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Impact evaluations of drug decriminalization and legal regulation: A systematic review

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ABSTRACT

Objectives: To review studies evaluating effects of drug decriminalization or legal regulation on drug availability, use, or related health and social harms globally.

Design: Systematic review with narrative synthesis.

Data sources: We searched MEDLINE, Embase, PsycINFO, Web of Science, and six additional databases for publications from 1 January 1970 through 4 October 2018.

Inclusion criteria: Peer-reviewed articles or published abstracts in any language with quantitative data on drug availability, use, or related health and social harms collected before and after implementation of *de jure* drug decriminalization or legal regulation. We excluded studies evaluating *de facto* decriminalization.

Data extraction and synthesis: Two independent reviewers screened titles, abstracts, and articles for inclusion. Extraction and quality appraisal (modified Downs and Black checklist) were performed by one reviewer and checked by a second, with discrepancies resolved by a third. We coded study-level outcome measures into metric groupings and categorized the estimated direction of association between the legal change and outcomes of interest.

Results: We screened 4860 titles and 221 full texts and included 114 articles. Most (n=104, 91.2%) were from the U.S., evaluated cannabis reform (n=109, 95.6%), and focused on legal regulation (n=96, 84.2%). 223 study outcome measures were categorized into 32 metrics, most commonly prevalence (39.5% of studies), frequency (14.0%), or perceived harmfulness (10.5%) of use of the decriminalized or regulated drug; or use of tobacco, alcohol, or other drugs (12.3%). Across all three substance use metrics, legal reform was most often statistically unassociated with use.

Conclusions: Studies evaluating drug decriminalization and legal regulation are concentrated in the U.S. and on cannabis legalization. Despite the range of outcomes potentially impacted by drug law reform, extant research is narrowly focused, with a particular emphasis on the prevalence of use. Metrics in drug law reform evaluations require improved alignment with relevant health and social outcomes.

Strengths and limitations of this study

- This is the first study to review all literature on the health and social impacts of decriminalization or legal regulation of drugs.
- We systematically searched 10 databases over a 38-year period, without language restrictions.
- The review was limited to study designs appropriate for evaluating interventions, nevertheless, most included studies used relatively weak evaluation designs.
- Given the study aim of characterizing metrics used in impact evaluations to date, included outcomes were heterogeneous and not quantitatively synthesized.
- Heterogeneity in the content and implementation of decriminalization and legal regulation policies was not considered in this review.

INTRODUCTION

An estimated 271 million people used an internationally scheduled ("illicit") drug in 2017, corresponding to 5.5% of the global population aged 15-64.[1] Despite decades of investment, policies aimed at reducing supply and demand have demonstrated limited effectiveness.[2,3] Moreover, prohibitive and punitive drug policies have had counterproductive effects by contributing to HIV and hepatitis C transmission,[4,5] fatal overdose,[6] mass incarceration and other human rights violations,[7,8] and drug market violence.[9] As a result, there have been growing calls for drug law reform [10–12] and in 2019, the United Nations Chief Executives Board endorsed decriminalization of drug use and possession.[13] Against this backdrop, as of 2017 approximately 23 countries had implemented *de jure* decriminalization or legal regulation of one or more previously illegal drugs.[14–16]

A wide range of health and social outcomes are affected by psychoactive drug production, sales, and use, and thus are potentially impacted by drug law reform. Nutt and colleagues have categorized these as physical harms (e.g., drug-related morbidity and mortality to users, injury to non-users), psychological harms (e.g., dependence), and social harms (e.g., loss of tangibles, environmental damage).[17,18] 2Concomitantly, a diverse and sometimes competing set of goals motivate drug policy development, including ameliorating the poor health and social marginalization experienced by people who use drugs problematically, shifting patterns of use to less harmful products or modes of administration, curtailing illegal markets and drug-related crime, and reducing the economic burden of drug-related harms.[19]

Given ongoing interest by states in drug law reform, a comprehensive understanding of their impacts to date is required. However, the scientific literature has not been well-characterized, and thus the state of the evidence related to these heterogenous policy targets remains largely unclear. While two meta-analyses have been published, both are narrowly focused on adolescent cannabis use. Sarvet et al. found that the implementation of medical cannabis policies in the United States (U.S.) did not lead to increases in the prevalence of past-month cannabis use among adolescents [20] and Melchior et al. found a small increase in use following recreational legalization that was reported only among lower-quality studies.[21]

Given increasing interest in drug law reform, as well as a lack of systematic assessment of outcomes beyond adolescent cannabis use to date, we conducted a systematic review of the effects of drug decriminalization or legal regulation on drug availability, use, or related health and social harms. We specifically aimed to characterize the topical and geographic range of existing studies, summarize the impacts of decriminalization and legal regulation, and identify gaps in the evidence.

METHODS

Consistent with our aim of synthesizing evidence on the impacts of decriminalization and legal regulation across the spectrum of potential health and social effects, we conducted a systematic review using narrative synthesis [22] without meta-analysis, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] The review protocol was registered in PROSPERO (CRD42017079681) and can be found online at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=79681.

Search Strategy and Selection Criteria

The review team developed, piloted, and refined the search strategy in consultation with a research librarian and content experts. We searched MEDLINE, Embase, PsycINFO, Web of Science, Criminal Justice Abstracts, Applied Social Sciences Index & Abstracts, International Bibliography of the Social Sciences, PAIS Index, Policy File Index, and Sociological Abstracts for publications from 1 January 1970 through 4 October 2018. We used MeSH terms and keywords related to (a) scheduled psychoactive drugs (b) legal regulation or decriminalization policies, and (c) quantitative study designs. See Appendix A for the final MEDLINE search strategy. For conference abstracts, we contacted authors for additional information on study methods and to identify subsequent relevant publications.

We included peer-reviewed journal articles or conference abstracts reporting on original quantitative studies that collected data both before and after the implementation of drug decriminalization or legal regulation. We defined decriminalization as the removal of criminal penalties for drug use and/or possession (allowing for civil or administrative sanctions) and legal

regulation as the development of a legal regulatory framework for the use, production, and sale of psychoactive drugs. Studies were excluded if they evaluated *de facto* (e.g., changes in enforcement practices) rather than *de jure* decriminalization or legal regulation (changes to the law). This exclusion applied to studies analyzing changes in outcomes following the U.S. Justice Department 2009 memo deprioritizing prosecution of cannabis-related offences legal under state medical cannabis laws. Eligible studies included outcome measures pertaining to drug availability, use, or related health and social harms, following the schema developed by Nutt and colleagues.[18]

Both observational studies and randomized controlled trials were eligible in principle, but no trials were identified. There were no geographic or language restrictions; titles, abstracts, and full-texts were translated on an as-needed basis for screening and data extraction. We excluded cross-sectional studies (unless they were repeated) and studies lacking pre- and post-implementation data collection because such designs are inappropriate for evaluating intervention effects.

Data Analysis

Screening and data extraction were conducted in DistillerSR (Evidence Partners, Ottawa, Ontario). We began with title-only screening to identify potentially relevant titles. Two reviewers screened each title. Unless both reviewers independently decided a title should be excluded, it was advanced to the next stage. Next, two reviewers independently screened each potentially eligible abstract. Inter-rater reliability was good (weighted Kappa at the question level=0.75). At this stage, we retrieved full-text copies of all remaining references, which were screened independently by two reviewers. Disagreements on inclusion were resolved through discussion with the first author. Finally, one reviewer extracted data from each included publication using a standardized, pre-piloted form and performed quality appraisal. A second reviewer double-checked data extraction and quality appraisal for every publication, and the first author resolved any discrepancies.

The data extraction form included information on study characteristics (author, title, year, geographic location), type of legal change studied and drug(s) impacted, details and timing of the legal change (e.g., medical vs. recreational cannabis regulation), study design, sampling

approach, sample characteristics (size, age range, proportion female), and quantitative estimates of association. We coded study-level outcome measures into metric groupings, using 24 pre-specified categories and a free-text field (see Figure 3 for full list). Examples of metrics include: prevalence of use of the decriminalized or regulated drug, overdose or poisoning, and non-drug crime.

We also categorized the estimated direction of association of the legal change on outcome measure(s) of interest (beneficial, harmful, mixed, or null).2 These associations were coded at the outcome (not study) level and classified as beneficial if a statistically significant increase in a positive outcome (e.g., educational attainment) or decrease in a negative outcome (e.g., substance use disorder) was attributed to implementation of decriminalization or legal regulation, and vice-versa for harmful associations. The association was categorized as mixed if associations were both harmful and beneficial across participant subgroups, exposure definitions (e.g., loosely vs. tightly regulated medical cannabis access), or timeframes. The association was categorized as null if no statistically significant changes following implementation of drug decriminalization or legal regulation were detected. We set statistical significance at a=0.05, including in cases where authors used more liberal criteria.

Quality assessment at the study level was conducted for each full-length article using a modified version of the Downs and Black checklist [24] for observational studies (see Appendix B). Each study could receive up to 18 points, with higher scores indicating more methodologically rigorous studies. Conference abstracts were not subjected to quality assessment due to limited methodologic details.

Patient and Public Involvement

This systematic review of existing studies did not include patient or public involvement.

RESULTS

Study Characteristics

As shown in the PRISMA Flow Diagram (Figure 1), we screened 4860 titles and abstracts and 213 full texts, with 114 articles meeting inclusion criteria (Appendix C). Key reasons for

Table 1. Characteristics of studies evaluating drug decriminalization or legal regulation, 1970-2018

Characteristic	Total (%) n (%) (*n* = 114)	Decriminalization[a] n (%) (*n* =19)	Legal regulation[a] n (%) (*n* =96)
Country			
United States	104 (91.2)	10 (52.6)	95 (99.0)
Australia	3 (2.6)	3 (15.8)	0 (0.0)
Portugal	2 (1.8)	2 (10.5)	0 (0.0)
China	1 (0.9)	0 (0.0)	1 (1.0)
Czech Republic	1 (0.9)	1 (5.3)	0 (0.0)
Mexico	1 (0.9)	1 (5.3)	0 (0.0)
Multi-country[b]	2 (1.8)	2 (10.5)	0 (0.0)
Focus of drug law reform			
Cannabis	109 (95.6)	15 (78.9)	95 (99.0)
Opium	1 (0.9)	0 (0.0)	1 (1.0)
Peyote	1 (0.9)	1 (5.3)	0 (0.0)
Multiple/All drugs	3 (2.6)	3 (15.8)	0 (0.0)

exclusion at the full-text screening stage were that the article did not report on original quantitative research (n=59) or did not evaluate decriminalization or legal regulation as defined herein (n=23). Details of each included study are presented in Supplementary Table 1. Included studies had final publication dates from 1976-2019; 44.7% (n=51) were first published in 2017-2018, 43.9% (n=50) were published in 2014-2016 and 11.4% (n=13) were published before 2014.

Characteristics of included studies are described in Table 1, both overall and stratified by whether they evaluated decriminalization (n=19) or legalization (n=96) policies (one study evaluated both policies). Most studies (n=104, 91.2%) were from the U.S. and examined impacts of liberalizing cannabis laws (n=109, 95.6%). Countries represented in non-U.S. studies included Australia, Belgium, China, Czech Republic, France, Mexico, and Portugal. The most common study designs were repeated cross-sectional (n=74, 64.9%) or controlled before-and-after (n=26, 22.8%) studies and the majority of studies (n=87, 76.3%) used population-based sampling methods. Figure 2 illustrates the geographic distribution of studies among countries where national or subnational governments had decriminalized or legally regulated one or more drugs

Study design			
Cohort	4 (3.5)	0 (0.0)	4 (4.2)
Controlled before-and-after	26 (22.8)	6 (31.6)	20 (20.8)
Interrupted time series	6 (5.3)	0 (0.0)	6 (6.3)
Repeated cross-sectional	74 (64.9)	11 (57.9)	64 (66.7)
Uncontrolled before-and-after	4 (3.5)	2 (10.5)	2 (2.1)
Sampling approach			
Convenience	22 (19.3)	5 (26.3)	18 (18.8)
Population-based	87 (76.3)	13 (68.4)	74 (77.1)
Administrative records	45 (39.5)	6 (31.6)	39 (40.6)
Household survey	25 (21.9)	5 (26.3)	20 (20.8)
School-based survey	17 (14.9)	2 (10.5)	15 (15.6)
Unspecified	5 (4.2)	1 (5.3)	4 (4.2)

a. Combined total exceeds number of studies because some evaluated both decriminalization and legal regulation.
b. One global study and one from Belgium, Portugal, and France

Study Quality

Quality assessment was performed for the 93 full-length articles included in the review, excluding 21 conference abstracts (Supplementary Table 1). Scores ranged from 7 to 18 of 18 possible points, with a mean of 14.4 (SD=2.56). Quality scores were similar comparing U.S. to non-U.S.-based studies (X=14.4 and 13.7, respectively, p=0.386) but higher for studies evaluating legal regulation (X=14.8) versus decriminalization (X=12.8) (p=0.003). Study quality did not appear to increase over time (e.g., X=14.0 in 2014 and 14.4 in 2018).

Study Outcome Measures and Metrics

Across 114 studies we extracted 223 outcome measures, which were coded into 32 metrics (Figure 3). The most common metric employed by studies was the prevalence of use of the decriminalized or legally regulated drug, which was examined in 39.5% of studies (n=45) and represented 22.4% of outcome measures (n=50). Of these studies, 14 (31.1%; 8 full-length articles and 6 abstracts) did not report any other metric [25–38] and an additional 5 articles

(11.1%) reported on the prevalence of use in addition to a single drug-related perception metric (either harmfulness or availability).[39–43] The second most common metric was the frequency of use of the decriminalized or legally regulated drug (14.0% of studies, n=16) and the third was the prevalence or frequency of use of tobacco, alcohol, or drugs that remained illegal (12.3% of studies, n=14; 9.4% of outcome measures, n=21). The fourth most commonly employed metric was any change in the perceived harmfulness of the decriminalized or regulated drug (10.5% of studies, n=12), which was assessed among adolescents or young adults in all studies except for one that assessed this metric among parents.[44]

All other metrics were assessed in <10% of included studies. Health service utilization was evaluated in 7.9% of studies (n=9) using 12 outcome measures, primarily related to emergency department visits and/or hospitalizations. Prescribed (primarily opioid) drug use and perceived availability of the decriminalized or legally regulated drug were reported in 7.0% of studies each (n=8). Overdose or poisoning by the decriminalized or regulated drug, and by other drugs (predominantly opioids), were examined in 5.3% (n=6) and 6.1% of studies (n=7), respectively. Driving while under the influence of the decriminalized or regulated drug (cannabis) was examined in seven studies (6.1%) inclusive of eight outcome measures. Notably, some studies assessed the proportion of fatally injured drivers screening cannabis-positive, versus the overall prevalence of impaired driving. Remaining metrics were measured in less than 5% of studies (Figure 3). Some pre-specified metrics were not represented in any of the articles, including infectious disease incidence (e.g., HIV, Hepatitis C), environmental impacts (e.g., drug production waste, discarded needles), and labor market participation.

Of the ten studies conducted outside the U.S., six focused on cannabis decriminalization. All three studies from Australia examined the prevalence of cannabis use post-decriminalization,[30,33,45] while one also measured perceived cannabis availability.[45] Following cannabis decriminalization, one European multi-country study (Belgium, Portugal, France) examined the prevalence of cannabis use and uptake of cannabis-related addictions treatment [46] and one Czech study considered the age of first cannabis use.[47] An international study using United Nations Office on Drugs and Crime data from 102 countries compared availability, as reflected by cannabis seizures and plant eradication, in countries that had

decriminalized cannabis versus those that had not.[48] Three non-U.S. studies evaluated decriminalization of all psychoactive drugs. Two studies from Portugal examined health care and non-health-care costs and psychoactive drug prices, respectively.[49,50] One study from Mexico examined drug-related criminal justice involvement (arrests) and (violent) crimes.[51] Finally, a study of historic opium legalization in China (1801-1902) measured the price and availability (quantity of exports) of opium before and after legalization.[52]

Impacts of Decriminalization and Legal Regulation

Supplementary Table 2 tallies findings for each of the metrics; here we focus on those examined in more than 5% of studies. Across all three substance use metrics (prevalence of use, frequency of use, and use of other alcohol or drugs), drug law reform was most often statistically unassociated with use (with null findings for 48.0-52.4% of outcome measures falling under these metrics). With respect to change in perceived harmfulness of the decriminalized or regulated drug, mixed results were found in half of cases, with heterogeneity detected on the basis of age, gender, and state.[39,43,53–55] For example, legal regulation of cannabis for medical use was associated with greater perceived harmfulness of cannabis among eighth graders but not older students in an analysis of U.S. Monitoring the Future data [39] while a study employing U.S. National Survey on Drug Use and Health data found greater perceived harmfulness of cannabis among young adults aged 18-25 but not adolescents aged 12-17.[55]

Among nine studies that employed health service utilization metrics, harmful effects were reported for six of nine outcome measures, with increases in emergency department visits and/or hospitalizations attributed to decriminalization or legal regulation.[56–61] However, all but one of those studies [58] assessed change over time in one jurisdiction, without a control group. In contrast, six of nine prescription drug use associations were beneficial, with reductions observed in rates of opioid [62–66] and other drug prescribing [67,68] attributed to legal regulation of cannabis for medical use. Perceived availability of the decriminalized or regulated drug appeared largely unaffected by decriminalization (null associations for five of eight outcome measures) but one study indicated increased perceived availability of cannabis among Colorado, U.S. adolescents following legal regulation for adult use.[69] Across the subset of seven outcome

measures for overdose or poisoning by the decriminalized or regulated drug (cannabis), in all cases an increase in calls to poison control centers or unintentional pediatric exposures was reported.[57,70–74] However, studies assessing the impacts of cannabis regulation on overdose or poisoning by drugs other than cannabis concluded that the effects were either beneficial (four outcome measures[73,75–77]) or mixed/null (three outcome measures[78–80]). Driving while under the influence of cannabis was most often found to increase following decriminalization or legal regulation (five of eight outcome measures; [81–85]).

DISCUSSION

This systematic review identified 114 peer-reviewed publications and conference abstracts evaluating the impacts of drug decriminalization or legal regulation from 1970-2018. Within this search period, 88.6% were published in 2014 or later. This rapid growth in scholarship was driven by the implementation and subsequent evaluation of cannabis legalization in a number of U.S. states beginning in 2012, and knowledge production will surely continue to accelerate as longer-term data become available and as other jurisdictions (e.g., Canada, Uruguay) analyze the effects of recently implemented cannabis legalization. The present study provides an overview of the emerging literature based on our systematic review and suggests three key patterns.

First, peer-reviewed evaluations of drug decriminalization and legal regulation are overwhelmingly geographically concentrated in the U.S. and focused on cannabis legalization. It is notable that decriminalization in the absence of legal regulation was evaluated in only 18 studies (15.8%), despite being far more common globally than legal regulation. These gaps may hamper evidence-based drug law reform in countries that are less well-developed, play a substantial role in drug production and transit, or have different baseline levels of substance (mis)use as compared to the U.S.

Second, prevalence of use was the predominant metric used to assess the impact of drug law reform, despite its limited clinical significance (e.g., much cannabis use is non-problematic) and limited responsiveness to drug policy. This is because ecological analyses have indicated little relationship between drug policies and prevalence of use,[2] as have studies assessing within-state change in use related to legal regulation;[20] these findings are further confirmed by the

preponderance of evidence synthesized in this review, which suggests that population prevalence of use is largely unaffected by drug policy. By contrast, drug policies may be able to influence the types of drugs that people use, drug-related risk behaviors, and modes of drug consumption.[86] Metrics to assess these outcomes, however, were lacking in the reviewed literature. For example, only one study (0.8%) investigated whether legal regulation of cannabis was associated with changes in the mode of cannabis consumption.[69] Although the prevalence of use was often measured alongside more clinically or socially significant metrics (e.g., prevalence of substance use disorders, educational outcomes among young adults), 42.2% of studies assessing substance use prevalence included that metric alone or in combination with a single drug-related attitude metric.

Third, there was a lack of alignment between the stated policy objectives of drug law reform and the metrics used to assess its impact in the scientific literature. For instance, removal of criminal sanctions to prevent their negative sequelae is a key rationale for decriminalization and legal regulation,[12,13,87] but only four studies (3.5%) evaluated changes in drug-related criminal justice involvement following drug law reform. As a result, there is a risk that decisions on drug policy may be informed by inappropriate metrics. Promisingly, in recent months, additional studies assessing legal regulation that employ a range of criminal justice metrics have been published.[88,89] Finally, despite ample evidence of the impact of criminalization on infectious disease transmission and acquisition risks,[5] we found no studies evaluating the impact of decriminalization on these outcomes.

Strengths and Limitations

Both the included studies and our systematic review have important strengths and limitations. To our knowledge, we conducted the first review of all global literature on decriminalization and legal regulation and applied no language restrictions. All eligible articles identified were published in English; this may reflect a paucity of evaluation research published in other languages and/or limitations of our search strategy. In addition, we excluded grey literature and study designs that are not suited to evaluating policy effects (e.g., cross-sectional studies), but these restrictions may have narrowed the geographic scope of included studies. Nevertheless,

most included studies used weaker eligible study designs that are vulnerable to pre-existing trends and confounding; only 22.8% and 5.3% respectively used controlled before-and-after or interrupted time series designs to address these threats to validity.

This narrative synthesis did not focus on estimating the outcome-specific effects of particular decriminalization or legal regulation policies but instead sought to characterize the metrics employed to date. With respect to both the individual studies and our synthesis, the implementation and specific provisions of drug policies vary widely. Decriminalization policies vary in their definitions of quantities for personal use, application of administrative penalties, and the extent to which the law "on the books" is reflected in policing and criminal justice practice. Indeed, in some jurisdictions with nominal decriminalization, arrests for possession of small quantities of the decriminalized drugs remain routine.[51] Legal regulation models for cannabis are also heterogenous. For example, policies legally regulating cannabis for medical use may or may not allow for legal dispensaries, and this provision has been shown to substantially modify the impact of legal regulation on cannabis use.[90] To the extent that individual studies employed crude exposure measures (e.g., presence versus absence of a law), they may have obscured context-dependent effects of drug law liberalization.

Our use of vote-counting in this synthesis (i.e., categorizing individual outcome measures as indicating beneficial, harmful, mixed/subgroup-specific, or no statistically significant associations) is subject to the same limitation. Vote-counting should also be interpreted with caution in light of the heterogeneity of outcome definitions and the inherent arbitrariness of statistical significance thresholds. Moreover, as illustrated by a recently published extension of the included article by Bachhuber et al.,[76] multiple high-quality studies may generate results that are later revealed to be spurious as additional follow-up data become availability. Specifically, Shover et al. demonstrated that the positive association reported between medical cannabis legalization and opioid overdose mortality in 1999-2010 reversed direction in later years, suggesting that earlier findings of a protective effect should not be given causal interpretations.[91]

Conclusions

The findings of this review indicate a need for a broadening of the metrics used to assess the impacts of drug decriminalization and legal regulation. Given the growing number of jurisdictions considering decriminalization or legal regulation of psychoactive drugs,[14–16] the disproportionate emphasis on metrics assessing drug use prevalence, as well as the limited geo-cultural diversity in evaluations, are concerning. Experts have called for a more fulsome approach to evaluating drug policies in line with public health and the United Nations Sustainable Development Goals, with attention to the full breath of health and social domains potentially impacted, including human rights and social inclusion (e.g., stigma), peace and security (e.g., drug market violence), development (e.g., labor market participation) drug market regulation (e.g., safety of the drug supply), and clinically-significant health metrics (e.g., drug-related morbidity).[92] Drawing on methods such as multi-criterion decision analysis,[19] the engagement of both scientists and policymakers in priority-setting may help to produce evidence that provides a more comprehensive understanding of the breadth of impacts that should be anticipated with drug law reform efforts.

Figure 1 Legend

PRISMA Flow Diagram

Figure 2 Legend

Number of included studies from countries that implemented decriminalization or legal regulation by 2017

Note: Policy changes were classified, following the review inclusion criteria, based on the implementation of a change to national or subnational law to decriminalize drug use and/or possession or to legalize at least one class of drugs. We did not evaluate the extent to which legal changes were reflected in policing and criminal justice practice. Implementation of cannabis legalization for medical purposes only is not reflected in this map.

Figure 3 Legend

Metrics examined by included studies.

Author contributions

DW and AIS conceptualized and supervised the review. CZ designed and conducted the literature searches. AIS drafted the manuscript. SC, ZM, and AIS conducted screening and data extraction. NZ contributed to drafting the manuscript and developing figures. All authors

contributed to interpretation of findings and revising the manuscript for important intellectual content.

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Competing interests

We have no competing interests to declare.

Data sharing statement

All relevant data are contained within the article and supplementary materials.

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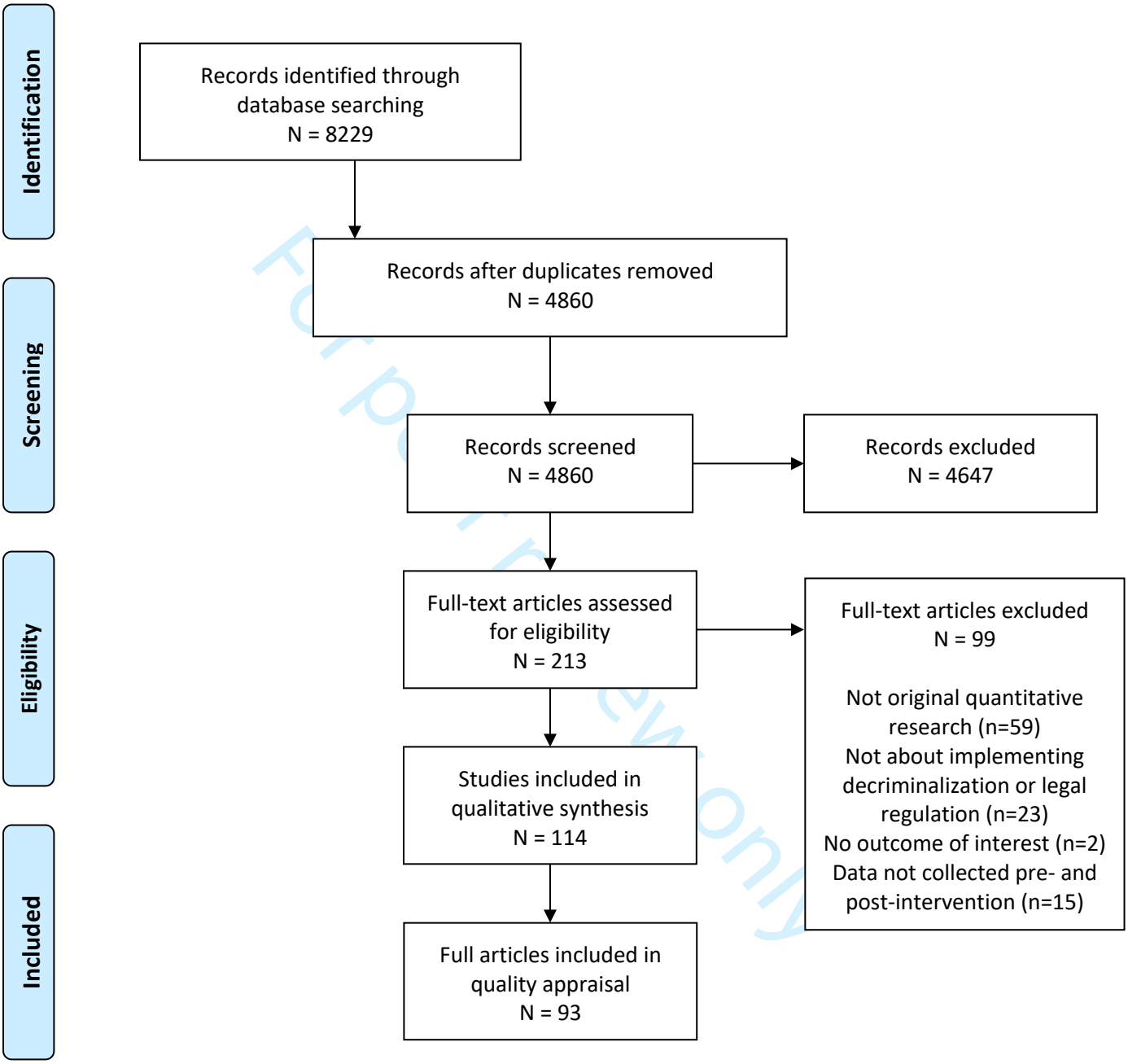
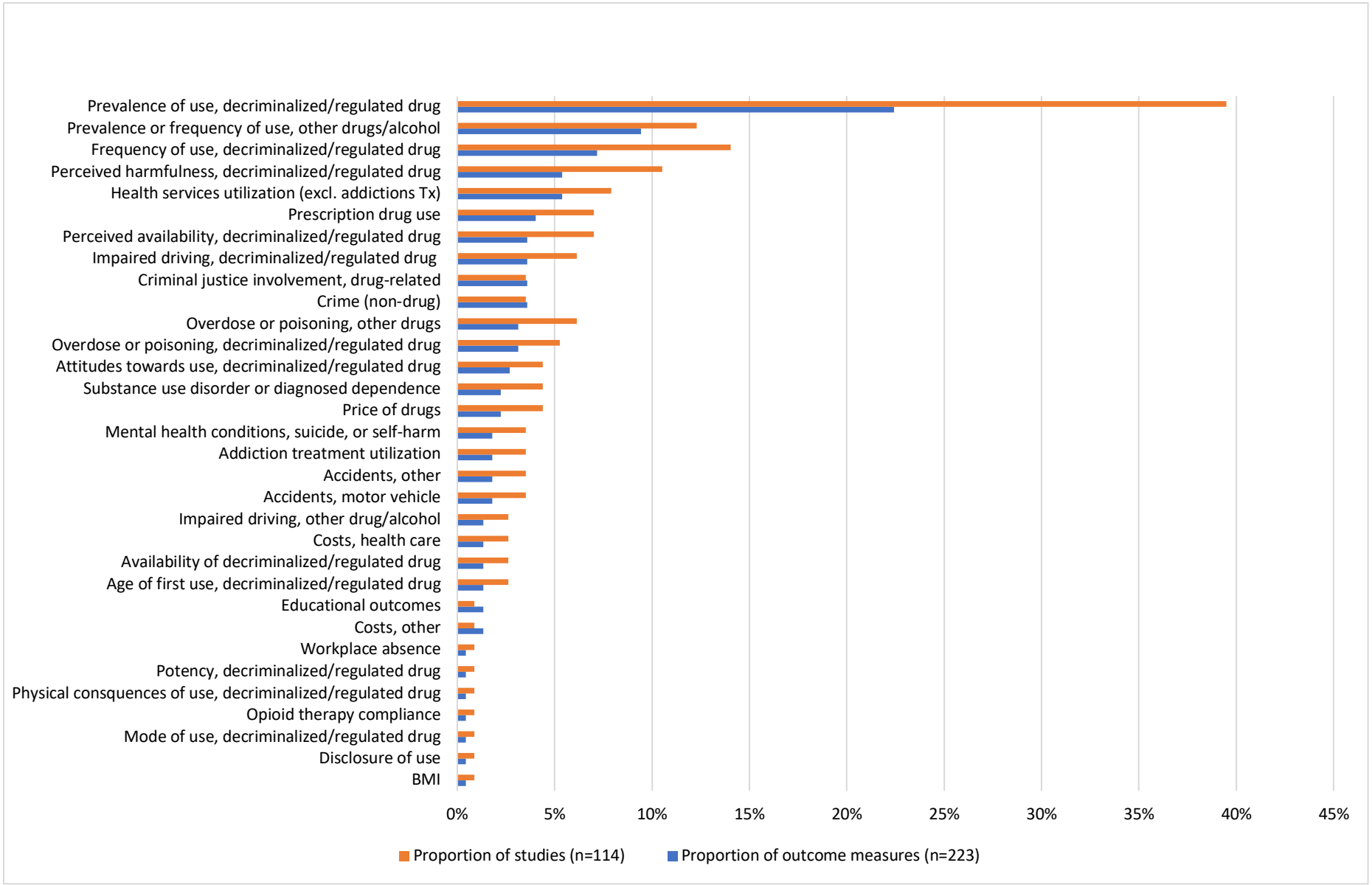


Number of included studies from countries that implemented decriminalization or legal regulation by 2017
Note: Policy changes were classified, following the review inclusion criteria, based on the implementation of a change to national or subnational law to decriminalize drug use and/or possession or to legalize at least one class of drugs. We did not evaluate the extent to which legal changes were reflected in policing and criminal justice practice. Implementation of cannabis legalization for medical purposes only is not reflected in this map.

619x332mm (96 x 96 DPI)


Prevalence of use, decriminalized/regulated drug
Prevalence or frequency of use, other drugs/alcohol
Frequency of use, decriminalized/regulated drug
Perceived harmfulness, decriminalized/regulated drug
Health services utilization (excl. addictions Tx)
Prescription drug use
Perceived availability, decriminalized/regulated drug
Impaired driving, decriminalized/regulated drug
Criminal justice involvement, drug-related
Crime (non-drug)
Overdose or poisoning, other drugs
Overdose or poisoning, decriminalized/regulated drug
Attitudes towards use, decriminalized/regulated drug
Substance use disorder or diagnosed dependence
Price of drugs
Mental health conditions, suicide, or self-harm
Addiction treatment utilization
Accidents, other
Accidents, motor vehicle
Impaired driving, other drug/alcohol
Costs, health care
Availability of decriminalized/regulated drug
Age of first use, decriminalized/regulated drug
Educational outcomes
Costs, other
Workplace absence
Potency, decriminalized/regulated drug
Physical consquences of use, decriminalized/regulated drug
Opioid therapy compliance
Mode of use, decriminalized/regulated drug
Disclosure of use
BMI
0%
5%
10%
15%
20%
25%
30%
35%
40%
45%
Proportion of studies (n=114)
Proportion of outcome measures (n=223)

Supplementary Table 1. Included Studies

	Reference	Setting Legal change	Study design, dates [Comparison group or condition]	Sampling approach Sample size	Outcomes	Effects	Quality
1.	Adam 2017	Belgium, Portugal, France Cannabis decriminalization	Controlled before-and-after, 1996-2010 [Austria, Germany, Greece, Ireland, Italy, Netherlands, Spain, Sweden]	Convenience sampling 89 treatment units	*Addiction treatment utilization:* # of first-time drug treatment clients reporting cannabis as primary indication, per reporting treatment unit	No significant effect of decriminalization. *B*= 2.66, *SE*=8.72, *P*=0.770	13
					Prevalence of use, decriminalized/regulated drug(s): past-year cannabis use	No significant effect of decriminalization. *B* = 1.88, *SE*=1.77, *P*=0.310	
2.	Allshouse 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2013; 2014	Population-based; Admin record data N=743	*Prevalence of use, decriminalized/regulated drug(s)*: self-reported cannabis use during pregnancy	No significant effect of RCL (from 4.5% to 7.5%, *p*=0.06)	A *
					Prevalence of use, decriminalized/regulated drug(s): cannabis-positive urine screen during pregnancy	No significant effect of RCL. Adjusted prevalence difference = 0.03, *P*=0.99.	
3.	Anderson 2013	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1990-2010	Convenience sampling *Study A*: 8,271 cannabis purchases *Study B*: 1071 fatalities	*Price of drugs*: median price of cannabis in state and year	9.8% decrease in price of high-quality cannabis, controlling for state-specific time trends. Lagged models indicate price reductions not significant until 4th year after MCL. Effects on price of low-quality cannabis largely statistically insignificant.	11
					Accidents, motor vehicle: traffic fatality outcomes per 100,000; primary outcome is total fatalities.	No significant change in fatalities, controlling for state-specific time trends. In lagged models, MCL associated with 8-13% fatality reductions in years 1-4, with reduction attenuated and no longer significant after 5 years, controlling for state-specific time trends.	

4.	Anderson 2014	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1990-2007 [States that did not implement MCL]	Population-based; Admin record data	*Mental health conditions, suicide, or self-harm*: annual suicide rates per 100,000 among individuals 15+	No difference in suicide rate overall. Reduction among males, (log) rate difference =0.047* (95% CI: –0.089, –0.005). By age, significant reductions among males from 20-39 and among females >=60.	16
5.	Anderson 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1992-2015	Population-based; Admin record data N= 1224 state-years	*Accidents, other*: Workplace fatalities by state from the Bureau of Labor Statistics	No difference in fatality rate overall. Reduction among those aged 25-44 only. Adjusted rate ratio = 0.805 (95% CI: 0.662, 0.979).	15
6.	Anderson 2015	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1993-2011	Population-based; School-based survey N=862,695	*Prevalence of use, decriminalized/regulated drug(s)*: past 30 day use	No significant effect of MCL: % difference, combined national and state YRBS = -0.007, SE=0.011, p>0.05.	15
					Frequency of use, decriminalized/regulated drug(s): used ≥ 10 times in past 30 days	No significant effect of MCL: % difference, combined national and state YRBS = -0.004, SE=0.006, p>0.05.	
					Actual availability of decriminalized/regulated drug(s): offered, sold, or given an illegal drug on school property in past year	MCL associated with reduction in availability, % difference, combined national and state YRBS = -0.020, SE=0.008, p<0.05;	
7.	Arredondo 2018	Mexico Decriminalization of all drugs	Repeated cross-sectional study, 2009-2014	Population-based; Admin record data	*Criminal justice involvement*: Monthly number of drug possession arrests per precinct.	Decriminalization law not associated with arrests, Beta for ln(possession arrests)=0.187, SE=0.151, p>0.05.	14
					Crime (non-drug): Violent crime arrests (injuries, robbery, homicides)	Law not associated with arrests, b=0.001, SE=0.090, p>0.05.	

					Crime (non-drug): Non-violent arrests (theft, possession of stolen car)	Law not associated with arrests, b=-0.043, SE=0.071, p>0.05.	
8.	Aydelotte 2017	United States Legal regulation of cannabis for recreational use (RCL)	Controlled before-and-after study, 2009-2015 [8 similar states without MCL or RCL]	Population-based; Admin record data N=60,737	*Accidents, motor vehicle*: Annual number of motor vehicle crash fatalities	RCL not associated with crash fatalities, adjusted difference in difference coefficient: +0.2 (95% CI: -0.4, +0.9).	15
9.	Bachhuber 2014	United States Legal regulation of cannabis for medical use (MCL)	Interrupted time series study, 1999-2010	Population-based; Admin record data	*Overdose or poisoning, other drug*: opioid analgesic overdose mortality rate	MCL associated with reduced mortality, adjusted percentage change in annual rate= -24.8% (95% CI: -37.5, -9.5), p = .003.	16
10.	Banerji 2017	United States Legal regulation of cannabis for recreational use	Repeated cross-sectional study, 2011-2015	Population-based; Admin record data N=777 exposures	*Overdose or poisoning, decriminalized/regulated drug*: cannabis calls to poison control center	Apparent increase (from 86 in 2011 to 231 in 2015); no statistical tests reported.	A *
					Overdose or poisoning, other drug: synthetic cannabinoid calls to poison control center	Apparent decrease (100 in 2013 and 17 in 2014); no statistical tests reported.	
11.	Bell 2015	United States Legal regulation of cannabis for medical use (MCL) and recreational use	Repeated cross-sectional study, 2008-2014	Population-based; Admin record data N=29	*Accidents, other*: hydrocarbon burns referred to the University of Colorado Hospital	Before MCL (Jan 2008-Aug 2009): 0 cases During MCL (Oct 2009-Dec 2013): 19 cases During recreational legalization (Dec 2013-Aug 2014): 12 cases No statistical tests reported.	11
12.	Bjordal 2015	United States Legal regulation of cannabis for recreational use	Repeated cross-sectional study, 2013-2014	Population-based; Admin record data N=245 exposures	*Overdose or poisoning, decriminalized/regulated drug*: Cannabis calls to poison control center (p.694)	Apparent increase (from 158 in 2013 to 245 in 2014); no statistical tests reported.	A *

13.	Blachly 1976	United States Cannabis decriminalizatio n	Uncontrolled before-and-after study, 1970; 1975	Convenience sampling N=627 admissions	*Health services utilization*: % of drug abuse admissions to Dammasch State Hospital due to cannabis	Prevalence from 6.7% (1970) to 2.5% (1975); no statistical tests reported.	8
14.	Boyle 2014	United States Cannabis decriminalizatio n	Repeated cross-sectional study, 2011-2013	Population-based; Admin record data N=11 incidents	*Accidents, other*: explosions of gases related to hash oil manufacturing	Two events in 2 years prior, nine events in 7 months post-decriminalization (before legal sales); no statistical tests reported.	A *
15.	Bradford 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2010-2015	Population-based; Admin record data N=132.6 million physician-drug-year observations	*Prescription drug use*: total number of daily opioid dose prescriptions filled (in millions)	MCL associated with fewer daily doses filled in states with active dispensaries (-3.742 million, 95% CI: -6.289, -1.194) and in states with home cultivation (-1.792 million, 95% CI: -3.532, -0.052). Results also varied by type of opioid.	18
16.	Bradford 2016	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 2010-2013 [States without a medical marijuana law at a given time]	Population-based; Admin record data N= 588,808-2,496,608	*Prescription drug use*: among Medicaid Part D enrollees, average daily doses filled annually per physician for FDA-approved drugs treating conditions that cannabis may be used to treat (anxiety, depression, glaucoma, nausea, pain, psychosis, seizures, sleep disorders, spasticity)	MCL associated with statistically significant ($p<0.05$) reductions in daily doses filled for 7 of 9 conditions (difference-in-difference coefficients from -265 daily doses for depression to -1826 for pain), no significant effects for glaucoma or spasticity.	17
					Costs, health care: estimated annual change in Medicaid Part D spending (program and enrollee)	Estimated prescription drug cost savings from 2010-2013 attributed to MCL = $515,194,125.	

17.	Bradford 2017	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 2007-2014 [States without MCL in a given quarter]	Population-based; Admin record data	*Prescription drug use*: average number of daily prescription drug doses dispensed per fee-for-service Medicaid beneficiary for FDA-approved drugs treating conditions that cannabis may be used to treat.	MCL associated with statistically significant ($p<0.05$) reductions in daily doses per beneficiary for 5 of 9 conditions (depression, nausea, pain, psychosis, and seizures). Estimated proportion reductions in dispensed doses ranged from 11% for pain to 17% for nausea.	17
					Costs, health care: estimated annual change in Medicaid fee-for-service spending on prescription drugs with medical cannabis indications	Estimated Medicaid fee-for-service prescription drug cost savings from 2007-2014 attributed to MCL = 2,694.1 million	
18.	Brooks-Russell 2019	United States Legal regulation of cannabis for recreational use	Repeated cross-sectional study, 2013-2015	Population-based; School-based survey N = 26,019 (2013) N = 15,970 (2015)	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime use; past 30-day use.	No significant change in lifetime or past 30-day use following legal regulation.	15
					Prevalence of use, other drugs or alcohol: past 30-day use of cigarettes; past 30-day use alcohol; lifetime non-medical prescription drug use; lifetime cocaine use.	Decrease in past 30-day cigarette use from 2013 to 2015 (12.1 to 8.6%, $p<0.01$). No significant changes in other drug or alcohol use.	
					Perceived harmfulness of decriminalized/regulated drug(s): high vs. low perceived accessibility, wrongfulness, parental disapproval, and harmfulness.	Decrease in high perceived harmfulness (52.9% to 47.7%, $p<0.01$). No significant changes in other perceptions.	
					Frequency of use, decriminalized/legalized drug(s): >20 occasions of use in past 30 days, among those who reported past 30-day use.	Decrease in frequent use among past-30-day users (33.2% to 26.8%, $p<0.01$).	
					Prevalence of use, decriminalized/regulated drug(s): use on school property, among those who reported past 30-day use.	Decrease in use on school property among past-30-day users (5.7% to 4.4%, $p=0.03$).	

19.	Calcaterra 2018	United States Legal regulation of cannabis for recreational use (RCL)	Interrupted time series study, 2009-2015	Population-based; Admin record data N=370,612	*Health services utilization*: cannabis-related hospitalizations	RCL associated with an increase in hospitalizations: adjusted annual rates of inpatient and emergent hospitalizations were 2.4 and 4.3 times higher in 2015 as compared to 2009 ($p<0.001$). A reduced segmented regression model shows a significant increase in slope post-RCL ($b= 1.835$, $SE=0.218$, $p< 0.0001$).	A *
20.	Cassidy 2015	United States Legal regulation of cannabis for recreational use	Uncontrolled before-and-after study, 2008-2014	Convenience sampling N=13,945	*Prevalence of use, decriminalized/regulated drug(s)*: among substance use treatment clients	Increase from 21.3% in 2008 to 32.8% in 2014 ($p<0.001$).	A *
					Prevalence of use, decriminalized/regulated drug(s): past-year initiation	No significant change in past-year initiation.	
21.	Cerda 2018	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1991-2015 [States without MCL]	Population-based; School-based survey N=1,179,372	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	Decrease in 8th grade (aOR=0.72; 95% CI: 0.62, 0.84). No significant changes in 10th or 12th.	18
					Prevalence of use, other drugs or alcohol: binge drinking in past two weeks	Decrease in 8th grade (aOR=0.72; 95% CI: 0.65, 0.79). No significant changes in 10th or 12th.	
					Prevalence of use, other drugs or alcohol: past 30-day cigarette use	Decrease in 8th grade (aOR=0.74; 95% CI: 0.66, 0.82) and increase in 12th grade (aOR=1.17; 95% CI: 1.06, 1.29).	
					Prevalence of use, other drugs or alcohol: past 30-day non-medical prescription drug use	Decrease in non-medical prescription opioid use in 8th grade (aOR=0.43; 95% CI: 0.36, 0.52) and increase in 12th grade (aOR=1.42; 95% CI: 1.21, 1.66). Decrease in prescription amphetamine use (aOR=0.71; 95% CI: 0.63, 0.81) and prescription tranquilizer use (aOR=0.83; 95% CI: 0.71, 0.98) in 8th grade only.	
					Prevalence of use, other drugs or alcohol: past 30-day non-cannabis illicit drug use	Decrease in 8th grade only (aOR=0.77; 95% CI: 0.69, 0.86).	

22.	Cerda 2017	United States Legal regulation of cannabis for recreational use (RCL)	Controlled before-and-after study, 2010-2015	Population-based; School-based survey N=253,902	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	Increase in 8th and 10th grade in Washington but not Colorado (difference-in-difference WA vs. non-RCL= 3.2% in 8th grade, p=0.03; 5.0% in 10th, p=0.01).	18
					Perceived harmfulness of decriminalized/regulated drug(s): great or moderate vs. low or no risk	Decreased perceived harmfulness in 8th and 10th grade in Washington but not Colorado (difference-in-difference WA vs. non-RCL= -9.3% in 8th grade, p=0.01; -9.0% in 10th, p=0.02).	
23.	Cerveny 2017	Czech Republic Cannabis decriminalizatio n	Repeated cross-sectional study, 2008; 2012	Population-based; Household survey N=1524	*Age of first use, decriminalized/regulated drug*	No significant effect of decriminalization on hazard of initiation.	13
24.	Choo 2014	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1991-2011 [Matched to state in geographic proximity without MCL]	Population-based; School-based survey N= 11,703,100	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	No significant effect of MCL.	16
25.	Chu 2014	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1988-2008 [Non-MCL state years]	Population-based; Admin record data N=12,157 city-years	*Criminal justice involvement*: adult male cannabis possession arrest rates	No significant effect of MCL.	15
					Criminal justice involvement: ratio of cannabis possession arrests to all arrests among adult males	MCL associated with 9.3-12.1% increase in ratio of cannabis to non-cannabis arrests.	
					Addiction treatment utilization: ratio of cannabis-related to all treatment admissions among adult male non-criminal justice referrals	MCL associated with 9.1-10.5% increase in ratio of cannabis to non-cannabis admissions.	

26.	Couper 2014	United States Cannabis decriminalization	Repeated cross-sectional study, 2009-2013	Convenience sampling N=25,719	*Impaired driving, decriminalized/regulated drug(s)*: prevalence of THC in blood toxicology results from suspected impaired driving cases in Washington State	Increased prevalence of active THC after decriminalization (24.9% vs. 19.1%, p<0.05).	9
27.	Donnelly 1995	Australia Cannabis decriminalization	Repeated cross-sectional study, 1985-1993	Population-based; Household survey N= 2257 to 3500	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime cannabis use	No significant interaction between survey year and state: lifetime use did not increase at a significantly greater rate in South Australia (decriminalized).	15
					Perceived availability of decriminalized/regulated drug(s): been offered cannabis	No significant interaction between survey year and state.	
					Attitudes towards use, decriminalized/regulated drug(s): would take cannabis if offered by a trusted friend	Proportion reporting willingness to try increased from 10% in 1985 to 18% in 1991 in South Australia, significant positive interaction between survey year and state (p<0.05).	
					Prevalence of use, decriminalized/regulated drug(s): weekly use of cannabis	No significant interaction between survey year and state.	
28.	Donnelly 2000	Australia Cannabis decriminalization	Repeated cross-sectional study, 1985; 1988; 1991; 1993; 1995	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime use	Greater increase in lifetime use in South Australia (decriminalized) than the rest of Australia (test for trend, p<0.05).	11
					Prevalence of use, decriminalized/regulated drug(s): weekly use	Rate of change for South Australia not significantly different from rest of the country.	
29.	Dutra 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2008-2015	Population-based; Household survey N= 91,123 to 10,1973	*Mental health conditions, suicide, or self-harm*: state prevalence of serious mental illness	Liberal MCL associated with 0.2% increase in state prevalence of mental illness (b=0.002, SE=0.001, p=0.015). No significant effect of restrictive MCL.	17

30.	Estoup 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2010-2015	Convenience sampling N=262	*Mental health conditions, suicide, or self-harm*: # of reported psychological, behavioral, relational consequences of cannabis use	RCL associated with increased negative consequences of use, mediated by increased perceived harmfulness (*b* for indirect effect=3.73; 95% CI=0.33, 9.55).	11
					Perceived harmfulness of decriminalized/regulated drug(s): # of cons of continued cannabis use endorsed in decisional balance matrix	RCL associated with increased perceived harmfulness.	
					Frequency of use, decriminalized/legalized drug(s): # of times used in past 3 months	No significant effect of RCL.	
31.	Feige 2008	China Legal regulation of opium	Repeated cross-sectional study, 1801-1902	Unspecified	*Actual availability of decriminalized/regulated drug(s):* Quantity of opium exports (number of chests per capita)	No significant effect of legal regulation.	16
					Price of drugs: Price of opium at the scales in India	No significant effect of legal regulation.	
32.	Félix 2017	Portugal Decriminalization of all drugs	Controlled before-and-after study, 1990-2010 [13 EU countries and Norway]	Convenience sampling	*Price of drugs*: price data from (1) EU country reports to the Commission on Narcotic Drugs and (2) the European Monitoring Center for Drugs and Drug Addiction	Drug prices increased in Portugal following decriminalization, but difference-in-difference and synthetic control analyses indicate no statistically significant change in slope of drug prices.	14
33.	Gonçalves 2015	Portugal Decriminalization of all drugs	Repeated cross-sectional study, 1999-2010	Population-based; Admin record data	*Costs, health care*: combined direct costs of (1) drug treatment, prevention and harm reduction and (2) hospital treatment for hepatitis and HIV	12% increase over first 5 years following decriminalization, 9% over first 11 years.	13

					Costs, non-health care: combined indirect costs of lost income and production due to (1) drug addiction treatment and (2) drug-related death.	37% reduction over first 5 years following decriminalization, 29% over first 11 years.	
					Costs, non-health care: combined direct costs of social rehabilitation and legal system costs related to drugs	17% reduction over first 11 years.	
					Costs, non-health care: indirect costs of lost income and production of individuals arrested for drug-related crimes	5% reduction over first 5 years following decriminalization, 24% over first 11 years.	
34.	Gorman 2007	United States Legal regulation of cannabis for medical use (MCL)	Interrupted time series study, 1994-2002	Convenience sampling	*Prevalence of use, decriminalized/regulated drug(s)*: prevalence of positive cannabis urine screen among arrestees.	No significant effect of MCL on positive cannabis tests in CA or OR.	12
					Health services utilization: proportion of emergency department visits in which cannabis was mentioned in CA, WA, and CO DAWN sites	No significant effect of MCL on ED visits mentioning cannabis.	
35.	Grant 2018	United States Legal regulation of cannabis for medical use (MCL)	Cohort study, 1998-2012	Convenience sampling N=1359	*Prevalence of use, decriminalized/regulated drug(s)*: use in last 30 days of substance use case management program	Participants exiting case management after MCL were more likely to report past 30-day use (AOR = 2.1, $p < 0.0001$).	12
					Prevalence of use, other drugs or alcohol: # of days of use, in past 30 days, of alcohol or drugs	Participants exiting case management after MCL used alcohol ($b = 0.48$, SE=0.24, $p < 0.05$), illicit methadone ($b = 0.67$, SE=0.22, $p < 0.005$), and other opioids ($b = 0.52$, SE=0.15), $p < 0.01$) more frequently than the pre-MCL cohort.	
36.	Grucza 2018	United States Cannabis	Controlled before-and-after study,	Population-based; School-	*Criminal justice involvement*: arrest rates for cannabis	Arrest rates decreased by 75% among youth (95% CI: -0.89, -0.44) and 78% among adults (95% CI: -0.89, -0.52).	18

		decriminalizatio n	2007-2015 [States without decriminalizatio n, legal regulation, or change in penalties related to cannabis]	based survey N= 622,848	possession among minors (18 or under) and adults		
					Prevalence of use, decriminalized/regulated drug(s): past 30-day use	Decriminalization was not significantly associated with use.	
					Frequency of use, decriminalized/regulated drug(s): frequency of past 30-day use	Decriminalization was not significantly associated with frequency of use.	
37.	Grucza 2015	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1990-2010 [States without MCL]	Population-based; Admin record data N=662,993	*Mental health conditions, suicide, or self-harm*: suicide deaths	MCL not significantly associated with suicide rate overall, or when stratified by sex.	16
38.	Harper 2012	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 2002-2009 [States without MCL]	Population-based Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use among adolescents	*Reanalysis of Wall 2011 (#106) Difference-in-difference estimates indicate no significant effects of MCL, after accounting for state-level covariates and measurement error.	15
					Perceived harmfulness of decriminalized/regulated drug(s): perceived riskiness of monthly use among adolescents	No significant effects of MCL.	
39.	Harpin 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2013-2014	Population-based; School-based survey N=11,931 to 12,240	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime and past 30-day use	No significant change after RCL.	13
					Mode of use, decriminalized/regulated drug(s): smoking vs. other modes, among past-month users	No significant change after RCL.	
					Perceived harmfulness of decriminalized/regulated drug(s): high versus low	No significant change after RCL.	

					perceived harmfulness and wrongfulness of use		
					Perceived availability of decriminalized/regulated drug(s): high versus low perceived ease of access	Post-RCL year associated with high perceived access, (AOR= 1.21, 95% CI: 1.09, 1.34).	
40.	Hasin 2017	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1991-1992; 2001-2001; 2012-2013 [late MCL states, never MCL states]	Population-based; Household survey N=118,497	*Prevalence of use, decriminalized/regulated drug(s):* past-year use	MCL associated with greater increase in past-year use (difference-in-difference coefficient=1.4 percentage points, SE=0.5, p=0.004). Results varied by state and early vs. late MCL adoption.	17
					Substance use disorder or diagnosed dependence: DSM-IV Cannabis Use Disorder in past year	MCL associated with greater increase in CUD (difference-in-difference coefficient=0.7, SE=0.3, p=0.03).	
41.	Hasin 2015	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1991-2014	Population-based; School-based survey N=1,098,270	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	No significant effect of MCL overall, but interaction with grade: reduced use among 8th graders post-MCL (AOR=0.73, 95% CI: 0.63, 0.84), but not 10th or 12th graders.	18
42.	Hasin 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1991-1992; 2001-2002; 2012-2013	Population-based Household survey	*Impaired driving, decriminalized/regulated drug(s)*	Prevalence of cannabis-impaired driving increased more in states that passed MCL, but not significantly so (p=0.07).	A *
					Impaired driving, other drugs or alcohol: driving under the influence of alcohol	No significant effect of MCL.	
43.	Hoyte 2015	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2007-2014	Population-based; Admin record data N= 42 fatalities	*Accidents, motor vehicle*: THC-positive motor driver fatalities in Denver County, CO	Fatalities increased from 0.28/month from July 1, 2007 to Dec 31, 2008 to 0.5/month from 2009-2012 to 0.56/month from Jan 1, 2013 to June 30, 2014 (post-RCL). No statistical tests reported.	A *
44.	Huber 2016	United States Legal regulation of cannabis for	Repeated cross-sectional study, 1970-2012	Population-based; Admin record data	*Crime (non-drug)*: state violent crime rates (FBI Uniform Crime Reports)	MCL associated with 12.9% reduction in rate (*b*=-0.129, SE= 0.036, p<0.01).	14

		medical use (MCL)			*Crime (non-drug)*: state property crime rates	MCL associated with 9.2% reduction in rate (b=-0.092, SE= 0.032, p<0.01).	
45.	Hunt 2017	United States Legal regulation of cannabis for recreational use (RCL)	Controlled before-and-after study, 2013;2014 [WA and OR before RCL implementation]	Population-based; Household survey N=5576	*Price of* drugs: consumer-reported price per gram	No statistically significant effects of implementing legal retail cannabis sales in CO and WA on prices paid for recreational or medical purposes, 4-5 months later.	16
46.	Johnson 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1991-2011	Population-based; School-based survey N=715,014	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use among adolescents	MCL associated with decreased odds of past 30-day use (AOR=0.93, 95% CI: 0.86, 0.99). Policy details associated with lower (e.g., years since MCL and liberal provisions) and higher (e.g., voluntary vs. mandatory patient registration) use.	17
					Frequency of use, decriminalized/regulated drug(s): past 30-day heavy use (≥20 times)	MCL not associated with odds of heavy use (AOR=1.00, 95% CI: 0.89, 1.13).	
47.	Jones 2015	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2012; 2014	Unspecified	*Prevalence of use, decriminalized/regulated drug(s)*: THCA-positive meconium specimens from high-risk newborns in Colorado	RCL associated with increase in THCA-positive specimens (from 10.6% to 11.7%) and with increased mean THCA concentrations in positive specimens.	A *
48.	Jones 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2013-2015	Convenience sampling N=1413	*Frequency of use, decriminalized/regulated drug(s)*: Categories from no use to daily use.	No statistically significant difference in use frequency between pre- and post-RCL periods.	10
					Prevalence of use, other drugs or alcohol: Frequency of cannabis use within alcohol use frequency groups	Strength of the relationship between alcohol and cannabis use decreased after RCL (from r=0.54 in Nov 2013 to 0.33 in Mar 2015).	
49.	Kerr DCR 2017	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2012-2016	Population-based; School-based survey N=10,924	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	No significant association between RCL and past 30-day use overall (AOR=1.21, p=0.48) but increasing secular trend. RCL associated with increased cannabis use among heavy alcohol users (AOR=1.73, p=0.0076).	17

					Prevalence of use, other drugs or alcohol: past 30-day cigarette use	No significant association with RCL.	
					Prevalence of use, other drugs or alcohol: past 30-day heavy alcohol use	No significant association with RCL.	
50.	Kerr WC 2018	United States Legal regulation of cannabis for medical (MCL) and recreational use (RCL)	Repeated cross-sectional study, 1984-2015	Population-based; Household survey N=37,359	*Prevalence of use, decriminalized/regulated drug(s)*: past-year use	No significant association between MCL (home growing or dispensaries) or RCL and past-year use, among both women and men.	17
51.	Kerr DCR 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2008-2016	Population-based; School-based survey N=281,752	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	RCL associated with increased past 30-day use among university students (AOR= 1.29, 95% CI: 1.13, 1.48).	17
					Prevalence of use, other drugs or alcohol: past 30-day tobacco use	RCL associated with decreased tobacco use (AOR= 0.71, p=0.0001).	
					Prevalence of use, other drugs or alcohol: past 30-day alcohol use	RCL not associated with alcohol use (p=0.59).	
					Prevalence of use, other drugs or alcohol: past 30-day illicit drug use (non-cannabis)	RCL not associated with illicit drug use (p=0.78).	
52.	Keyes 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1991-2014	Population-based; School-based survey N=973,089	*Perceived harmfulness of decriminalized/regulated drug(s)*: great or moderate vs. low perceived risk of physical harm due to occasional use	No significant association with MCL in all grades, 10th or 12th, but increased perceived harm in 8th (AOR= 1.21, 95% CI: 1.08, 1.36).	15
					Prevalence of use, decriminalized/regulated drug(s): past 30-day use	Adjusting for perceived harmfulness, significant negative association between MCL and use in 8th grade only (AOR= 0.81, 95% CI: 0.72, 0.92).	
53.	Khatapoush 2004	United States Legal regulation	Repeated cross-sectional study, 1995;1997;1999	Population-based; Household	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use	No statistically significant change over time in California (MCL state) or other states.	10

		of cannabis for medical use (MCL)		survey N=15,567	*Perceived availability of decriminalized/regulated drug(s)*	No statistically significant change over time in California (MCL state) or other states.	
					Prevalence of use, other drugs or alcohol: past-year use of other drugs.	No statistically significant change over time in California (MCL state) or other states.	
54.	Kim, Anderson et al. 2015	United States Cannabis decriminalizatio n	Repeated cross-sectional study, 2008-2009; 2010-2011	Population-based; Admin record data N=2574	*Health services utilization*: emergency department visits for cyclic vomiting	Decriminalization associated with increase in visits (prevalence ratio= 1.92, 95% CI: 1.33, 2.79).	15
55.	Kim, Hall, et al. 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2012-2014	Population-based; Admin record data	*Health services utilization*: cannabis-related emergency department visits	RCL associated with increase in cannabis-related ED visits by Colorado residents (rate ratio; RR=1.46, $p>0.001$) and non-residents (RR=1.17, $p>0.001$).	14
56.	Kim, Santaella et al. 2015	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1999-2011	Population-based; Admin record data	*Prescription drug use*: annual opioid sales in morphine-equivalent doses	Adjusting for increasing secular trend, MCL associated with 1% reduction in opioid sales per year of MCL (b=-0.01, p=0.0016).	A *
57.	Kim 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2004-2013	Population-based; Household survey	*Prevalence of use, other drugs or alcohol*: past-month nonmedical use of prescription opioids	No significant difference in prevalence post-MCL for youth, young adults, or adults 26+.	A *
58.	Kim, Santaella-Tenorio, et al. 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1999-2013	Population-based; Admin record data N=68,394	*Impaired driving, other drugs or alcohol*: positive opioid tests among driver fatalities in motor vehicle accidents	MCL not significantly associated with opioid presence overall, but with reduction among decedents age 24-40 (AOR post-MCL vs. pre=0.50, 95% CI=0.37, 0.67).	17
59.	Kosterman 2016	United States Legal regulation of cannabis for	Interrupted time series study, 1985-2014	Convenience sampling N=395	*Frequency of use, decriminalized/regulated drug(s)*: past-month frequency	Frequency of use increased post-RCL (from 4-6 to 10 times/month, $p<0.05$).	8

		recreational use (RCL)			among WA parents with any past-year use		
					Substance use disorder or diagnosed dependence: meets DSM-IV criteria for cannabis use disorder	No statistically significant change post-RCL.	
					Perceived harmfulness of decriminalized/regulated drug(s): approval and perceived harmfulness of cannabis use	Approval increased and perceived harmfulness decreased following RCL (p<0.05).	
60.	Larimer 2015	United States Legal regulation of cannabis for recreational use (RCL)	Cohort study	Unspecified N= 1095	*Frequency of use, decriminalized/regulated drug(s)*: # of times used in past month among 12-17 year olds	No significant change associated with RCL.	A *
					Perceived harmfulness of decriminalized/regulated drug(s): perceived risk due to regular and occasional use	Perceived risk from regular use decreased among males but not females (p for interaction=0.017).	
					Perceived availability of decriminalized/regulated drug(s)	No significant change associated with RCL.	
					Prevalence of use, other drugs or alcohol: number of drinks consumed per week.	RCL associated with increased number of drinks per week (p<0.01), beyond time trends.	
61.	Liang 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1993-2014	Population-based; Admin record data	*Prescription drug use*: # of filled opioid prescriptions, dosage of filled prescriptions in morphine-equivalent doses, and related Medicaid spending for Schedule II opioids (e.g., hydrocodone, oxycodone).	MCL not associated not associated with Schedule II opioid use.	15
					Prescription drug use: as above, for Schedule III opioids (e.g. codeine).	MCL associated with reductions in Schedule III opioid prescriptions (-29.6%, 95% CI: -2.4%, -56.7%), doses, and spending.	

62.	Livingston 2017	United States Legal regulation of cannabis for recreational use (RCL)	Interrupted time series study, 2000-2015	Population-based; Admin record data	*Overdose or poisoning*, *other drugs*: deaths with ICD-10 code indicating opioid poisoning	RCL associated with reduction in opioid poisoning deaths, adjusting for comparison state trends (-0.68 deaths per month, 95% CI: -1.35, -0.03).	16
63.	Lo 2015	United States Legal regulation of cannabis for recreational use (RCL)	Uncontrolled before-and-after study, 2013-2015	Convenience sampling N= 2186	*Prevalence of use, decriminalized/regulated drug(s)*: positive cannabinoid screen among high-risk opioid therapy patients	RCL associated with increase in positive THC screens (30% of visits to 36%, p=0.0003).	A *
					Opioid therapy compliance: non-compliance (illicit opioids use or non-use of prescription)	RCL not associated with compliance.	
64.	Lynne-Landsman 2013	United States Legal regulation of cannabis for medical use (MCL)	Switching replications study, 2003-2011	Population-based; School-based survey	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime and past-month	MCL not associated with use (1 of 20 planned comparisons significant, expected by chance alone).	15
					Frequency of use, decriminalized/legalized drug(s): daily or weekly use among lifetime users	MCL not associated with frequency (1 of 20 planned comparisons significant, expected by chance alone).	
65.	Martins 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2004-2013	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use	MCL associated with greater past-month use among adults 26+ (AOR=1.24, 95% CI: 1.16, 1.31), but not among ages 12-17 or 18-25.	16
					Perceived availability of decriminalized/regulated drug(s): fairly or very easy to obtain vs. other	MCL associated with greater availability among adults 26+ (AOR=1.11, 95% CI: 1.07, 1.15), but not among ages 12-17 or 18-25.	
66.	Mason 2016	United States Legal regulation of cannabis for recreational use (RCL)	Controlled before-and-after study, 2010-2013 [students completed follow up before RCL]	Convenience sampling N= 238	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	Post-RCL subject group not significantly associated with use (AOR= 2.80, 95% CI: 0.94–8.34).	13
					Prevalence of use, other drugs or alcohol: use of cigarettes or alcohol vs. cannabis (indicating substitution effect)	Post-RCL subject group significantly less likely to use cigarettes or alcohol versus cannabis (p<0.05).	

67.	Masten 2014	United States Legal regulation of cannabis for medical use (MCL)	Interrupted time series study, 1992-2009	Population-based; Admin record data N=245,495	*Impaired driving, decriminalized/regulated drug(s)*: proportion of fatal-crash-involved drivers (decedents and survivors) who test cannabinoid-positive	Significant policy effect found in 3 of 12 MCL states, with increases of 2.1-6.0 percentage points among all drivers and 4.6-9.6 among fatally injured drivers in CA, HI, and OR (adjusted for changes in testing and national trends). These were step increases rather than upward trends.	14
68.	Mauro 2019	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2004-2013	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use	No significant effect of MCL among men or women aged 12-17 or 18-25, but significant increases for ages 26+ among men (+1.7 percentage points, $p < 0.001$) and women (+ 1.1%, $p = 0.013$).	16
					Frequency of use, decriminalized/legalized drug(s): daily use among past-year users	Significant effect of MCL among men aged 18-25 (+ 2.4%, $p = 0.047$), and both men and women age 26+ (men + 2.8%, $p = 0.014$; women + 3.4 %, $p = 0.003$).	
					Substance use disorder or diagnosed dependence: met DSM-IV criteria for cannabis use disorder	No statistically significant effect of MCL for any age-gender group.	
69.	Mauro 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2004-2013	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use	MCL associated with increased use among adults 26-39 [AOR=1.2, 95% CI: 1.1, 1.3], 40-64 [AOR=1.4, 95% CI: 1.2, 1.5], and 65+ [AOR=2.6, 95% CI: 1.5, 4.6]. Association partially mediated by perceived access.	A *
70.	Merker 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2012-2017	Convenience sampling N=302	*Prevalence of use, decriminalized/regulated drug(s)*: current use among Inflammatory Bowel Disease patients	Increase in use post-MCL (12.3% to 22.8% of patients, p=0.0008), but no significant increase in reported medical use.	12
71.	Miech 2015	United States Cannabis decriminalizatio n	Repeated cross-sectional study, 2007-2013	Population-based; School-based survey	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime, past-year, past 30-day use	[Decriminalization in CA in 2010] 8th and 10th grades: differences in use between CA residents and other states limited to select years, not sustained over time. 12th grade: past-year use higher	12

				N=320,809		among CA residents vs. other states in 2010-2013.	
					Perceived harmfulness of decriminalized/regulated drug(s): great vs. less-than-great perceived risk of regular use	8th and 10th grades: only one significant difference (8th grade in 2012). 12th grade: lower perceived risk among CA residents vs. other states in 2012-2013.	
					Perceived availability of decriminalized/regulated drug(s): easy vs. less-than-easy perceived access	8th and 10th grades: only one significant difference (8th grade in 2011). 12th grade: higher perceived availability among CA residents vs. other states in 2012 only.	
					Attitudes towards use, decriminalized/regulated drug(s): strong disapproval of adult use vs. other	8th and 10th grades: only one significant difference (8th grade in 2012). 12th grade: less strong disapproval among CA residents vs. other states in 2012-2013	
					Attitudes towards use, decriminalized/regulated drug(s): definitely or probably expect to use five years from present (only 12th graders)	12th grade: greater expected use among CA residents vs. other states in 2012-2013.	
72.	Miller 2017	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2005-2015	Population-based; School-based survey N=13,335	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	RCL associated with increase of 2.0-3.5 percentage points (12-22%), adjusting for linear secular trend [passage of RCL, additional effect of legal store openings not statistically significant].	16
					Frequency of use, decriminalized/legalized drug(s): past 30-day frequency	RCL associated with increase of 0.5 days per month, adjusting for linear secular trend [passage of RCL, additional effect of legal store openings not significant].	
					Prevalence of use, other drugs or alcohol	RCL passage not associated with changes. In 2015 (legal stores), decrease in tobacco and increase in other illegal drugs, but findings not robust.	
73.	Model 1993	United States Cannabis decriminalizatio	Controlled before-and-after study, 1975-1978	Population-based; Admin record data	*Health services utilization:* non-cannabis drug mentions at ER visits	Decriminalization associated with 12% fewer drug mentions at ER visits (b=-0.133, SE=0.053, p<0.01), with stronger effects in initial years.	16

		n [States that did not not decriminalize]			*Health services utilization*: cannabis drug mentions at ER visits	Decriminalization associated with 64% more cannabis mentions (*b*=-0.642, SE=0.112, *p*<0.01), with stronger effects in later years.	
74.	Morris 2014	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1990-2006	Population-based; Admin record data	*Crime (non-drug)*: rates of violent crime (homicide, rape, robbery, assault)	MCL associated with 2.4% reduction in homicide rate (*p*<0.01).	16
					Crime (non-drug): rates of property crime (burglary, larceny, auto theft)	No significant association between MCL and property crimes.	
75.	Nappe 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study. 2010-2015	Population-based; Admin record data N=5231 exposures	*Overdose or poisoning, decriminalized/regulated drug*: cannabis exposures reported to the National Poison Data System in Colorado	RCL associated with increase in cannabis exposures (86 in 2011 to 231 in 2015).	A *
76.	Onders 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study 2000-2013	Population-based; Admin record data N= 1969 exposures	*Overdose or poisoning, decriminalized/regulated drug*: cannabis exposures among children <6 reported to the National Poison Data System	MCL associated with increased exposures (rate ratio for post vs. pre-MCL=2.25, 95% CI: 1.45, 3.51). Exposures peaked in the year following RCL.	13
77.	Pacula 2010	United States Cannabis decriminalization and legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1987-2003	Convenience sampling	*Price of drugs*: price per gram paid at the last transaction among arrestees	Decriminalization and MCL associated with higher prices (indicating increased demand). .	13
78.	Pacula 2015	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1992-2011 and 1997-2011	Population-based; Admin record data N=973	*Addiction treatment utilization*: number of treatment admissions with cannabis as primary indication	MCL associated with 14% reduction in cannabis admissions (difference-in-difference = -0.136, SE=0.067, *p*<0.05). Larger effect size for non-criminal justice referrals. Partially offset by	15

			[State-years without MML]	Household survey N=112,926		increase in admissions associated with dispensaries.	
					Prevalence of use, decriminalized/regulated drug(s): past 30-day use	No overall significant association between MCL and use.	
					Frequency of use, decriminalized/regulated drug(s): heavy use (>20 of last 30 days), # of days of use in past 30	No significant association between MCL and frequency of use.	
79.	Parnes 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2013-2015	Convenience sampling N=5241	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	No significant association between RCL and use among CO undergraduates.	12
80.	Phillips 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2011-2014	Population-based; Admin record data N=188,266	*Overdose or poisoning*, *other drugs*: state-level age-adjusted opioid-related mortality rate	MCL associated with 21.7% increase in opioid-related mortality ($p < 0.0001$) but interacted with prescription drug monitoring programs such that rates decreased in states with both policies.	15
81.	Plunk 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2000-2014	Population-based; Household survey N=5,483,715	*Educational outcomes*: high school non-completion	High-school age exposure to MCL not associated with non-completion overall, but with increase in probability of failing to complete conditioned on completing the 12th grade (AOR=1.11, 95% CI: 1.05, 1.17).	16
					Educational outcomes: college non-enrollment among high school graduates	High-school age exposure to MCL associated with college non-enrollment (AOR = 1.09, 95% CI: 1.04, 1.14). Dose-response relationship with years of exposure.	
					Educational outcomes: college non-completion among college entrants aged 25+	High-school age exposure to MCL associated with increase in probability of degree non-completion (AOR = 1.03, 95% CI: 1.01, 1.06).	

					Prevalence of use, decriminalized/regulated drug(s): past-month use	High-school age exposure to MCL not significantly associated with use.	
					Frequency of use, decriminalized/regulated drug(s): daily use (40 or more times/month)	High-school age exposure to MCL not significantly associated with use overall, but among 12th graders only (AOR=1.62, 95% CI: 1.04, 2.54).	
82.	Pollini 2015	United States Cannabis decriminalizatio n	Repeated cross-sectional study Roadside Survey, 2010; 2012 Fatality Analysis Reporting System, 2008-2012	Population-based; Admin record data Roadside Survey, N=379-515 FARS, N=2860	*Impaired driving, decriminalized/regulated drug(s)*: proportion of drivers testing THC-positive in roadside survey	No statistically significant change in THC-positivity following decriminalization.	13
					Impaired driving, decriminalized/regulated drug(s): presence of cannabinoids among fatally injured drivers	Increase in cannabinoid prevalence in 2012 as compared to the pre-decriminalization period (AOR = 1.67, 95% CI: 1.28, 2.18).	
83.	Powell 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1999-2013	Population-based; Admin record data	*Overdose or poisoning, other drugs*: deaths related to prescription opioids and heroin	Existence of MCL not significantly associated with overdose mortality (only active dispensaries associated with reduction in deaths).	15
					Addiction treatment utilization: number of treatment episodes related to pain reliever misuse	Existence of MCL not significantly associated with overdose mortality (only active dispensaries associated with reduction).	
					Prevalence of use, other drugs or alcohol: self-reported nonmedical use of pain relievers (National Survey on Drug Use and Health)	No statistically significant association between MCL and use.	
					Prescription drug use: morphine-equivalent doses of opioids distributed to legal medical markets	No statistically significant association between MCL and use over full time period.	
84.	Prue 2014	United States Peyote decriminalizatio	Repeated cross-sectional study, 1985-2010	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: peyote use	Use among American Indians increased from 1% in 1994 (year of American Indian Religious Freedom Act) to 10% in	7

		n		N=886,088		1999. Use among non-American Indians remained steady <2%.	
					Age of first use, decriminalized/regulated drug: age at first use of peyote	No significant change in age at first use among American Indians or non-American Indians following decriminalization.	
85.	Ramirez 2017	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2014;2015	Unspecified N=2400	*Impaired driving, decriminalized/regulated drug(s)*: daytime prevalence of cannabis-positive drivers	Statistically significant increase post-RCL (7.8% to 18.9% after one year).	A *
86.	Reith 2015	International Cannabis decriminalization	Controlled before-and-after study, 1980-2012 [Country-years without decriminalization]	Unspecified N=102 countries	*Actual availability of decriminalized/regulated drug(s)*: kg of cannabis seized and number of plants eradicated divided by population in millions	Decriminalization associated with increased plant eradication (p<0.05), but not seizures.	10
87.	Rodriguez 2016	United States Legal regulation of cannabis for recreational use (RCL)	Cohort study, 2009-2015	Convenience sampling N= 1698	*Prevalence of use, decriminalized/regulated drug(s)*: positive urine toxicology among pregnant young women *Disclosure of use, decriminalized/regulated drug(s)*: agreement between self-reported use and urine toxicology	Increased cannabis-positive screens post-RCL (16.2 to 20.2%, p=0.048). Improved agreement post-RCL (kappa = 0.504 vs. 0.191).	A *

88.	Rohda 2017	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2011-2016	Population-based; Admin record data N=29,044 exposures	*Overdose or poisoning, other drugs:* synthetic cannabinoid receptor agonist (SCRA) exposures reported to poison control centers	SCRA exposures declined in WA (175 to 28, p=0.017*)* and OR (39 to 14, p=0.012) following RCL, but not in all RCL states combined (p=0.41).	A *
89.	Rusby 2018	United States Legal regulation of cannabis for recreational use (RCL)	Cohort study, 2014-2016	Population-based; School-based survey N=444	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	RCL not significantly associated with use.	12
					Frequency of use, decriminalized/regulated drug(s): number of days use in past 30	RCL associated with greater number of days of use (ARR=1.26, 95% CI: 1.10, 1.45).	
					Attitudes towards use, decriminalized/regulated drug(s): willingness and intention to use (any vs. none)	RCL not significantly associated with willingness or intention to use.	
90.	Sabia 2017	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study. 1990-2012 [State-years without MML]	Population-based; Household survey N=5,428,399	*BMI*	MCL associated with reduction in BMI (adjusted difference-in-differences for contemporaneous effect = -0.084, SE=0.034, p<0.05).	16
91.	Santaella-Tenorio 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1985-2014	Population-based; Admin record data N=1,220,610 deaths	*Accidents, motor vehicle*: age-adjusted traffic fatality rates (all road users)	MCL associated with 10.8% reduction in traffic fatality rates (95% CI = 9.0%, 12.5%).	17
92.	Schmidt 2016	United States Legal regulation of cannabis for medical use	Repeated cross-sectional study, 2014-2013	Population-based; Household survey	*Perceived harmfulness of decriminalized/regulated drug(s)*: belief that weekly/ monthly use is “not a great risk”	Living in MCL state not associated with perceived harmfulness. (Secular trend towards greater permissiveness for all outcomes, but no significant effects MCL after control for state fixed effects).	17

		(MCL)		N=450,300	*Attitudes towards use, decriminalized/regulated drug(s)*: belief that parents/ friends don't disapprove of trying cannabis	Living in MCL state not associated with perceived attitudes.	
					Perceived availability of decriminalized/regulated drug(s): belief that cannabis is fairly or very easy to obtain	Living in MCL state not associated with perceived availability.	
93.	Sevigny 2014	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1990-2010 [State-years without MCL]	Convenience sampling N=39,157	*Potency of decriminalized/regulated drug(s)*: concentration of THC in cannabis seized by law enforcement	MCL not significantly associated with potency (adjusted difference in %THC=0.53, $p>0.05$), but legal dispensaries associated with higher potency.	16
94.	Shah 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2006-2014	Population-based; Admin record data	*Prescription drug use*: opioid use among commercially insured population.	MCL associated with lower odds of any opioid use (AOR=0.95, 95% CI: 0.94, 0.96), chronic opioid use (AOR=0.93, 95% CI: 0.91, 0.95) and high-risk opioid use (AOR=0.98, 95% CI: 0.96, 0.99).	A *
95.	Shepard 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1997-2009	Population-based; Admin record data	*Crime (non-drug)*: property crime (burglary, larceny, and vehicle theft arrests per 1000 residents)	MCL not associated with property crime.	12
					Crime (non-drug): violent crime (assault, homicide, rape, and robbery arrests)	MCL associated with reduction in violent crimes (-0.254 crimes per 1000 residents, SE=0.089, $p<0.05$).	
96.	Shi 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1997-2014	Population-based; Admin record data N= 0.4M to 2.2M records	*Health services utilization*: annual hospitalization rate for cannabis dependence or abuse (ICD-9)	MCL not significantly associated with hospitalizations.	16
					Overdose or poisoning, other drugs: hospitalization rate for opioid pain reliever overdose	MCL associated with reduction in hospitalizations related to opioid overdose (adjusted prevalence difference = −0.13, 95% CI: −0.25, −0.018).	

					Health services utilization: hospitalization rate for opioid dependence or abuse	MCL associated with reduction in hospitalizations related to opioid dependence (adjusted prevalence difference = −0.23, 95% CI: −0.41, −0.068).	
97.	Sokoya 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2012-2015	Convenience sampling N=2164	*Accidents, other*: types of bony facial trauma among patients presenting to two CO hospitals	RCL not associated with significant difference in mechanisms of facial fracture.	12
98.	Steinemann 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1993-2000; 2001-2015	Population-based; Admin record data N=1578	*Impaired driving, decriminalized/regulated drug(s)*: proportion of fatally injured drivers who were cannabis-positive in HI	MCL associated with increase in THC positivity (5.5% in 1993-2000; 16.3% in 2011-2015, $p<0.001$).	12
					Impaired driving, other drugs or alcohol: proportion of fatally injured drivers who were methamphetamine- or alcohol-positive	MCL not associated with significant difference in positivity rates.	
99.	Stolzenberg 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2002-2003; 2004-2005; 2006-2007; 2008-2009; 2010-2011	Population-based; School-based survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use among adolescents	Living in MCL state associated with greater use (adjusted coefficient=0.861, SE=0.298, $p<0.01$).	14
					Prevalence of use, other drugs or alcohol: past-month non-cannabis illicit drug use	No significant association between living in MCL state and use.	
100.	Straub 2017	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2011-2012; 2012-2014; 2014-2016	Population-based; Admin record data N=25,763	*Prevalence of use, decriminalized/regulated drug(s)*: positive urine screen or documented use during pregnancy	No significant change in cannabis-positivity post-RCL.	A *
101.	Suggs 1981	United States Cannabis decriminalizatio	Uncontrolled before-and-after study, 1977-1979	Population-based; Admin record data	*Criminal justice involvement*: possession arrests and citations for adults and minors in two NE cities	No significant difference in mean monthly arrests following decriminalization.	12

		n		N=719	*Criminal justice involvement*: possession prosecutions for adults and minors	Significant increase in prosecutions following decriminalization among minors (from mean of 1.92 to 5.75/month, $p<0.05$), but not adults (26.71 to 36.25, $p>0.05$).	
					Criminal justice involvement: defendants representing themselves	Significant increase following decriminalization (from 18.07 to 30.75/month, $p<0.05$).	
					Criminal justice involvement: case dismissal before trial	Significant decrease following decriminalization (from 9.14 to 2.37/month, $p<0.001$).	
102.	Ullman 2017	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1992-2012 [State-years without MCL]	Population-based; Household survey N=757,677	*Workplace absence*: self-reported absence for medical reasons in the past week	MCL associated with lower probability of absence (b= -0.0013, SE=0.0007, p<0.10), with effects concentrated in loosely regulated MCL states, men and people aged 30-49.	16
103.	Urfer 2014	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2011-2014	Convenience sampling N=12,082	*Impaired driving, decriminalized/regulated drug(s)*: Proportion of THC-positive blood samples collected from CO drivers	Increase in THC-positive screens from 2011 (28%) to 2012 (59%) to 2013 (65%), p=0.001. No significant change in first two months of legal cannabis sales.	11
104.	Wagner 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2012-2015	Convenience sampling N=34	*Physical health consequences of use, decriminalized/ regulated drug(s)*: Reversible Cerebral Vasoconstriction Syndrome (RCVS) cases secondary to cannabis	Of 18 RCVS cases before RCL, 1 patient used cannabis. Of 16 cases after RCL, 5 used cannabis. No statistical tests reported.	A *
105.	Wall 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2002-2010	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use among adolescents	*Reanalysis of Stolzenberg 2016 (#99) After appropriate adjustment for pre-MCL prevalence, MCL not associated with adolescent use (b = 0.33%; SE= 0.29%, p = 0.25).	18

106.	Wall 2011	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2002-2008	Population-based; Household survey N=23,300	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use among adolescents	Use was significantly higher in MCL states (average of 8.7% vs. 6.9%) but among states that passed MCL from 2004-2008, baseline use (pre-MCL) was already higher than in non-MCL states.	13
					Perceived harmfulness of decriminalized/regulated drug(s): perceived "great risk" of using monthly or more	Perceived harmfulness was significantly lower in MCL states each year (average of 8.7% vs. 6.9%), but among states that passed MCL, baseline perceived risk (pre-MCL) was already lower than non-MCL states.	
107.	Wang 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2005-2015	Population-based; Admin record data N=4202	*Health services utilization:* emergency or urgent care visits with a cannabis-related discharge code or THC-positive urine toxicology among adolescents	Cannabis-related visits increased from 1.8 per 1000 visits in 2009 to 4.9 per 1000 in 2015, following RCL (p<0.0001).	11
108.	Wang 2017	United States Legal regulation of cannabis for medical (MCL) and recreational use (RCL)	Repeated cross-sectional study, 2000-2015	Population-based; Admin record data N=7,432,254	*Health services utilization*: hospitalizations with cannabis-related billing codes	Hospitalizations increased from 274 per 100,000 in 2000 (prior to MCL) to 593 in 2015 (after RCL). Statistically significant 25% increase in 2014 (RCL implementation with legal sales).	14
					Health services utilization: emergency department visits with cannabis-related billing codes	ED visits increased from 313 per 100,000 in 2011 to 478 in 2015, with highest rate in 2014 (554). Statistically significant increase in 2014 (p=0.0005).	
					Overdose or poisoning, decriminalized/regulated drug: cannabis exposure calls to CO poison control centers	Poison control calls increased by 79.9% following RCL implementation in 2014, from 123 to 221 (p=0.0001).	
109.	Wang 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2009-2015	Population-based; Admin record data N=62	*Overdose or poisoning, decriminalized/regulated drug*: children's hospital visits related to cannabis exposure	RCL associated with increased cannabis-related visits (1.2 per 100,000 in 2012-2013 to 2.3 per 100,000 in 2014-2015, p=0.02).	13
					Overdose or poisoning, decriminalized/regulated drug: poison control calls related to cannabis exposure among children 0-9	RCL associated with increased cannabis-related calls in CO (2.7 per 100,000 in 2012-2013 to 5.3 per 100,000 in 2014-2015, p<0.001) and in comparison to rest	

						of the US (34% increase in CO vs. 19% increase in remainder of US, p=0.04).	
110.	Wen 2018	United States Legal regulation of cannabis for medical (MCL) and recreational use (RCL)	Controlled before-and-after study, 2011-2016 [States without MCL or RCL over the study period]	Population-based; Admin record data N=1059 state-quarter observations	*Prescription drug use*: number of opioid prescriptions covered by Medicaid on a quarterly, per-1000-Medicaid-enrollee basis in each state	MCL and RCL associated with reductions in prescriptions of 5.88% (95% CI: -11.55%, -0.21%) and 6.38% (95% CI: -12.20, -0.56%) respectively.	17
111.	Wen 2015	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2004-2012	Population-based; Household survey N=593,400	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use; past-year initiation	MCL associated with increase in past-month use among adults 21+ (+1.32%, p<0.05) but not ages 12-20. MCL associated with increased risk of past-year initiation among ages 12-20 only (+0.32%, p<0.05).	17
					Frequency of use, decriminalized/regulated drug(s): daily/almost daily use (>20 days in month); # of days among past-month users	MCL associated with increase in (almost) daily use among adults 21+ (+0.58%, p<0.05) but not ages 12-20.	
					Prevalence of use, other drugs or alcohol: # of drinks in past month; # of binge drinking days; met DSM-IV alcohol use disorder criteria in past year; both cannabis use and binge drinking in past month; use of cannabis and alcohol on same occasion in past month	MCL associated with frequency of binge drinking (+0.16 days, p<0.05) and past-month use of both cannabis and alcohol (+1.44%, p<0.01) among adults 21+. No associations with alcohol use among ages 12-20, or with alcohol use disorders.	
					Prevalence of use, other drugs or alcohol; past-year use of non-medical prescription painkillers, heroin, cocaine	No immediate or lagged associations between MCL and illicit drug use in either age group.	
					Substance use disorder or diagnosed dependence: met DSM-IV cannabis use disorder criteria in past year	Lagged associations between MCL and cannabis use disorder among adults 21+ (+0.25% at 1 year, p<0.05) but not among ages 12-20.	

112.	Wen 2019	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 2004-2012 [Non-MCL states]	Population-based; Household survey N=388,200	*Perceived availability of decriminalized/regulated drug(s)*: (very) easy to obtain, among adolescents and young adults	No significant association between MCL and perceived availability among ages 12-17 or 18-25.	16
					Attitudes towards use, decriminalized/regulated drug(s): acceptance of use by other adolescents/young adults; perceived parental acceptance (ages 12-17 only)	MCL significantly associated with lower perceived parental acceptance among ages 12-17 (-0.37%, 95% CI: -0.72, -0.03).	
					Perceived harmfulness of decriminalized/regulated drug(s): no/low health risk of using once or twice per week	MCL significantly associated with higher perceived harmlessness among ages 18-25 only (+4.72%, 95% CI: 0.15, 9.28).	
113.	Williams 2017	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 2004-2013 [State-years without MCL]	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use	Only loosely regulated MCL associated with higher use, among adults 26+ only (adjusted prevalence difference = +1.46%, 95% CI: 0.33, 2.58).	15
					Frequency of use, decriminalized/legalized drug(s): heavy use in past year (>300 days), among past-year users	Tightly regulated MCL associated with less heavy use, among ages 12-17 only (adjusted prevalence difference = -3.67%, 95% CI: -7.24, -0.11).	
					Substance use disorder or diagnosed dependence met DSM-IV criteria for cannabis use disorder	Loosely regulated MCL associated with lower prevalence of cannabis use disorder, among ages 18-25 only (-0.80%, 95% CI: -1.45, -0.16).	
114.	Williams 2014	Australia Cannabis decriminalization	Controlled before-and-after study, 1998;2001;2004;2007;2010 [state-years without decriminalization)	Population-based; Household survey N=39,087	*Age of first use, decriminalized/regulated drug(s)*: age at initiation	Decriminalization not associated with hazard of cannabis uptake overall but interacts with age such that minors under decriminalization have a 12% higher hazard rate of uptake while adults under decriminalization have an 11% lower hazard rate of uptake (p<0.01).	18

*A = abstract; no quality appraisal performed.

Supplementary Table 2. Direction of effect of decriminalization or legal regulation, by outcome category

Outcomes	Number of outcomes	# reporting beneficial effects	# reporting harmful effects	# reporting mixed effects	# reporting no effect	Article # (See Included Studies)
Accidents, motor vehicle	4	1	1	1	1	3, 8, 43, 91
Accidents, other	4	0	2	1	1	5, 11, 14, 97
Addiction treatment utilization	4	0	1	1	2	1, 25, 78, 83
Age of first use, decriminalized/regulated drug	3	0	0	1	2	23, 84, 114
Attitudes towards use, decriminalized/regulated drug	6	0	1	3	2	27, 71, 89, 92, 112
Availability of decriminalized/regulated drug	3	0	0	1	2	6, 31, 86
BMI	1	1	0	0	0	90
Costs, health care	3	2	1	0	0	15, 17, 33
Costs, other	3	3	0	0	0	33
Crime (non-drug)	9	5	0	0	4	7, 44, 74, 95
Criminal justice involvement	8	1	3	1	3	7, 25, 36, 101
Disclosure of use to healthcare provider	1	1	0	0	0	87
Educational outcomes	3	0	2	1	0	81
Frequency of use, decriminalized/regulated drug	16	1	3	4	8	6, 18, 30, 36, 46, 47, 59, 60, 64, 69, 72, 78, 81, 89, 111, 113
Health services utilization (excluding addictions treatment)	12	2	6	1	3	13, 19, 34, 54, 55, 73, 96, 107, 108
Impaired driving, decriminalized/regulated drug	8	0	5	1	2	26, 42, 67, 82, 85, 98, 103
Impaired driving, other drug/alcohol	3	0	0	1	2	42, 58, 98
Mental health conditions, suicide, or self-harm	4	0	1	2	1	4, 29, 30, 37

Outcomes	Number of outcomes	# reporting beneficial effects	# reporting harmful effects	# reporting mixed effects	# reporting no effect	Article # (See Included Studies)
Mode of use, decriminalized/regulated drug	1	0	0	0	1	39
Opioid therapy compliance	1	0	0	0	1	63
Overdose or poisoning (incl. unintentional exposures) decriminalized/regulated drug	7	0	7	0	0	10, 12, 75, 76, 108, 109
Overdose or poisoning, other drugs	7	4	0	2	1	9, 10, 62, 80, 83, 88, 96
Perceived availability, decriminalized/regulated drug	8	0	1	2	5	27, 39, 53, 60, 65, 71, 92, 112
Perceived harmfulness, decriminalized/regulated drug	12	1	2	6	3	18, 22, 30, 38, 39, 52, 59, 60, 71, 92, 106, 112
Physical health consequences of use, decriminalized/regulated drug	1	0	0	0	1	104
Potency, decriminalized/regulated drug	1	0	0	0	1	93
Prescription drug use (medical use)	9	6	0	1	2	15, 16, 17, 56, 61, 83, 94, 110
Prevalence of use, decriminalized/regulated drug	50	2	13	11	24	1, 2, 6, 18, 20, 21, 22, 24, 27, 28, 34, 35, 36, 38, 39, 40, 41, 46, 48, 49, 50, 51, 52, 53, 63, 64, 65, 66, 68, 69, 70, 71, 72, 78, 79, 81, 84, 87, 89, 99, 100, 105, 106, 111, 113

Outcomes	Number of outcomes	# reporting beneficial effects	# reporting harmful effects	# reporting mixed effects	# reporting no effect	Article # (See Included Studies)
Prevalence or frequency of use, other drugs/alcohol	21	2	2	6	11	18, 21, 35, 47, 49, 50, 53, 57, 60, 66, 72, 83, 99, 111
Price of drugs	5	0	1	1	3	3, 31, 32, 45, 77
Substance use disorder or diagnosed dependence	5	0	1	2	2	40, 59, 69, 111, 113
Workplace absence	1	1	0	0	0	102

Appendix A: Search Strategy and Results

Database: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946-Present>
Search Strategy:
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1 ((Marijuana or marihuana or cannabis or cannabinoid* or psychoactive product* or psychoactive substances* or narcotic*) adj5 (Legaliz* or legalis* or decriminal* or depenaliz* or depenalis* or deregulat* or liberaliz* or liberalis*)).tw,kf.
2 ((marijuana or marihuana or cannabis or cannabinoid*) adj1 (policy or policies or law or laws or licens* or legislation or dispensar* or store or stores or regulat* or recreational or medical or medicinal or nonmedical or legal*)).tw,kf.
3 (legal high or legal highs).tw,kf.
4 Psychoactive Substances Act.tw,kf.
5 2 or 3 or 4
6 new psychoactive product*.tw,kf.
7 novel psychoactive product*.tw,kf.
8 novel psychoactive substance*.tw,kf.
9 new psychoactive substance*.tw,kf.
10 novel psychoactive drug*.tw,kf.
11 new psychoactive substances*.tw,kf.
12 Designer Drugs/sd [Supply & Distribution]
13 Medical Marijuana/sd [Supply & Distribution]
14 exp Street Drugs/lj, sd [Legislation & Jurisprudence, Supply & Distribution]
15 Marijuana Smoking/lj [Legislation & Jurisprudence]
16 Drug Users/lj, sn [Legislation & Jurisprudence, Statistics & Numerical Data]
17 "Drug and Narcotic Control"/lj [Legislation & Jurisprudence]
18 or/6-17
19 (Legal* or decriminal* or depenaliz* or depenalis* or deregulat* or liberaliz* or liberalis* or policy or policies or law or laws or licens* or legislation or regulat*).ti.
20 18 and 19
21 5 or 20
22 limit 21 to (clinical study or clinical trial, all or comparative study or evaluation studies or meta analysis or multicenter study or observational study or pragmatic clinical trial or systematic reviews or validation studies)
23 Epidemiologic studies/
24 exp case control studies/
25 exp cohort studies/
26 Case control.tw.
27 (cohort adj (study or studies)).tw.
28 Cohort analy$.tw.
29 (Follow up adj (study or studies)).tw.
30 (observational adj (study or studies)).tw.
31 Longitudinal.tw.
32 Retrospective.tw.
33 Cross sectional.tw.
34 Cross-sectional studies/

Appendix A: Search Strategy and Results

35 or/23-34 [Observational Studies search filter used by SIGN (Scottish Intercollegiate Guidelines Network http://www.sign.ac.uk/methodology/filters.html#obs]
36 21 and 35
37 exp Epidemiologic Methods/
38 amphetamine-related disorders/ep or cocaine-related disorders/ep or drug overdose/ep or inhalant abuse/ep or marijuana abuse/ep or exp opioid-related disorders/ep or phencyclidine abuse/ep or psychoses, substance-induced/ep or substance abuse, intravenous/ep
39 Prevalence/
40 Incidence/ or incidence.ti,ab,kw.
41 (harm or harms).tw,kf.
42 ("marijuana use" or "marijuana availability" or "cannabis use" or cannabis availability or "drug use").tw,kf.
43 or/37-42
44 21 and 43
45 1 or 22 or 36 or 44
46 45 not (exp animals/ not humans.sh.)
47 limit 46 to (comment or editorial or letter)
48 46 not 47
49 limit 48 to yr="1970 -Current"

Database	**Number of Results**
Medline (OVID)	2041
Embase (OVID)	1453
PsycINFO (OVID)	1393
Web of Science: Science Citation Index Social Sciences Citation Index Conference Proceedings Citation Index- Science Conference Proceedings Citation Index- Social Science & Humanities	1358
Criminal Justice Abstracts (EBSCO)	1074
ProQuest Databases: Applied Social Sciences Index & Abstracts (ASSIA), International Bibliography of the Social Sciences (IBSS), PAIS Index, Policy File Index, Sociological Abstracts	910
Total Number of Results	**8229**
Total number of results after duplicates removed in EndNote	**4860**

Appendix B: Quality Appraisal Checklist

Adapted from: Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52(6):377-384.

1. Is the hypothesis/aim/objective of the study clearly described?

☐ Yes (1)

☐ No (0)

2. Are the main outcomes to be measured clearly described in the Introduction or Methods section? *If the main outcomes are first mentioned in the Results section, the question should be answered no.*

☐ Yes (1)

☐ No (0)

3. Are the characteristics of the individuals included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given.

☐ Yes (1)

☐ No (0)

4. Are the interventions of interest clearly described?

☐ Yes (1)

☐ No (0)

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?

☐ Yes (2)

☐ Partially (1)

☐ No (0)

6. Are the main findings of the study clearly described? *Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).*

☐ Yes (1)

☐ No (0)

7. Does the study provide estimates of the random variability in the data for the main outcome *(e.g., IQR, standard deviation, confidence interval, etc.)?*

☐ Yes (1)

☐ No (0)

☐ N/A [there is no variability because data come from the entire population] (1)

Appendix B: Quality Appraisal Checklist

8. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001? (*Confidence intervals are acceptable in place of p-values*)

□ Yes (1)

□ No (0)

9. Were the subjects that were asked to participate in the study representative of the entire population from which they were recruited? *The study must identify the source population for participants and describe how they were selected. Participants would be representative if they comprised the entire source population or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

10. Were those subjects who agreed to participate representative of the entire population from which they were recruited? *The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

11. If any of the results of the study were based on "data dredging", was this made clear? *Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

12. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of participants, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? *Where follow-up was the same for all study participants the answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.*

□ Yes or N/A (1)

□ No (0)

□ Unable to determine (0)

13. Were the statistical tests used to assess the main outcomes appropriate? *The statistical techniques used must be appropriate to the data. For example non- parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data*

Appendix B: Quality Appraisal Checklist

(normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

□ Yes (1)

□ No (0)

□ Unable to determine from article (0)

14. Were the main outcome measures used accurate (valid and reliable)? *For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

15. Were the participants in different comparison groups recruited from the same population or from comparable populations? *Answer NO for studies without a comparison/control group.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

16. Were study subjects in different intervention groups recruited over the same period of time? *Answer NO for studies without a comparison/control group.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

17. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

□ Yes (1)

□ No (0)

□ Unable to determine (0)

Appendix C: Included Studies

INCLUDED STUDIES

1. Adam C, Raschzok A. Cannabis policy and the uptake of treatment for cannabis-related problems. *Drug Alcohol Rev*. 2017;36(2):171-177.
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Appendix C: Included Studies

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22. Cerda M, Wall M, Feng T, et al. Association of state recreational marijuana laws with adolescent marijuana use. *JAMA Pediatr*. 2017;171(2):142-149.
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Appendix C: Included Studies

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Appendix C: Included Studies

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Appendix C: Included Studies

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Appendix C: Included Studies

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Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title			
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
Introduction			
Rationale	#3	Describe the rationale for the review in the context of what is already known.	4
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5

Methods

Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	5
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	5-6
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	5
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	6
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	6-7
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	7
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	7
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A

Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
Results			
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8, Figure 1
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	Supplementary Table 1
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Supplementary Table 1
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary Table 1
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	9-12
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
Discussion			
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	12-14
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15

Funding

Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	16

Notes:

- 17: 7-8, Figure 1
- 18: Supplementary Table 1
- 19: Supplementary Table 1
- 20: Supplementary Table 1 This checklist was completed on 19. October 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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Impact evaluations of drug decriminalization and legal regulation on drug use, health and social harms: A systematic review

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ABSTRACT

Objectives: To review the metrics and findings of studies evaluating effects of drug decriminalization or legal regulation on drug availability, use, or related health and social harms globally.

Design: Systematic review with narrative synthesis.

Data sources: We searched MEDLINE, Embase, PsycINFO, Web of Science, and six additional databases for publications from 1 January 1970 through 4 October 2018.

Inclusion criteria: Peer-reviewed articles or published abstracts in any language with quantitative data on drug availability, use, or related health and social harms collected before and after implementation of *de jure* drug decriminalization or legal regulation.

Data extraction and synthesis: Two independent reviewers screened titles, abstracts, and articles for inclusion. Extraction and quality appraisal (modified Downs and Black checklist) were performed by one reviewer and checked by a second, with discrepancies resolved by a third. We coded study-level outcome measures into metric groupings and categorized the estimated direction of association between the legal change and outcomes of interest.

Results: We screened 4860 titles and 221 full texts and included 114 articles. Most (n=104, 91.2%) were from the U.S., evaluated cannabis reform (n=109, 95.6%), and focused on legal regulation (n=96, 84.2%). 224 study outcome measures were categorized into 32 metrics, most commonly prevalence (39.5% of studies), frequency (14.0%), or perceived harmfulness (10.5%) of use of the decriminalized or regulated drug; or use of tobacco, alcohol, or other drugs (12.3%). Across all substance use metrics, legal reform was most often not associated with changes in use.

Conclusions: Studies evaluating drug decriminalization and legal regulation are concentrated in the U.S. and on cannabis legalization. Despite the range of outcomes potentially impacted by drug law reform, extant research is narrowly focused, with a particular emphasis on the prevalence of use. Metrics in drug law reform evaluations require improved alignment with relevant health and social outcomes.

Strengths and limitations of this study

- This is the first study to review all literature on the health and social impacts of decriminalization or legal regulation of drugs.
- We systematically searched 10 databases over a 38-year period, without language restrictions.
- The review was limited to study designs appropriate for evaluating interventions, nevertheless, most included studies used relatively weak evaluation designs.
- Included outcomes were heterogeneous and not quantitatively synthesized.
- Heterogeneity in the details and implementation of decriminalization or legal regulation policies was not considered in this review.

INTRODUCTION

An estimated 271 million people used an internationally scheduled ("illicit") drug in 2017, corresponding to 5.5% of the global population aged 15-64.[1] Despite decades of investment, policies aimed at reducing supply and demand have demonstrated limited effectiveness.[2,3] Moreover, prohibitive and punitive drug policies have had counterproductive effects by contributing to HIV and hepatitis C transmission,[4,5] fatal overdose,[6] mass incarceration and other human rights violations,[7,8] and drug market violence.[9] As a result, there have been growing calls for drug law reform [10–12] and in 2019, the United Nations Chief Executives Board endorsed decriminalization of drug use and possession.[13] Against this backdrop, as of 2017 approximately 23 countries had implemented *de jure* decriminalization or legal regulation of one or more previously illegal drugs.[14–16]

A wide range of health and social outcomes are affected by psychoactive drug production, sales, and use, and thus are potentially impacted by drug law reform. Nutt and colleagues have categorized these as physical harms (e.g., drug-related morbidity and mortality to users, injury to non-users), psychological harms (e.g., dependence), and social harms (e.g., loss of tangibles, environmental damage).[17,18] 2Concomitantly, a diverse and sometimes competing set of goals motivate drug policy development, including ameliorating the poor health and social marginalization experienced by people who use drugs problematically, shifting patterns of use to less harmful products or modes of administration, curtailing illegal markets and drug-related crime, and reducing the economic burden of drug-related harms.[19]

Given ongoing interest by states in drug law reform, as well as the recent position statement by the UN Chief Executives Board endorsing drug decriminalization,[13] a comprehensive understanding of their impacts to date is required. However, the scientific literature has not been well-characterized, and thus the state of the evidence related to these heterogenous policy targets remains largely unclear. Reviews in the scientific literature, including two meta-analyses, are narrowly focused on adolescent cannabis use. Dirisu et al. found no conclusive evidence that cannabis legalization for medical or recreational purposes increases cannabis use by young people.[20] In the two meta-analyses, Sarvet et al. found that the implementation of medical

cannabis policies in the United States (U.S.) did not lead to increases in the prevalence of past-month cannabis use among adolescents [21] and Melchior et al. found a small increase in use following recreational legalization that was reported only among lower-quality studies.[22]

Given increasing interest in quantifying the impact of drug law reform, as well as a lack of systematic assessment of outcomes beyond adolescent cannabis use to date, we conducted a systematic review of original peer-reviewed research evaluating the impacts of (a) legal regulation and (b) drug decriminalization on drug availability, use, or related health and social harms. Our primary aim is to characterize studies with respect to metrics and indicators used. The secondary aim is to summarize the findings and methodologic quality of studies to date.

METHODS

Consistent with our aim of synthesizing evidence on the impacts of decriminalization and legal regulation across the spectrum of potential health and social effects, we conducted a systematic review using narrative synthesis [23] without meta-analysis. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in preparing this manuscript.[24] The review protocol was registered in PROSPERO (CRD42017079681) and can be found online at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=79681.

Search Strategy and Selection Criteria

The review team developed, piloted, and refined the search strategy in consultation with a research librarian and content experts. We searched MEDLINE, Embase, PsycINFO, Web of Science, Criminal Justice Abstracts, Applied Social Sciences Index & Abstracts, International Bibliography of the Social Sciences, PAIS Index, Policy File Index, and Sociological Abstracts for publications from 1 January 1970 through 4 October 2018. We used MeSH terms and keywords related to (a) scheduled psychoactive drugs (b) legal regulation or decriminalization policies, and (c) quantitative study designs. Search terms specific to health and social outcomes were not employed so that the search would capture the broad range of outcomes of interest. See Appendix A for the final MEDLINE search strategy. For conference abstracts, we contacted

authors for additional information on study methods and to identify subsequent relevant publications.

We included peer-reviewed journal articles or conference abstracts reporting on original quantitative studies that collected data both before and after the implementation of drug decriminalization or legal regulation. We did not consider as original research studies that reproduced secondary data without conducting original statistical analyses of the data. We defined decriminalization as the removal of criminal penalties for drug use and/or possession (allowing for civil or administrative sanctions) and legal regulation as the development of a legal regulatory framework for the use, production, and sale of formerly illegal psychoactive drugs. Studies were excluded if they evaluated *de facto* (e.g., changes in enforcement practices) rather than *de jure* decriminalization or legal regulation (changes to the law). This exclusion applied to studies analyzing changes in outcomes following the U.S. Justice Department 2009 memo deprioritizing prosecution of cannabis-related offences legal under state medical cannabis laws. Eligible studies included outcome measures pertaining to drug availability, use, or related health and social harms. We used the schema developed by Nutt and colleagues to conceptualize health and social harms, including those to users (physical, psychological, and social) and to others (injury or social harm).[18]

Both observational studies and randomized controlled trials were eligible in principle, but no trials were identified. There were no geographic or language restrictions; titles, abstracts, and full-texts were translated on an as-needed basis for screening and data extraction. We excluded cross-sectional studies (unless they were repeated) and studies lacking pre- and post-implementation data collection because such designs are inappropriate for evaluating intervention effects.

Data Analysis

Screening and data extraction were conducted in DistillerSR (Evidence Partners, Ottawa, Ontario). We began with title-only screening to identify potentially relevant titles. Two reviewers screened each title. Unless both reviewers independently decided a title should be excluded, it was advanced to the next stage. Next, two reviewers independently screened each potentially eligible abstract. Inter-rater reliability was good (weighted Kappa at the question level=0.75). At

this stage, we retrieved full-text copies of all remaining references, which were screened independently by two reviewers. Disagreements on inclusion were resolved through discussion with the first author. Finally, one reviewer extracted data from each included publication using a standardized, pre-piloted form and performed quality appraisal. A second reviewer double-checked data extraction and quality appraisal for every publication, and the first author resolved any discrepancies.

The data extraction form included information on study characteristics (author, title, year, geographic location), type of legal change studied and drug(s) impacted, details and timing of the legal change (e.g., medical vs. recreational cannabis regulation), study design, sampling approach, sample characteristics (size, age range, proportion female), and quantitative estimates of association. We coded each study-level outcome measure into one metric grouping, using 24 pre-specified categories and a free-text field (see Figure 1 for full list). Examples of metrics include: prevalence of use of the decriminalized or regulated drug, overdose or poisoning, and non-drug crime.

We also categorized the estimated direction of association of the legal change on outcome measure(s) of interest (beneficial, harmful, mixed, or null).2 These associations were coded at the outcome (not study) level and classified as beneficial if a statistically significant increase in a positive outcome (e.g., educational attainment) or decrease in a negative outcome (e.g., substance use disorder) was attributed to implementation of decriminalization or legal regulation, and vice-versa for harmful associations. The association was categorized as mixed if associations were both harmful and beneficial across participant subgroups, exposure definitions (e.g., loosely vs. tightly regulated medical cannabis access), or timeframes. Although any use of cannabis and other psychoactive drugs need not be problematic at the individual level, we categorized drug use as a negative outcome given that population-level increases in use may correspond to increases in negative consequences; we thought that this cautious approach to categorization was appropriate given that such increases are generally conceptualized as negative within the scientific literature. For outcomes that are not unambiguously negative or positive, the coding approach was pre-determined taking a societal perspective. For example, increased healthcare utilization (e.g., hospital visits due to cannabis use) was coded as negative because of the increased burden placed on healthcare systems. The association was categorized as null if no

statistically significant changes following implementation of drug decriminalization or legal regulation were detected. We set statistical significance at a=0.05, including in cases where authors used more liberal criteria.

Quality assessment at the study level was conducted for each full-length article using a modified version of the Downs and Black checklist [25] for observational studies (see Appendix B), which assesses internal validity (bias), external validity, and reporting. Each study could receive up to 18 points, with higher scores indicating more methodologically rigorous studies. Conference abstracts were not subjected to quality assessment due to limited methodologic details.

Patient and Public Involvement

This systematic review of existing studies did not include patient or public involvement.

RESULTS

Study Characteristics

As shown in the PRISMA Flow Diagram (Figure 2), we screened 4860 titles and abstracts and 213 full texts, with 114 articles meeting inclusion criteria (Appendix C). Key reasons for exclusion at the full-text screening stage were that the article did not report on original quantitative research (n=59) or did not evaluate decriminalization or legal regulation as defined herein (n=23). Details of each included study are presented in Supplementary Table 1. Included studies had final publication dates from 1976-2019; 44.7% (n=51) were first published in 2017-2018, 43.9% (n=50) were published in 2014-2016 and 11.4% (n=13) were published before 2014.

Characteristics of included studies are described in Table 1, both overall and stratified by whether they evaluated decriminalization (n=19) or legalization (n=96) policies (one study evaluated both policies). Most studies (n=104, 91.2%) were from the U.S. and examined impacts of liberalizing cannabis laws (n=109, 95.6%). Countries represented in non-U.S. studies included Australia, Belgium, China, Czech Republic, Mexico, and Portugal. The most common study designs were repeated cross-sectional (n=74, 64.9%) or controlled before-and-after (n=26, 22.8%) studies and the majority of studies (n=87, 76.3%) used population-based sampling

Table 1. Characteristics of studies evaluating drug decriminalization or legal regulation, 1970-2018

Characteristic	Total (%) n (%) (*n* = 114)	Decriminalization[a] n (%) (*n* =19)	Legal regulation[a] n (%) (*n* =96)
Country			
United States	104 (91.2)	10 (52.6)	95 (99.0)
Australia	3 (2.6)	3 (15.8)	0 (0.0)
Portugal	2 (1.8)	2 (10.5)	0 (0.0)
China	1 (0.9)	0 (0.0)	1 (1.0)
Czech Republic	1 (0.9)	1 (5.3)	0 (0.0)
Mexico	1 (0.9)	1 (5.3)	0 (0.0)
Multi-country[b]	2 (1.8)	2 (10.5)	0 (0.0)
Focus of drug law reform			
Cannabis	109 (95.6)	15 (78.9)	95 (99.0)
Opium	1 (0.9)	0 (0.0)	1 (1.0)
Peyote	1 (0.9)	1 (5.3)	0 (0.0)
Multiple/All drugs	3 (2.6)	3 (15.8)	0 (0.0)
Study design			
Cohort	4 (3.5)	0 (0.0)	4 (4.2)
Controlled before-and-after	26 (22.8)	6 (31.6)	20 (20.8)
Interrupted time series	6 (5.3)	0 (0.0)	6 (6.3)
Repeated cross-sectional	74 (64.9)	11 (57.9)	64 (66.7)
Uncontrolled before-and-after	4 (3.5)	2 (10.5)	2 (2.1)
Sampling approach			
Convenience	22 (19.3)	5 (26.3)	18 (18.8)
Population-based	87 (76.3)	13 (68.4)	74 (77.1)
Administrative records	45 (39.5)	6 (31.6)	39 (40.6)
Household survey	25 (21.9)	5 (26.3)	20 (20.8)
School-based survey	17 (14.9)	2 (10.5)	15 (15.6)
Unspecified	5 (4.2)	1 (5.3)	4 (4.2)

a. Combined total exceeds number of studies because some evaluated both decriminalization and legal regulation.
b. One global study and one multi-country European study including Belgium and Portugal.

methods. Figure 3 illustrates the geographic distribution of studies among countries where national or subnational governments had decriminalized or legally regulated one or more drugs.

Study Quality

Quality assessment was performed for the 93 full-length articles included in the review, excluding 21 conference abstracts (Supplementary Table 1). Scores ranged from 7 to 18 of 18

possible points, with a mean of 14.4 (SD=2.56). Quality scores were similar comparing U.S. to non-U.S.-based studies (*X*=14.4 and 13.7, respectively, p=0.386) but higher for studies evaluating legal regulation (*X*=14.8) versus decriminalization (*X*=12.8) (p=0.003). Study quality differed significantly (p<0.001) by the direction of the association with the outcome of interest, with higher quality scores among studies estimating mixed (*X*=15.4) or beneficial (*X*=15.2) versus null (*X*=14.2) or harmful (*X*=13.1) effects of legal change on the outcome of interest. Study quality did not appear to increase over time (e.g., *X*=14.0 in 2014 and 14.4 in 2018).

Study Outcome Measures and Metrics

Across 114 studies we extracted 224 outcome measures, which were coded into 32 metrics (Figure 1). The most common metric employed by studies was the prevalence of use of the decriminalized or legally regulated drug, which was examined in 39.5% of studies (n=45) and represented 22.3% of outcome measures (n=50). Of these studies, 13 (28.9%; 8 full-length articles and 5 abstracts) did not report any other metric [26–38] and an additional 6 studies (13.3%) reported on the prevalence of use in addition to a single drug-related perception metric (either harmfulness or availability).[39–44] The second most common metric was the frequency of use of the decriminalized or legally regulated drug (14.0% of studies, n=16) and the third was the prevalence or frequency of use of tobacco, alcohol, or drugs that remained illegal (12.3% of studies, n=14; 9.4% of outcome measures, n=21). The fourth most commonly employed metric was any change in the perceived health harmfulness of using the decriminalized or regulated drug (10.5% of studies, n=12), which was assessed among adolescents or young adults in all studies except for one that assessed this metric among parents.[45]

All other metrics were assessed in <10% of included studies. Health service utilization was evaluated in 7.9% of studies (n=9) using 12 outcome measures, primarily related to emergency department visits and/or hospitalizations. Prescribed (primarily opioid) drug use and perceived availability of the decriminalized or legally regulated drug were reported in 7.0% of studies each (n=8). Overdose or poisoning by the decriminalized or regulated drug, and by other drugs (predominantly opioids), were examined in 5.3% (n=6) and 6.1% of studies (n=7), respectively. Driving while under the influence or with detectable concentrations of the decriminalized or regulated drug (cannabis) was examined in seven studies (6.1%) inclusive of eight outcome

measures. Notably, one study assessed self-reported impaired driving,[46] while others assessed the proportion of fatally injured drivers screening cannabis-positive or the overall prevalence of driving with detectable THC concentrations in blood. Remaining metrics were measured in less than 5% of studies (Figure 1). Some pre-specified metrics were not represented in any of the articles, including infectious disease incidence (e.g., HIV, Hepatitis C), environmental impacts (e.g., drug production waste, discarded needles), and labor market participation.

Studies Outside the U.S.

Of the ten studies conducted outside the U.S., six focused on cannabis decriminalization. All three studies from Australia examined the prevalence of cannabis use post-decriminalization,[31,34,47] while one also measured perceived cannabis availability.[47] Following cannabis decriminalization, one European multi-country study including Belgium and Portugal examined the prevalence of cannabis use and uptake of cannabis-related addictions treatment [48] and one Czech study considered the age of first cannabis use.[49] An international study using United Nations Office on Drugs and Crime data from 102 countries compared availability, as reflected by cannabis seizures and plant eradication, in countries that had decriminalized cannabis versus those that had not.[50] Three non-U.S. studies evaluated decriminalization of all psychoactive drugs. Two studies from Portugal examined health care and non-health-care costs and psychoactive drug prices, respectively.[51,52] One study from Mexico examined drug-related criminal justice involvement (arrests) and (violent) crimes.[53] Finally, a study of historic opium legalization in China (1801-1902) measured the price and availability (quantity of exports) of opium before and after legalization.[54]

Impacts of Decriminalization and Legal Regulation

Results of individual studies are provided in Supplementary Table 1. Supplementary Table 2 tallies findings and average quality scores for each of the metrics; here we summarize findings for metrics examined in more than 5% of studies, in descending order based on the number of datapoints. Across all three substance use metrics (prevalence of use, frequency of use, and use of other alcohol or drugs), drug law reform was most often not associated with use (with null findings for 48.0-52.4% of outcome measures falling under these metrics). With respect to change in perceived harmfulness of the decriminalized or regulated drug, mixed results were

found in half of cases, with heterogeneity detected on the basis of age, gender, and state.[39,43,55–57] For example, legal regulation of cannabis for medical use was associated with greater perceived harmfulness of cannabis among eighth graders but not older students in an analysis of U.S. Monitoring the Future data [39] while a study employing U.S. National Survey on Drug Use and Health data found greater perceived harmfulness of cannabis among young adults aged 18-25 but not adolescents aged 12-17.[57]

Among nine studies that employed health service utilization metrics, harmful effects were reported for six of twelve outcome measures, with increases in emergency department visits and/or hospitalizations attributed to decriminalization or legal regulation.[58–63] However, all but one of those studies [58] assessed change over time in one jurisdiction, without a control group. In contrast, six of nine prescription drug use associations were beneficial, with reductions observed in rates of opioid [64–68] and other drug prescribing [69,70] attributed to legal regulation of cannabis for medical use; outcomes in this category came from studies of higher average quality (X=16.3) . Perceived availability of the decriminalized or regulated drug appeared largely unaffected by decriminalization (null associations for five of nine outcome measures) but two studies indicated increased perceived availability of cannabis among Colorado, U.S. adolescents following legal regulation for adult use [71] and among adults in U.S. states with legal regulation for medical use.[44] Across the subset of seven outcome measures for overdose or poisoning by the decriminalized or regulated drug (cannabis), in all cases an increase in calls to poison control centers or unintentional pediatric exposures was reported.[59,72–76] However, studies assessing the impacts of cannabis regulation on overdose or poisoning by drugs other than cannabis concluded that the effects were either beneficial (four outcome measures[75,77–79]) or mixed/null (three outcome measures[80–82]). Driving with detectable concentrations of THC was most often found to increase following decriminalization or legal regulation (five of eight outcome measures; [83–87]), but these studies were of lower average quality (X=12.0).

Impacts of Decriminalization

Of the 19 studies evaluating impacts of decriminalization, six measured the prevalence of use of the decriminalized substance with eight unique outcome measures. No association was

detected for all but three outcomes; following cannabis decriminalization lifetime use increased among adults in South Australia,[31] while past-month use increased among 12th graders but not younger students in California,[56] relative to the rest of the country in both cases. After peyote use for ceremonial purposes was decriminalized in the U.S. in 1994, self-reported use increased among American Indians.[88] Three studies evaluated relationships between decriminalization and drug-related criminal justice involvement in Mexico and the United States. One high-quality study found that decriminalization positively influenced criminal justice involvement: in five U.S. states, arrests for cannabis possession decreased amongst youth and adults.[89] When possession of small amounts of cannabis was decriminalized in the 1970s in Nebraska, however, the mean monthly number of arrests did not change, while cannabis-related prosecutions increased among youth.[90] In Tijuana, Mexico, decriminalization of all drugs had no apparent impact on the number of drug possession arrests.[53] Two historic and one recent study measured health care utilization. U.S. states that decriminalized cannabis in the 1970s saw greater emergency department visits related to cannabis, but decreased visits related to other drugs.[60] In Colorado, U.S., decriminalization was associated with increased emergency department visits for cyclic vomiting.[62] Addiction treatment utilization, health care and non-health-care costs, driving after use, price of drugs, availability of drugs, frequency of use, and attitudes towards use and perceived harmfulness were each evaluated in only one or two studies of decriminalization.

DISCUSSION

This systematic review identified 114 peer-reviewed publications and conference abstracts evaluating the impacts of drug decriminalization or legal regulation from 1970-2018. Within this search period, 88.6% were published in 2014 or later. This rapid growth in scholarship was driven by the implementation and subsequent evaluation of cannabis legalization in a number of U.S. states beginning in 2012, and knowledge production will surely continue to accelerate as longer-term data become available and as other jurisdictions (e.g., Canada, Uruguay) analyze the effects of recently implemented cannabis legalization. The present study provides an overview of the emerging literature based on our systematic review and suggests three key patterns.

First, peer-reviewed evaluations of drug decriminalization and legal regulation are overwhelmingly geographically concentrated in the U.S. and focused on cannabis legalization. Importantly, the lack of non-U.S. studies evaluating legal regulation of cannabis for medical use may reflect the more tightly controlled nature of medical cannabis regulation in other countries, and thus the more limited potential for population-level effects. It is notable that decriminalization in the absence of legal regulation was evaluated in only 18 studies (15.8%), despite being far more common globally than legal regulation. These gaps may hamper evidence-based drug law reform in countries that are less well-developed, play a substantial role in drug production and transit, or have different baseline levels of substance (mis)use as compared to the U.S.

Second, prevalence of use was the predominant metric used to assess the impact of drug law reform, despite its limited clinical significance (e.g., much cannabis use is non-problematic) and limited responsiveness to drug policy. This is because ecological analyses have indicated little relationship between drug policies and prevalence of use,[52] as have studies assessing within-state change in use related to legal regulation.[21] These findings are supported by the preponderance of evidence synthesized in this review, although some variation is evident in relation to the specific provisions of legal reforms (e.g., liberal versus tightly regulated medical markets [91]). Impacts of legal cannabis regulation on prevalence and frequency of use continue to be evaluated, with recent data suggesting small increases among adults, but not youth.[92] Drug policies may be more able to influence the types of drugs that people use, drug-related risk behaviors, and modes of drug consumption.[93] Metrics to assess these outcomes, however, were lacking in the reviewed literature. For example, only one study (0.8%) investigated whether legal regulation of cannabis was associated with changes in the mode of cannabis consumption.[71] Although the prevalence of use was often measured alongside more clinically or socially significant metrics (e.g., prevalence of substance use disorders, educational outcomes among young adults), 42.2% of studies assessing substance use prevalence included that metric alone or in combination with a single drug-related attitude metric.

Third, there was a lack of alignment between the stated policy objectives of drug law reform and the metrics used to assess its impact in the scientific literature. For instance, removal of criminal

sanctions to prevent their negative sequelae is a key rationale for decriminalization and legal regulation,[12,13,94] but only four studies (3.5%) evaluated changes in drug-related criminal justice involvement following drug law reform. Similarly. improving the physical and mental health of people who (already) use drugs is a motivation for drug policy reform but no included studies examined mental or physical health outcomes (aside from substance use disorders) in this population. As a result, there is a risk that decisions on drug policy may be informed by inappropriate metrics. Promisingly, in recent months, additional studies assessing legal regulation that employ a range of criminal justice metrics have been published.[95,96] Finally, despite ample evidence of the impact of criminalization on infectious disease transmission and acquisition risks,[5] we found no studies evaluating the impact of decriminalization on these outcomes.

Both the included studies and our systematic review have important strengths and limitations. To our knowledge, we conducted the first review of all global literature on decriminalization and legal regulation and applied no language restrictions. All eligible articles identified were published in English; this may reflect a paucity of evaluation research published in other languages and/or limitations of our search strategy (e.g., some non-English journals may not be indexed in the 10 databases searched). In addition, we excluded grey literature, non-original research, and study designs that are not suited to evaluating policy effects (e.g., cross-sectional studies), but these restrictions may have narrowed the geographic scope of included studies. Scoping reviews inclusive of grey literature would be valuable for describing the full range of evaluations that have been conducted globally. Nevertheless, most included studies used weaker eligible study designs that are vulnerable to pre-existing trends and confounding; only 22.8% and 5.3% respectively used controlled before-and-after or interrupted time series designs to address these threats to validity. The use of these study designs may be related to limited resources for prospective drug policy evaluations, with many studies relying on publicly available, routinely collected data.

This narrative synthesis did not focus on estimating the outcome-specific effects of particular decriminalization or legal regulation policies but instead sought to characterize the metrics employed to date. With respect to both the individual studies and our synthesis, the

implementation and specific provisions of drug policies vary widely. Decriminalization policies vary in their definitions of quantities for personal use, application of administrative penalties, and the extent to which the law "on the books" is reflected in policing and criminal justice practice. Indeed, in some jurisdictions with nominal decriminalization, arrests for possession of small quantities of the decriminalized drugs remain routine.[53] Legal regulation models for cannabis are also heterogenous. For example, policies legally regulating cannabis for medical use may or may not allow for legal dispensaries, and this provision has been shown to substantially modify the impact of legal regulation on cannabis use.[97] To the extent that individual studies employed crude exposure measures (e.g., presence versus absence of a law), they may have obscured context-dependent effects of drug law liberalization. Further, the impact of drug laws on drug use and related outcomes may be limited by a lack of public awareness of the details of local laws.[98]

Our use of vote-counting in this synthesis (i.e., categorizing individual outcome measures as indicating beneficial, harmful, mixed/subgroup-specific, or no statistically significant associations) is subject to the same limitation. Vote-counting should also be interpreted with caution in light of the heterogeneity of outcome definitions, the inherent arbitrariness of statistical significance thresholds, and the key distinction between statistical and clinical significance. In addition, many included studies are evaluating the same policies (e.g., cannabis legalization in western U.S. states), sometimes using overlapping data but drawing different conclusions based on analytic choices and timeframes. The existence of multiple datapoints for a particular outcome does not imply that the outcome has been well-studied across diverse contexts such that scientific consensus on its effects has been reached. Moreover, as illustrated by a recently published extension of the included article by Bachhuber et al.,[78] multiple high-quality studies may generate results that are later revealed to be spurious as additional follow-up data become availability. Specifically, Shover et al. demonstrated that the positive association reported between medical cannabis legalization and opioid overdose mortality in 1999-2010 reversed direction in later years, suggesting that earlier findings of a protective effect should not be given causal interpretations.[99] This was foreshadowed in the included article by Powell et al., which found that the purportedly positive effect of medical cannabis legalization was attenuated in 2010-2013.[82] This scientific back-and-forth can be expected given that most

included articles are evaluating legal changes introduced rather recently, and thus are examining early impacts with limited years of follow-up. Longer-term impacts of non-medical cannabis legalization, and how they might be influenced by increased commercialization, are yet to be seen.[100]

Conclusions

The findings of this review indicate a need for a broadening of the metrics used to assess the impacts of drug decriminalization and legal regulation. Given the growing number of jurisdictions considering decriminalization or legal regulation of psychoactive drugs,[14–16] the disproportionate emphasis on metrics assessing drug use prevalence, as well as the limited geo-cultural diversity in evaluations, are concerning. Experts have called for a more fulsome approach to evaluating drug policies in line with public health and the United Nations Sustainable Development Goals, with attention to the full breath of health and social domains potentially impacted, including human rights and social inclusion (e.g., stigma), peace and security (e.g., drug market violence), development (e.g., labor market participation) drug market regulation (e.g., safety of the drug supply), and clinically-significant health metrics (e.g., drug-related morbidity).[101] Drawing on methods such as multi-criterion decision analysis,[19] the engagement of both scientists and policymakers in priority-setting may help to produce evidence that provides a more comprehensive understanding of the breadth of impacts that should be anticipated with drug law reform efforts. Funding will also be required to support rigorous prospective evaluations of legal reforms.

Figure 1 Legend

Metrics examined by included studies.

Figure 2 Legend

PRISMA Flow Diagram

Figure 3 Legend

Number of included studies from countries that implemented decriminalization or legal regulation by 2017

Note: Policy changes were classified, following the review inclusion criteria, based on the implementation of a change to national or subnational law to decriminalize drug use and/or possession or to legalize at least one class of drugs. We did not evaluate the extent to which legal changes were reflected in policing and criminal justice practice. Implementation of cannabis legalization for medical purposes only is not reflected in this map.

Author contributions

DW and AIS conceptualized and supervised the review. CZ designed and conducted the literature searches. AIS drafted the manuscript. SC, ZM, and AIS conducted screening and data extraction. NZ contributed to drafting the manuscript and developing figures. All authors contributed to interpretation of findings and revising the manuscript for important intellectual content.

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Competing interests

We have no competing interests to declare.

Data sharing statement

All relevant data are contained within the article and supplementary materials.

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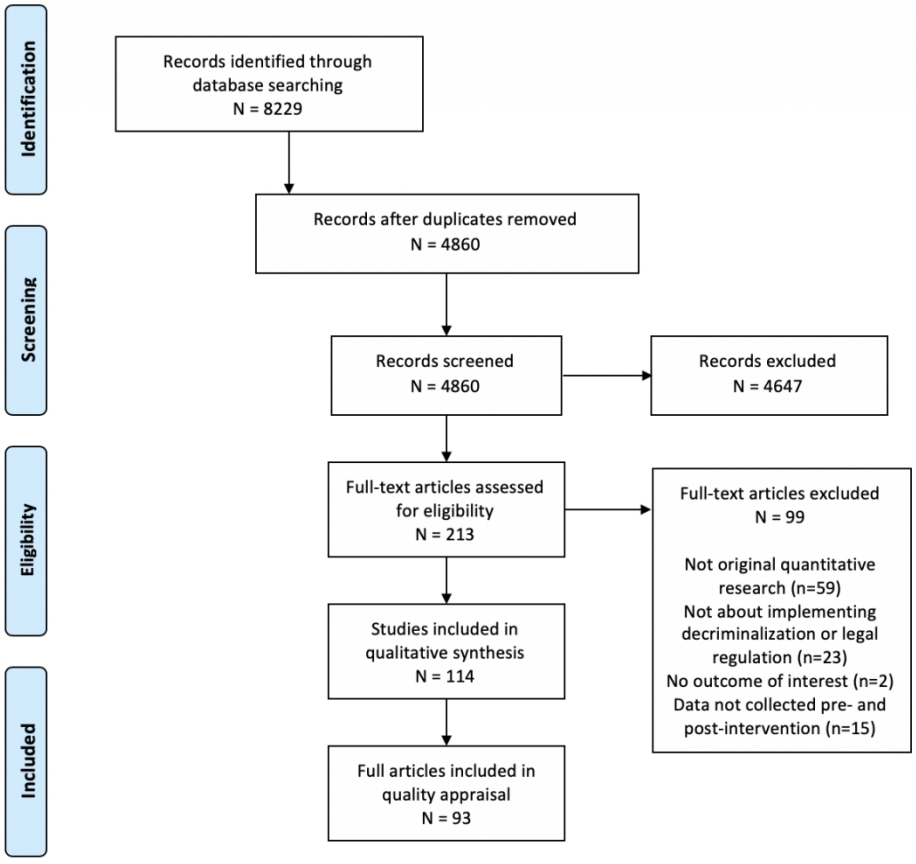
Metrics examined by included studies.



PRISMA Flow Diagram

Number of included studies from countries that implemented decriminalization or legal regulation by 2017
Note: Policy changes were classified, following the review inclusion criteria, based on the implementation of a change to national or subnational law to decriminalize drug use and/or possession or to legalize at least one class of drugs. We did not evaluate the extent to which legal changes were reflected in policing and criminal justice practice. Implementation of cannabis legalization for medical purposes only is not reflected in this map.

Supplementary Table 1. Included Studies

	Reference	Setting Legal change	Study design, dates [Comparison group or condition]	Sampling approach Sample size	Outcomes	Effects	Quality
1.	Adam 2017	Belgium, Portugal Cannabis decriminalization	Controlled before-and-after, 1996-2010 [Austria, Germany, Greece, Ireland, Italy, Netherlands, Spain, Sweden]	Convenience sampling 89 treatment units	*Addiction treatment utilization:* # of first-time drug treatment clients reporting cannabis as primary indication, per reporting treatment unit	No significant effect of decriminalization. *B*= 2.66, *SE*=8.72, *P*=0.770	13
					Prevalence of use, decriminalized/regulated drug(s): past-year cannabis use	No significant effect of decriminalization. *B* = 1.88, *SE*=1.77, *P*=0.310	
2.	Allshouse 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2013; 2014	Population-based; Admin record data N=743	*Prevalence of use, decriminalized/regulated drug(s)*: self-reported cannabis use during pregnancy	No significant effect of RCL (from 4.5% to 7.5%, *p*=0.06)	A *
					Prevalence of use, decriminalized/regulated drug(s): cannabis-positive urine screen during pregnancy	No significant effect of RCL. Adjusted prevalence difference = 0.03, *P*=0.99.	
3.	Anderson 2013	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1990-2010	Convenience sampling *Study A*: 8,271 cannabis purchases *Study B*: 1071 fatalities	*Price of drugs*: median price of cannabis in state and year	9.8% decrease in price of high-quality cannabis, controlling for state-specific time trends. Lagged models indicate price reductions not significant until 4th year after MCL. Effects on price of low-quality cannabis largely statistically insignificant.	11
					Accidents, motor vehicle: traffic fatality outcomes per 100,000; primary outcome is total fatalities.	No significant change in fatalities, controlling for state-specific time trends. In lagged models, MCL associated with 8-13% fatality reductions in years 1-4, with reduction attenuated and no longer significant after 5 years, controlling for state-specific time trends.	

4.	Anderson 2014	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1990-2007 [States that did not implement MCL]	Population-based; Admin record data	*Mental health conditions, suicide, or self-harm*: annual suicide rates per 100,000 among individuals 15+	No difference in suicide rate overall. Reduction among males, (log) rate difference =0.047* (95% CI: –0.089, –0.005). By age, significant reductions among males from 20-39 and among females >=60.	16
5.	Anderson 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1992-2015	Population-based; Admin record data N= 1224 state-years	*Accidents, other*: Workplace fatalities by state from the Bureau of Labor Statistics	No difference in fatality rate overall. Reduction among those aged 25-44 only. Adjusted rate ratio = 0.805 (95% CI: 0.662, 0.979).	15
6.	Anderson 2015	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1993-2011	Population-based; School-based survey N=862,695	*Prevalence of use, decriminalized/regulated drug(s)*: past 30 day use	No significant effect of MCL: % difference, combined national and state YRBS = -0.007, SE=0.011, p>0.05.	15
					Frequency of use, decriminalized/regulated drug(s): used ≥ 10 times in past 30 days	No significant effect of MCL: % difference, combined national and state YRBS = -0.004, SE=0.006, p>0.05.	
					Actual availability of decriminalized/regulated drug(s): offered, sold, or given an illegal drug on school property in past year	MCL associated with reduction in availability, % difference, combined national and state YRBS = -0.020, SE=0.008, p<0.05;	
7.	Arredondo 2018	Mexico Decriminalization of all drugs	Repeated cross-sectional study, 2009-2014	Population-based; Admin record data	*Criminal justice involvement*: Monthly number of drug possession arrests per precinct.	Decriminalization law not associated with arrests, Beta for ln(possession arrests)=0.187, SE=0.151, p>0.05.	14
					Crime (non-drug): Violent crime arrests (injuries, robbery, homicides)	Law not associated with arrests, b=0.001, SE=0.090, p>0.05.	

					Crime (non-drug): Non-violent arrests (theft, possession of stolen car)	Law not associated with arrests, b=-0.043, SE=0.071, p>0.05.	
8.	Aydelotte 2017	United States Legal regulation of cannabis for recreational use (RCL)	Controlled before-and-after study, 2009-2015 [8 similar states without MCL or RCL]	Population-based; Admin record data N=60,737	*Accidents, motor vehicle*: Annual number of motor vehicle crash fatalities	RCL not associated with crash fatalities, adjusted difference in difference coefficient: +0.2 (95% CI: -0.4, +0.9).	15
9.	Bachhuber 2014	United States Legal regulation of cannabis for medical use (MCL)	Interrupted time series study, 1999-2010	Population-based; Admin record data	*Overdose or poisoning, other drug*: opioid analgesic overdose mortality rate	MCL associated with reduced mortality, adjusted percentage change in annual rate= -24.8% (95% CI: -37.5, -9.5), p = .003.	16
10.	Banerji 2017	United States Legal regulation of cannabis for recreational use	Repeated cross-sectional study, 2011-2015	Population-based; Admin record data N=777 exposures	*Overdose or poisoning, decriminalized/regulated drug*: cannabis calls to poison control center	Apparent increase (from 86 in 2011 to 231 in 2015); no statistical tests reported.	A *
					Overdose or poisoning, other drug: synthetic cannabinoid calls to poison control center	Apparent decrease (100 in 2013 and 17 in 2014); no statistical tests reported.	
11.	Bell 2015	United States Legal regulation of cannabis for medical use (MCL) and recreational use	Repeated cross-sectional study, 2008-2014	Population-based; Admin record data N=29	*Accidents, other*: hydrocarbon burns referred to the University of Colorado Hospital	Before MCL (Jan 2008-Aug 2009): 0 cases During MCL (Oct 2009-Dec 2013): 19 cases During recreational legalization (Dec 2013-Aug 2014): 12 cases No statistical tests reported.	11
12.	Bjordal 2015	United States Legal regulation of cannabis for recreational use	Repeated cross-sectional study, 2013-2014	Population-based; Admin record data N=245 exposures	*Overdose or poisoning, decriminalized/regulated drug*: Cannabis calls to poison control center (p.694)	Apparent increase (from 158 in 2013 to 245 in 2014); no statistical tests reported.	A *

13.	Blachly 1976	United States Cannabis decriminalization	Uncontrolled before-and-after study, 1970; 1975	Convenience sampling N=627 admissions	*Health services utilization*: % of drug abuse admissions to Dammasch State Hospital due to cannabis	Prevalence from 6.7% (1970) to 2.5% (1975); no statistical tests reported.	8
14.	Boyle 2014	United States Cannabis decriminalization	Repeated cross-sectional study, 2011-2013	Population-based; Admin record data N=11 incidents	*Accidents, other*: explosions of gases related to hash oil manufacturing	Two events in 2 years prior, nine events in 7 months post-decriminalization (before legal sales); no statistical tests reported.	A *
15.	Bradford 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2010-2015	Population-based; Admin record data N=132.6 million physician-drug-year observations	*Prescription drug use*: total number of daily opioid dose prescriptions filled (in millions)	MCL associated with fewer daily doses filled in states with active dispensaries (-3.742 million, 95% CI: -6.289, -1.194) and in states with home cultivation (-1.792 million, 95% CI: -3.532, -0.052). Results also varied by type of opioid.	18
16.	Bradford 2016	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 2010-2013 [States without a medical marijuana law at a given time]	Population-based; Admin record data N= 588,808-2,496,608	*Prescription drug use*: among Medicaid Part D enrollees, average daily doses filled annually per physician for FDA-approved drugs treating conditions that cannabis may be used to treat (anxiety, depression, glaucoma, nausea, pain, psychosis, seizures, sleep disorders, spasticity)	MCL associated with statistically significant ($p<0.05$) reductions in daily doses filled for 7 of 9 conditions (difference-in-difference coefficients from -265 daily doses for depression to -1826 for pain), no significant effects for glaucoma or spasticity.	17
					Costs, health care: estimated annual change in Medicaid Part D spending (program and enrollee)	Estimated prescription drug cost savings from 2010-2013 attributed to MCL = $515,194,125.	

17.	Bradford 2017	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 2007-2014 [States without MCL in a given quarter]	Population-based; Admin record data	*Prescription drug use*: average number of daily prescription drug doses dispensed per fee-for-service Medicaid beneficiary for FDA-approved drugs treating conditions that cannabis may be used to treat.	MCL associated with statistically significant ($p<0.05$) reductions in daily doses per beneficiary for 5 of 9 conditions (depression, nausea, pain, psychosis, and seizures). Estimated proportion reductions in dispensed doses ranged from 11% for pain to 17% for nausea.	17
					Costs, health care: estimated annual change in Medicaid fee-for-service spending on prescription drugs with medical cannabis indications	Estimated Medicaid fee-for-service prescription drug cost savings from 2007-2014 attributed to MCL = 2,694.1 million	
18.	Brooks-Russell 2019	United States Legal regulation of cannabis for recreational use	Repeated cross-sectional study, 2013-2015	Population-based; School-based survey N = 26,019 (2013) N = 15,970 (2015)	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime use; past 30-day use.	No significant change in lifetime or past 30-day use following legal regulation.	15
					Prevalence of use, other drugs or alcohol: past 30-day use of cigarettes; past 30-day use alcohol; lifetime non-medical prescription drug use; lifetime cocaine use.	Decrease in past 30-day cigarette use from 2013 to 2015 (12.1 to 8.6%, $p<0.01$). No significant changes in other drug or alcohol use.	
					Perceived harmfulness of decriminalized/regulated drug(s): high vs. low perceived accessibility, wrongfulness, parental disapproval, and harmfulness.	Decrease in high perceived harmfulness (52.9% to 47.7%, $p<0.01$). No significant changes in other perceptions.	
					Frequency of use, decriminalized/legalized drug(s): >20 occasions of use in past 30 days, among those who reported past 30-day use.	Decrease in frequent use among past-30-day users (33.2% to 26.8%, $p<0.01$).	
					Prevalence of use, decriminalized/regulated drug(s): use on school property, among those who reported past 30-day use.	Decrease in use on school property among past-30-day users (5.7% to 4.4%, $p=0.03$).	

19.	Calcaterra 2018	United States Legal regulation of cannabis for recreational use (RCL)	Interrupted time series study, 2009-2015	Population-based; Admin record data N=370,612	*Health services utilization*: cannabis-related hospitalizations	RCL associated with an increase in hospitalizations: adjusted annual rates of inpatient and emergent hospitalizations were 2.4 and 4.3 times higher in 2015 as compared to 2009 ($p<0.001$). A reduced segmented regression model shows a significant increase in slope post-RCL ($b= 1.835$, $SE=0.218$, $p< 0.0001$).	A *
20.	Cassidy 2015	United States Legal regulation of cannabis for recreational use	Uncontrolled before-and-after study, 2008-2014	Convenience sampling N=13,945	*Prevalence of use, decriminalized/regulated drug(s)*: among substance use treatment clients	Increase from 21.3% in 2008 to 32.8% in 2014 ($p<0.001$).	A *
					Prevalence of use, decriminalized/regulated drug(s): past-year initiation	No significant change in past-year initiation.	
21.	Cerda 2018	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1991-2015 [States without MCL]	Population-based; School-based survey N=1,179,372	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	Decrease in 8th grade (aOR=0.72; 95% CI: 0.62, 0.84). No significant changes in 10th or 12th.	18
					Prevalence of use, other drugs or alcohol: binge drinking in past two weeks	Decrease in 8th grade (aOR=0.72; 95% CI: 0.65, 0.79). No significant changes in 10th or 12th.	
					Prevalence of use, other drugs or alcohol: past 30-day cigarette use	Decrease in 8th grade (aOR=0.74; 95% CI: 0.66, 0.82) and increase in 12th grade (aOR=1.17; 95% CI: 1.06, 1.29).	
					Prevalence of use, other drugs or alcohol: past 30-day non-medical prescription drug use	Decrease in non-medical prescription opioid use in 8th grade (aOR=0.43; 95% CI: 0.36, 0.52) and increase in 12th grade (aOR=1.42; 95% CI: 1.21, 1.66). Decrease in prescription amphetamine use (aOR=0.71; 95% CI: 0.63, 0.81) and prescription tranquilizer use (aOR=0.83; 95% CI: 0.71, 0.98) in 8th grade only.	
					Prevalence of use, other drugs or alcohol: past 30-day non-cannabis illicit drug use	Decrease in 8th grade only (aOR=0.77; 95% CI: 0.69, 0.86).	

22.	Cerda 2017	United States Legal regulation of cannabis for recreational use (RCL)	Controlled before-and-after study, 2010-2015	Population-based; School-based survey N=253,902	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	Increase in 8th and 10th grade in Washington but not Colorado (difference-in-difference WA vs. non-RCL= 3.2% in 8th grade, p=0.03; 5.0% in 10th, p=0.01).	18
					Perceived harmfulness of decriminalized/regulated drug(s): great or moderate vs. low or no risk	Decreased perceived harmfulness in 8th and 10th grade in Washington but not Colorado (difference-in-difference WA vs. non-RCL= -9.3% in 8th grade, p=0.01; -9.0% in 10th, p=0.02).	
23.	Cerveny 2017	Czech Republic Cannabis decriminalization	Repeated cross-sectional study, 2008; 2012	Population-based; Household survey N=1524	*Age of first use, decriminalized/regulated drug*	No significant effect of decriminalization on hazard of initiation.	13
24.	Choo 2014	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1991-2011 [Matched to state in geographic proximity without MCL]	Population-based; School-based survey N= 11,703,100	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	No significant effect of MCL.	16
25.	Chu 2014	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1988-2008 [Non-MCL state years]	Population-based; Admin record data N=12,157 city-years	*Criminal justice involvement*: adult male cannabis possession arrest rates	No significant effect of MCL.	15
					Criminal justice involvement: ratio of cannabis possession arrests to all arrests among adult males	MCL associated with 9.3-12.1% increase in ratio of cannabis to non-cannabis arrests.	
					Addiction treatment utilization: ratio of cannabis-related to all treatment admissions among adult male non-criminal justice referrals	MCL associated with 9.1-10.5% increase in ratio of cannabis to non-cannabis admissions.	

26.	Couper 2014	United States Cannabis decriminalization	Repeated cross-sectional study, 2009-2013	Convenience sampling N=25,719	*Driving under the influence or with detectable concentration, decriminalized/regulated drug(s)*: prevalence of THC in blood toxicology results from suspected impaired driving cases in Washington State	Increased prevalence of active THC after decriminalization (24.9% vs. 19.1%, p<0.05).	9
27.	Donnelly 1995	Australia Cannabis decriminalization	Repeated cross-sectional study, 1985-1993	Population-based; Household survey N= 2257 to 3500	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime cannabis use	No significant interaction between survey year and state: lifetime use did not increase at a significantly greater rate in South Australia (decriminalized).	15
					Perceived availability of decriminalized/regulated drug(s): been offered cannabis	No significant interaction between survey year and state.	
					Attitudes towards use, decriminalized/regulated drug(s): would take cannabis if offered by a trusted friend	Proportion reporting willingness to try increased from 10% in 1985 to 18% in 1991 in South Australia, significant positive interaction between survey year and state (p<0.05).	
					Prevalence of use, decriminalized/regulated drug(s): weekly use of cannabis	No significant interaction between survey year and state.	
28.	Donnelly 2000	Australia Cannabis decriminalization	Repeated cross-sectional study, 1985; 1988; 1991; 1993; 1995	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime use	Greater increase in lifetime use in South Australia (decriminalized) than the rest of Australia (test for trend, p<0.05).	11
					Prevalence of use, decriminalized/regulated drug(s): weekly use	Rate of change for South Australia not significantly different from rest of the country.	
29.	Dutra 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2008-2015	Population-based; Household survey N= 91,123 to 10,1973	*Mental health conditions, suicide, or self-harm*: state prevalence of serious mental illness	Liberal MCL associated with 0.2% increase in state prevalence of mental illness (b=0.002, SE=0.001, p=0.015). No significant effect of restrictive MCL.	17

30.	Estoup 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2010-2015	Convenience sampling N=262	*Mental health conditions, suicide, or self-harm*: # of reported psychological, behavioral, relational consequences of cannabis use	RCL associated with increased negative consequences of use, mediated by increased perceived harmfulness (*b* for indirect effect=3.73; 95% CI=0.33, 9.55).	11
					Perceived harmfulness of decriminalized/regulated drug(s): # of cons of continued cannabis use endorsed in decisional balance matrix	RCL associated with increased perceived harmfulness.	
					Frequency of use, decriminalized/legalized drug(s): # of times used in past 3 months	No significant effect of RCL.	
31.	Feige 2008	China Legal regulation of opium	Repeated cross-sectional study, 1801-1902	Unspecified	*Actual availability of decriminalized/regulated drug(s):* Quantity of opium exports (number of chests per capita)	No significant effect of legal regulation.	16
					Price of drugs: Price of opium at the scales in India	No significant effect of legal regulation.	
32.	Félix 2017	Portugal Decriminalization of all drugs	Controlled before-and-after study, 1990-2010 [13 EU countries and Norway]	Convenience sampling	*Price of drugs*: price data from (1) EU country reports to the Commission on Narcotic Drugs and (2) the European Monitoring Center for Drugs and Drug Addiction	Drug prices increased in Portugal following decriminalization, but difference-in-difference and synthetic control analyses indicate no statistically significant change in slope of drug prices.	14
33.	Gonçalves 2015	Portugal Decriminalization of all drugs	Repeated cross-sectional study, 1999-2010	Population-based; Admin record data	*Costs, health care*: combined direct costs of (1) drug treatment, prevention and harm reduction and (2) hospital treatment for hepatitis and HIV	12% increase over first 5 years following decriminalization, 9% over first 11 years.	13

					Costs, non-health care: combined indirect costs of lost income and production due to (1) drug addiction treatment and (2) drug-related death.	37% reduction over first 5 years following decriminalization, 29% over first 11 years.	
					Costs, non-health care: combined direct costs of social rehabilitation and legal system costs related to drugs	17% reduction over first 11 years.	
					Costs, non-health care: indirect costs of lost income and production of individuals arrested for drug-related crimes	5% reduction over first 5 years following decriminalization, 24% over first 11 years.	
34.	Gorman 2007	United States Legal regulation of cannabis for medical use (MCL)	Interrupted time series study, 1994-2002	Convenience sampling	*Prevalence of use, decriminalized/regulated drug(s)*: prevalence of positive cannabis urine screen among arrestees.	No significant effect of MCL on positive cannabis tests in CA or OR.	12
					Health services utilization: proportion of emergency department visits in which cannabis was mentioned in CA, WA, and CO DAWN sites	No significant effect of MCL on ED visits mentioning cannabis.	
35.	Grant 2018	United States Legal regulation of cannabis for medical use (MCL)	Cohort study, 1998-2012	Convenience sampling N=1359	*Prevalence of use, decriminalized/regulated drug(s)*: use in last 30 days of substance use case management program	Participants exiting case management after MCL were more likely to report past 30-day use (AOR = 2.1, $p < 0.0001$).	12
					Prevalence of use, other drugs or alcohol: # of days of use, in past 30 days, of alcohol or drugs	Participants exiting case management after MCL used alcohol ($b = 0.48$, SE=0.24, $p < 0.05$), illicit methadone ($b = 0.67$, SE=0.22, $p < 0.005$), and other opioids ($b = 0.52$, SE=0.15), $p < 0.01$) more frequently than the pre-MCL cohort.	
36.	Grucza 2018	United States	Controlled before-and-after study,	Population-based;	*Criminal justice involvement*: arrest rates for cannabis	Arrest rates decreased by 75% among youth (95% CI: -0.89, -0.44) and 78% among adults (95% CI: -0.89, -0.52).	18

		Cannabis decriminalization	2007-2015 [States without decriminalization, legal regulation, or change in penalties related to cannabis]	School-based survey N= 622,848	possession among minors (18 or under) and adults		
					Prevalence of use, decriminalized/regulated drug(s): past 30-day use	Decriminalization was not significantly associated with use.	
					Frequency of use, decriminalized/regulated drug(s): frequency of past 30-day use	Decriminalization was not significantly associated with frequency of use.	
37.	Grucza 2015	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1990-2010 [States without MCL]	Population-based; Admin record data N=662,993	*Mental health conditions, suicide, or self-harm*: suicide deaths	MCL not significantly associated with suicide rate overall, or when stratified by sex.	16
38.	Harper 2012	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 2002-2009 [States without MCL]	Population-based Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use among adolescents	*Reanalysis of Wall 2011 (#106) Difference-in-difference estimates indicate no significant effects of MCL, after accounting for state-level covariates and measurement error.	15
					Perceived harmfulness of decriminalized/regulated drug(s): perceived riskiness of monthly use among adolescents	No significant effects of MCL.	
39.	Harpin 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2013-2014	Population-based; School-based survey N=11,931 to 12,240	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime and past 30-day use	No significant change after RCL.	13
					Mode of use, decriminalized/regulated drug(s): smoking vs. other modes, among past-month users	No significant change after RCL.	
					Perceived harmfulness of decriminalized/regulated drug(s): high versus low	No significant change after RCL.	

					perceived harmfulness and wrongfulness of use		
					Perceived availability of decriminalized/regulated drug(s): high versus low perceived ease of access	Post-RCL year associated with high perceived access, (AOR= 1.21, 95% CI: 1.09, 1.34).	
40.	Hasin 2017	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1991-1992; 2001-2001; 2012-2013 [late MCL states, never MCL states]	Population-based; Household survey N=118,497	*Prevalence of use, decriminalized/regulated drug(s):* past-year use	MCL associated with greater increase in past-year use (difference-in-difference coefficient=1.4 percentage points, SE=0.5, p=0.004). Results varied by state and early vs. late MCL adoption.	17
					Substance use disorder or diagnosed dependence: DSM-IV Cannabis Use Disorder in past year	MCL associated with greater increase in CUD (difference-in-difference coefficient=0.7, SE=0.3, p=0.03).	
41.	Hasin 2015	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1991-2014	Population-based; School-based survey N=1,098,270	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	No significant effect of MCL overall, but interaction with grade: reduced use among 8th graders post-MCL (AOR=0.73, 95% CI: 0.63, 0.84), but not 10th or 12th graders.	18
42.	Hasin 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1991-1992; 2001-2002; 2012-2013	Population-based Household survey	*Driving under the influence or with detectable concentration, decriminalized/regulated drug(s)*	Prevalence of cannabis-impaired driving increased more in states that passed MCL, but not significantly so (p=0.07).	A *
					Driving under the influence or with detectable concentration,: driving under the influence of alcohol	No significant effect of MCL.	
43.	Hoyte 2015	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2007-2014	Population-based; Admin record data N= 42 fatalities	*Accidents, motor vehicle*: THC-positive motor driver fatalities in Denver County, CO	Fatalities increased from 0.28/month from July 1, 2007 to Dec 31, 2008 to 0.5/month from 2009-2012 to 0.56/month from Jan 1, 2013 to June 30, 2014 (post-RCL). No statistical tests reported.	A *

44.	Huber 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1970-2012	Population-based; Admin record data	*Crime (non-drug)*: state violent crime rates (FBI Uniform Crime Reports)	MCL associated with 12.9% reduction in rate (b=-0.129, SE= 0.036, p<0.01).	14
					Crime (non-drug): state property crime rates	MCL associated with 9.2% reduction in rate (b=-0.092, SE= 0.032, p<0.01).	
45.	Hunt 2017	United States Legal regulation of cannabis for recreational use (RCL)	Controlled before-and-after study, 2013;2014 [WA and OR before RCL implementation]	Population-based; Household survey N=5576	*Price of* drugs: consumer-reported price per gram	No statistically significant effects of implementing legal retail cannabis sales in CO and WA on prices paid for recreational or medical purposes, 4-5 months later.	16
46.	Johnson 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1991-2011	Population-based; School-based survey N=715,014	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use among adolescents	MCL associated with decreased odds of past 30-day use (AOR=0.93, 95% CI: 0.86, 0.99). Policy details associated with lower (e.g., years since MCL and liberal provisions) and higher (e.g., voluntary vs. mandatory patient registration) use.	17
					Frequency of use, decriminalized/regulated drug(s): past 30-day heavy use (≥20 times)	MCL not associated with odds of heavy use (AOR=1.00, 95% CI: 0.89, 1.13).	
47.	Jones 2015	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2012; 2014	Unspecified	*Prevalence of use, decriminalized/regulated drug(s)*: THCA-positive meconium specimens from high-risk newborns in Colorado	RCL associated with increase in THCA-positive specimens (from 10.6% to 11.7%) and with increased mean THCA concentrations in positive specimens.	A *
48.	Jones 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2013-2015	Convenience sampling N=1413	*Frequency of use, decriminalized/regulated drug(s)*: Categories from no use to daily use.	No statistically significant difference in use frequency between pre- and post-RCL periods.	10
					Prevalence of use, other drugs or alcohol: Frequency of cannabis use within alcohol use frequency groups	Strength of the relationship between alcohol and cannabis use decreased after RCL (from r=0.54 in Nov 2013 to 0.33 in Mar 2015).	

49.	Kerr DCR 2017	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2012-2016	Population-based; School-based survey N=10,924	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	No significant association between RCL and past 30-day use overall (AOR=1.21, *p*=0.48) but increasing secular trend. RCL associated with increased cannabis use among heavy alcohol users (AOR=1.73, *p*=0.0076).	17
					Prevalence of use, other drugs or alcohol: past 30-day cigarette use	No significant association with RCL.	
					Prevalence of use, other drugs or alcohol: past 30-day heavy alcohol use	No significant association with RCL.	
50.	Kerr WC 2018	United States Legal regulation of cannabis for medical (MCL) and recreational use (RCL)	Repeated cross-sectional study, 1984-2015	Population-based; Household survey N=37,359	*Prevalence of use, decriminalized/regulated drug(s)*: past-year use	No significant association between MCL (home growing or dispensaries) or RCL and past-year use, among both women and men.	17
51.	Kerr DCR 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2008-2016	Population-based; School-based survey N=281,752	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	RCL associated with increased past 30-day use among university students (AOR= 1.29, 95% CI: 1.13, 1.48).	17
					Prevalence of use, other drugs or alcohol: past 30-day tobacco use	RCL associated with decreased tobacco use (AOR= 0.71, *p*=0.0001).	
					Prevalence of use, other drugs or alcohol: past 30-day alcohol use	RCL not associated with alcohol use (*p*=0.59).	
					Prevalence of use, other drugs or alcohol: past 30-day illicit drug use (non-cannabis)	RCL not associated with illicit drug use (*p*=0.78).	
52.	Keyes 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1991-2014	Population-based; School-based survey N=973,089	*Perceived harmfulness of decriminalized/regulated drug(s)*: great or moderate vs. low perceived risk of physical harm due to occasional use	No significant association with MCL in all grades, 10th or 12th, but increased perceived harm in 8th (AOR= 1.21, 95% CI: 1.08, 1.36).	15
					Prevalence of use, decriminalized/regulated drug(s): past 30-day use	Adjusting for perceived harmfulness, significant negative association between	

						MCL and use in 8th grade only (AOR= 0.81, 95% CI: 0.72, 0.92).	
53.	Khatapoush 2004	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1995;1997;1999	Population-based; Household survey N=15,567	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use	No statistically significant change over time in California (MCL state) or other states.	10
					Perceived availability of decriminalized/regulated drug(s)	No statistically significant change over time in California (MCL state) or other states.	
					Prevalence of use, other drugs or alcohol: past-year use of other drugs.	No statistically significant change over time in California (MCL state) or other states.	
54.	Kim, Anderson et al. 2015	United States Cannabis decriminalization	Repeated cross-sectional study, 2008-2009; 2010-2011	Population-based; Admin record data N=2574	*Health services utilization*: emergency department visits for cyclic vomiting	Decriminalization associated with increase in visits (prevalence ratio= 1.92, 95% CI: 1.33, 2.79).	15
55.	Kim, Hall, et al. 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2012-2014	Population-based; Admin record data	*Health services utilization*: cannabis-related emergency department visits	RCL associated with increase in cannabis-related ED visits by Colorado residents (rate ratio; RR=1.46, $p>0.001$) and non-residents (RR=1.17, $p>0.001$).	14
56.	Kim, Santaella et al. 2015	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1999-2011	Population-based; Admin record data	*Prescription drug use*: annual opioid sales in morphine-equivalent doses	Adjusting for increasing secular trend, MCL associated with 1% reduction in opioid sales per year of MCL (b=-0.01, p=0.0016).	A *
57.	Kim 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2004-2013	Population-based; Household survey	*Prevalence of use, other drugs or alcohol*: past-month nonmedical use of prescription opioids	No significant difference in prevalence post-MCL for youth, young adults, or adults 26+.	A *

58.	Kim, Santaella-Tenorio, et al. 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1999-2013	Population-based; Admin record data N=68,394	*Driving under the influence or with detectable concentration, other drugs or alcohol*: positive opioid tests among driver fatalities in motor vehicle accidents	MCL not significantly associated with opioid presence overall, but with reduction among decedents age 24-40 (AOR post-MCL vs. pre=0.50, 95% CI=0.37, 0.67).	17
59.	Kosterman 2016	United States Legal regulation of cannabis for recreational use (RCL)	Interrupted time series study, 1985-2014	Convenience sampling N=395	*Frequency of use, decriminalized/regulated drug(s)*: past-month frequency among WA parents with any past-year use	Frequency of use increased post-RCL (from 4-6 to 10 times/month, $p<0.05$).	8
					Substance use disorder or diagnosed dependence: meets DSM-IV criteria for cannabis use disorder	No statistically significant change post-RCL.	
					Perceived harmfulness of decriminalized/regulated drug(s): approval and perceived harmfulness of cannabis use	Approval increased and perceived harmfulness decreased following RCL ($p<0.05$).	
60.	Larimer 2015	United States Legal regulation of cannabis for recreational use (RCL)	Cohort study	Unspecified N= 1095	*Frequency of use, decriminalized/regulated drug(s)*: # of times used in past month among 12-17 year olds	No significant change associated with RCL.	A *
					Perceived harmfulness of decriminalized/regulated drug(s): perceived risk due to regular and occasional use	Perceived risk from regular use decreased among males but not females (p for interaction=0.017).	
					Perceived availability of decriminalized/regulated drug(s)	No significant change associated with RCL.	
					Prevalence of use, other drugs or alcohol: number of drinks consumed per week.	RCL associated with increased number of drinks per week ($p<0.01$), beyond time trends.	
61.	Liang 2018	United States Legal regulation of cannabis for	Repeated cross-sectional study, 1993-2014	Population-based; Admin record data	*Prescription drug use*: # of filled opioid prescriptions, dosage of filled prescriptions in morphine-equivalent doses, and related Medicaid spending	MCL not associated not associated with Schedule II opioid use.	15

		medical use (MCL)			for Schedule II opioids (e.g., hydrocodone, oxycodone).		
					Prescription drug use: as above, for Schedule III opioids (e.g. codeine).	MCL associated with reductions in Schedule III opioid prescriptions (-29.6%, 95% CI: -2.4%, -56.7%), doses, and spending.	
62.	Livingston 2017	United States Legal regulation of cannabis for recreational use (RCL)	Interrupted time series study, 2000-2015	Population-based; Admin record data	*Overdose or poisoning*, *other drugs*: deaths with ICD-10 code indicating opioid poisoning	RCL associated with reduction in opioid poisoning deaths, adjusting for comparison state trends (-0.68 deaths per month, 95% CI: -1.35, -0.03).	16
63.	Lo 2015	United States Legal regulation of cannabis for recreational use (RCL)	Uncontrolled before-and-after study, 2013-2015	Convenience sampling N= 2186	*Prevalence of use, decriminalized/regulated drug(s)*: positive cannabinoid screen among high-risk opioid therapy patients	RCL associated with increase in positive THC screens (30% of visits to 36%, p=0.0003).	A *
					Opioid therapy compliance: non-compliance (illicit opioids use or non-use of prescription)	RCL not associated with compliance.	
64.	Lynne-Landsman 2013	United States Legal regulation of cannabis for medical use (MCL)	Switching replications study, 2003-2011	Population-based; School-based survey	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime and past-month	MCL not associated with use (1 of 20 planned comparisons significant, expected by chance alone).	15
					Frequency of use, decriminalized/legalized drug(s): daily or weekly use among lifetime users	MCL not associated with frequency (1 of 20 planned comparisons significant, expected by chance alone).	
65.	Martins 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2004-2013	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use	MCL associated with greater past-month use among adults 26+ (AOR=1.24, 95% CI: 1.16, 1.31), but not among ages 12-17 or 18-25.	16
					Perceived availability of decriminalized/regulated drug(s): fairly or very easy to obtain vs. other	MCL associated with greater availability among adults 26+ (AOR=1.11, 95% CI: 1.07, 1.15), but not among ages 12-17 or 18-25.	
66.	Mason 2016	United States	Controlled before-and-after study,	Convenience sampling	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	Post-RCL subject group not significantly associated with use (AOR= 2.80, 95% CI: 0.94–8.34).	13

		Legal regulation of cannabis for recreational use (RCL)	2010-2013 [students completed follow up before RCL]	N= 238	*Prevalence of use, other drugs or alcohol*: use of cigarettes or alcohol vs. cannabis (indicating substitution effect)	Post-RCL subject group significantly less likely to use cigarettes or alcohol versus cannabis (p<0.05).	
67.	Masten 2014	United States Legal regulation of cannabis for medical use (MCL)	Interrupted time series study, 1992-2009	Population-based; Admin record data N=245,495	*Driving under the influence or with detectable concentration, decriminalized/regulated drug(s)*: proportion of fatal-crash-involved drivers (decedents and survivors) who test cannabinoid-positive	Significant policy effect found in 3 of 12 MCL states, with increases of 2.1-6.0 percentage points among all drivers and 4.6-9.6 among fatally injured drivers in CA, HI, and OR (adjusted for changes in testing and national trends). These were step increases rather than upward trends.	14
68.	Mauro 2019	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2004-2013	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use	No significant effect of MCL among men or women aged 12-17 or 18-25, but significant increases for ages 26+ among men (+1.7 percentage points, $p < 0.001$) and women (+ 1.1%, $p = 0.013$).	16
					Frequency of use, decriminalized/legalized drug(s): daily use among past-year users	Significant effect of MCL among men aged 18-25 (+ 2.4%, $p = 0.047$), and both men and women age 26+ (men + 2.8%, $p = 0.014$; women + 3.4 %, $p = 0.003$).	
					Substance use disorder or diagnosed dependence: met DSM-IV criteria for cannabis use disorder	No statistically significant effect of MCL for any age-gender group.	
69.	Mauro 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2004-2013	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use	MCL associated with increased use among adults 26-39 [AOR=1.2, 95% CI: 1.1, 1.3], 40-64 [AOR=1.4, 95% CI: 1.2, 1.5], and 65+ [AOR=2.6, 95% CI: 1.5, 4.6].	A *
					Perceived availability of decriminalized/regulated drug(s)	MCL associated with increased perceived accessibility of cannabis, which partially mediated association between MCL and use.	

70.	Merker 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2012-2017	Convenience sampling N=302	*Prevalence of use, decriminalized/regulated drug(s)*: current use among Inflammatory Bowel Disease patients	Increase in use post-MCL (12.3% to 22.8% of patients, p=0.0008), but no significant increase in reported medical use.	12
71.	Miech 2015	United States Cannabis decriminalization	Repeated cross-sectional study, 2007-2013	Population-based; School-based survey N=320,809	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime, past-year, past 30-day use	[Decriminalization in CA in 2010] 8th and 10th grades: differences in use between CA residents and other states limited to select years, not sustained over time. 12th grade: past-year use higher among CA residents vs. other states in 2010-2013.	12
					Perceived harmfulness of decriminalized/regulated drug(s): great vs. less-than-great perceived risk of regular use	8th and 10th grades: only one significant difference (8th grade in 2012). 12th grade: lower perceived risk among CA residents vs. other states in 2012-2013.	
					Perceived availability of decriminalized/regulated drug(s): easy vs. less-than-easy perceived access	8th and 10th grades: only one significant difference (8th grade in 2011). 12th grade: higher perceived availability among CA residents vs. other states in 2012 only.	
					Attitudes towards use, decriminalized/regulated drug(s): strong disapproval of adult use vs. other	8th and 10th grades: only one significant difference (8th grade in 2012). 12th grade: less strong disapproval among CA residents vs. other states in 2012-2013	
					Attitudes towards use, decriminalized/regulated drug(s): definitely or probably expect to use five years from present (only 12th graders)	12th grade: greater expected use among CA residents vs. other states in 2012-2013.	
72.	Miller 2017	United States Legal regulation of cannabis for	Repeated cross-sectional study, 2005-2015	Population-based; School-based survey	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	RCL associated with increase of 2.0-3.5 percentage points (12-22%), adjusting for linear secular trend [passage of RCL, additional effect of legal store openings not statistically significant].	16

		recreational use (RCL)		N=13,335	*Frequency of use, decriminalized/legalized drug(s)*: past 30-day frequency	RCL associated with increase of 0.5 days per month, adjusting for linear secular trend [passage of RCL, additional effect of legal store openings not significant].	
					Prevalence of use, other drugs or alcohol	RCL passage not associated with changes. In 2015 (legal stores), decrease in tobacco and increase in other illegal drugs, but findings not robust.	
73.	Model 1993	United States Cannabis decriminalizatio n	Controlled before-and-after study, 1975-1978 [States that did not not decriminalize]	Population-based; Admin record data	*Health services utilization:* non-cannabis drug mentions at ER visits	Decriminalization associated with 12% fewer drug mentions at ER visits (b=-0.133, SE=0.053, p<0.01), with stronger effects in initial years.	16
					Health services utilization: cannabis drug mentions at ER visits	Decriminalization associated with 64% more cannabis mentions (b=-0.642, SE=0.112, p<0.01), with stronger effects in later years.	
74.	Morris 2014	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1990-2006	Population-based; Admin record data	*Crime (non-drug)*: rates of violent crime (homicide, rape, robbery, assault)	MCL associated with 2.4% reduction in homicide rate (p<0.01).	16
					Crime (non-drug): rates of property crime (burglary, larceny, auto theft)	No significant association between MCL and property crimes.	
75.	Nappe 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study. 2010-2015	Population-based; Admin record data N=5231 exposures	*Overdose or poisoning, decriminalized/regulated drug*: cannabis exposures reported to the National Poison Data System in Colorado	RCL associated with increase in cannabis exposures (86 in 2011 to 231 in 2015).	A *
76.	Onders 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study 2000-2013	Population-based; Admin record data N= 1969 exposures	*Overdose or poisoning, decriminalized/regulated drug*: cannabis exposures among children <6 reported to the National Poison Data System	MCL associated with increased exposures (rate ratio for post vs. pre-MCL=2.25, 95% CI: 1.45, 3.51). Exposures peaked in the year following RCL.	13

77.	Pacula 2010	United States Cannabis decriminalization and legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1987-2003	Convenience sampling	*Price of drugs*: price per gram paid at the last transaction among arrestees	Decriminalization and MCL associated with higher prices (indicating increased demand). .	13
78.	Pacula 2015	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1992-2011 and 1997-2011 [State-years without MML]	Population-based; Admin record data N=973 Household survey N=112,926	*Addiction treatment utilization*: number of treatment admissions with cannabis as primary indication	MCL associated with 14% reduction in cannabis admissions (difference-in-difference = -0.136, SE=0.067, $p<0.05$). Larger effect size for non-criminal justice referrals. Partially offset by increase in admissions associated with dispensaries.	15
					Prevalence of use, decriminalized/regulated drug(s): past 30-day use	No overall significant association between MCL and use.	
					Frequency of use, decriminalized/regulated drug(s): heavy use (>20 of last 30 days), # of days of use in past 30	No significant association between MCL and frequency of use.	
79.	Parnes 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2013-2015	Convenience sampling N=5241	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	No significant association between RCL and use among CO undergraduates.	12
80.	Phillips 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2011-2014	Population-based; Admin record data N=188,266	*Overdose or poisoning, other drugs*: state-level age-adjusted opioid-related mortality rate	MCL associated with 21.7% increase in opioid-related mortality ($p < 0.0001$) but interacted with prescription drug monitoring programs such that rates decreased in states with both policies.	15

81.	Plunk 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2000-2014	Population-based; Household survey N=5,483,715	*Educational outcomes*: high school non-completion	High-school age exposure to MCL not associated with non-completion overall, but with increase in probability of failing to complete conditioned on completing the 12th grade (AOR=1.11, 95% CI: 1.05, 1.17).	16
					Educational outcomes: college non-enrollment among high school graduates	High-school age exposure to MCL associated with college non-enrollment (AOR = 1.09, 95% CI: 1.04, 1.14). Dose-response relationship with years of exposure.	
					Educational outcomes: college non-completion among college entrants aged 25+	High-school age exposure to MCL associated with increase in probability of degree non-completion (AOR = 1.03, 95% CI: 1.01, 1.06).	
					Prevalence of use, decriminalized/regulated drug(s): past-month use	High-school age exposure to MCL not significantly associated with use.	
					Frequency of use, decriminalized/regulated drug(s): daily use (40 or more times/month)	High-school age exposure to MCL not significantly associated with use overall, but among 12th graders only (AOR=1.62, 95% CI: 1.04, 2.54).	
82.	Pollini 2015	United States Cannabis decriminalization	Repeated cross-sectional study Roadside Survey, 2010; 2012 Fatality Analysis Reporting System, 2008-2012	Population-based; Admin record data Roadside Survey, N=379-515 FARS, N=2860	*Driving under the influence or with detectable concentration, decriminalized/regulated drug(s)*: proportion of drivers testing THC-positive in roadside survey	No statistically significant change in THC-positivity following decriminalization.	13
					Driving under the influence or with detectable concentration, decriminalized/regulated drug(s): presence of cannabinoids among fatally injured drivers	Increase in cannabinoid prevalence in 2012 as compared to the pre-decriminalization period (AOR = 1.67, 95% CI: 1.28, 2.18).	
83.	Powell 2018	United States Legal regulation of cannabis for	Repeated cross-sectional study, 1999-2013	Population-based; Admin record data	*Overdose or poisoning, other drugs*: deaths related to prescription opioids and heroin	Existence of MCL not significantly associated with overdose mortality (only active dispensaries associated with reduction in deaths).	15

		medical use (MCL)			*Addiction treatment utilization*: number of treatment episodes related to pain reliever misuse	Existence of MCL not significantly associated with overdose mortality (only active dispensaries associated with reduction).	
					Prevalence of use, other drugs or alcohol: self-reported nonmedical use of pain relievers (National Survey on Drug Use and Health)	No statistically significant association between MCL and use.	
					Prescription drug use: morphine-equivalent doses of opioids distributed to legal medical markets	No statistically significant association between MCL and use over full time period.	
84.	Prue 2014	United States Peyote decriminalization	Repeated cross-sectional study, 1985-2010	Population-based; Household survey N=886,088	*Prevalence of use, decriminalized/regulated drug(s)*: peyote use	Use among American Indians increased from 1% in 1994 (year of American Indian Religious Freedom Act) to 10% in 1999. Use among non-American Indians remained steady <2%.	7
					Age of first use, decriminalized/regulated drug: age at first use of peyote	No significant change in age at first use among American Indians or non-American Indians following decriminalization.	
85.	Ramirez 2017	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2014;2015	Unspecified N=2400	*Driving under the influence or with detectable concentration, decriminalized/regulated drug(s)*: daytime prevalence of cannabis-positive drivers	Statistically significant increase post-RCL (7.8% to 18.9% after one year).	A *
86.	Reith 2015	International Cannabis decriminalization	Controlled before-and-after study, 1980-2012 [Country-years without decriminalization]	Unspecified N=102 countries	*Actual availability of decriminalized/regulated drug(s)*: kg of cannabis seized and number of plants eradicated divided by population in millions	Decriminalization associated with increased plant eradication (p<0.05), but not seizures.	10

87.	Rodriguez 2016	United States Legal regulation of cannabis for recreational use (RCL)	Cohort study, 2009-2015	Convenience sampling N= 1698	*Prevalence of use, decriminalized/regulated drug(s)*: positive urine toxicology among pregnant young women *Disclosure of use, decriminalized/regulated drug(s)*: agreement between self-reported use and urine toxicology	Increased cannabis-positive screens post-RCL (16.2 to 20.2%, p=0.048). Improved agreement post-RCL (kappa = 0.504 vs. 0.191).	A *
88.	Rohda 2017	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2011-2016	Population-based; Admin record data N=29,044 exposures	*Overdose or poisoning, other drugs:* synthetic cannabinoid receptor agonist (SCRA) exposures reported to poison control centers	SCRA exposures declined in WA (175 to 28, p=0.017*)* and OR (39 to 14, p=0.012) following RCL, but not in all RCL states combined (p=0.41).	A *
89.	Rusby 2018	United States Legal regulation of cannabis for recreational use (RCL)	Cohort study, 2014-2016	Population-based; School-based survey N=444	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	RCL not significantly associated with use.	12
					Frequency of use, decriminalized/regulated drug(s): number of days use in past 30	RCL associated with greater number of days of use (ARR=1.26, 95% CI: 1.10, 1.45).	
					Attitudes towards use, decriminalized/regulated drug(s): willingness and intention to use (any vs. none)	RCL not significantly associated with willingness or intention to use.	
90.	Sabia 2017	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study. 1990-2012 [State-years without MML]	Population-based; Household survey N=5,428,399	*BMI*	MCL associated with reduction in BMI (adjusted difference-in-differences for contemporaneous effect = -0.084, SE=0.034, p<0.05).	16

91.	Santaella-Tenorio 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1985-2014	Population-based; Admin record data N=1,220,610 deaths	*Accidents, motor vehicle*: age-adjusted traffic fatality rates (all road users)	MCL associated with 10.8% reduction in traffic fatality rates (95% CI = 9.0%, 12.5%).	17
92.	Schmidt 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2014-2013	Population-based; Household survey N=450,300	*Perceived harmfulness of decriminalized/regulated drug(s)*: belief that weekly/ monthly use is "not a great risk"	Living in MCL state not associated with perceived harmfulness. (Secular trend towards greater permissiveness for all outcomes, but no significant effects MCL after control for state fixed effects).	17
					Attitudes towards use, decriminalized/regulated drug(s): belief that parents/ friends don't disapprove of trying cannabis	Living in MCL state not associated with perceived attitudes.	
					Perceived availability of decriminalized/regulated drug(s): belief that cannabis is fairly or very easy to obtain	Living in MCL state not associated with perceived availability.	
93.	Sevigny 2014	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1990-2010 [State-years without MCL]	Convenience sampling N=39,157	*Potency of decriminalized/regulated drug(s)*: concentration of THC in cannabis seized by law enforcement	MCL not significantly associated with potency (adjusted difference in %THC=0.53, p>0.05), but legal dispensaries associated with higher potency.	16
94.	Shah 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2006-2014	Population-based; Admin record data	*Prescription drug use*: opioid use among commercially insured population.	MCL associated with lower odds of any opioid use (AOR=0.95, 95% CI: 0.94, 0.96), chronic opioid use (AOR=0.93, 95% CI: 0.91, 0.95) and high-risk opioid use (AOR=0.98, 95% CI: 0.96, 0.99).	A *
95.	Shepard 2016	United States Legal regulation of cannabis for	Repeated cross-sectional study, 1997-2009	Population-based; Admin record data	*Crime (non-drug)*: property crime (burglary, larceny, and vehicle theft arrests per 1000 residents)	MCL not associated with property crime.	12

		medical use (MCL)			*Crime (non-drug)*: violent crime (assault, homicide, rape, and robbery arrests)	MCL associated with reduction in violent crimes (-0.254 crimes per 1000 residents, SE=0.089, $p<0.05$).	
96.	Shi 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1997-2014	Population-based; Admin record data N= 0.4M to 2.2M records	*Health services utilization*: annual hospitalization rate for cannabis dependence or abuse (ICD-9)	MCL not significantly associated with hospitalizations.	16
					Overdose or poisoning, other drugs: hospitalization rate for opioid pain reliever overdose	MCL associated with reduction in hospitalizations related to opioid overdose (adjusted prevalence difference = −0.13, 95% CI: −0.25, −0.018).	
					Health services utilization: hospitalization rate for opioid dependence or abuse	MCL associated with reduction in hospitalizations related to opioid dependence (adjusted prevalence difference = −0.23, 95% CI: −0.41, −0.068).	
97.	Sokoya 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2012-2015	Convenience sampling N=2164	*Accidents, other*: types of bony facial trauma among patients presenting to two CO hospitals	RCL not associated with significant difference in mechanisms of facial fracture.	12
98.	Steinemann 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1993-2000; 2001-2015	Population-based; Admin record data N=1578	*Driving under the influence or with detectable concentration, decriminalized/regulated drug(s)*: proportion of fatally injured drivers who were cannabis-positive in HI	MCL associated with increase in THC positivity (5.5% in 1993-2000; 16.3% in 2011-2015, $p<0.001$).	12
					Driving under the influence or with detectable concentration, other drugs or alcohol: proportion of fatally injured drivers who were methamphetamine- or alcohol-positive	MCL not associated with significant difference in positivity rates.	
99.	Stolzenberg 2016	United States Legal regulation of cannabis for	Repeated cross-sectional study, 2002-2003; 2004-2005;	Population-based; School-based survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use among adolescents	Living in MCL state associated with greater use (adjusted coefficient=0.861, SE=0.298, $p<0.01$).	14

		medical use (MCL)	2006-2007; 2008-2009; 2010-2011		*Prevalence of use, other drugs or alcohol*: past-month non-cannabis illicit drug use	No significant association between living in MCL state and use.	
100.	Straub 2017	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2011-2012; 2012-2014; 2014-2016	Population-based; Admin record data N=25,763	*Prevalence of use, decriminalized/regulated drug(s)*: positive urine screen or documented use during pregnancy	No significant change in cannabis-positivity post-RCL.	A *
101.	Suggs 1981	United States Cannabis decriminalization	Uncontrolled before-and-after study, 1977-1979	Population-based; Admin record data N=719	*Criminal justice involvement*: possession arrests and citations for adults and minors in two NE cities	No significant difference in mean monthly arrests following decriminalization.	12
					Criminal justice involvement: possession prosecutions for adults and minors	Significant increase in prosecutions following decriminalization among minors (from mean of 1.92 to 5.75/month, $p<0.05$), but not adults (26.71 to 36.25, $p>0.05$).	
					Criminal justice involvement: defendants representing themselves	Significant increase following decriminalization (from 18.07 to 30.75/month, $p<0.05$).	
					Criminal justice involvement: case dismissal before trial	Significant decrease following decriminalization (from 9.14 to 2.37/month, $p<0.001$).	
102.	Ullman 2017	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1992-2012 [State-years without MCL]	Population-based; Household survey N=757,677	*Workplace absence*: self-reported absence for medical reasons in the past week	MCL associated with lower probability of absence (b= -0.0013, SE=0.0007, $p<0.10$), with effects concentrated in loosely regulated MCL states, men and people aged 30-49.	16
103.	Urfer 2014	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2011-2014	Convenience sampling N=12,082	*Driving under the influence or with detectable concentration, decriminalized/regulated drug(s)*: Proportion of THC-positive blood samples collected from CO drivers	Increase in THC-positive screens from 2011 (28%) to 2012 (59%) to 2013 (65%), p=0.001. No significant change in first two months of legal cannabis sales.	11

104.	Wagner 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2012-2015	Convenience sampling N=34	*Physical health consequences of use, decriminalized/ regulated drug(s)*: Reversible Cerebral Vasoconstriction Syndrome (RCVS) cases secondary to cannabis	Of 18 RCVS cases before RCL, 1 patient used cannabis. Of 16 cases after RCL, 5 used cannabis. No statistical tests reported.	A *
105.	Wall 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2002-2010	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use among adolescents	*Reanalysis of Stolzenberg 2016 (#99) After appropriate adjustment for pre-MCL prevalence, MCL not associated with adolescent use (b = 0.33%; SE= 0.29%, p = 0.25).	18
106.	Wall 2011	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2002-2008	Population-based; Household survey N=23,300	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use among adolescents	Use was significantly higher in MCL states (average of 8.7% vs. 6.9%) but among states that passed MCL from 2004-2008, baseline use (pre-MCL) was already higher than in non-MCL states.	13
					Perceived harmfulness of decriminalized/regulated drug(s): perceived "great risk" of using monthly or more	Perceived harmfulness was significantly lower in MCL states each year (average of 8.7% vs. 6.9%), but among states that passed MCL, baseline perceived risk (pre-MCL) was already lower than non-MCL states.	
107.	Wang 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2005-2015	Population-based; Admin record data N=4202	*Health services utilization:* emergency or urgent care visits with a cannabis-related discharge code or THC-positive urine toxicology among adolescents	Cannabis-related visits increased from 1.8 per 1000 visits in 2009 to 4.9 per 1000 in 2015, following RCL (p<0.0001).	11
108.	Wang 2017	United States Legal regulation of cannabis for medical (MCL) and recreational use (RCL)	Repeated cross-sectional study, 2000-2015	Population-based; Admin record data N=7,432,254	*Health services utilization*: hospitalizations with cannabis-related billing codes	Hospitalizations increased from 274 per 100,000 in 2000 (prior to MCL) to 593 in 2015 (after RCL). Statistically significant 25% increase in 2014 (RCL implementation with legal sales).	14
					Health services utilization: emergency department visits with cannabis-related billing codes	ED visits increased from 313 per 100,000 in 2011 to 478 in 2015, with highest rate in 2014 (554). Statistically significant increase in 2014 (p=0.0005).	

					Overdose or poisoning, decriminalized/regulated drug: cannabis exposure calls to CO poison control centers	Poison control calls increased by 79.9% following RCL implementation in 2014, from 123 to 221 (p=0.0001).	
109.	Wang 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2009-2015	Population-based; Admin record data N=62	*Overdose or poisoning, decriminalized/regulated drug*: children's hospital visits related to cannabis exposure	RCL associated with increased cannabis-related visits (1.2 per 100,000 in 2012-2013 to 2.3 per 100,000 in 2014-2015, p=0.02).	13
					Overdose or poisoning, decriminalized/regulated drug: poison control calls related to cannabis exposure among children 0-9	RCL associated with increased cannabis-related calls in CO (2.7 per 100,000 in 2012-2013 to 5.3 per 100,000 in 2014-2015, p<0.001) and in comparison to rest of the US (34% increase in CO vs. 19% increase in remainder of US, p=0.04).	
110.	Wen 2018	United States Legal regulation of cannabis for medical (MCL) and recreational use (RCL)	Controlled before-and-after study, 2011-2016 [States without MCL or RCL over the study period]	Population-based; Admin record data N=1059 state-quarter observations	*Prescription drug use*: number of opioid prescriptions covered by Medicaid on a quarterly, per-1000-Medicaid-enrollee basis in each state	MCL and RCL associated with reductions in prescriptions of 5.88% (95% CI: -11.55%, -0.21%) and 6.38% (95% CI: -12.20, -0.56%) respectively.	17
111.	Wen 2015	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2004-2012	Population-based; Household survey N=593,400	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use; past-year initiation	MCL associated with increase in past-month use among adults 21+ (+1.32%, p<0.05) but not ages 12-20. MCL associated with increased risk of past-year initiation among ages 12-20 only (+0.32%, p<0.05).	17
					Frequency of use, decriminalized/regulated drug(s): daily/almost daily use (>20 days in month); # of days among past-month users	MCL associated with increase in (almost) daily use among adults 21+ (+0.58%, p<0.05) but not ages 12-20.	
					Prevalence of use, other drugs or alcohol: # of drinks in past month; # of binge drinking days; met DSM-IV alcohol use disorder criteria in past year; both cannabis use and	MCL associated with frequency of binge drinking (+0.16 days, p<0.05) and past-month use of both cannabis and alcohol (+1.44%, p<0.01) among adults 21+. No associations with alcohol use among ages	

					binge drinking in past month; use of cannabis and alcohol on same occasion in past month	12-20, or with alcohol use disorders.	
					Prevalence of use, other drugs or alcohol; past-year use of non-medical prescription painkillers, heroin, cocaine	No immediate or lagged associations between MCL and illicit drug use in either age group.	
					Substance use disorder or diagnosed dependence: met DSM-IV cannabis use disorder criteria in past year	Lagged associations between MCL and cannabis use disorder among adults 21+ (+0.25% at 1 year, $p<0.05$) but not among ages 12-20.	
112.	Wen 2019	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 2004-2012 [Non-MCL states]	Population-based; Household survey N=388,200	*Perceived availability of decriminalized/regulated drug(s)*: (very) easy to obtain, among adolescents and young adults	No significant association between MCL and perceived availability among ages 12-17 or 18-25.	16
					Attitudes towards use, decriminalized/regulated drug(s): acceptance of use by other adolescents/young adults; perceived parental acceptance (ages 12-17 only)	MCL significantly associated with lower perceived parental acceptance among ages 12-17 (-0.37%, 95% CI: -0.72, -0.03).	
					Perceived harmfulness of decriminalized/regulated drug(s): no/low health risk of using once or twice per week	MCL significantly associated with higher perceived harmlessness among ages 18-25 only (+4.72%, 95% CI: 0.15, 9.28).	
113.	Williams 2017	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 2004-2013 [State-years without MCL]	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use	Only loosely regulated MCL associated with higher use, among adults 26+ only (adjusted prevalence difference = +1.46%, 95% CI: 0.33, 2.58).	15
					Frequency of use, decriminalized/legalized drug(s): heavy use in past year (>300 days), among past-year users	Tightly regulated MCL associated with less heavy use, among ages 12-17 only (adjusted prevalence difference = -3.67%, 95% CI: -7.24, -0.11).	
					Substance use disorder or diagnosed dependence met DSM-IV criteria for cannabis use disorder	Loosely regulated MCL associated with lower prevalence of cannabis use disorder, among ages 18-25 only (-0.80%, 95% CI: -1.45, -0.16).	

114.	Williams 2014	Australia Cannabis decriminalization	Controlled before-and-after study, 1998;2001;2004;2007;2010 [state-years without decriminalization)	Population-based; Household survey N=39,087	*Age of first use, decriminalized/regulated drug(s)*: age at initiation	Decriminalization not associated with hazard of cannabis uptake overall but interacts with age such that minors under decriminalization have a 12% higher hazard rate of uptake while adults under decriminalization have an 11% lower hazard rate of uptake ($p<0.01$).	18

*A = abstract; no quality appraisal performed.

Supplementary Table 2. Direction of effect of decriminalization or legal regulation, by outcome category

Outcomes	**# of outcomes**	**# reporting beneficial effects**	**# reporting harmful effects**	**# reporting mixed effects**	**# reporting no effect**	**Article #** (See Included Studies)	**Average quality** (of 18, excluding abstracts)
Accidents, motor vehicle	4	1	1	1	1	3, 8, 43, 91	14.3
Accidents, other	4	0	2	1	1	5, 11, 14, 97	12.7
Addiction treatment utilization	4	0	1	1	2	1, 25, 78, 83	14.5
Age of first use, decriminalized/regulated drug	3	0	0	1	2	23, 84, 114	12.7
Attitudes towards use, decriminalized/regulated drug	6	0	1	3	2	27, 71, 89, 92, 112	14.0
Availability of decriminalized/regulated drug	3	0	0	1	2	6, 31, 86	13.3
BMI	1	1	0	0	0	90	16.0
Costs, health care	3	2	1	0	0	15, 17, 33	15.7
Costs, other	3	3	0	0	0	33	13.0
Crime (non-drug)	9	5	0	0	4	7, 44, 74, 95	14.0
Criminal justice involvement	8	1	3	1	3	7, 25, 36, 101	13.8
Disclosure of use to healthcare provider	1	1	0	0	0	87	N/A
Educational outcomes	3	0	2	1	0	81	16.0
Frequency of use, decriminalized/regulated drug	16	1	3	4	8	6, 18, 30, 36, 46, 47, 59, 60, 64, 69, 72, 78, 81, 89, 111, 113	14.4
Health services utilization (excluding addictions treatment)	12	2	6	1	3	13, 19, 34, 54, 55, 73, 96, 107, 108	13.8
Driving under the influence or with detectable concentrations of the decriminalized/regulated drug	8	0	5	1	2	26, 42, 67, 82, 85, 98, 103	12.0

Outcomes	Number of outcomes	# reporting beneficial effects	# reporting harmful effects	# reporting mixed effects	# reporting no effect	Article # (See Included Studies)	Average quality score
Driving under the influence or with detectable concentrations, other drug/alcohol	3	0	0	1	2	42, 58, 98	14.5
Mental health conditions, suicide, or self-harm	4	0	1	2	1	4, 29, 30, 37	15.0
Mode of use, decriminalized/regulated drug	1	0	0	0	1	39	13.0
Opioid therapy compliance	1	0	0	0	1	63	N/A
Overdose or poisoning (incl. unintentional exposures) decriminalized/regulated drug	7	0	7	0	0	10, 12, 75, 76, 108, 109	13.3
Overdose or poisoning, other drugs	7	4	0	2	1	9, 10, 62, 80, 83, 88, 96	15.6
Perceived availability, decriminalized/regulated drug	9	0	2	2	5	27, 39, 53, 60, 65, 68, 71, 92, 112	14.1
Perceived harmfulness, decriminalized/regulated drug	12	1	2	6	3	18, 22, 30, 38, 39, 52, 59, 60, 71, 92, 106, 112	13.9
Physical health consequences of use, decriminalized/regulated drug	1	0	0	0	1	104	N/A
Potency, decriminalized/regulated drug	1	0	0	0	1	93	16.0
Prescription drug use (medical use)	9	6	0	1	2	15, 16, 17, 56, 61, 83, 94, 110	16.3
Prevalence of use, decriminalized/regulated drug	50	2	13	11	24	1, 2, 6, 18, 20, 21, 22, 24, 27, 28, 34, 35, 36, 38, 39, 40, 41, 46, 48, 49, 50, 51, 52, 53, 63, 64, 65, 66, 68, 69, 70, 71, 72, 78, 79, 81, 84, 87, 89, 99, 100, 105, 106, 111, 113	14.6

Outcomes	Number of outcomes	# reporting beneficial effects	# reporting harmful effects	# reporting mixed effects	# reporting no effect	Article # (See Included Studies)	Average quality score
Prevalence or frequency of use, other drugs/alcohol	21	2	2	6	11	18, 21, 35, 47, 49, 50, 53, 57, 60, 66, 72, 83, 99, 111	15.6
Price of drugs	5	0	1	1	3	3, 31, 32, 45, 77	14.0
Substance use disorder or diagnosed dependence	5	0	1	2	2	40, 59, 69, 111, 113	14.6
Workplace absence	1	1	0	0	0	102	16.0

Appendix A: Search Strategy and Results

Database: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946-Present>
Search Strategy:
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1 ((Marijuana or marihuana or cannabis or cannabinoid* or psychoactive product* or psychoactive substances* or narcotic*) adj5 (Legaliz* or legalis* or decriminal* or depenaliz* or depenalis* or deregulat* or liberaliz* or liberalis*)).tw,kf.
2 ((marijuana or marihuana or cannabis or cannabinoid*) adj1 (policy or policies or law or laws or licens* or legislation or dispensar* or store or stores or regulat* or recreational or medical or medicinal or nonmedical or legal*)).tw,kf.
3 (legal high or legal highs).tw,kf.
4 Psychoactive Substances Act.tw,kf.
5 2 or 3 or 4
6 new psychoactive product*.tw,kf.
7 novel psychoactive product*.tw,kf.
8 novel psychoactive substance*.tw,kf.
9 new psychoactive substance*.tw,kf.
10 novel psychoactive drug*.tw,kf.
11 new psychoactive substances*.tw,kf.
12 Designer Drugs/sd [Supply & Distribution]
13 Medical Marijuana/sd [Supply & Distribution]
14 exp Street Drugs/lj, sd [Legislation & Jurisprudence, Supply & Distribution]
15 Marijuana Smoking/lj [Legislation & Jurisprudence]
16 Drug Users/lj, sn [Legislation & Jurisprudence, Statistics & Numerical Data]
17 "Drug and Narcotic Control"/lj [Legislation & Jurisprudence]
18 or/6-17
19 (Legal* or decriminal* or depenaliz* or depenalis* or deregulat* or liberaliz* or liberalis* or policy or policies or law or laws or licens* or legislation or regulat*).ti.
20 18 and 19
21 5 or 20
22 limit 21 to (clinical study or clinical trial, all or comparative study or evaluation studies or meta analysis or multicenter study or observational study or pragmatic clinical trial or systematic reviews or validation studies)
23 Epidemiologic studies/
24 exp case control studies/
25 exp cohort studies/
26 Case control.tw.
27 (cohort adj (study or studies)).tw.
28 Cohort analy$.tw.
29 (Follow up adj (study or studies)).tw.
30 (observational adj (study or studies)).tw.
31 Longitudinal.tw.
32 Retrospective.tw.
33 Cross sectional.tw.
34 Cross-sectional studies/

Appendix A: Search Strategy and Results

35 or/23-34 [Observational Studies search filter used by SIGN (Scottish Intercollegiate Guidelines Network http://www.sign.ac.uk/methodology/filters.html#obs]
36 21 and 35
37 exp Epidemiologic Methods/
38 amphetamine-related disorders/ep or cocaine-related disorders/ep or drug overdose/ep or inhalant abuse/ep or marijuana abuse/ep or exp opioid-related disorders/ep or phencyclidine abuse/ep or psychoses, substance-induced/ep or substance abuse, intravenous/ep
39 Prevalence/
40 Incidence/ or incidence.ti,ab,kw.
41 (harm or harms).tw,kf.
42 ("marijuana use" or "marijuana availability" or "cannabis use" or cannabis availability or "drug use").tw,kf.
43 or/37-42
44 21 and 43
45 1 or 22 or 36 or 44
46 45 not (exp animals/ not humans.sh.)
47 limit 46 to (comment or editorial or letter)
48 46 not 47
49 limit 48 to yr="1970 -Current"

Database	**Number of Results**
Medline (OVID)	2041
Embase (OVID)	1453
PsycINFO (OVID)	1393
Web of Science: Science Citation Index Social Sciences Citation Index Conference Proceedings Citation Index- Science Conference Proceedings Citation Index- Social Science & Humanities	1358
Criminal Justice Abstracts (EBSCO)	1074
ProQuest Databases: Applied Social Sciences Index & Abstracts (ASSIA), International Bibliography of the Social Sciences (IBSS), PAIS Index, Policy File Index, Sociological Abstracts	910
Total Number of Results	**8229**
Total number of results after duplicates removed in EndNote	**4860**

Appendix B: Quality Appraisal Checklist

Adapted from: Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52(6):377-384.

1. Is the hypothesis/aim/objective of the study clearly described?

☐ Yes (1)

☐ No (0)

2. Are the main outcomes to be measured clearly described in the Introduction or Methods section? *If the main outcomes are first mentioned in the Results section, the question should be answered no.*

☐ Yes (1)

☐ No (0)

3. Are the characteristics of the individuals included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given.

☐ Yes (1)

☐ No (0)

4. Are the interventions of interest clearly described?

☐ Yes (1)

☐ No (0)

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?

☐ Yes (2)

☐ Partially (1)

☐ No (0)

6. Are the main findings of the study clearly described? *Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).*

☐ Yes (1)

☐ No (0)

7. Does the study provide estimates of the random variability in the data for the main outcome *(e.g., IQR, standard deviation, confidence interval, etc.)?*

☐ Yes (1)

☐ No (0)

☐ N/A [there is no variability because data come from the entire population] (1)

Appendix B: Quality Appraisal Checklist

8. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001? (*Confidence intervals are acceptable in place of p-values*)

□ Yes (1)

□ No (0)

9. Were the subjects that were asked to participate in the study representative of the entire population from which they were recruited? *The study must identify the source population for participants and describe how they were selected. Participants would be representative if they comprised the entire source population or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

10. Were those subjects who agreed to participate representative of the entire population from which they were recruited? *The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

11. If any of the results of the study were based on "data dredging", was this made clear? *Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

12. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of participants, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? *Where follow-up was the same for all study participants the answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.*

□ Yes or N/A (1)

□ No (0)

□ Unable to determine (0)

13. Were the statistical tests used to assess the main outcomes appropriate? *The statistical techniques used must be appropriate to the data. For example non- parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data*

Appendix B: Quality Appraisal Checklist

(normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

□ Yes (1)

□ No (0)

□ Unable to determine from article (0)

14. Were the main outcome measures used accurate (valid and reliable)? *For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

15. Were the participants in different comparison groups recruited from the same population or from comparable populations? *Answer NO for studies without a comparison/control group.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

16. Were study subjects in different intervention groups recruited over the same period of time? *Answer NO for studies without a comparison/control group.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

17. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

□ Yes (1)

□ No (0)

□ Unable to determine (0)

Appendix C: Included Studies

INCLUDED STUDIES

1. Adam C, Raschzok A. Cannabis policy and the uptake of treatment for cannabis-related problems. *Drug Alcohol Rev*. 2017;36(2):171-177.
2. Allshouse AA, Metz TD. Trends in self-reported and urine toxicology (UTOX)-detected maternal marijuana use before and after legalization. *Am J Obstet Gynecol*. 2016;1:S444-S445.
3. Anderson DM, Hansen B, Rees DI. Medical marijuana laws, traffic fatalities, and alcohol consumption. *J Law Econ*. 2013;56(2):333-369.
4. Anderson DM, Rees DI, Sabia JJ. Medical marijuana laws and suicides by gender and age. *Am J Public Health*. 2014;104(12):2369-2376.
5. Anderson DM, Rees DI, Tekin E. Medical marijuana laws and workplace fatalities in the United States. *Int J Drug Policy*. 2018;60:33-39.
6. Anderson MD, Hansen B, Rees DI. Medical marijuana laws and teen marijuana use. *Am Law Econ Rev*. 2015;17(2):495-528.
7. Arredondo J, Gaines T, Manian S, et al. The law on the streets: evaluating the impact of Mexico's drug decriminalization reform on drug possession arrests in Tijuana, Mexico. *Int J Drug Policy*. 2018;54:1-8. doi:10.1016/j.drugpo.2017.12.006.
8. Aydelotte JD, Brown LH, Luftman KM, et al. Crash fatality rates after recreational marijuana legalization in Washington and Colorado. *Am J Public Health*. 2017;107(8):1329-1331.
9. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med*. 2014;174(10):1668-1673.
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Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMAreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title			
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
Introduction			
Rationale	#3	Describe the rationale for the review in the context of what is already known.	4
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5

Methods

Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	5
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	5-6
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	5
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	6
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	6-7
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	7
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	7
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A

Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
Results			
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8, Figure 1
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	Supplementary Table 1
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Supplementary Table 1
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary Table 1
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	9-12
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
Discussion			
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	12-14
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15

Funding

Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	16

Notes:

- 17: 7-8, Figure 1
- 18: Supplementary Table 1
- 19: Supplementary Table 1
- 20: Supplementary Table 1 This checklist was completed on 19. October 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Impact evaluations of drug decriminalization and legal regulation on drug use, health and social harms: A systematic review

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Impact evaluations of drug decriminalization and legal regulation on drug use, health and social harms: A systematic review

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ABSTRACT

Objectives: To review the metrics and findings of studies evaluating effects of drug decriminalization or legal regulation on drug availability, use, or related health and social harms globally.

Design: Systematic review with narrative synthesis.

Data sources: We searched MEDLINE, Embase, PsycINFO, Web of Science, and six additional databases for publications from 1 January 1970 through 4 October 2018.

Inclusion criteria: Peer-reviewed articles or published abstracts in any language with quantitative data on drug availability, use, or related health and social harms collected before and after implementation of *de jure* drug decriminalization or legal regulation.

Data extraction and synthesis: Two independent reviewers screened titles, abstracts, and articles for inclusion. Extraction and quality appraisal (modified Downs and Black checklist) were performed by one reviewer and checked by a second, with discrepancies resolved by a third. We coded study-level outcome measures into metric groupings and categorized the estimated direction of association between the legal change and outcomes of interest.

Results: We screened 4860 titles and 221 full texts and included 114 articles. Most (n=104, 91.2%) were from the U.S., evaluated cannabis reform (n=109, 95.6%), and focused on legal regulation (n=96, 84.2%). 224 study outcome measures were categorized into 32 metrics, most commonly prevalence (39.5% of studies), frequency (14.0%), or perceived harmfulness (10.5%) of use of the decriminalized or regulated drug; or use of tobacco, alcohol, or other drugs (12.3%). Across all substance use metrics, legal reform was most often not associated with changes in use.

Conclusions: Studies evaluating drug decriminalization and legal regulation are concentrated in the U.S. and on cannabis legalization. Despite the range of outcomes potentially impacted by drug law reform, extant research is narrowly focused, with a particular emphasis on the prevalence of use. Metrics in drug law reform evaluations require improved alignment with relevant health and social outcomes.

Strengths and limitations of this study

- This is the first study to review all literature on the health and social impacts of decriminalization or legal regulation of drugs.
- We systematically searched 10 databases over a 38-year period, without language restrictions.
- The review was limited to study designs appropriate for evaluating interventions, nevertheless, most included studies used relatively weak evaluation designs.
- Included outcomes were heterogeneous and not quantitatively synthesized.
- Heterogeneity in the details and implementation of decriminalization or legal regulation policies was not considered in this review.

INTRODUCTION

An estimated 271 million people used an internationally scheduled ("illicit") drug in 2017, corresponding to 5.5% of the global population aged 15-64.[1] Despite decades of investment, policies aimed at reducing supply and demand have demonstrated limited effectiveness.[2,3] Moreover, prohibitive and punitive drug policies have had counterproductive effects by contributing to HIV and hepatitis C transmission,[4,5] fatal overdose,[6] mass incarceration and other human rights violations,[7,8] and drug market violence.[9] As a result, there have been growing calls for drug law reform [10–12] and in 2019, the United Nations Chief Executives Board endorsed decriminalization of drug use and possession.[13] Against this backdrop, as of 2017 approximately 23 countries had implemented *de jure* decriminalization or legal regulation of one or more previously illegal drugs.[14–16]

A wide range of health and social outcomes are affected by psychoactive drug production, sales, and use, and thus are potentially impacted by drug law reform. Nutt and colleagues have categorized these as physical harms (e.g., drug-related morbidity and mortality to users, injury to non-users), psychological harms (e.g., dependence), and social harms (e.g., loss of tangibles, environmental damage).[17,18] 2Concomitantly, a diverse and sometimes competing set of goals motivate drug policy development, including ameliorating the poor health and social marginalization experienced by people who use drugs problematically, shifting patterns of use to less harmful products or modes of administration, curtailing illegal markets and drug-related crime, and reducing the economic burden of drug-related harms.[19]

Given ongoing interest by states in drug law reform, as well as the recent position statement by the UN Chief Executives Board endorsing drug decriminalization,[13] a comprehensive understanding of their impacts to date is required. However, the scientific literature has not been well-characterized, and thus the state of the evidence related to these heterogenous policy targets remains largely unclear. Systematic reviews, including two meta-analyses, are narrowly focused on adolescent cannabis use. Dirisu et al. found no conclusive evidence that cannabis legalization for medical or recreational purposes increases cannabis use by young people.[20] In the two meta-analyses, Sarvet et al. found that the implementation of medical cannabis policies in the

United States (U.S.) did not lead to increases in the prevalence of past-month cannabis use among adolescents [21] and Melchior et al. found a small increase in use following recreational legalization that was reported only among lower-quality studies.[22]

Given increasing interest in quantifying the impact of drug law reform, as well as a lack of systematic assessment of outcomes beyond adolescent cannabis use to date, we conducted a systematic review of original peer-reviewed research evaluating the impacts of (a) legal regulation and (b) drug decriminalization on drug availability, use, or related health and social harms. Our primary aim is to characterize studies with respect to metrics and indicators used. The secondary aim is to summarize the findings and methodologic quality of studies to date.

METHODS

Consistent with our aim of synthesizing evidence on the impacts of decriminalization and legal regulation across the spectrum of potential health and social effects, we conducted a systematic review using narrative synthesis [23] without meta-analysis. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in preparing this manuscript.[24] The review protocol was registered in PROSPERO (CRD42017079681) and can be found online at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=79681.

Search Strategy and Selection Criteria

The review team developed, piloted, and refined the search strategy in consultation with a research librarian and content experts. We searched MEDLINE, Embase, PsycINFO, Web of Science, Criminal Justice Abstracts, Applied Social Sciences Index & Abstracts, International Bibliography of the Social Sciences, PAIS Index, Policy File Index, and Sociological Abstracts for publications from 1 January 1970 through 4 October 2018. We used MeSH terms and keywords related to (a) scheduled psychoactive drugs (b) legal regulation or decriminalization policies, and (c) quantitative study designs. Search terms specific to health and social outcomes were not employed so that the search would capture the broad range of outcomes of interest. See Appendix A for the final MEDLINE search strategy. For conference abstracts, we contacted

authors for additional information on study methods and to identify subsequent relevant publications.

We included peer-reviewed journal articles or conference abstracts reporting on original quantitative studies that collected data both before and after the implementation of drug decriminalization or legal regulation. We did not consider as original research studies that reproduced secondary data without conducting original statistical analyses of the data. We defined decriminalization as the removal of criminal penalties for drug use and/or possession (allowing for civil or administrative sanctions) and legal regulation as the development of a legal regulatory framework for the use, production, and sale of formerly illegal psychoactive drugs. Studies were excluded if they evaluated *de facto* (e.g., changes in enforcement practices) rather than *de jure* decriminalization or legal regulation (changes to the law). This exclusion applied to studies analyzing changes in outcomes following the U.S. Justice Department 2009 memo deprioritizing prosecution of cannabis-related offences legal under state medical cannabis laws. Eligible studies included outcome measures pertaining to drug availability, use, or related health and social harms. We used the schema developed by Nutt and colleagues to conceptualize health and social harms, including those to users (physical, psychological, and social) and to others (injury or social harm).[18]

Both observational studies and randomized controlled trials were eligible in principle, but no trials were identified. There were no geographic or language restrictions; titles, abstracts, and full-texts were translated on an as-needed basis for screening and data extraction. We excluded cross-sectional studies (unless they were repeated) and studies lacking pre- and post-implementation data collection because such designs are inappropriate for evaluating intervention effects.

Data Analysis

Screening and data extraction were conducted in DistillerSR (Evidence Partners, Ottawa, Ontario). We began with title-only screening to identify potentially relevant titles. Two reviewers screened each title. Unless both reviewers independently decided a title should be excluded, it was advanced to the next stage. Next, two reviewers independently screened each potentially eligible abstract. Inter-rater reliability was good (weighted Kappa at the question level=0.75). At

this stage, we retrieved full-text copies of all remaining references, which were screened independently by two reviewers. Disagreements on inclusion were resolved through discussion with the first author. Finally, one reviewer extracted data from each included publication using a standardized, pre-piloted form and performed quality appraisal. A second reviewer double-checked data extraction and quality appraisal for every publication, and the first author resolved any discrepancies.

The data extraction form included information on study characteristics (author, title, year, geographic location), type of legal change studied and drug(s) impacted, details and timing of the legal change (e.g., medical vs. recreational cannabis regulation), study design, sampling approach, sample characteristics (size, age range, proportion female), and quantitative estimates of association. We coded each study-level outcome measure into one metric grouping, using 24 pre-specified categories and a free-text field (see Figure 1 for full list). Examples of metrics include: prevalence of use of the decriminalized or regulated drug, overdose or poisoning, and non-drug crime.

We also categorized the estimated direction of association of the legal change on outcome measure(s) of interest (beneficial, harmful, mixed, or null).2 These associations were coded at the outcome (not study) level and classified as beneficial if a statistically significant increase in a positive outcome (e.g., educational attainment) or decrease in a negative outcome (e.g., substance use disorder) was attributed to implementation of decriminalization or legal regulation, and vice-versa for harmful associations. The association was categorized as mixed if associations were both harmful and beneficial across participant subgroups, exposure definitions (e.g., loosely vs. tightly regulated medical cannabis access), or timeframes. Although any use of cannabis and other psychoactive drugs need not be problematic at the individual level, we categorized drug use as a negative outcome given that population-level increases in use may correspond to increases in negative consequences; we thought that this cautious approach to categorization was appropriate given that such increases are generally conceptualized as negative within the scientific literature. For outcomes that are not unambiguously negative or positive, the coding approach was pre-determined taking a societal perspective. For example, increased healthcare utilization (e.g., hospital visits due to cannabis use) was coded as negative because of the increased burden placed on healthcare systems. The association was categorized as null if no

statistically significant changes following implementation of drug decriminalization or legal regulation were detected. We set statistical significance at a=0.05, including in cases where authors used more liberal criteria.

Quality assessment at the study level was conducted for each full-length article using a modified version of the Downs and Black checklist [25] for observational studies (see Appendix B), which assesses internal validity (bias), external validity, and reporting. Each study could receive up to 18 points, with higher scores indicating more methodologically rigorous studies. Conference abstracts were not subjected to quality assessment due to limited methodologic details.

Patient and Public Involvement

This systematic review of existing studies did not include patient or public involvement.

RESULTS

Study Characteristics

As shown in the PRISMA Flow Diagram (Figure 2), we screened 4860 titles and abstracts and 213 full texts, with 114 articles meeting inclusion criteria (Appendix C). Key reasons for exclusion at the full-text screening stage were that the article did not report on original quantitative research (n=59) or did not evaluate decriminalization or legal regulation as defined herein (n=23). Details of each included study are presented in Supplementary Table 1. Included studies had final publication dates from 1976-2019; 44.7% (n=51) were first published in 2017-2018, 43.9% (n=50) were published in 2014-2016 and 11.4% (n=13) were published before 2014.

Characteristics of included studies are described in Table 1, both overall and stratified by whether they evaluated decriminalization (n=19) or legalization (n=96) policies (one study evaluated both policies). Most studies (n=104, 91.2%) were from the U.S. and examined impacts of liberalizing cannabis laws (n=109, 95.6%). Countries represented in non-U.S. studies included Australia, Belgium, China, Czech Republic, Mexico, and Portugal. The most common study designs were repeated cross-sectional (n=74, 64.9%) or controlled before-and-after (n=26, 22.8%) studies and the majority of studies (n=87, 76.3%) used population-based sampling

Table 1. Characteristics of studies evaluating drug decriminalization or legal regulation, 1970-2018

Characteristic	Total (%) n (%) (*n* = 114)	Decriminalization[a] n (%) (*n* =19)	Legal regulation[a] n (%) (*n* =96)
Country			
United States	104 (91.2)	10 (52.6)	95 (99.0)
Australia	3 (2.6)	3 (15.8)	0 (0.0)
Portugal	2 (1.8)	2 (10.5)	0 (0.0)
China	1 (0.9)	0 (0.0)	1 (1.0)
Czech Republic	1 (0.9)	1 (5.3)	0 (0.0)
Mexico	1 (0.9)	1 (5.3)	0 (0.0)
Multi-country[b]	2 (1.8)	2 (10.5)	0 (0.0)
Focus of drug law reform			
Cannabis	109 (95.6)	15 (78.9)	95 (99.0)
Opium	1 (0.9)	0 (0.0)	1 (1.0)
Peyote	1 (0.9)	1 (5.3)	0 (0.0)
Multiple/All drugs	3 (2.6)	3 (15.8)	0 (0.0)
Study design			
Cohort	4 (3.5)	0 (0.0)	4 (4.2)
Controlled before-and-after	26 (22.8)	6 (31.6)	20 (20.8)
Interrupted time series	6 (5.3)	0 (0.0)	6 (6.3)
Repeated cross-sectional	74 (64.9)	11 (57.9)	64 (66.7)
Uncontrolled before-and-after	4 (3.5)	2 (10.5)	2 (2.1)
Sampling approach			
Convenience	22 (19.3)	5 (26.3)	18 (18.8)
Population-based	87 (76.3)	13 (68.4)	74 (77.1)
Administrative records	45 (39.5)	6 (31.6)	39 (40.6)
Household survey	25 (21.9)	5 (26.3)	20 (20.8)
School-based survey	17 (14.9)	2 (10.5)	15 (15.6)
Unspecified	5 (4.2)	1 (5.3)	4 (4.2)

a. Combined total exceeds number of studies because some evaluated both decriminalization and legal regulation.
b. One global study and one multi-country European study including Belgium and Portugal.

methods. Figure 3 illustrates the geographic distribution of studies among countries where national or subnational governments had decriminalized or legally regulated one or more drugs.

Study Quality

Quality assessment was performed for the 93 full-length articles included in the review, excluding 21 conference abstracts (Supplementary Table 1). Scores ranged from 7 to 18 of 18

possible points, with a mean of 14.4 (SD=2.56). Quality scores were similar comparing U.S. to non-U.S.-based studies (*X*=14.4 and 13.7, respectively, p=0.386) but higher for studies evaluating legal regulation (*X*=14.8) versus decriminalization (*X*=12.8) (p=0.003). Study quality differed significantly (p<0.001) by the direction of the association with the outcome of interest, with higher quality scores among studies estimating mixed (*X*=15.4) or beneficial (*X*=15.2) versus null (*X*=14.2) or harmful (*X*=13.1) effects of legal change on the outcome of interest. Study quality did not appear to increase over time (e.g., *X*=14.0 in 2014 and 14.4 in 2018).

Study Outcome Measures and Metrics

Across 114 studies we extracted 224 outcome measures, which were coded into 32 metrics (Figure 1). The most common metric employed by studies was the prevalence of use of the decriminalized or legally regulated drug, which was examined in 39.5% of studies (n=45) and represented 22.3% of outcome measures (n=50). Of these studies, 13 (28.9%; 8 full-length articles and 5 abstracts) did not report any other metric [26–38] and an additional 6 studies (13.3%) reported on the prevalence of use in addition to a single drug-related perception metric (either harmfulness or availability).[39–44] The second most common metric was the frequency of use of the decriminalized or legally regulated drug (14.0% of studies, n=16) and the third was the prevalence or frequency of use of tobacco, alcohol, or drugs that remained illegal (12.3% of studies, n=14; 9.4% of outcome measures, n=21). The fourth most commonly employed metric was any change in the perceived health harmfulness of using the decriminalized or regulated drug (10.5% of studies, n=12), which was assessed among adolescents or young adults in all studies except for one that assessed this metric among parents.[45]

All other metrics were assessed in <10% of included studies. Health service utilization was evaluated in 7.9% of studies (n=9) using 12 outcome measures, primarily related to emergency department visits and/or hospitalizations. Prescribed (primarily opioid) drug use and perceived availability of the decriminalized or legally regulated drug were reported in 7.0% of studies each (n=8). Overdose or poisoning by the decriminalized or regulated drug, and by other drugs (predominantly opioids), were examined in 5.3% (n=6) and 6.1% of studies (n=7), respectively. Driving while under the influence or with detectable concentrations of the decriminalized or regulated drug (cannabis) was examined in seven studies (6.1%) inclusive of eight outcome

measures. Notably, one study assessed self-reported impaired driving,[46] while others assessed the proportion of fatally injured drivers screening cannabis-positive or the overall prevalence of driving with detectable THC concentrations in blood. Remaining metrics were measured in less than 5% of studies (Figure 1). Some pre-specified metrics were not represented in any of the articles, including infectious disease incidence (e.g., HIV, Hepatitis C), environmental impacts (e.g., drug production waste, discarded needles), and labor market participation.

Studies Outside the U.S.

Of the ten studies conducted outside the U.S., six focused on cannabis decriminalization. All three studies from Australia examined the prevalence of cannabis use post-decriminalization,[31,34,47] while one also measured perceived cannabis availability.[47] Following cannabis decriminalization, one European multi-country study including Belgium and Portugal examined the prevalence of cannabis use and uptake of cannabis-related addictions treatment [48] and one Czech study considered the age of first cannabis use.[49] An international study using United Nations Office on Drugs and Crime data from 102 countries compared availability, as reflected by cannabis seizures and plant eradication, in countries that had decriminalized cannabis versus those that had not.[50] Three non-U.S. studies evaluated decriminalization of all psychoactive drugs. Two studies from Portugal examined health care and non-health-care costs and psychoactive drug prices, respectively.[51,52] One study from Mexico examined drug-related criminal justice involvement (arrests) and (violent) crimes.[53] Finally, a study of historic opium legalization in China (1801-1902) measured the price and availability (quantity of exports) of opium before and after legalization.[54]

Impacts of Decriminalization and Legal Regulation

Results of individual studies are provided in Supplementary Table 1. Supplementary Table 2 tallies findings and average quality scores for each of the metrics; here we summarize findings for metrics examined in more than 5% of studies, in descending order based on the number of datapoints. Across all three substance use metrics (prevalence of use, frequency of use, and use of other alcohol or drugs), drug law reform was most often not associated with use (with null findings for 48.0-52.4% of outcome measures falling under these metrics). With respect to change in perceived harmfulness of the decriminalized or regulated drug, mixed results were

found in half of cases, with heterogeneity detected on the basis of age, gender, and state.[39,43,55–57] For example, legal regulation of cannabis for medical use was associated with greater perceived harmfulness of cannabis among eighth graders but not older students in an analysis of U.S. Monitoring the Future data [39] while a study employing U.S. National Survey on Drug Use and Health data found greater perceived harmfulness of cannabis among young adults aged 18-25 but not adolescents aged 12-17.[57]

Among nine studies that employed health service utilization metrics, harmful effects were reported for six of twelve outcome measures, with increases in emergency department visits and/or hospitalizations attributed to decriminalization or legal regulation.[58–63] However, all but one of those studies [58] assessed change over time in one jurisdiction, without a control group. Further, two studies that also examined changes in acute care use for non-cannabis drugs found reductions in those visits or admissions following cannabis decriminalization or legal regulation [60, 64]. In contrast, six of nine prescription drug use associations were beneficial, with reductions observed in rates of opioid [65–69] and other drug prescribing [70,71] attributed to legal regulation of cannabis for medical use; outcomes in this category came from studies of higher average quality (X=16.3) . Perceived availability of the decriminalized or regulated drug appeared largely unaffected by decriminalization (null associations for five of nine outcome measures) but two studies indicated increased perceived availability of cannabis among Colorado, U.S. adolescents following legal regulation for adult use [72] and among adults in U.S. states with legal regulation for medical use.[44] Across the subset of seven outcome measures for overdose or poisoning by the decriminalized or regulated drug (cannabis), in all cases an increase in calls to poison control centers or unintentional pediatric exposures was reported.[59,73–77] However, studies assessing the impacts of cannabis regulation on overdose or poisoning by drugs other than cannabis concluded that the effects were either beneficial (four outcome measures[64, 76, 78, 79]) or mixed/null (three outcome measures[80–82]). Driving with detectable concentrations of THC was most often found to increase following decriminalization or legal regulation (five of eight outcome measures; [83–87]), but these studies were of lower average quality (X=12.0).

Impacts of Decriminalization

Of the 19 studies evaluating impacts of decriminalization, six measured the prevalence of use of the decriminalized substance with eight unique outcome measures. No association was detected for all but three outcomes; following cannabis decriminalization lifetime use increased among adults in South Australia,[31] while past-month use increased among 12th graders but not younger students in California,[56] relative to the rest of the country in both cases. After peyote use for ceremonial purposes was decriminalized in the U.S. in 1994, self-reported use increased among American Indians.[88] Three studies evaluated relationships between decriminalization and drug-related criminal justice involvement in Mexico and the United States. One high-quality study found that decriminalization positively influenced criminal justice involvement: in five U.S. states, arrests for cannabis possession decreased amongst youth and adults.[89] When possession of small amounts of cannabis was decriminalized in the 1970s in Nebraska, however, the mean monthly number of arrests did not change, while cannabis-related prosecutions increased among youth.[90] In Tijuana, Mexico, decriminalization of all drugs had no apparent impact on the number of drug possession arrests.[53] Two historic and one recent study measured health care utilization. U.S. states that decriminalized cannabis in the 1970s saw greater emergency department visits related to cannabis, but decreased visits related to other drugs.[60] In Colorado, U.S., decriminalization was associated with increased emergency department visits for cyclic vomiting.[62] Addiction treatment utilization, health care and non-health-care costs, driving after use, price of drugs, availability of drugs, frequency of use, and attitudes towards use and perceived harmfulness were each evaluated in only one or two studies of decriminalization.

DISCUSSION

This systematic review identified 114 peer-reviewed publications and conference abstracts evaluating the impacts of drug decriminalization or legal regulation from 1970-2018. Within this search period, 88.6% were published in 2014 or later. This rapid growth in scholarship was driven by the implementation and subsequent evaluation of cannabis legalization in a number of U.S. states beginning in 2012, and knowledge production will surely continue to accelerate as longer-term data become available and as other jurisdictions (e.g., Canada, Uruguay) analyze the effects of recently implemented cannabis legalization. Indeed, a first study on the impacts of cannabis legalization on adolescent use in Uruguay was published in May 2020 (finding no

impact on risk of use [91]). The present study provides an overview of the emerging literature based on our systematic review and suggests three key patterns.

First, peer-reviewed longitudinal evaluations of drug decriminalization and legal regulation are overwhelmingly geographically concentrated in the U.S. and focused on cannabis legalization. Importantly, the lack of non-U.S. studies evaluating legal regulation of cannabis for medical use may reflect the more tightly controlled nature of medical cannabis regulation in other countries, and thus the more limited potential for population-level effects. It is notable that decriminalization in the absence of legal regulation was evaluated in only 18 studies (15.8%), despite being far more common globally than legal regulation. These gaps may hamper evidence-based drug law reform in countries that are less well-developed, play a substantial role in drug production and transit, or have different baseline levels of substance (mis)use as compared to the U.S.

Second, prevalence of use was the predominant metric used to assess the impact of drug law reform, despite its limited clinical significance (e.g., much cannabis use is non-problematic) and limited responsiveness to drug policy. This is because ecological analyses have indicated little relationship between drug policies and prevalence of use,[52] as have studies assessing within-state change in use related to legal regulation.[21] These findings are supported by the preponderance of evidence synthesized in this review, although some variation is evident in relation to the specific provisions of legal reforms (e.g., liberal versus tightly regulated medical markets [92]). Impacts of legal cannabis regulation on prevalence and frequency of use continue to be evaluated, with recent data suggesting small increases among adults, but not youth.[93] Drug policies may be more able to influence the types of drugs that people use, drug-related risk behaviors, and modes of drug consumption.[94] Metrics to assess these outcomes, however, were lacking in the reviewed literature. For example, only one study (0.8%) investigated whether legal regulation of cannabis was associated with changes in the mode of cannabis consumption.[72] Although the prevalence of use was often measured alongside more clinically or socially significant metrics (e.g., prevalence of substance use disorders, educational outcomes among young adults), 42.2% of studies assessing substance use prevalence included that metric alone or in combination with a single drug-related attitude metric.

Third, there was a lack of alignment between the stated policy objectives of drug law reform and the metrics used to assess its impact in the scientific literature. For instance, removal of criminal sanctions to prevent their negative sequelae is a key rationale for decriminalization and legal regulation,[12,13,95] but only four studies (3.5%) evaluated changes in drug-related criminal justice involvement following drug law reform. Similarly. improving the physical and mental health of people who (already) use drugs is a motivation for drug policy reform but no included studies examined mental or physical health outcomes (aside from substance use disorders) in this population. As a result, there is a risk that decisions on drug policy may be informed by inappropriate metrics. Promisingly, in recent months, additional studies assessing legal regulation that employ a range of criminal justice metrics have been published.[96,97, 98] Finally, despite ample evidence of the impact of criminalization on infectious disease transmission and acquisition risks,[5] we found no studies evaluating the impact of decriminalization on these outcomes.

Both the included studies and our systematic review have important strengths and limitations. To our knowledge, we conducted the first review of all global literature on decriminalization and legal regulation and applied no language restrictions. All eligible articles identified were published in English; this may reflect a paucity of evaluation research published in other languages and/or limitations of our search strategy (e.g., some non-English journals may not be indexed in the 10 databases searched). In addition, we excluded grey literature, non-original research, and study designs that are not suited to evaluating policy effects (e.g., cross-sectional studies), but these restrictions narrowed the geographic scope of included studies. For example, two articles on Portugal were excluded as non-original research, but nevertheless provide important insight on impacts of decriminalization [99,100]. Despite restricting eligibility to more rigorous study designs, most included studies used relatively weaker eligible designs that are known to be vulnerable to pre-existing trends and confounding; only 22.8% and 5.3% respectively used controlled before-and-after or interrupted time series designs to address these threats to validity. The use of these study designs may be related to limited resources for prospective drug policy evaluations, with many studies relying on publicly available, routinely collected data. That the U.S. is unique in the extent to which data on drug use and related harms

are routinely collected helps to explain its over-representation in our review. Scoping reviews inclusive of grey literature and cross-sectional designs would be valuable for describing the full range of evaluations that have been conducted globally.

While beyond the scope of our high-level synthesis, the implementation and specific provisions of drug policies vary widely. Decriminalization policies vary in their definitions of quantities for personal use, application of administrative penalties, and the extent to which the law "on the books" is reflected in policing and criminal justice practice. Indeed, in some jurisdictions with nominal decriminalization, arrests for possession of small quantities of the decriminalized drugs remain routine.[53] Legal regulation models for cannabis are also heterogenous. For example, policies legally regulating cannabis for medical use may or may not allow for legal dispensaries, and this provision has been shown to substantially modify the impact of legal regulation on cannabis use.[101] To the extent that individual studies employed crude exposure measures (e.g., presence versus absence of a law), they may have obscured context-dependent effects of drug law liberalization. Further, the impact of drug laws on drug use and related outcomes may be limited by a lack of public awareness of the details of local laws.[102]

Our use of vote-counting in this synthesis (i.e., categorizing individual outcome measures as indicating beneficial, harmful, mixed/subgroup-specific, or no statistically significant associations) is subject to the same limitation. Vote-counting should also be interpreted with caution in light of the heterogeneity of outcome definitions, the inherent arbitrariness of statistical significance thresholds, and the key distinction between statistical and clinical significance. In addition, many included studies are evaluating the same policies (e.g., cannabis legalization in western U.S. states), sometimes using overlapping data but drawing different conclusions based on analytic choices and timeframes. The existence of multiple datapoints for a particular outcome does not imply that the outcome has been well-studied across diverse contexts such that scientific consensus on its effects has been reached. Moreover, as illustrated by a recently published extension of the included article by Bachhuber et al.,[79] multiple high-quality studies may generate results that are later revealed to be spurious as additional follow-up data become availability. Specifically, Shover et al. demonstrated that the positive association reported between medical cannabis legalization and opioid overdose mortality in 1999-2010

reversed direction in later years, suggesting that earlier findings of a protective effect should not be given causal interpretations.[103] This was foreshadowed in the included article by Powell et al., which found that the purportedly positive effect of medical cannabis legalization was attenuated in 2010-2013.[82] This scientific back-and-forth can be expected given that most included articles are evaluating legal changes introduced rather recently, and thus are examining early impacts with limited years of follow-up. Longer-term impacts of non-medical cannabis legalization, and how they might be influenced by increased commercialization, are yet to be seen.[104]

Conclusions

The findings of this review indicate a need for a broadening of the metrics used to assess the impacts of drug decriminalization and legal regulation. Given the growing number of jurisdictions considering decriminalization or legal regulation of psychoactive drugs,[14–16] the disproportionate emphasis on metrics assessing drug use prevalence, as well as the limited geo-cultural diversity in evaluations, are concerning. Experts have called for a more fulsome approach to evaluating drug policies in line with public health and the United Nations Sustainable Development Goals, with attention to the full breath of health and social domains potentially impacted, including human rights and social inclusion (e.g., stigma), peace and security (e.g., drug market violence), development (e.g., labor market participation) drug market regulation (e.g., safety of the drug supply), and clinically-significant health metrics (e.g., drug-related morbidity).[105] Drawing on methods such as multi-criterion decision analysis,[19] the engagement of both scientists and policymakers in priority-setting may help to produce evidence that provides a more comprehensive understanding of the breadth of impacts that should be anticipated with drug law reform efforts. Funding will also be required to support rigorous prospective evaluations of legal reforms.

Figure 1 Legend

Metrics examined by included studies.

Figure 2 Legend

PRISMA Flow Diagram

Figure 3 Legend

Number of included studies from countries that implemented decriminalization or legal regulation by 2017

Note: Policy changes were classified, following the review inclusion criteria, based on the implementation of a change to national or subnational law to decriminalize drug use and/or possession or to legalize at least one class of drugs. We did not evaluate the extent to which legal changes were reflected in policing and criminal justice practice. Implementation of cannabis legalization for medical purposes only is not reflected in this map.

Author contributions

DW and AIS conceptualized and supervised the review. CZ designed and conducted the literature searches. AIS drafted the manuscript. SC, ZM, and AIS conducted screening and data extraction. NM contributed to drafting the manuscript and developing figures. All authors contributed to interpretation of findings and revising the manuscript for important intellectual content.

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Competing interests

We have no competing interests to declare.

Data sharing statement

All relevant data are contained within the article and supplementary materials.

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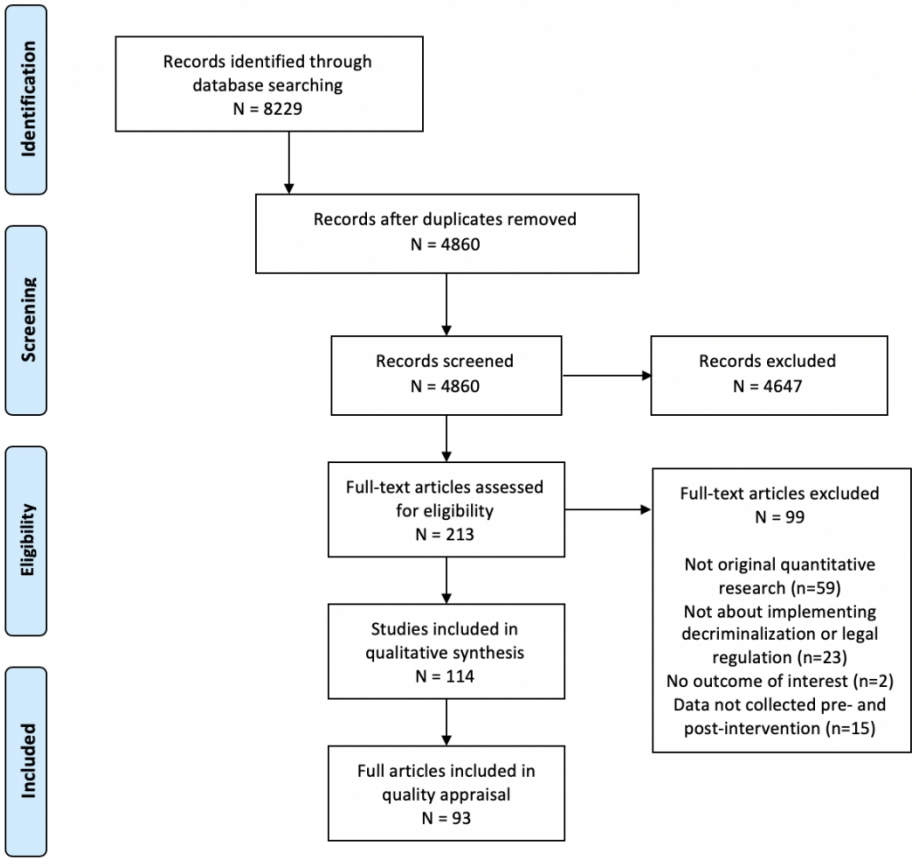
Metrics examined by included studies.



PRISMA Flow Diagram

Number of included studies from countries that implemented decriminalization or legal regulation by 2017
Note: Policy changes were classified, following the review inclusion criteria, based on the implementation of a change to national or subnational law to decriminalize drug use and/or possession or to legalize at least one class of drugs. We did not evaluate the extent to which legal changes were reflected in policing and criminal justice practice. Implementation of cannabis legalization for medical purposes only is not reflected in this map.

Supplementary Table 1. Included Studies

	Reference	Setting Legal change	Study design, dates [Comparison group or condition]	Sampling approach Sample size	Outcomes	Effects	Quality
1.	Adam 2017	Belgium, Portugal Cannabis decriminalization	Controlled before-and-after, 1996-2010 [Austria, Germany, Greece, Ireland, Italy, Netherlands, Spain, Sweden]	Convenience sampling 89 treatment units	*Addiction treatment utilization:* # of first-time drug treatment clients reporting cannabis as primary indication, per reporting treatment unit	No significant effect of decriminalization. *B*= 2.66, *SE*=8.72, *P*=0.770	13
					Prevalence of use, decriminalized/regulated drug(s): past-year cannabis use	No significant effect of decriminalization. *B* = 1.88, *SE*=1.77, *P*=0.310	
2.	Allshouse 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2013; 2014	Population-based; Admin record data N=743	*Prevalence of use, decriminalized/regulated drug(s)*: self-reported cannabis use during pregnancy	No significant effect of RCL (from 4.5% to 7.5%, *p*=0.06)	A *
					Prevalence of use, decriminalized/regulated drug(s): cannabis-positive urine screen during pregnancy	No significant effect of RCL. Adjusted prevalence difference = 0.03, *P*=0.99.	
3.	Anderson 2013	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1990-2010	Convenience sampling *Study A*: 8,271 cannabis purchases *Study B*: 1071 fatalities	*Price of drugs*: median price of cannabis in state and year	9.8% decrease in price of high-quality cannabis, controlling for state-specific time trends. Lagged models indicate price reductions not significant until 4th year after MCL. Effects on price of low-quality cannabis largely statistically insignificant.	11
					Accidents, motor vehicle: traffic fatality outcomes per 100,000; primary outcome is total fatalities.	No significant change in fatalities, controlling for state-specific time trends. In lagged models, MCL associated with 8-13% fatality reductions in years 1-4, with reduction attenuated and no longer significant after 5 years, controlling for state-specific time trends.	

4.	Anderson 2014	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1990-2007 [States that did not implement MCL]	Population-based; Admin record data	*Mental health conditions, suicide, or self-harm*: annual suicide rates per 100,000 among individuals 15+	No difference in suicide rate overall. Reduction among males, (log) rate difference =0.047* (95% CI: –0.089, –0.005). By age, significant reductions among males from 20-39 and among females >=60.	16
5.	Anderson 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1992-2015	Population-based; Admin record data N= 1224 state-years	*Accidents, other*: Workplace fatalities by state from the Bureau of Labor Statistics	No difference in fatality rate overall. Reduction among those aged 25-44 only. Adjusted rate ratio = 0.805 (95% CI: 0.662, 0.979).	15
6.	Anderson 2015	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1993-2011	Population-based; School-based survey N=862,695	*Prevalence of use, decriminalized/regulated drug(s)*: past 30 day use	No significant effect of MCL: % difference, combined national and state YRBS = -0.007, SE=0.011, p>0.05.	15
					Frequency of use, decriminalized/regulated drug(s): used ≥ 10 times in past 30 days	No significant effect of MCL: % difference, combined national and state YRBS = -0.004, SE=0.006, p>0.05.	
					Actual availability of decriminalized/regulated drug(s): offered, sold, or given an illegal drug on school property in past year	MCL associated with reduction in availability, % difference, combined national and state YRBS = -0.020, SE=0.008, p<0.05;	
7.	Arredondo 2018	Mexico Decriminalization of all drugs	Repeated cross-sectional study, 2009-2014	Population-based; Admin record data	*Criminal justice involvement*: Monthly number of drug possession arrests per precinct.	Decriminalization law not associated with arrests, Beta for ln(possession arrests)=0.187, SE=0.151, p>0.05.	14
					Crime (non-drug): Violent crime arrests (injuries, robbery, homicides)	Law not associated with arrests, b=0.001, SE=0.090, p>0.05.	

					Crime (non-drug): Non-violent arrests (theft, possession of stolen car)	Law not associated with arrests, b=-0.043, SE=0.071, p>0.05.	
8.	Aydelotte 2017	United States Legal regulation of cannabis for recreational use (RCL)	Controlled before-and-after study, 2009-2015 [8 similar states without MCL or RCL]	Population-based; Admin record data N=60,737	*Accidents, motor vehicle*: Annual number of motor vehicle crash fatalities	RCL not associated with crash fatalities, adjusted difference in difference coefficient: +0.2 (95% CI: -0.4, +0.9).	15
9.	Bachhuber 2014	United States Legal regulation of cannabis for medical use (MCL)	Interrupted time series study, 1999-2010	Population-based; Admin record data	*Overdose or poisoning, other drug*: opioid analgesic overdose mortality rate	MCL associated with reduced mortality, adjusted percentage change in annual rate= -24.8% (95% CI: -37.5, -9.5), p = .003.	16
10.	Banerji 2017	United States Legal regulation of cannabis for recreational use	Repeated cross-sectional study, 2011-2015	Population-based; Admin record data N=777 exposures	*Overdose or poisoning, decriminalized/regulated drug*: cannabis calls to poison control center	Apparent increase (from 86 in 2011 to 231 in 2015); no statistical tests reported.	A *
					Overdose or poisoning, other drug: synthetic cannabinoid calls to poison control center	Apparent decrease (100 in 2013 and 17 in 2014); no statistical tests reported.	
11.	Bell 2015	United States Legal regulation of cannabis for medical use (MCL) and recreational use	Repeated cross-sectional study, 2008-2014	Population-based; Admin record data N=29	*Accidents, other*: hydrocarbon burns referred to the University of Colorado Hospital	Before MCL (Jan 2008-Aug 2009): 0 cases During MCL (Oct 2009-Dec 2013): 19 cases During recreational legalization (Dec 2013-Aug 2014): 12 cases No statistical tests reported.	11
12.	Bjordal 2015	United States Legal regulation of cannabis for recreational use	Repeated cross-sectional study, 2013-2014	Population-based; Admin record data N=245 exposures	*Overdose or poisoning, decriminalized/regulated drug*: Cannabis calls to poison control center (p.694)	Apparent increase (from 158 in 2013 to 245 in 2014); no statistical tests reported.	A *

13.	Blachly 1976	United States Cannabis decriminalization	Uncontrolled before-and-after study, 1970; 1975	Convenience sampling N=627 admissions	*Health services utilization*: % of drug abuse admissions to Dammasch State Hospital due to cannabis	Prevalence from 6.7% (1970) to 2.5% (1975); no statistical tests reported.	8
14.	Boyle 2014	United States Cannabis decriminalization	Repeated cross-sectional study, 2011-2013	Population-based; Admin record data N=11 incidents	*Accidents, other*: explosions of gases related to hash oil manufacturing	Two events in 2 years prior, nine events in 7 months post-decriminalization (before legal sales); no statistical tests reported.	A *
15.	Bradford 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2010-2015	Population-based; Admin record data N=132.6 million physician-drug-year observations	*Prescription drug use*: total number of daily opioid dose prescriptions filled (in millions)	MCL associated with fewer daily doses filled in states with active dispensaries (-3.742 million, 95% CI: -6.289, -1.194) and in states with home cultivation (-1.792 million, 95% CI: -3.532, -0.052). Results also varied by type of opioid.	18
16.	Bradford 2016	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 2010-2013 [States without a medical marijuana law at a given time]	Population-based; Admin record data N= 588,808-2,496,608	*Prescription drug use*: among Medicaid Part D enrollees, average daily doses filled annually per physician for FDA-approved drugs treating conditions that cannabis may be used to treat (anxiety, depression, glaucoma, nausea, pain, psychosis, seizures, sleep disorders, spasticity)	MCL associated with statistically significant ($p<0.05$) reductions in daily doses filled for 7 of 9 conditions (difference-in-difference coefficients from -265 daily doses for depression to -1826 for pain), no significant effects for glaucoma or spasticity.	17
					Costs, health care: estimated annual change in Medicaid Part D spending (program and enrollee)	Estimated prescription drug cost savings from 2010-2013 attributed to MCL = $515,194,125.	

17.	Bradford 2017	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 2007-2014 [States without MCL in a given quarter]	Population-based; Admin record data	*Prescription drug use*: average number of daily prescription drug doses dispensed per fee-for-service Medicaid beneficiary for FDA-approved drugs treating conditions that cannabis may be used to treat.	MCL associated with statistically significant ($p<0.05$) reductions in daily doses per beneficiary for 5 of 9 conditions (depression, nausea, pain, psychosis, and seizures). Estimated proportion reductions in dispensed doses ranged from 11% for pain to 17% for nausea.	17
					Costs, health care: estimated annual change in Medicaid fee-for-service spending on prescription drugs with medical cannabis indications	Estimated Medicaid fee-for-service prescription drug cost savings from 2007-2014 attributed to MCL = 2,694.1 million	
18.	Brooks-Russell 2019	United States Legal regulation of cannabis for recreational use	Repeated cross-sectional study, 2013-2015	Population-based; School-based survey N = 26,019 (2013) N = 15,970 (2015)	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime use; past 30-day use.	No significant change in lifetime or past 30-day use following legal regulation.	15
					Prevalence of use, other drugs or alcohol: past 30-day use of cigarettes; past 30-day use alcohol; lifetime non-medical prescription drug use; lifetime cocaine use.	Decrease in past 30-day cigarette use from 2013 to 2015 (12.1 to 8.6%, $p<0.01$). No significant changes in other drug or alcohol use.	
					Perceived harmfulness of decriminalized/regulated drug(s): high vs. low perceived accessibility, wrongfulness, parental disapproval, and harmfulness.	Decrease in high perceived harmfulness (52.9% to 47.7%, $p<0.01$). No significant changes in other perceptions.	
					Frequency of use, decriminalized/legalized drug(s): >20 occasions of use in past 30 days, among those who reported past 30-day use.	Decrease in frequent use among past-30-day users (33.2% to 26.8%, $p<0.01$).	
					Prevalence of use, decriminalized/regulated drug(s): use on school property, among those who reported past 30-day use.	Decrease in use on school property among past-30-day users (5.7% to 4.4%, $p=0.03$).	

19.	Calcaterra 2018	United States Legal regulation of cannabis for recreational use (RCL)	Interrupted time series study, 2009-2015	Population-based; Admin record data N=370,612	*Health services utilization*: cannabis-related hospitalizations	RCL associated with an increase in hospitalizations: adjusted annual rates of inpatient and emergent hospitalizations were 2.4 and 4.3 times higher in 2015 as compared to 2009 ($p<0.001$). A reduced segmented regression model shows a significant increase in slope post-RCL ($b= 1.835$, $SE=0.218$, $p< 0.0001$).	A *
20.	Cassidy 2015	United States Legal regulation of cannabis for recreational use	Uncontrolled before-and-after study, 2008-2014	Convenience sampling N=13,945	*Prevalence of use, decriminalized/regulated drug(s)*: among substance use treatment clients	Increase from 21.3% in 2008 to 32.8% in 2014 ($p<0.001$).	A *
					Prevalence of use, decriminalized/regulated drug(s): past-year initiation	No significant change in past-year initiation.	
21.	Cerda 2018	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1991-2015 [States without MCL]	Population-based; School-based survey N=1,179,372	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	Decrease in 8th grade (aOR=0.72; 95% CI: 0.62, 0.84). No significant changes in 10th or 12th.	18
					Prevalence of use, other drugs or alcohol: binge drinking in past two weeks	Decrease in 8th grade (aOR=0.72; 95% CI: 0.65, 0.79). No significant changes in 10th or 12th.	
					Prevalence of use, other drugs or alcohol: past 30-day cigarette use	Decrease in 8th grade (aOR=0.74; 95% CI: 0.66, 0.82) and increase in 12th grade (aOR=1.17; 95% CI: 1.06, 1.29).	
					Prevalence of use, other drugs or alcohol: past 30-day non-medical prescription drug use	Decrease in non-medical prescription opioid use in 8th grade (aOR=0.43; 95% CI: 0.36, 0.52) and increase in 12th grade (aOR=1.42; 95% CI: 1.21, 1.66). Decrease in prescription amphetamine use (aOR=0.71; 95% CI: 0.63, 0.81) and prescription tranquilizer use (aOR=0.83; 95% CI: 0.71, 0.98) in 8th grade only.	
					Prevalence of use, other drugs or alcohol: past 30-day non-cannabis illicit drug use	Decrease in 8th grade only (aOR=0.77; 95% CI: 0.69, 0.86).	

22.	Cerda 2017	United States Legal regulation of cannabis for recreational use (RCL)	Controlled before-and-after study, 2010-2015	Population-based; School-based survey N=253,902	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	Increase in 8th and 10th grade in Washington but not Colorado (difference-in-difference WA vs. non-RCL= 3.2% in 8th grade, p=0.03; 5.0% in 10th, p=0.01).	18
					Perceived harmfulness of decriminalized/regulated drug(s): great or moderate vs. low or no risk	Decreased perceived harmfulness in 8th and 10th grade in Washington but not Colorado (difference-in-difference WA vs. non-RCL= -9.3% in 8th grade, p=0.01; -9.0% in 10th, p=0.02).	
23.	Cerveny 2017	Czech Republic Cannabis decriminalization	Repeated cross-sectional study, 2008; 2012	Population-based; Household survey N=1524	*Age of first use, decriminalized/regulated drug*	No significant effect of decriminalization on hazard of initiation.	13
24.	Choo 2014	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1991-2011 [Matched to state in geographic proximity without MCL]	Population-based; School-based survey N= 11,703,100	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	No significant effect of MCL.	16
25.	Chu 2014	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1988-2008 [Non-MCL state years]	Population-based; Admin record data N=12,157 city-years	*Criminal justice involvement*: adult male cannabis possession arrest rates	No significant effect of MCL.	15
					Criminal justice involvement: ratio of cannabis possession arrests to all arrests among adult males	MCL associated with 9.3-12.1% increase in ratio of cannabis to non-cannabis arrests.	
					Addiction treatment utilization: ratio of cannabis-related to all treatment admissions among adult male non-criminal justice referrals	MCL associated with 9.1-10.5% increase in ratio of cannabis to non-cannabis admissions.	

26.	Couper 2014	United States Cannabis decriminalization	Repeated cross-sectional study, 2009-2013	Convenience sampling N=25,719	*Driving under the influence or with detectable concentration, decriminalized/regulated drug(s)*: prevalence of THC in blood toxicology results from suspected impaired driving cases in Washington State	Increased prevalence of active THC after decriminalization (24.9% vs. 19.1%, p<0.05).	9
27.	Donnelly 1995	Australia Cannabis decriminalization	Repeated cross-sectional study, 1985-1993	Population-based; Household survey N= 2257 to 3500	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime cannabis use	No significant interaction between survey year and state: lifetime use did not increase at a significantly greater rate in South Australia (decriminalized).	15
					Perceived availability of decriminalized/regulated drug(s): been offered cannabis	No significant interaction between survey year and state.	
					Attitudes towards use, decriminalized/regulated drug(s): would take cannabis if offered by a trusted friend	Proportion reporting willingness to try increased from 10% in 1985 to 18% in 1991 in South Australia, significant positive interaction between survey year and state (p<0.05).	
					Prevalence of use, decriminalized/regulated drug(s): weekly use of cannabis	No significant interaction between survey year and state.	
28.	Donnelly 2000	Australia Cannabis decriminalization	Repeated cross-sectional study, 1985; 1988; 1991; 1993; 1995	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime use	Greater increase in lifetime use in South Australia (decriminalized) than the rest of Australia (test for trend, p<0.05).	11
					Prevalence of use, decriminalized/regulated drug(s): weekly use	Rate of change for South Australia not significantly different from rest of the country.	
29.	Dutra 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2008-2015	Population-based; Household survey N= 91,123 to 10,1973	*Mental health conditions, suicide, or self-harm*: state prevalence of serious mental illness	Liberal MCL associated with 0.2% increase in state prevalence of mental illness (b=0.002, SE=0.001, p=0.015). No significant effect of restrictive MCL.	17

30.	Estoup 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2010-2015	Convenience sampling N=262	*Mental health conditions, suicide, or self-harm*: # of reported psychological, behavioral, relational consequences of cannabis use	RCL associated with increased negative consequences of use, mediated by increased perceived harmfulness (*b* for indirect effect=3.73; 95% CI=0.33, 9.55).	11
					Perceived harmfulness of decriminalized/regulated drug(s): # of cons of continued cannabis use endorsed in decisional balance matrix	RCL associated with increased perceived harmfulness.	
					Frequency of use, decriminalized/legalized drug(s): # of times used in past 3 months	No significant effect of RCL.	
31.	Feige 2008	China Legal regulation of opium	Repeated cross-sectional study, 1801-1902	Unspecified	*Actual availability of decriminalized/regulated drug(s):* Quantity of opium exports (number of chests per capita)	No significant effect of legal regulation.	16
					Price of drugs: Price of opium at the scales in India	No significant effect of legal regulation.	
32.	Félix 2017	Portugal Decriminalization of all drugs	Controlled before-and-after study, 1990-2010 [13 EU countries and Norway]	Convenience sampling	*Price of drugs*: price data from (1) EU country reports to the Commission on Narcotic Drugs and (2) the European Monitoring Center for Drugs and Drug Addiction	Drug prices increased in Portugal following decriminalization, but difference-in-difference and synthetic control analyses indicate no statistically significant change in slope of drug prices.	14
33.	Gonçalves 2015	Portugal Decriminalization of all drugs	Repeated cross-sectional study, 1999-2010	Population-based; Admin record data	*Costs, health care*: combined direct costs of (1) drug treatment, prevention and harm reduction and (2) hospital treatment for hepatitis and HIV	12% increase over first 5 years following decriminalization, 9% over first 11 years.	13

					Costs, non-health care: combined indirect costs of lost income and production due to (1) drug addiction treatment and (2) drug-related death.	37% reduction over first 5 years following decriminalization, 29% over first 11 years.	
					Costs, non-health care: combined direct costs of social rehabilitation and legal system costs related to drugs	17% reduction over first 11 years.	
					Costs, non-health care: indirect costs of lost income and production of individuals arrested for drug-related crimes	5% reduction over first 5 years following decriminalization, 24% over first 11 years.	
34.	Gorman 2007	United States Legal regulation of cannabis for medical use (MCL)	Interrupted time series study, 1994-2002	Convenience sampling	*Prevalence of use, decriminalized/regulated drug(s)*: prevalence of positive cannabis urine screen among arrestees.	No significant effect of MCL on positive cannabis tests in CA or OR.	12
					Health services utilization: proportion of emergency department visits in which cannabis was mentioned in CA, WA, and CO DAWN sites	No significant effect of MCL on ED visits mentioning cannabis.	
35.	Grant 2018	United States Legal regulation of cannabis for medical use (MCL)	Cohort study, 1998-2012	Convenience sampling N=1359	*Prevalence of use, decriminalized/regulated drug(s)*: use in last 30 days of substance use case management program	Participants exiting case management after MCL were more likely to report past 30-day use (AOR = 2.1, $p < 0.0001$).	12
					Prevalence of use, other drugs or alcohol: # of days of use, in past 30 days, of alcohol or drugs	Participants exiting case management after MCL used alcohol ($b = 0.48$, SE=0.24, $p < 0.05$), illicit methadone ($b = 0.67$, SE=0.22, $p < 0.005$), and other opioids ($b = 0.52$, SE=0.15), $p < 0.01$) more frequently than the pre-MCL cohort.	
36.	Grucza 2018	United States	Controlled before-and-after study,	Population-based;	*Criminal justice involvement*: arrest rates for cannabis	Arrest rates decreased by 75% among youth (95% CI: -0.89, -0.44) and 78% among adults (95% CI: -0.89, -0.52).	18

		Cannabis decriminalization	2007-2015 [States without decriminalization, legal regulation, or change in penalties related to cannabis]	School-based survey N= 622,848	possession among minors (18 or under) and adults		
					Prevalence of use, decriminalized/regulated drug(s): past 30-day use	Decriminalization was not significantly associated with use.	
					Frequency of use, decriminalized/regulated drug(s): frequency of past 30-day use	Decriminalization was not significantly associated with frequency of use.	
37.	Grucza 2015	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1990-2010 [States without MCL]	Population-based; Admin record data N=662,993	*Mental health conditions, suicide, or self-harm*: suicide deaths	MCL not significantly associated with suicide rate overall, or when stratified by sex.	16
38.	Harper 2012	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 2002-2009 [States without MCL]	Population-based Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use among adolescents	*Reanalysis of Wall 2011 (#106) Difference-in-difference estimates indicate no significant effects of MCL, after accounting for state-level covariates and measurement error.	15
					Perceived harmfulness of decriminalized/regulated drug(s): perceived riskiness of monthly use among adolescents	No significant effects of MCL.	
39.	Harpin 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2013-2014	Population-based; School-based survey N=11,931 to 12,240	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime and past 30-day use	No significant change after RCL.	13
					Mode of use, decriminalized/regulated drug(s): smoking vs. other modes, among past-month users	No significant change after RCL.	
					Perceived harmfulness of decriminalized/regulated drug(s): high versus low	No significant change after RCL.	

					perceived harmfulness and wrongfulness of use		
					Perceived availability of decriminalized/regulated drug(s): high versus low perceived ease of access	Post-RCL year associated with high perceived access, (AOR= 1.21, 95% CI: 1.09, 1.34).	
40.	Hasin 2017	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1991-1992; 2001-2001; 2012-2013 [late MCL states, never MCL states]	Population-based; Household survey N=118,497	*Prevalence of use, decriminalized/regulated drug(s):* past-year use	MCL associated with greater increase in past-year use (difference-in-difference coefficient=1.4 percentage points, SE=0.5, p=0.004). Results varied by state and early vs. late MCL adoption.	17
					Substance use disorder or diagnosed dependence: DSM-IV Cannabis Use Disorder in past year	MCL associated with greater increase in CUD (difference-in-difference coefficient=0.7, SE=0.3, p=0.03).	
41.	Hasin 2015	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1991-2014	Population-based; School-based survey N=1,098,270	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	No significant effect of MCL overall, but interaction with grade: reduced use among 8th graders post-MCL (AOR=0.73, 95% CI: 0.63, 0.84), but not 10th or 12th graders.	18
42.	Hasin 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1991-1992; 2001-2002; 2012-2013	Population-based Household survey	*Driving under the influence or with detectable concentration, decriminalized/regulated drug(s)*	Prevalence of cannabis-impaired driving increased more in states that passed MCL, but not significantly so (p=0.07).	A *
					Driving under the influence or with detectable concentration,: driving under the influence of alcohol	No significant effect of MCL.	
43.	Hoyte 2015	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2007-2014	Population-based; Admin record data N= 42 fatalities	*Accidents, motor vehicle*: THC-positive motor driver fatalities in Denver County, CO	Fatalities increased from 0.28/month from July 1, 2007 to Dec 31, 2008 to 0.5/month from 2009-2012 to 0.56/month from Jan 1, 2013 to June 30, 2014 (post-RCL). No statistical tests reported.	A *

44.	Huber 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1970-2012	Population-based; Admin record data	*Crime (non-drug)*: state violent crime rates (FBI Uniform Crime Reports)	MCL associated with 12.9% reduction in rate (b=-0.129, SE= 0.036, p<0.01).	14
					Crime (non-drug): state property crime rates	MCL associated with 9.2% reduction in rate (b=-0.092, SE= 0.032, p<0.01).	
45.	Hunt 2017	United States Legal regulation of cannabis for recreational use (RCL)	Controlled before-and-after study, 2013;2014 [WA and OR before RCL implementation]	Population-based; Household survey N=5576	*Price of* drugs: consumer-reported price per gram	No statistically significant effects of implementing legal retail cannabis sales in CO and WA on prices paid for recreational or medical purposes, 4-5 months later.	16
46.	Johnson 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1991-2011	Population-based; School-based survey N=715,014	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use among adolescents	MCL associated with decreased odds of past 30-day use (AOR=0.93, 95% CI: 0.86, 0.99). Policy details associated with lower (e.g., years since MCL and liberal provisions) and higher (e.g., voluntary vs. mandatory patient registration) use.	17
					Frequency of use, decriminalized/regulated drug(s): past 30-day heavy use (≥20 times)	MCL not associated with odds of heavy use (AOR=1.00, 95% CI: 0.89, 1.13).	
47.	Jones 2015	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2012; 2014	Unspecified	*Prevalence of use, decriminalized/regulated drug(s)*: THCA-positive meconium specimens from high-risk newborns in Colorado	RCL associated with increase in THCA-positive specimens (from 10.6% to 11.7%) and with increased mean THCA concentrations in positive specimens.	A *
48.	Jones 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2013-2015	Convenience sampling N=1413	*Frequency of use, decriminalized/regulated drug(s)*: Categories from no use to daily use.	No statistically significant difference in use frequency between pre- and post-RCL periods.	10
					Prevalence of use, other drugs or alcohol: Frequency of cannabis use within alcohol use frequency groups	Strength of the relationship between alcohol and cannabis use decreased after RCL (from r=0.54 in Nov 2013 to 0.33 in Mar 2015).	

49.	Kerr DCR 2017	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2012-2016	Population-based; School-based survey N=10,924	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	No significant association between RCL and past 30-day use overall (AOR=1.21, *p*=0.48) but increasing secular trend. RCL associated with increased cannabis use among heavy alcohol users (AOR=1.73, *p*=0.0076).	17
					Prevalence of use, other drugs or alcohol: past 30-day cigarette use	No significant association with RCL.	
					Prevalence of use, other drugs or alcohol: past 30-day heavy alcohol use	No significant association with RCL.	
50.	Kerr WC 2018	United States Legal regulation of cannabis for medical (MCL) and recreational use (RCL)	Repeated cross-sectional study, 1984-2015	Population-based; Household survey N=37,359	*Prevalence of use, decriminalized/regulated drug(s)*: past-year use	No significant association between MCL (home growing or dispensaries) or RCL and past-year use, among both women and men.	17
51.	Kerr DCR 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2008-2016	Population-based; School-based survey N=281,752	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	RCL associated with increased past 30-day use among university students (AOR= 1.29, 95% CI: 1.13, 1.48).	17
					Prevalence of use, other drugs or alcohol: past 30-day tobacco use	RCL associated with decreased tobacco use (AOR= 0.71, *p*=0.0001).	
					Prevalence of use, other drugs or alcohol: past 30-day alcohol use	RCL not associated with alcohol use (*p*=0.59).	
					Prevalence of use, other drugs or alcohol: past 30-day illicit drug use (non-cannabis)	RCL not associated with illicit drug use (*p*=0.78).	
52.	Keyes 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1991-2014	Population-based; School-based survey N=973,089	*Perceived harmfulness of decriminalized/regulated drug(s)*: great or moderate vs. low perceived risk of physical harm due to occasional use	No significant association with MCL in all grades, 10th or 12th, but increased perceived harm in 8th (AOR= 1.21, 95% CI: 1.08, 1.36).	15
					Prevalence of use, decriminalized/regulated drug(s): past 30-day use	Adjusting for perceived harmfulness, significant negative association between	

						MCL and use in 8th grade only (AOR= 0.81, 95% CI: 0.72, 0.92).	
53.	Khatapoush 2004	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1995;1997;1999	Population-based; Household survey N=15,567	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use	No statistically significant change over time in California (MCL state) or other states.	10
					Perceived availability of decriminalized/regulated drug(s)	No statistically significant change over time in California (MCL state) or other states.	
					Prevalence of use, other drugs or alcohol: past-year use of other drugs.	No statistically significant change over time in California (MCL state) or other states.	
54.	Kim, Anderson et al. 2015	United States Cannabis decriminalization	Repeated cross-sectional study, 2008-2009; 2010-2011	Population-based; Admin record data N=2574	*Health services utilization*: emergency department visits for cyclic vomiting	Decriminalization associated with increase in visits (prevalence ratio= 1.92, 95% CI: 1.33, 2.79).	15
55.	Kim, Hall, et al. 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2012-2014	Population-based; Admin record data	*Health services utilization*: cannabis-related emergency department visits	RCL associated with increase in cannabis-related ED visits by Colorado residents (rate ratio; RR=1.46, $p>0.001$) and non-residents (RR=1.17, $p>0.001$).	14
56.	Kim, Santaella et al. 2015	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1999-2011	Population-based; Admin record data	*Prescription drug use*: annual opioid sales in morphine-equivalent doses	Adjusting for increasing secular trend, MCL associated with 1% reduction in opioid sales per year of MCL (b=-0.01, p=0.0016).	A *
57.	Kim 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2004-2013	Population-based; Household survey	*Prevalence of use, other drugs or alcohol*: past-month nonmedical use of prescription opioids	No significant difference in prevalence post-MCL for youth, young adults, or adults 26+.	A *

58.	Kim, Santaella-Tenorio, et al. 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1999-2013	Population-based; Admin record data N=68,394	*Driving under the influence or with detectable concentration, other drugs or alcohol*: positive opioid tests among driver fatalities in motor vehicle accidents	MCL not significantly associated with opioid presence overall, but with reduction among decedents age 24-40 (AOR post-MCL vs. pre=0.50, 95% CI=0.37, 0.67).	17
59.	Kosterman 2016	United States Legal regulation of cannabis for recreational use (RCL)	Interrupted time series study, 1985-2014	Convenience sampling N=395	*Frequency of use, decriminalized/regulated drug(s)*: past-month frequency among WA parents with any past-year use	Frequency of use increased post-RCL (from 4-6 to 10 times/month, $p<0.05$).	8
					Substance use disorder or diagnosed dependence: meets DSM-IV criteria for cannabis use disorder	No statistically significant change post-RCL.	
					Perceived harmfulness of decriminalized/regulated drug(s): approval and perceived harmfulness of cannabis use	Approval increased and perceived harmfulness decreased following RCL ($p<0.05$).	
60.	Larimer 2015	United States Legal regulation of cannabis for recreational use (RCL)	Cohort study	Unspecified N= 1095	*Frequency of use, decriminalized/regulated drug(s)*: # of times used in past month among 12-17 year olds	No significant change associated with RCL.	A *
					Perceived harmfulness of decriminalized/regulated drug(s): perceived risk due to regular and occasional use	Perceived risk from regular use decreased among males but not females (p for interaction=0.017).	
					Perceived availability of decriminalized/regulated drug(s)	No significant change associated with RCL.	
					Prevalence of use, other drugs or alcohol: number of drinks consumed per week.	RCL associated with increased number of drinks per week ($p<0.01$), beyond time trends.	
61.	Liang 2018	United States Legal regulation of cannabis for	Repeated cross-sectional study, 1993-2014	Population-based; Admin record data	*Prescription drug use*: # of filled opioid prescriptions, dosage of filled prescriptions in morphine-equivalent doses, and related Medicaid spending	MCL not associated not associated with Schedule II opioid use.	15

		medical use (MCL)			for Schedule II opioids (e.g., hydrocodone, oxycodone).		
					Prescription drug use: as above, for Schedule III opioids (e.g. codeine).	MCL associated with reductions in Schedule III opioid prescriptions (-29.6%, 95% CI: -2.4%, -56.7%), doses, and spending.	
62.	Livingston 2017	United States Legal regulation of cannabis for recreational use (RCL)	Interrupted time series study, 2000-2015	Population-based; Admin record data	*Overdose or poisoning*, *other drugs*: deaths with ICD-10 code indicating opioid poisoning	RCL associated with reduction in opioid poisoning deaths, adjusting for comparison state trends (-0.68 deaths per month, 95% CI: -1.35, -0.03).	16
63.	Lo 2015	United States Legal regulation of cannabis for recreational use (RCL)	Uncontrolled before-and-after study, 2013-2015	Convenience sampling N= 2186	*Prevalence of use, decriminalized/regulated drug(s)*: positive cannabinoid screen among high-risk opioid therapy patients	RCL associated with increase in positive THC screens (30% of visits to 36%, p=0.0003).	A *
					Opioid therapy compliance: non-compliance (illicit opioids use or non-use of prescription)	RCL not associated with compliance.	
64.	Lynne-Landsman 2013	United States Legal regulation of cannabis for medical use (MCL)	Switching replications study, 2003-2011	Population-based; School-based survey	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime and past-month	MCL not associated with use (1 of 20 planned comparisons significant, expected by chance alone).	15
					Frequency of use, decriminalized/legalized drug(s): daily or weekly use among lifetime users	MCL not associated with frequency (1 of 20 planned comparisons significant, expected by chance alone).	
65.	Martins 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2004-2013	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use	MCL associated with greater past-month use among adults 26+ (AOR=1.24, 95% CI: 1.16, 1.31), but not among ages 12-17 or 18-25.	16
					Perceived availability of decriminalized/regulated drug(s): fairly or very easy to obtain vs. other	MCL associated with greater availability among adults 26+ (AOR=1.11, 95% CI: 1.07, 1.15), but not among ages 12-17 or 18-25.	
66.	Mason 2016	United States	Controlled before-and-after study,	Convenience sampling	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	Post-RCL subject group not significantly associated with use (AOR= 2.80, 95% CI: 0.94–8.34).	13

		Legal regulation of cannabis for recreational use (RCL)	2010-2013 [students completed follow up before RCL]	N= 238	*Prevalence of use, other drugs or alcohol*: use of cigarettes or alcohol vs. cannabis (indicating substitution effect)	Post-RCL subject group significantly less likely to use cigarettes or alcohol versus cannabis (p<0.05).	
67.	Masten 2014	United States Legal regulation of cannabis for medical use (MCL)	Interrupted time series study, 1992-2009	Population-based; Admin record data N=245,495	*Driving under the influence or with detectable concentration, decriminalized/regulated drug(s)*: proportion of fatal-crash-involved drivers (decedents and survivors) who test cannabinoid-positive	Significant policy effect found in 3 of 12 MCL states, with increases of 2.1-6.0 percentage points among all drivers and 4.6-9.6 among fatally injured drivers in CA, HI, and OR (adjusted for changes in testing and national trends). These were step increases rather than upward trends.	14
68.	Mauro 2019	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2004-2013	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use	No significant effect of MCL among men or women aged 12-17 or 18-25, but significant increases for ages 26+ among men (+1.7 percentage points, $p < 0.001$) and women (+ 1.1%, $p = 0.013$).	16
					Frequency of use, decriminalized/legalized drug(s): daily use among past-year users	Significant effect of MCL among men aged 18-25 (+ 2.4%, $p = 0.047$), and both men and women age 26+ (men + 2.8%, $p = 0.014$; women + 3.4 %, $p = 0.003$).	
					Substance use disorder or diagnosed dependence: met DSM-IV criteria for cannabis use disorder	No statistically significant effect of MCL for any age-gender group.	
69.	Mauro 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2004-2013	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use	MCL associated with increased use among adults 26-39 [AOR=1.2, 95% CI: 1.1, 1.3], 40-64 [AOR=1.4, 95% CI: 1.2, 1.5], and 65+ [AOR=2.6, 95% CI: 1.5, 4.6].	A *
					Perceived availability of decriminalized/regulated drug(s)	MCL associated with increased perceived accessibility of cannabis, which partially mediated association between MCL and use.	

70.	Merker 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2012-2017	Convenience sampling N=302	*Prevalence of use, decriminalized/regulated drug(s)*: current use among Inflammatory Bowel Disease patients	Increase in use post-MCL (12.3% to 22.8% of patients, p=0.0008), but no significant increase in reported medical use.	12
71.	Miech 2015	United States Cannabis decriminalization	Repeated cross-sectional study, 2007-2013	Population-based; School-based survey N=320,809	*Prevalence of use, decriminalized/regulated drug(s)*: lifetime, past-year, past 30-day use	[Decriminalization in CA in 2010] 8th and 10th grades: differences in use between CA residents and other states limited to select years, not sustained over time. 12th grade: past-year use higher among CA residents vs. other states in 2010-2013.	12
					Perceived harmfulness of decriminalized/regulated drug(s): great vs. less-than-great perceived risk of regular use	8th and 10th grades: only one significant difference (8th grade in 2012). 12th grade: lower perceived risk among CA residents vs. other states in 2012-2013.	
					Perceived availability of decriminalized/regulated drug(s): easy vs. less-than-easy perceived access	8th and 10th grades: only one significant difference (8th grade in 2011). 12th grade: higher perceived availability among CA residents vs. other states in 2012 only.	
					Attitudes towards use, decriminalized/regulated drug(s): strong disapproval of adult use vs. other	8th and 10th grades: only one significant difference (8th grade in 2012). 12th grade: less strong disapproval among CA residents vs. other states in 2012-2013	
					Attitudes towards use, decriminalized/regulated drug(s): definitely or probably expect to use five years from present (only 12th graders)	12th grade: greater expected use among CA residents vs. other states in 2012-2013.	
72.	Miller 2017	United States Legal regulation of cannabis for	Repeated cross-sectional study, 2005-2015	Population-based; School-based survey	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	RCL associated with increase of 2.0-3.5 percentage points (12-22%), adjusting for linear secular trend [passage of RCL, additional effect of legal store openings not statistically significant].	16

		recreational use (RCL)		N=13,335	*Frequency of use, decriminalized/legalized drug(s)*: past 30-day frequency	RCL associated with increase of 0.5 days per month, adjusting for linear secular trend [passage of RCL, additional effect of legal store openings not significant].	
					Prevalence of use, other drugs or alcohol	RCL passage not associated with changes. In 2015 (legal stores), decrease in tobacco and increase in other illegal drugs, but findings not robust.	
73.	Model 1993	United States Cannabis decriminalizatio n	Controlled before-and-after study, 1975-1978 [States that did not not decriminalize]	Population-based; Admin record data	*Health services utilization:* non-cannabis drug mentions at ER visits	Decriminalization associated with 12% fewer drug mentions at ER visits (b=-0.133, SE=0.053, p<0.01), with stronger effects in initial years.	16
					Health services utilization: cannabis drug mentions at ER visits	Decriminalization associated with 64% more cannabis mentions (b=-0.642, SE=0.112, p<0.01), with stronger effects in later years.	
74.	Morris 2014	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1990-2006	Population-based; Admin record data	*Crime (non-drug)*: rates of violent crime (homicide, rape, robbery, assault)	MCL associated with 2.4% reduction in homicide rate (p<0.01).	16
					Crime (non-drug): rates of property crime (burglary, larceny, auto theft)	No significant association between MCL and property crimes.	
75.	Nappe 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study. 2010-2015	Population-based; Admin record data N=5231 exposures	*Overdose or poisoning, decriminalized/regulated drug*: cannabis exposures reported to the National Poison Data System in Colorado	RCL associated with increase in cannabis exposures (86 in 2011 to 231 in 2015).	A *
76.	Onders 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study 2000-2013	Population-based; Admin record data N= 1969 exposures	*Overdose or poisoning, decriminalized/regulated drug*: cannabis exposures among children <6 reported to the National Poison Data System	MCL associated with increased exposures (rate ratio for post vs. pre-MCL=2.25, 95% CI: 1.45, 3.51). Exposures peaked in the year following RCL.	13

77.	Pacula 2010	United States Cannabis decriminalization and legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1987-2003	Convenience sampling	*Price of drugs*: price per gram paid at the last transaction among arrestees	Decriminalization and MCL associated with higher prices (indicating increased demand). .	13
78.	Pacula 2015	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1992-2011 and 1997-2011 [State-years without MML]	Population-based; Admin record data N=973 Household survey N=112,926	*Addiction treatment utilization*: number of treatment admissions with cannabis as primary indication	MCL associated with 14% reduction in cannabis admissions (difference-in-difference = -0.136, SE=0.067, $p<0.05$). Larger effect size for non-criminal justice referrals. Partially offset by increase in admissions associated with dispensaries.	15
					Prevalence of use, decriminalized/regulated drug(s): past 30-day use	No overall significant association between MCL and use.	
					Frequency of use, decriminalized/regulated drug(s): heavy use (>20 of last 30 days), # of days of use in past 30	No significant association between MCL and frequency of use.	
79.	Parnes 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2013-2015	Convenience sampling N=5241	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	No significant association between RCL and use among CO undergraduates.	12
80.	Phillips 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2011-2014	Population-based; Admin record data N=188,266	*Overdose or poisoning, other drugs*: state-level age-adjusted opioid-related mortality rate	MCL associated with 21.7% increase in opioid-related mortality ($p < 0.0001$) but interacted with prescription drug monitoring programs such that rates decreased in states with both policies.	15

81.	Plunk 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2000-2014	Population-based; Household survey N=5,483,715	*Educational outcomes*: high school non-completion	High-school age exposure to MCL not associated with non-completion overall, but with increase in probability of failing to complete conditioned on completing the 12th grade (AOR=1.11, 95% CI: 1.05, 1.17).	16
					Educational outcomes: college non-enrollment among high school graduates	High-school age exposure to MCL associated with college non-enrollment (AOR = 1.09, 95% CI: 1.04, 1.14). Dose-response relationship with years of exposure.	
					Educational outcomes: college non-completion among college entrants aged 25+	High-school age exposure to MCL associated with increase in probability of degree non-completion (AOR = 1.03, 95% CI: 1.01, 1.06).	
					Prevalence of use, decriminalized/regulated drug(s): past-month use	High-school age exposure to MCL not significantly associated with use.	
					Frequency of use, decriminalized/regulated drug(s): daily use (40 or more times/month)	High-school age exposure to MCL not significantly associated with use overall, but among 12th graders only (AOR=1.62, 95% CI: 1.04, 2.54).	
82.	Pollini 2015	United States Cannabis decriminalization	Repeated cross-sectional study Roadside Survey, 2010; 2012 Fatality Analysis Reporting System, 2008-2012	Population-based; Admin record data Roadside Survey, N=379-515 FARS, N=2860	*Driving under the influence or with detectable concentration, decriminalized/regulated drug(s)*: proportion of drivers testing THC-positive in roadside survey	No statistically significant change in THC-positivity following decriminalization.	13
					Driving under the influence or with detectable concentration, decriminalized/regulated drug(s): presence of cannabinoids among fatally injured drivers	Increase in cannabinoid prevalence in 2012 as compared to the pre-decriminalization period (AOR = 1.67, 95% CI: 1.28, 2.18).	
83.	Powell 2018	United States Legal regulation of cannabis for	Repeated cross-sectional study, 1999-2013	Population-based; Admin record data	*Overdose or poisoning, other drugs*: deaths related to prescription opioids and heroin	Existence of MCL not significantly associated with overdose mortality (only active dispensaries associated with reduction in deaths).	15

		medical use (MCL)			*Addiction treatment utilization*: number of treatment episodes related to pain reliever misuse	Existence of MCL not significantly associated with overdose mortality (only active dispensaries associated with reduction).	
					Prevalence of use, other drugs or alcohol: self-reported nonmedical use of pain relievers (National Survey on Drug Use and Health)	No statistically significant association between MCL and use.	
					Prescription drug use: morphine-equivalent doses of opioids distributed to legal medical markets	No statistically significant association between MCL and use over full time period.	
84.	Prue 2014	United States Peyote decriminalization	Repeated cross-sectional study, 1985-2010	Population-based; Household survey N=886,088	*Prevalence of use, decriminalized/regulated drug(s)*: peyote use	Use among American Indians increased from 1% in 1994 (year of American Indian Religious Freedom Act) to 10% in 1999. Use among non-American Indians remained steady <2%.	7
					Age of first use, decriminalized/regulated drug: age at first use of peyote	No significant change in age at first use among American Indians or non-American Indians following decriminalization.	
85.	Ramirez 2017	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2014;2015	Unspecified N=2400	*Driving under the influence or with detectable concentration, decriminalized/regulated drug(s)*: daytime prevalence of cannabis-positive drivers	Statistically significant increase post-RCL (7.8% to 18.9% after one year).	A *
86.	Reith 2015	International Cannabis decriminalization	Controlled before-and-after study, 1980-2012 [Country-years without decriminalization]	Unspecified N=102 countries	*Actual availability of decriminalized/regulated drug(s)*: kg of cannabis seized and number of plants eradicated divided by population in millions	Decriminalization associated with increased plant eradication (p<0.05), but not seizures.	10

87.	Rodriguez 2016	United States Legal regulation of cannabis for recreational use (RCL)	Cohort study, 2009-2015	Convenience sampling N= 1698	*Prevalence of use, decriminalized/regulated drug(s)*: positive urine toxicology among pregnant young women *Disclosure of use, decriminalized/regulated drug(s)*: agreement between self-reported use and urine toxicology	Increased cannabis-positive screens post-RCL (16.2 to 20.2%, p=0.048). Improved agreement post-RCL (kappa = 0.504 vs. 0.191).	A *
88.	Rohda 2017	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2011-2016	Population-based; Admin record data N=29,044 exposures	*Overdose or poisoning, other drugs:* synthetic cannabinoid receptor agonist (SCRA) exposures reported to poison control centers	SCRA exposures declined in WA (175 to 28, p=0.017*)* and OR (39 to 14, p=0.012) following RCL, but not in all RCL states combined (p=0.41).	A *
89.	Rusby 2018	United States Legal regulation of cannabis for recreational use (RCL)	Cohort study, 2014-2016	Population-based; School-based survey N=444	*Prevalence of use, decriminalized/regulated drug(s)*: past 30-day use	RCL not significantly associated with use.	12
					Frequency of use, decriminalized/regulated drug(s): number of days use in past 30	RCL associated with greater number of days of use (ARR=1.26, 95% CI: 1.10, 1.45).	
					Attitudes towards use, decriminalized/regulated drug(s): willingness and intention to use (any vs. none)	RCL not significantly associated with willingness or intention to use.	
90.	Sabia 2017	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study. 1990-2012 [State-years without MML]	Population-based; Household survey N=5,428,399	*BMI*	MCL associated with reduction in BMI (adjusted difference-in-differences for contemporaneous effect = -0.084, SE=0.034, p<0.05).	16

91.	Santaella-Tenorio 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1985-2014	Population-based; Admin record data N=1,220,610 deaths	*Accidents, motor vehicle*: age-adjusted traffic fatality rates (all road users)	MCL associated with 10.8% reduction in traffic fatality rates (95% CI = 9.0%, 12.5%).	17
92.	Schmidt 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2014-2013	Population-based; Household survey N=450,300	*Perceived harmfulness of decriminalized/regulated drug(s)*: belief that weekly/ monthly use is "not a great risk"	Living in MCL state not associated with perceived harmfulness. (Secular trend towards greater permissiveness for all outcomes, but no significant effects MCL after control for state fixed effects).	17
					Attitudes towards use, decriminalized/regulated drug(s): belief that parents/ friends don't disapprove of trying cannabis	Living in MCL state not associated with perceived attitudes.	
					Perceived availability of decriminalized/regulated drug(s): belief that cannabis is fairly or very easy to obtain	Living in MCL state not associated with perceived availability.	
93.	Sevigny 2014	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1990-2010 [State-years without MCL]	Convenience sampling N=39,157	*Potency of decriminalized/regulated drug(s)*: concentration of THC in cannabis seized by law enforcement	MCL not significantly associated with potency (adjusted difference in %THC=0.53, p>0.05), but legal dispensaries associated with higher potency.	16
94.	Shah 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2006-2014	Population-based; Admin record data	*Prescription drug use*: opioid use among commercially insured population.	MCL associated with lower odds of any opioid use (AOR=0.95, 95% CI: 0.94, 0.96), chronic opioid use (AOR=0.93, 95% CI: 0.91, 0.95) and high-risk opioid use (AOR=0.98, 95% CI: 0.96, 0.99).	A *
95.	Shepard 2016	United States Legal regulation of cannabis for	Repeated cross-sectional study, 1997-2009	Population-based; Admin record data	*Crime (non-drug)*: property crime (burglary, larceny, and vehicle theft arrests per 1000 residents)	MCL not associated with property crime.	12

		medical use (MCL)			*Crime (non-drug)*: violent crime (assault, homicide, rape, and robbery arrests)	MCL associated with reduction in violent crimes (-0.254 crimes per 1000 residents, SE=0.089, $p<0.05$).	
96.	Shi 2017	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1997-2014	Population-based; Admin record data N= 0.4M to 2.2M records	*Health services utilization*: annual hospitalization rate for cannabis dependence or abuse (ICD-9)	MCL not significantly associated with hospitalizations.	16
					Overdose or poisoning, other drugs: hospitalization rate for opioid pain reliever overdose	MCL associated with reduction in hospitalizations related to opioid overdose (adjusted prevalence difference = −0.13, 95% CI: −0.25, −0.018).	
					Health services utilization: hospitalization rate for opioid dependence or abuse	MCL associated with reduction in hospitalizations related to opioid dependence (adjusted prevalence difference = −0.23, 95% CI: −0.41, −0.068).	
97.	Sokoya 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2012-2015	Convenience sampling N=2164	*Accidents, other*: types of bony facial trauma among patients presenting to two CO hospitals	RCL not associated with significant difference in mechanisms of facial fracture.	12
98.	Steinemann 2018	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 1993-2000; 2001-2015	Population-based; Admin record data N=1578	*Driving under the influence or with detectable concentration, decriminalized/regulated drug(s)*: proportion of fatally injured drivers who were cannabis-positive in HI	MCL associated with increase in THC positivity (5.5% in 1993-2000; 16.3% in 2011-2015, $p<0.001$).	12
					Driving under the influence or with detectable concentration, other drugs or alcohol: proportion of fatally injured drivers who were methamphetamine- or alcohol-positive	MCL not associated with significant difference in positivity rates.	
99.	Stolzenberg 2016	United States Legal regulation of cannabis for	Repeated cross-sectional study, 2002-2003; 2004-2005;	Population-based; School-based survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use among adolescents	Living in MCL state associated with greater use (adjusted coefficient=0.861, SE=0.298, $p<0.01$).	14

		medical use (MCL)	2006-2007; 2008-2009; 2010-2011		*Prevalence of use, other drugs or alcohol*: past-month non-cannabis illicit drug use	No significant association between living in MCL state and use.	
100.	Straub 2017	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2011-2012; 2012-2014; 2014-2016	Population-based; Admin record data N=25,763	*Prevalence of use, decriminalized/regulated drug(s)*: positive urine screen or documented use during pregnancy	No significant change in cannabis-positivity post-RCL.	A *
101.	Suggs 1981	United States Cannabis decriminalization	Uncontrolled before-and-after study, 1977-1979	Population-based; Admin record data N=719	*Criminal justice involvement*: possession arrests and citations for adults and minors in two NE cities	No significant difference in mean monthly arrests following decriminalization.	12
					Criminal justice involvement: possession prosecutions for adults and minors	Significant increase in prosecutions following decriminalization among minors (from mean of 1.92 to 5.75/month, $p<0.05$), but not adults (26.71 to 36.25, $p>0.05$).	
					Criminal justice involvement: defendants representing themselves	Significant increase following decriminalization (from 18.07 to 30.75/month, $p<0.05$).	
					Criminal justice involvement: case dismissal before trial	Significant decrease following decriminalization (from 9.14 to 2.37/month, $p<0.001$).	
102.	Ullman 2017	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 1992-2012 [State-years without MCL]	Population-based; Household survey N=757,677	*Workplace absence*: self-reported absence for medical reasons in the past week	MCL associated with lower probability of absence (b= -0.0013, SE=0.0007, $p<0.10$), with effects concentrated in loosely regulated MCL states, men and people aged 30-49.	16
103.	Urfer 2014	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2011-2014	Convenience sampling N=12,082	*Driving under the influence or with detectable concentration, decriminalized/regulated drug(s)*: Proportion of THC-positive blood samples collected from CO drivers	Increase in THC-positive screens from 2011 (28%) to 2012 (59%) to 2013 (65%), p=0.001. No significant change in first two months of legal cannabis sales.	11

104.	Wagner 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2012-2015	Convenience sampling N=34	*Physical health consequences of use, decriminalized/ regulated drug(s)*: Reversible Cerebral Vasoconstriction Syndrome (RCVS) cases secondary to cannabis	Of 18 RCVS cases before RCL, 1 patient used cannabis. Of 16 cases after RCL, 5 used cannabis. No statistical tests reported.	A *
105.	Wall 2016	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2002-2010	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use among adolescents	*Reanalysis of Stolzenberg 2016 (#99) After appropriate adjustment for pre-MCL prevalence, MCL not associated with adolescent use (b = 0.33%; SE= 0.29%, p = 0.25).	18
106.	Wall 2011	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2002-2008	Population-based; Household survey N=23,300	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use among adolescents	Use was significantly higher in MCL states (average of 8.7% vs. 6.9%) but among states that passed MCL from 2004-2008, baseline use (pre-MCL) was already higher than in non-MCL states.	13
					Perceived harmfulness of decriminalized/regulated drug(s): perceived "great risk" of using monthly or more	Perceived harmfulness was significantly lower in MCL states each year (average of 8.7% vs. 6.9%), but among states that passed MCL, baseline perceived risk (pre-MCL) was already lower than non-MCL states.	
107.	Wang 2018	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2005-2015	Population-based; Admin record data N=4202	*Health services utilization:* emergency or urgent care visits with a cannabis-related discharge code or THC-positive urine toxicology among adolescents	Cannabis-related visits increased from 1.8 per 1000 visits in 2009 to 4.9 per 1000 in 2015, following RCL (p<0.0001).	11
108.	Wang 2017	United States Legal regulation of cannabis for medical (MCL) and recreational use (RCL)	Repeated cross-sectional study, 2000-2015	Population-based; Admin record data N=7,432,254	*Health services utilization*: hospitalizations with cannabis-related billing codes	Hospitalizations increased from 274 per 100,000 in 2000 (prior to MCL) to 593 in 2015 (after RCL). Statistically significant 25% increase in 2014 (RCL implementation with legal sales).	14
					Health services utilization: emergency department visits with cannabis-related billing codes	ED visits increased from 313 per 100,000 in 2011 to 478 in 2015, with highest rate in 2014 (554). Statistically significant increase in 2014 (p=0.0005).	

					Overdose or poisoning, decriminalized/regulated drug: cannabis exposure calls to CO poison control centers	Poison control calls increased by 79.9% following RCL implementation in 2014, from 123 to 221 (p=0.0001).	
109.	Wang 2016	United States Legal regulation of cannabis for recreational use (RCL)	Repeated cross-sectional study, 2009-2015	Population-based; Admin record data N=62	*Overdose or poisoning, decriminalized/regulated drug*: children's hospital visits related to cannabis exposure	RCL associated with increased cannabis-related visits (1.2 per 100,000 in 2012-2013 to 2.3 per 100,000 in 2014-2015, p=0.02).	13
					Overdose or poisoning, decriminalized/regulated drug: poison control calls related to cannabis exposure among children 0-9	RCL associated with increased cannabis-related calls in CO (2.7 per 100,000 in 2012-2013 to 5.3 per 100,000 in 2014-2015, p<0.001) and in comparison to rest of the US (34% increase in CO vs. 19% increase in remainder of US, p=0.04).	
110.	Wen 2018	United States Legal regulation of cannabis for medical (MCL) and recreational use (RCL)	Controlled before-and-after study, 2011-2016 [States without MCL or RCL over the study period]	Population-based; Admin record data N=1059 state-quarter observations	*Prescription drug use*: number of opioid prescriptions covered by Medicaid on a quarterly, per-1000-Medicaid-enrollee basis in each state	MCL and RCL associated with reductions in prescriptions of 5.88% (95% CI: -11.55%, -0.21%) and 6.38% (95% CI: -12.20, -0.56%) respectively.	17
111.	Wen 2015	United States Legal regulation of cannabis for medical use (MCL)	Repeated cross-sectional study, 2004-2012	Population-based; Household survey N=593,400	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use; past-year initiation	MCL associated with increase in past-month use among adults 21+ (+1.32%, p<0.05) but not ages 12-20. MCL associated with increased risk of past-year initiation among ages 12-20 only (+0.32%, p<0.05).	17
					Frequency of use, decriminalized/regulated drug(s): daily/almost daily use (>20 days in month); # of days among past-month users	MCL associated with increase in (almost) daily use among adults 21+ (+0.58%, p<0.05) but not ages 12-20.	
					Prevalence of use, other drugs or alcohol: # of drinks in past month; # of binge drinking days; met DSM-IV alcohol use disorder criteria in past year; both cannabis use and	MCL associated with frequency of binge drinking (+0.16 days, p<0.05) and past-month use of both cannabis and alcohol (+1.44%, p<0.01) among adults 21+. No associations with alcohol use among ages	

					binge drinking in past month; use of cannabis and alcohol on same occasion in past month	12-20, or with alcohol use disorders.	
					Prevalence of use, other drugs or alcohol; past-year use of non-medical prescription painkillers, heroin, cocaine	No immediate or lagged associations between MCL and illicit drug use in either age group.	
					Substance use disorder or diagnosed dependence: met DSM-IV cannabis use disorder criteria in past year	Lagged associations between MCL and cannabis use disorder among adults 21+ (+0.25% at 1 year, $p<0.05$) but not among ages 12-20.	
112.	Wen 2019	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 2004-2012 [Non-MCL states]	Population-based; Household survey N=388,200	*Perceived availability of decriminalized/regulated drug(s)*: (very) easy to obtain, among adolescents and young adults	No significant association between MCL and perceived availability among ages 12-17 or 18-25.	16
					Attitudes towards use, decriminalized/regulated drug(s): acceptance of use by other adolescents/young adults; perceived parental acceptance (ages 12-17 only)	MCL significantly associated with lower perceived parental acceptance among ages 12-17 (-0.37%, 95% CI: -0.72, -0.03).	
					Perceived harmfulness of decriminalized/regulated drug(s): no/low health risk of using once or twice per week	MCL significantly associated with higher perceived harmlessness among ages 18-25 only (+4.72%, 95% CI: 0.15, 9.28).	
113.	Williams 2017	United States Legal regulation of cannabis for medical use (MCL)	Controlled before-and-after study, 2004-2013 [State-years without MCL]	Population-based; Household survey	*Prevalence of use, decriminalized/regulated drug(s)*: past-month use	Only loosely regulated MCL associated with higher use, among adults 26+ only (adjusted prevalence difference = +1.46%, 95% CI: 0.33, 2.58).	15
					Frequency of use, decriminalized/legalized drug(s): heavy use in past year (>300 days), among past-year users	Tightly regulated MCL associated with less heavy use, among ages 12-17 only (adjusted prevalence difference = -3.67%, 95% CI: -7.24, -0.11).	
					Substance use disorder or diagnosed dependence met DSM-IV criteria for cannabis use disorder	Loosely regulated MCL associated with lower prevalence of cannabis use disorder, among ages 18-25 only (-0.80%, 95% CI: -1.45, -0.16).	

114.	Williams 2014	Australia Cannabis decriminalization	Controlled before-and-after study, 1998;2001;2004;2007;2010 [state-years without decriminalization)	Population-based; Household survey N=39,087	*Age of first use, decriminalized/regulated drug(s)*: age at initiation	Decriminalization not associated with hazard of cannabis uptake overall but interacts with age such that minors under decriminalization have a 12% higher hazard rate of uptake while adults under decriminalization have an 11% lower hazard rate of uptake ($p<0.01$).	18

*A = abstract; no quality appraisal performed.

Supplementary Table 2. Direction of effect of decriminalization or legal regulation, by outcome category

Outcomes	**# of outcomes**	**# reporting beneficial effects**	**# reporting harmful effects**	**# reporting mixed effects**	**# reporting no effect**	**Article #** (See Included Studies)	**Average quality** (of 18, excluding abstracts)
Accidents, motor vehicle	4	1	1	1	1	3, 8, 43, 91	14.3
Accidents, other	4	0	2	1	1	5, 11, 14, 97	12.7
Addiction treatment utilization	4	0	1	1	2	1, 25, 78, 83	14.5
Age of first use, decriminalized/regulated drug	3	0	0	1	2	23, 84, 114	12.7
Attitudes towards use, decriminalized/regulated drug	6	0	1	3	2	27, 71, 89, 92, 112	14.0
Availability of decriminalized/regulated drug	3	0	0	1	2	6, 31, 86	13.3
BMI	1	1	0	0	0	90	16.0
Costs, health care	3	2	1	0	0	15, 17, 33	15.7
Costs, other	3	3	0	0	0	33	13.0
Crime (non-drug)	9	5	0	0	4	7, 44, 74, 95	14.0
Criminal justice involvement	8	1	3	1	3	7, 25, 36, 101	13.8
Disclosure of use to healthcare provider	1	1	0	0	0	87	N/A
Educational outcomes	3	0	2	1	0	81	16.0
Frequency of use, decriminalized/regulated drug	16	1	3	4	8	6, 18, 30, 36, 46, 47, 59, 60, 64, 69, 72, 78, 81, 89, 111, 113	14.4
Health services utilization (excluding addictions treatment)	12	2	6	1	3	13, 19, 34, 54, 55, 73, 96, 107, 108	13.8
Driving under the influence or with detectable concentrations of the decriminalized/regulated drug	8	0	5	1	2	26, 42, 67, 82, 85, 98, 103	12.0

Outcomes	Number of outcomes	# reporting beneficial effects	# reporting harmful effects	# reporting mixed effects	# reporting no effect	Article # (See Included Studies)	Average quality score
Driving under the influence or with detectable concentrations, other drug/alcohol	3	0	0	1	2	42, 58, 98	14.5
Mental health conditions, suicide, or self-harm	4	0	1	2	1	4, 29, 30, 37	15.0
Mode of use, decriminalized/regulated drug	1	0	0	0	1	39	13.0
Opioid therapy compliance	1	0	0	0	1	63	N/A
Overdose or poisoning (incl. unintentional exposures) decriminalized/regulated drug	7	0	7	0	0	10, 12, 75, 76, 108, 109	13.3
Overdose or poisoning, other drugs	7	4	0	2	1	9, 10, 62, 80, 83, 88, 96	15.6
Perceived availability, decriminalized/regulated drug	9	0	2	2	5	27, 39, 53, 60, 65, 68, 71, 92, 112	14.1
Perceived harmfulness, decriminalized/regulated drug	12	1	2	6	3	18, 22, 30, 38, 39, 52, 59, 60, 71, 92, 106, 112	13.9
Physical health consequences of use, decriminalized/regulated drug	1	0	0	0	1	104	N/A
Potency, decriminalized/regulated drug	1	0	0	0	1	93	16.0
Prescription drug use (medical use)	9	6	0	1	2	15, 16, 17, 56, 61, 83, 94, 110	16.3
Prevalence of use, decriminalized/regulated drug	50	2	13	11	24	1, 2, 6, 18, 20, 21, 22, 24, 27, 28, 34, 35, 36, 38, 39, 40, 41, 46, 48, 49, 50, 51, 52, 53, 63, 64, 65, 66, 68, 69, 70, 71, 72, 78, 79, 81, 84, 87, 89, 99, 100, 105, 106, 111, 113	14.6

Outcomes	Number of outcomes	# reporting beneficial effects	# reporting harmful effects	# reporting mixed effects	# reporting no effect	Article # (See Included Studies)	Average quality score
Prevalence or frequency of use, other drugs/alcohol	21	2	2	6	11	18, 21, 35, 47, 49, 50, 53, 57, 60, 66, 72, 83, 99, 111	15.6
Price of drugs	5	0	1	1	3	3, 31, 32, 45, 77	14.0
Substance use disorder or diagnosed dependence	5	0	1	2	2	40, 59, 69, 111, 113	14.6
Workplace absence	1	1	0	0	0	102	16.0

Appendix A: Search Strategy and Results

Database: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946-Present>
Search Strategy:
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1 ((Marijuana or marihuana or cannabis or cannabinoid* or psychoactive product* or psychoactive substances* or narcotic*) adj5 (Legaliz* or legalis* or decriminal* or depenaliz* or depenalis* or deregulat* or liberaliz* or liberalis*)).tw,kf.
2 ((marijuana or marihuana or cannabis or cannabinoid*) adj1 (policy or policies or law or laws or licens* or legislation or dispensar* or store or stores or regulat* or recreational or medical or medicinal or nonmedical or legal*)).tw,kf.
3 (legal high or legal highs).tw,kf.
4 Psychoactive Substances Act.tw,kf.
5 2 or 3 or 4
6 new psychoactive product*.tw,kf.
7 novel psychoactive product*.tw,kf.
8 novel psychoactive substance*.tw,kf.
9 new psychoactive substance*.tw,kf.
10 novel psychoactive drug*.tw,kf.
11 new psychoactive substances*.tw,kf.
12 Designer Drugs/sd [Supply & Distribution]
13 Medical Marijuana/sd [Supply & Distribution]
14 exp Street Drugs/lj, sd [Legislation & Jurisprudence, Supply & Distribution]
15 Marijuana Smoking/lj [Legislation & Jurisprudence]
16 Drug Users/lj, sn [Legislation & Jurisprudence, Statistics & Numerical Data]
17 "Drug and Narcotic Control"/lj [Legislation & Jurisprudence]
18 or/6-17
19 (Legal* or decriminal* or depenaliz* or depenalis* or deregulat* or liberaliz* or liberalis* or policy or policies or law or laws or licens* or legislation or regulat*).ti.
20 18 and 19
21 5 or 20
22 limit 21 to (clinical study or clinical trial, all or comparative study or evaluation studies or meta analysis or multicenter study or observational study or pragmatic clinical trial or systematic reviews or validation studies)
23 Epidemiologic studies/
24 exp case control studies/
25 exp cohort studies/
26 Case control.tw.
27 (cohort adj (study or studies)).tw.
28 Cohort analy$.tw.
29 (Follow up adj (study or studies)).tw.
30 (observational adj (study or studies)).tw.
31 Longitudinal.tw.
32 Retrospective.tw.
33 Cross sectional.tw.
34 Cross-sectional studies/

Appendix A: Search Strategy and Results

35 or/23-34 [Observational Studies search filter used by SIGN (Scottish Intercollegiate Guidelines Network http://www.sign.ac.uk/methodology/filters.html#obs]
36 21 and 35
37 exp Epidemiologic Methods/
38 amphetamine-related disorders/ep or cocaine-related disorders/ep or drug overdose/ep or inhalant abuse/ep or marijuana abuse/ep or exp opioid-related disorders/ep or phencyclidine abuse/ep or psychoses, substance-induced/ep or substance abuse, intravenous/ep
39 Prevalence/
40 Incidence/ or incidence.ti,ab,kw.
41 (harm or harms).tw,kf.
42 ("marijuana use" or "marijuana availability" or "cannabis use" or cannabis availability or "drug use").tw,kf.
43 or/37-42
44 21 and 43
45 1 or 22 or 36 or 44
46 45 not (exp animals/ not humans.sh.)
47 limit 46 to (comment or editorial or letter)
48 46 not 47
49 limit 48 to yr="1970 -Current"

Database	**Number of Results**
Medline (OVID)	2041
Embase (OVID)	1453
PsycINFO (OVID)	1393
Web of Science: Science Citation Index Social Sciences Citation Index Conference Proceedings Citation Index- Science Conference Proceedings Citation Index- Social Science & Humanities	1358
Criminal Justice Abstracts (EBSCO)	1074
ProQuest Databases: Applied Social Sciences Index & Abstracts (ASSIA), International Bibliography of the Social Sciences (IBSS), PAIS Index, Policy File Index, Sociological Abstracts	910
Total Number of Results	**8229**
Total number of results after duplicates removed in EndNote	**4860**

Appendix B: Quality Appraisal Checklist

Adapted from: Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52(6):377-384.

1. Is the hypothesis/aim/objective of the study clearly described?

☐ Yes (1)

☐ No (0)

2. Are the main outcomes to be measured clearly described in the Introduction or Methods section? *If the main outcomes are first mentioned in the Results section, the question should be answered no.*

☐ Yes (1)

☐ No (0)

3. Are the characteristics of the individuals included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given.

☐ Yes (1)

☐ No (0)

4. Are the interventions of interest clearly described?

☐ Yes (1)

☐ No (0)

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?

☐ Yes (2)

☐ Partially (1)

☐ No (0)

6. Are the main findings of the study clearly described? *Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).*

☐ Yes (1)

☐ No (0)

7. Does the study provide estimates of the random variability in the data for the main outcome *(e.g., IQR, standard deviation, confidence interval, etc.)?*

☐ Yes (1)

☐ No (0)

☐ N/A [there is no variability because data come from the entire population] (1)

Appendix B: Quality Appraisal Checklist

8. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001? (*Confidence intervals are acceptable in place of p-values*)

□ Yes (1)

□ No (0)

9. Were the subjects that were asked to participate in the study representative of the entire population from which they were recruited? *The study must identify the source population for participants and describe how they were selected. Participants would be representative if they comprised the entire source population or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

10. Were those subjects who agreed to participate representative of the entire population from which they were recruited? *The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

11. If any of the results of the study were based on "data dredging", was this made clear? *Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

12. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of participants, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? *Where follow-up was the same for all study participants the answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.*

□ Yes or N/A (1)

□ No (0)

□ Unable to determine (0)

13. Were the statistical tests used to assess the main outcomes appropriate? *The statistical techniques used must be appropriate to the data. For example non- parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data*

Appendix B: Quality Appraisal Checklist

(normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

□ Yes (1)

□ No (0)

□ Unable to determine from article (0)

14. Were the main outcome measures used accurate (valid and reliable)? *For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

15. Were the participants in different comparison groups recruited from the same population or from comparable populations? *Answer NO for studies without a comparison/control group.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

16. Were study subjects in different intervention groups recruited over the same period of time? *Answer NO for studies without a comparison/control group.*

□ Yes (1)

□ No (0)

□ Unable to determine (0)

17. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

□ Yes (1)

□ No (0)

□ Unable to determine (0)

Appendix C: Included Studies

INCLUDED STUDIES

1. Adam C, Raschzok A. Cannabis policy and the uptake of treatment for cannabis-related problems. *Drug Alcohol Rev*. 2017;36(2):171-177.
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4. Anderson DM, Rees DI, Sabia JJ. Medical marijuana laws and suicides by gender and age. *Am J Public Health*. 2014;104(12):2369-2376.
5. Anderson DM, Rees DI, Tekin E. Medical marijuana laws and workplace fatalities in the United States. *Int J Drug Policy*. 2018;60:33-39.
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Appendix C: Included Studies

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21. Cerda M, Sarvet AL, Wall M, et al. Medical marijuana laws and adolescent use of marijuana and other substances: alcohol, cigarettes, prescription drugs, and other illicit drugs. *Drug Alcohol Depend*. 2018;183:62-68.
22. Cerda M, Wall M, Feng T, et al. Association of state recreational marijuana laws with adolescent marijuana use. *JAMA Pediatr*. 2017;171(2):142-149.
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Appendix C: Included Studies

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Appendix C: Included Studies

56. Kim JH, Santaella J, Cerda M, Martins SS. Medical marijuana laws and annual opioid analgesic sales in the United States. *Drug Alcohol Depend*. 2015;156:e111.
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Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMAreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title			
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
Introduction			
Rationale	#3	Describe the rationale for the review in the context of what is already known.	4
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5

Methods

Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	5
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	5-6
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	5
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	6
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	6-7
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	7
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	7
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A

Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
Results			
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8, Figure 1
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	Supplementary Table 1
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Supplementary Table 1
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary Table 1
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	9-12
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
Discussion			
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	12-14
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15

Funding

Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	16

Notes:

- 17: 7-8, Figure 1
- 18: Supplementary Table 1
- 19: Supplementary Table 1
- 20: Supplementary Table 1 This checklist was completed on 19. October 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai