Senate Federal and State Affairs Committee
In Opposition of Senate Bill 135
March 16, 2023

Testimony of Eric A. Voth, M.D., FACP
On Behalf of the Kansas Medical Society
Internal Medicine, Pain, and Addiction Medicine
President and Chairman of the Board
The International Academy on the Science
and Impact of Cannabis-IASIC-https://iasic1.org

Chairman Thompson and Members of the Committee:

SB135 continues to propagate dangerous elements that jeopardize Kansans and set the stage for serious problems with marijuana. Please keep in mind that the **hidden intent of this legislation is to take advantage of sick and suffering Kansans with the false hope of marijuana as a near miracle medicine. Instead, this legislation is a key to opening full legalization of marijuana as has been seen in many states.**

Specific concerns:
Leaf marijuana is allowed to contain up to 35% THC and oils or concentrates up to 60%. These levels are toxic and should never exceed 10% THC

The regulation and management of marijuana is placed upon the Kansas Department of Health and Environment. This adds huge responsibility to an organization that has no experience with marijuana for medical purposes.

The listed "medical" indications are vast and exceed medical research. The ONLY disorder that may have limited benefit is some forms of pain in far lower doses than this statute would allow.

Written recommendations for marijuana are treated essentially like prescriptions, yet allowed for a full year, do not spell out exact doses, concentrations, indications, nor risks.

Labeling is allowed to be very generic and should also contain exact analyses of toxins, chemicals, and other contaminants, and THC with labeled precautions as to the effects of cannabis.

Immunity should **NOT be afforded** to recommending providers especially when legitimate medical practitioners are burdened by malpractice insurance premiums and claims.

Statutes that allow the recommendation of medical marijuana present a real malpractice risk to physicians and medical providers. The remainder of my written testimony outlines the Standard of Care that is expected of medical providers when prescribing, much less "recommending" serious and potentially harmful medications. You will note that in no way does the recommending of marijuana meet these standards.

Despite a rapidly growing medical and recreational marijuana industry, there has been no definition of a standard of care for the use and recommendation of marijuana for medicinal purposes. This issue has been essentially ignored by the federal government and Congress has limited the ability of the Food and Drug Administration to enforce federal food and drugs law when it comes to "medical" marijuana. The marijuana industry has been allowed to run rampant.

Most of the medical opposition to medical marijuana is borne from concern over serious medical and social consequences in patients resulting from marijuana use. Additionally, the medicinal use of marijuana has been used by marijuana advocates as an intentional stair-step to legalization of the drug.

When considering what constitutes the "standard of care," it is important to embrace practices that reduce the risk to patients as well as reducing the risk of potential malpractice litigation of providers. Defining the standard of care should assist providers in determining appropriate therapeutic decisions. By necessity, providers must consider whether they have deviated from the standard of care and thus risk malpractice claims.

In legal terms, the "Standard of Care" is the level at which the average, prudent provider in a given community would practice. It is how **similarly qualified practitioners would have managed the patient's care under the same or similar circumstances.** In order to pursue litigation, the medical malpractice plaintiff must establish the appropriate standard of care and demonstrate that the standard of care has been breached (1).

Pure Cannabis-based medicines such as Marinol, Cesamet, Epidiolex, and Sativex are already FDA approved and on the market as medications that may be prescribed. Providers "recommending" state-approved cannabis are clearly recommending a non-FDA approved substance. **The recommendation of marijuana as a medicine generally has malpractice risk because "recommendations" for the use of marijuana are lacking the standard safe practices required of modern-day medicine**.

Thirty-seven states and four provinces have bypassed the Federal FDA authority and now allow medical marijuana "recommendations" well-beyond indications that have research to support them. For instance, Kansas is considering both House and Senate "Medical Marijuana" legislation that allows the following "qualifying" medical conditions:

In Kansas Senate Bill 135 Qualifying medical condition" means **any of the following**:

(1) Acquired immune deficiency syndrome;
(2) Alzheimer's disease;
(3) Amyotrophic lateral sclerosis;
(4) Cancer
(5) Chronic traumatic encephalopathy;
(6) Crohn's disease;
(7) Epilepsy or another seizure disorder;
(8) Fibromyalgia;

(9) Glaucoma;
(10) Hepatitis C;
(11) Inflammatory bowel disease;
(12) Multiple sclerosis;
(13) Pain that is either chronic and severe or intractable; (14) Parkinson's disease;
(15) Positive status for HIV;
(16) Post-traumatic stress disorder;
(17) Sickle cell anemia;
(18) Spinal cord disease or injury;
(19) Tourette's syndrome;
(20) Traumatic brain injury;
(21) Ulcerative colitis;
As well as "any other debilitating condition"

Research demonstrates that the use of marijuana even for pain has fallen into question (2). Extensive literature review and several international organizations have concluded that the use of cannabinoids for chronic non-cancer pain is not yet supported nor proven by research and its use for pain is considered limited (3,4).

Questions must also be answered as to what form of the drug is to be provided (smoked, vaped, gummies, oils etc.), what doses are safe and effective, what side effects should be expected, and what long-term side effects might be experienced. Patients must also be notified and cautioned of these side effects and the problem that such delivery vehicles present unreliable doses to the patient.

Several of the elements necessary for the standard of care to be met are listed below. Failure to meet these individual required elements of appropriate medical care open the door to malpractice claims:

Medical Evaluation- History and Physical Examination- As with any medical disorder, a thorough and complete medical evaluation must be performed, documented, and updated regularly by a licensed medical provider. This is a central and essential part of any medical evaluation. This process should also include specific documentation of other medical treatments and other successful or failed medications. The documentation of these elements must be entered into the patient's medical record which is appropriately retained, stored and made readily available for other providers also treating the patient. The patient's mental health history must be explored as cannabis use can damage mental health. (5)

The few Cannabinoid products that have been approved for use by the FDA, including Epidiolex (a CBD product) and Marinol and Cesamet (synthetic THC) have extensive warnings of the many risks of use. The FDA drug label for Marinol issues a warning that the drug "may cause psychiatric and cognitive effects and impair mental and/or physical abilities. Avoid use in patients with psychiatric history." (Table 1) While these boxed warnings exist on low potency prescription cannabis products, there may be no warnings on much higher potency federally illegal marijuana products sold at state marijuana stores or dispensaries.

Concentration/Dose- Research is now suggesting that THC concentrations should not exceed 10% (4), and that higher concentrations have been associated with psychosis and other psychiatric disorders. It is worth also noting that state statutes allowing "medical" applications of marijuana include smoking, oils, vaping for example that can be 70-90% THC concentrations. Typically, street preparations do not contain stable nor predictable doses of Delta-9-THC, **In no other medical realm would we accept a general guess as to the potency of a medication, or would we not specify a concentration/dose at all, particularly when the incorrect dose may have such severe and possibly irreversible, deleterious consequences,** yet that is exactly what is allowed with cannabis.

Failure to warn - Beyond the question of what indications fall within the standard of care for recommending marijuana is the question of side effects and whether a less problematic and less toxic medication might be an available alternative. Furthermore, that information must be made available to the patient, and there must also be a rationale provided if the practitioner proceeds in recommending marijuana over a less toxic medication. The patient must be warned on any drug drug interaction which may harm them or render a medically necessary drug for the patient (such as coumadin) dangerous or ineffective. This rationale and patient notification must be clearly documented in the medical record. A failure to do so by the practitioner constitutes a deviation from the standard of care.

Failure to monitor- Ongoing monitoring of symptoms, toxicity, need for dosage change, need for additional medication are all elements of good medical care. These monitored elements should then be documented in a readily available medical record as well.

REMS- Risk Evaluation and Mitigation Strategies are widely used for high-risk therapies such as opiates. While a REMS for marijuana administration is not widely used, as they become available it is strongly recommended to be a requirement for prescribing/recommending providers.

None of these elements are generally required at this time in medical marijuana statutes.

Summary:

1. In legal terms, the "Standard of Care" is the level at which the average, prudent provider in a given community would practice. It is how **similarly qualified practitioners would have managed the patient's care under the same or similar circumstances.** The medical malpractice plaintiff would seek to establish the appropriate standard of care and demonstrate that the standard of care has been breached.
2. Standard of care: A diagnostic and treatment process that a clinician should follow for a certain type of patient, illness, or clinical circumstance (6).
3. The fact that several states allow "Medical" marijuana should not impact a Standard of Care determination. It may, however, raise a question of conspiracy to harm such as with tobacco that could be pursued by plaintiff litigants.
4. Current medical marijuana statutes are generally in violation of the basic principle of "First Do No Harm". Intrinsic risks to the patient exist for marijuana use, and in order to

avoid violating the standard of care, statutes should require the provider to notify and educate the patient on potential harms and risks of:

    1. Impact on driving
    2. Psychosis
    3. Depression/suicide
    4. Violence
    5. Mania
    6. Persistent and uncontrolled vomiting (cannabis hyperemesis syndrome)
    7. Association with opiate abuse and overdose
    8. Cannabis Use Disorder and addiction

5. Marijuana is not an FDA-approved medication, and as such it should be used only under strict research protocols. There exist no clear guidelines for dosing nor contraindications or precautions.
6. Marijuana is highly impure, and the THC concentrations vary widely.
    1. The impact of dose may be significant for such complications as psychosis where there is a higher likelihood of psychosis with THC concentrations exceeding 10%
    2. Evidence exists that use of over 10% THC has increased side effects (4). Thus, vaped forms, oils, or highly concentrated forms of THC delivery have known complications.
7. Grounds exist for malpractice suits.
    1. Most prominent is failure to warn patients of potential direct harms
    2. Failure to use less problematic medications first
    3. Failure to monitor
    4. Knowingly exposing patients to a toxic substance.
    5. Failure to provide a thorough medical History and Physical examination
    6. Failure to document these elements in the medical record.

Bibliography

1. Moffett P, Moore G. The standard of care: legal history and definitions: the bad and good news. *West J Emerg Med*. 2011;12(1):109-112.
2. Why Marijuana Will Not Fix the Opioid Epidemic, by Kenneth Finn, MD. https://www.msma.org/uploads/6/2/5/3/62530417/why_marijuana_will_not_fix_the_opioid_epidemic_mayjune_2018_momed.pdf
3. Boland EG,Bennett MI, Allgar V, *et al*. *BMJ Supportive & Palliative Care* 2020;**10**:14–24.
4. Pratt et al. Systematic Reviews (2019) 8:320 https://doi.org/10.1186/s13643-019-1243-x
5. Di Forti et al Lancet Psychiatry 2019; 6: 427–36 Published Online March 19, 2019. http://dx.doi.org/10.1016/ S2215-0366(19)30048-3
6. Lieblich LM. N Engl J Med. 2004 Apr 22;350(17):1798. PMID: 15106274

Table 1.

Cesamet - has the potential to affect the central nervous system which might manifest itself in dizziness, drowsiness, euphoria “high”, ataxia, anxiety, disorientation, depression, hallucinations and psychosis.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018677s011lbl.pdf

Marinol -
https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018651s025s026lbl.pdf

Epidiolex - https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf

Leadership of the International Academy on the Science and Impact of Cannabis:

Eric A. Voth, MD, FACP is the President and Chairman of the Board of IASIC. He is a specialist in Internal Medicine, Pain management, and Addiction Medicine., is recognized as an international authority on drug use, and lectures on drug policy-related issues, pain management, and appropriate prescribing practices. He has been quoted by numerous international news media. Dr. Voth is a former member of the National Advisory Committee for the Center for Substance Abuse Treatment of HHS and has advised Reagan, Clinton, both Bush, and Obama administrations. He also advises on alcohol and drug abuse issues to the Kansas State Board of Healing Arts

Catherine Antley, M.D. is Treasurer of IASIC. She is board certified in Anatomic and Clinical Pathology and in Dermatopathology and was elected a Fellow of the American Society of Dermatopathology in December 2001. For 20 years she has served as laboratory director of Vermont Dermatopathology, the only independent dermatopathology lab in Vermont serving VT, NH and NY. She has a strong interest in public health and effective prevention as well as exploring the impact of policy on the prevention of use disorder and resulting health care costs. Dr. Antley has co-authored several Vermont Medical Society resolutions on cannabis. She recently contributed a chapter "Cannabis in Dermatology " to the textbook "Cannabis in Medicine, an Evidence Based Approach" edited by Dr. Ken Finn and published by Springer Nature.

Ken Finn, M.D., Pain Medicine and Drug Policy- is Vice-President of IASIC
Practicing medicine in Colorado Springs since 1994, Finn serves on the American Board of Pain Medicine Exam Council (’01) and is then President-Elect of the American Board of Pain Medicine (’20)., serves on the Appeals Committee (’14), and Executive Board (’14). Finn served on the Colorado Governor’s Task Force on Amendment 64, Consumer Safety and Social Issues Work Group (’12) and served 4 years on the Colorado Medical Marijuana Scientific Advisory Council (’14-’18). He was an Executive Board member of El Paso County Medical Society (’14-’18) and helped Colorado Medical Society andColorado Pain Society develop their position statement on cannabis (’18) as well as the El Paso County Board of Health (’14) and Medical Society (’14) on their statements. Finn is a voluntary clinical instructor for the University of Colorado Medical School-Colorado Springs Branch (‘17-’20).

Elizabeth Stuyt, M.D., Addiction Psychiatry is Secretary of IASIC
Dr. Stuyt is a board-certified Addiction Psychiatrist and has worked in the addiction/behavioral health field since 1990. She was the Medical Director for the Circle Program, a 90-day inpatient treatment program, funded by the state of Colorado, for persons with co-occurring mental illness and substance abuse who have failed other levels of treatment from June 1999 to May 2020. She was instrumental in helping the Circle Program to become tobacco free in January 2000 and has been a strong advocate of the need to address all addictions at the same time, including tobacco, to improve outcomes. She has been actively incorporating complementary treatments into treatment programs, including the 5-point ear acupuncture NADA (National Acupuncture Detoxification Association) protocol and BST (Brain Synchronization Therapy), to help patients recover from addiction as well as trauma which often underlie addiction and chronic pain issues. Her current mission is to educate as many people as possible on the unintended consequences of

the commercialization of marijuana in Colorado, focusing primarily on the deleterious effects of high potency THC on the developing brain.

CURRENT RESEARCH ON MENTAL HEALTH & HIGH POTENCY THC

1. Young-adult compared to adolescent onset of regular cannabis use: A 20-year prospective cohort study of later consequences

Chan GCK et al. Drug and Alcohol Review (2021) DOI: 10.1111/dar.13239

By the mid-30s, both young-adult and adolescent-onset regular users were more likely than minimal/non-users (63.5%) to have used other illicit drugs (odds ratio [OR] > 20.4), be a high-risk alcohol drinker (OR > 3.7), smoked daily (OR > 7.2) and less likely to be in relationships (OR < 0.4). As the prevalence of the young-adult-onset group was nearly double of the adolescent-onset group, it accounted for a higher proportion of adverse consequences than the adolescent-onset group. Cannabis users who began regular use in their teens had poorer later life outcomes than non-using peers. The larger group who began regular cannabis use after leaving high school accounted for most cannabis-related harms in adulthood. Given the legalisation of cannabis use in an increasing number of jurisdictions, we should increasingly expect harms from cannabis use to lie in those commencing use in young adulthood.

2. Association of High-Potency Cannabis Use With Mental Health and Substance Use in Adolescence

Hines LA et al. JAMA Psychiatry 2020;77(10):1044-1051.

In this cohort study of 1087 participants who reported cannabis use in the previous year, after adjusting for frequency of cannabis use and early adolescent mental health, use of high-potency cannabis was associated with a significant increase in the frequency of cannabis use, likelihood of cannabis problems, and likelihood of anxiety disorder. Those using high-potency cannabis had a small increase in the likelihood of psychotic experiences; however, this risk was attenuated after adjustment for frequency of cannabis use. Risks for cannabis use problems and anxiety disorders are higher among those reporting use of high-potency cannabis; provision of public health messaging regarding the importance of reducing both frequency of cannabis use and the potency of the drug, as well as limiting the availability of high-potency cannabis, may be effective for reducing these risks.

3. Association Between Recreational Marijuana Legalization in the United States and Changes in Marijuana Use and Cannabis Use Disorder From 2008 to 2016

Cerda M et al. JAMA Psychiatry. 2020;77(2):165-171.

This study's findings suggest that although marijuana legalization advanced social justice goals, the small post-RML increase in risk for CUD among respondents aged 12 to 17 years and increased frequent use and CUD among adults 26 years or older in this study are a potential public health concern. To undertake prevention efforts, further studies are warranted to assess how these increases occur and to identify subpopulations that may be especially vulnerable.

4. The Effects of Cannabis Use on the Development of Adolescents and Young Adults

Hall W et al. Annu. Rev. Dev. Psychol. 2020. 2:461–83

This review summarizes evidence on the effects of cannabis use on the development

of adolescents and young adults. It draws on epidemiological studies, neuroimaging studies, case-control studies, and twin and Mendelian randomization studies. The acute risks include psychiatric symptoms associated with the use of high THC (tetrahydrocannabinol) products and motor vehicle accidents. Daily cannabis use during adolescence is associated with cannabis dependence and poor cognitive function, which may affect educational attainment and occupational choice. Daily use of highly potent cannabis is associated with more severe psychological symptoms, such as psychoses, mania, and suicidality.

5. Trends in Cannabis Treatment Admissions in Adolescents/Young Adults: Analysis of TEDS-A 1992 to 2016

Standeven LR et al. J Addict Medicine 2020

Treatment admissions for cannabis among adolescents/YAs rose 3-fold from 1992 (49,996) to 1996 (125,858). The majority of referrals came from the criminal justice system (56%). Cannabis is increasingly the sole substance of use, with polysubstance use decreasing from 89% in 1992 to 59% in 2016. While alcohol-related treatment admissions were most common in 1992, admissions for treatment of cannabis use (followed by heroin and alcohol) were highest (38%) by 2016. Being an adolescent (odds ratio [OR] 3.1, 95% confidence interval [CI] 3.1–3.2), non-Hispanic black (OR 6.2, 95% CI 6.2–6.3), male (female OR 0.6, 95% CI 0.6–0.6) with co occurring alcohol use (OR 25.9, 95% CI 25.7–26.1) was associated with admission for treatment of primary cannabis use as compared with other substances.

6. Evaluation of THC-Related Neuropsychiatric Symptoms Among Adults Aged 50 Years and Older A Systematic Review and Metaregression Analysis

Velayudhan et al. JAMA Network Open. 2021;4(2):e2035913. doi:10.1001/jamanetworkopen.2020.35913

We used metaregression analyses to examine any association between THC dose and self-reported neuropsychiatric adverse events (AEs) using data from double masked, randomized clinical trials (RCTs) investigating CBMs in people aged 50 years or older.Higher THC dose was associated with a higher incidence of thinking or perception disorder and dizziness or light-headedness. Self-reported thinking or perception disorders reflect alterations in thinking and perception typically described under psychotic symptoms and suggest that older adults may also be at risk of psychotomimetic effects from THC.

7. Association of Cannabis Use With Self-harm and Mortality Risk Among Youths With Mood Disorders

Fontenella CA et al. JAMA Pediatrics 2020 doi:10.1001/jamapediatrics.2020.5494

A study of 204,780 (aged 10-24 years)Medicaid-enrolled youths with mood disorders found that the presence of cannabis use disorder was significantly associated with an increased risk of nonfatal self-harm, all-cause mortality, and death by unintentional overdose and homicide. Meaning Cannabis use disorder is common among adolescents and young adults with mood disorders and is associated with an elevated risk of self-harm, overall mortality, and death by unintentional overdose and homicide in this already vulnerable population.

8. Comorbid Cannabis Use Disorder with Major Depression and Generalized Anxiety Disorder: A Systematic Review with Meta-analysis of Nationally Representative Epidemiological Surveys

Onaemo VN et al. Journal of Affective Disorders 2021;281:467-475

In summary, our study findings provide further evidence on the strength of comorbid association of CUD with MD and CUD with GAD in the general population. The rates of comorbid MD and GAD is three times higher among those with CUD. This evidence should help guide clinical management of patients with comorbid CUD and mental health illness, which has often been associated with inadequate treatment, poor prognosis, and high levels of health service utilization (Hasin et al., 2016; Kessler, 2004). A thorough understanding of the way and reasons CUD co-occur with GAD and MD may provide effective prevention and treatment guidelines that focus on integrated shared-care approaches and/or psychosocial treatment in parallel systems (Horsfall et al., 2009; Mills et al., 2012; Tiet and Mausbach, 2007), as well as mitigate barriers in clinical management of patients with a comorbid diagnosis (Mills et al., 2012). Given the increasing prominence of cannabis use along with ongoing changes in cannabis legalization in legalization in many countries (Statistics Canada, 2019; Hawley et al., 2020), it is imperative to mitigate the serious health-related harms of CUD, such as increased risk of comorbid anxiety or depression (Patton et al., 2002); high risk of myocardial infarction, stroke, and transient ischemic attacks (Thomas et al., 2014); increased ER visits and fatal car accident (Brady and Li, 2014)); and crime (Schauer et al., 2016). There is a great need for stronger evidence-based policy interventions that include, public health education about potential harms and responsible use (Murray et al., 2007); increased clinicians training about treatment prognosis; more health care funding due to increase service utilization of comorbidity; and reduce social stigmatization of individuals who seek treatment.

9. Understanding Opioid Use Disorder (OUD) using tree-based classifiers

Wadekar AS. Drug and Alcohol Dependence 2020

https://doi.org/10.1016/j.drugalcdep.2020.107839

The proposed machine learning approach predicts adults at risk for OUD with remarkable accuracy. **The dominant predictor of OUD is first use of marijuana before the age of 18 years.** Socioeconomic and demographic groups affected by such early initiation are also identified.The machine learning models are capable of finding a “needle in a haystack”, given the low number of observations with OUD. Finally, it is shown how a combination of different machine learning methods can be used to comprehensively and synergistically predict Opioid UseDisorder in adults.

10. Examining Associations Between Licensed and Unlicensed Outlet Density and Cannabis Outcomes From Pre Opening to Postopening of Recreational Cannabis Outlets

Pedersen ER et al. American Journal of Addiction 2020 DOI: 10.1111/ajad.13132

This study expands beyond studies of outlet prevalence to find that, after controlling

for outcomes 1 year prior, licensed and unlicensed outlets were associated with young adults' cannabis outcomes. The current study is among the first to find associations between cannabis use outcomes and density of cannabis outlets among young adults using data from two time points: pre opening and post opening of recreational cannabis retailers. Findings can inform policies around the density and placement of cannabis outlets.

11. Mapping cannabis potency in medical and recreational programs in the United States

Cash MC et al. PLOS ONE 2020 https://doi.org/10.1371/journal.pone.0230167

A total of 8,505 cannabis products across 653 dispensaries were sampled.
Despite the clear differences between medicinal and recreational uses of cannabis, the average THC concentration advertised online in medicinal programs was similar (19.2% ±6.2) to recreational programs (21.5% ±6.0) when compared between states with different programs, or between medicinal and recreational programs within the same states (CO or WA). Lower CBD concentrations accompanied higher THC products. The majority of products, regardless of medicinal or recreational programs, were advertised to have >15% THC (70.3% - 91.4% of products). These stated concentrations seem unsuitable for medicinal purposes, particularly for patients with chronic neuropathic pain. Therefore, this information could induce the misconception that high potency cannabis is safe to treat pain. This data is consistent with reports in which THC and CBD in products from legal dispensaries or in nationwide products from the illegal market were actually measured, which indicates that patients consuming these products may be at risk of acute intoxication or long-term side effects. Our study offers grounds to develop policies that help prevent misconceptions toward cannabis and reduce risks in pain patients.

12. Risk of Persistence and Progression of Use of 5 Cannabis Products After Experimentation Among Adolescents

Barrington-Trimis JL et al. JAMA Network Open. 2020;3(1):e1919792

In this cohort study of 2685 adolescents with no history of heavy cannabis use, after accounting for polyuse of multiple products, the association of baseline experimental use with persistent use and progression of use of that product during a 12-month follow-up period was significantly stronger for cannabis concentrate than for other cannabis products. The rate of persistence and progression after experimentation among adolescents may be amplified with the use of cannabis concentrate compared with other cannabis products.

13. Knowledge of Tetrahydrocannabinol and Cannabidiol Levels Among Cannabis Consumers in the United States and Canada

Hammond D, Goodman S. Cannabis and Cannabinoid Research 2020 DOI: 10.1089/can.2020.0092

Few consumers knew and were able to report the numeric THC or CBD levels of their usual cannabis products. For example, only 10% of dried herb consumers reported the THC level, approximately 30% of whom reported implausible values. A greater proportion of consumers reported a descriptive THC:CBD ratio of their usual product, ranging from 50.9% of edible users to 78.2% of orally ingested oil users. Consumers were substantially more likely to report

products high in THC versus low in THC for all products except topicals and tinctures, whereas similar proportions reported using products high and low in CBD. Despite some evidence of greater knowledge in legal jurisdictions, knowledge was still low in states with legal cannabis markets.

14. Prevalence of Cannabis Withdrawal Symptoms Among People With Regular or Dependent Use of Cannabinoids A Systematic Review and Meta-analysis

Bahji A et al. JAMA Network Open. 2020;3(4):e202370

In this meta-analysis of observational studies including 23 518 participants, the prevalence of cannabis withdrawal syndrome was found to be 47%. Factors that were associated with higher cannabis withdrawal syndrome were clinical settings (particularly inpatient and outpatient vs population settings), concurrent tobacco or other substance use, and daily cannabis use. Cannabis withdrawal syndrome appears to be common among regular users of cannabis, particularly those in outpatient and inpatient settings and individuals with substance use disorders; clinicians should be aware of the high prevalence of cannabis withdrawal syndrome to counsel patients and support individuals who are reducing their use of cannabis

15. Progression of cannabis withdrawal symptoms in people using medical cannabis for chronic pain

Coughlin LN et al. Addiction 2021 doi:10.1111/add.15370

Adults with chronic pain seeking medical cannabis certification or recertification appear to experience mild to severe withdrawal symptoms. Withdrawal symptoms tend to be stable over a 2-year period, but younger age is predictive of worse symptoms and of an escalating withdrawal trajectory.

16. Association of Naturalistic Administration of Cannabis Flower and Concentrates With Intoxication and Impairment

Bidwell LC et al. JAMA Psychiatry 2020;77(8):787-796.

This study provides information about the association of pharmacological and neurobehavioral outcomes with legal market cannabis. Short-term use of concentrates was associated with higher levels of THC exposure. Across forms of cannabis and potencies, users' domains of verbal memory and proprioception-focused postural stability was primarily associated with THC administration.

17. Psychotic disorders hospitalizations associated with cannabis abuse or dependence: A nationwide big data analysis- Portugal

Gonçalves-Pinho M. et al. Int J Methods Psychiatr Res. 2020;29:e1813.

The number of hospitalizations with a primary diagnosis of psychotic disorder (PD) and schizophrenia associated with cannabis use (CU) rose 29.4 times during the study period, from 20 to 588 hospitalizations yearly (2000 and 2015, respectively) with a total of 3,233 hospitalizations and an average episode cost of €3,500. Male patients represented 89.8% of all episodes, and the mean/median age at discharge were 30.66/29.00 years, respectively. From all hospitalizations with a primary diagnosis of PD or schizophrenia, the ones with a secondary

diagnosis of CU rose from 0.87% in 2000 to 10.60% in 2015. Conclusions: The increase on secondary diagnosis coding and the change on cannabis patterns of consumption in Portuguese population with an increasing frequency of moderate/high dosage cannabis consumers may explain the rise on PD Hospitalizations.

18. A genetically informed study on the association of cannabis, alcohol, and tobacco smoking with suicide attempt

Orri M et al. Molecular Psychiatry 2020 **https://doi.org/10.1038/s41380-020-0785-6**

To evaluate the potential causal contributions of cannabis use, alcohol use, and tobacco smoking to suicide attempt, we applied two-sample Mendelian randomization, an instrumental variable approach using single-nucleotide polymorphisms (SNPs) as instrumental variables for three exposures: lifetime cannabis use (yes/no; 42 instrument SNPs; GWAS sample size [N] = 162,082), alcohol use (drinks-per-week; 53 instrument SNPs; N = 941,280), and tobacco smoking (initiation, yes/no; 156 instrument SNPs; N = 1,232,091; heaviness; 27 instrument SNPs; N = 337,334). The main outcome was suicide attempt measured from hospital records (N = 50,264).Using multivariable Mendelian randomization, we found that only cannabis showed a direct pathway to suicide attempt (P = 0.001), suggesting that the effect of alcohol and smoking was mediated by the other substance use phenotypes. No evidence was found for reverse causation, i.e., associations of suicide attempt on cannabis (P = 0.483), alcohol (P = 0.234), smoking initiation (P = 0.144), and heaviness (P = 0.601). In conclusion, evidence from this quasiexperimental study based on genetic data from large-scale GWASs are consistent with a causal role of cannabis, alcohol, andtobacco smoking on suicide attempt.

19. Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood-A Systematic Review and Meta-analysis

Gobbi G et al. JAMA Psychiatry 2019 doi:10.1001/jamapsychiatry.2018.4500

In this systematic review and meta-analysis of 11 studies and 23 317 individuals, adolescent cannabis consumption was associated with increased risk of developing depression and suicidal behavior later in life, even in the absence of a premorbid condition. There was no association with anxiety. Preadolescents and adolescents should avoid using cannabis as use is associated with a significantly increased risk of developing depression or suicidality in young adulthood; these findings should inform public health policy and governments to apply preventive strategies to reduce the use of cannabis among youth.

20. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study

Di Forti M et al. The Lancet Psychiatry 2019
http://dx.doi.org/10.1016/S2215-0366(19)30048-3

This multicentre case-control study across ten European and one Brazilian site replicates the strong effect of daily use of high-potency cannabis (>10%THC) on the odds for psychotic disorder in the whole sample—which, to our knowledge, is the largest to date to address this question. This effect was particularly visible in London and Amsterdam. Additionally, we show that, assuming causality, if high-potency cannabis types were no longer available, then 12% of

cases of first-episode psychosis could be prevented across Europe, rising to 30% in London and 50% in Amsterdam. Most importantly, we provide the first direct evidence that cannabis use has an effect on variation in the incidence of psychotic disorders. We show that differences in the prevalence of daily use of cannabis, and in use of high-potency cannabis, among the controls from the different study sites made a major contribution to the striking variations in the incidence rates of psychotic disorder that we have previously reported across the same sites.

21. Association between medical cannabis laws and opioid overdose mortality has reversed over time

Shover CL et al. PNAS 2019 **www.pnas.org/cgi/doi/10.1073/pnas.1903434116**

Medical cannabis has been touted as a solution to the US opioid overdose crisis since Bachhuber et al. [M. A. Bachhuber, B. Saloner, C. O. Cunningham, C. L. Barry, JAMA Intern. Med. 174,1668–1673] found that from 1999 to 2010 states with medical cannabis laws experienced slower increases in opioid analgesic overdose mortality.In this study, we used the same methods to extend Bachhuber et al.'s analysis through 2017. Not only did findings from the original analysis not hold over the longer period, but the association between state medical cannabis laws and opioid overdose mortality reversed direction from −21% to +23% and remained positive after accounting for recreational cannabis laws. We also uncovered no evidence that either broader (recreational) or more restrictive (low-tetrahydrocannabinol) cannabis laws were associated with changes in opioid overdose mortality. We find it unlikely that medical cannabis—used by about 2.5% of the US population—has exerted large conflicting effects on opioid overdose mortality. A more plausible interpretation is that this association is spurious. Moreover, if such relationships do exist, they cannot be rigorously discerned with aggregate data. Research into therapeutic potential of cannabis should continue, but the claim that enacting medical cannabis laws will reduce opioid overdose death should be met with skepticism.

22. Medical Marijuana Users are More Likely to Use Prescription Drugs Medically and Nonmedically

Caputi TL, Humphreys K. J Addict Med 2018 DOI: 10.1097/ADM.0000000000000405

Medical marijuana users were significantly more likely (RR 1.62, 95% confidence interval [CI] 1.50–1.74) to report medical use of prescription drugs in the past 12 months. Individuals who used medical marijuana were also significantly more likely to report nonmedical use in the past 12 months of any prescription drug (RR 2.12, 95% CI 1.67–2.62), with elevated risks for pain relievers (RR 1.95, 95% CI 1.41–2.62), stimulants (RR 1.86, 95% CI 1.09–3.02), and tranquilizers (RR 2.18, 95% CI 1.45–3.16). Our findings disconfirm the hypothesis that a population-level negative correlation between medical marijuana use and prescription drug harms occurs because medical marijuana users are less likely to use prescription drugs, either medically or nonmedically. Medical marijuana users should be a target population in efforts to combat nonmedical prescription drug use.

23. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study

Campbell G et al. www.thelancet.com/public-health Vol 3 July 2018

Cannabis use was common in people with chronic non-cancer pain who had been prescribed opioids, but we found no evidence that cannabis use improved patient outcomes. People who used cannabis had greater pain and lower self-efficacy in managing pain, and there was no evidence that cannabis use reduced pain severity or interference or exerted an opioid-sparing effect. As cannabis use for medicinal purposes increases globally, it is important that large well designed clinical trials, which include people with complex comorbidities, are conducted to determine the efficacy of cannabis for chronic non-cancer pain.

24. Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States

Olfson M et al. AJP in Advance 2017 doi: 10.1176/appi.ajp.2017.17040413

In a nationally representative sample of adults evaluated at waves 3 years apart, cannabis use was strongly associated with subsequent onset of nonmedical prescription opioid use and opioid use disorder. These results remained robust after controlling for the potentially confounding effects of several demographic and clinical covariates that were strongly associated with cannabis use. The association of cannabis use with the development of nonmedical opioid use was evident among adults without cannabis use disorders and among adults with moderate or more severe pain. Among adults with nonmedical prescription opioid use, cannabis use was associated with an increase in the level of nonmedical prescription opioid use at follow-up.

25. Maternal and paternal cannabis use during pregnancy and the risk of psychotic-like experiences in the offspring

Bolhuis K et al. Schizophrenia Research 2018;202: 322-327.

In this prospective cohort, we examined the relationship between parental cannabis use during pregnancy and offspring psychotic-like experiences. Comparisons were made between maternal and paternal cannabis use during pregnancy to investigate causal influences of intrauterine cannabis exposure during foetal neurodevelopmental. This study was embedded in the Generation R birth cohort and included N = 3692 participants.We demonstrated that both maternal and paternal cannabis use were associated with more offspring psychotic-like experiences at age ten years. This may suggest that common aetiologies, rather than solely causal intra-uterine mechanisms, underlie the association between parental cannabis use and offspring psychotic-like experiences. These common backgrounds most likely reflect genetic vulnerabilities and shared familial mechanisms, shedding a potential new light on the debated causal path from cannabis use to psychotic-like phenomena. Our findings indicate that diagnostic screening and preventative measures need to be adapted for young people at risk for severe mental illness

25. Cannabis-associated psychosis: Neural substrate and clinical impact

Murray RM et al. Neuropharmacology 2017 doi.org/10.1016/j.neuropharm.2017.06.018

In our opinion, the epidemiological evidence clearly demonstrates that heavy cannabis use, particularly of high potency types, or of synthetic cannabinoids, increases the risk of psychosis, especially in those who start their use in their early teens.

27. Cannabis induced psychosis and subsequent psychiatric disorders

Shah D et al. Asian Journal of Psychiatry 2017;30:180–184.

Patients who completely abstained from cannabis after the 1st episode had no relapse of psychiatric illness. They showed marked improvement in socio-occupational functioning as well. All those who relapsed to cannabis use had a recurrence of illness. Half the patients with predominantly non-affective psychosis progressed to an independent psychiatric disorder; while only 7.7% of patients with predominantly affective psychosis developed an independent disorder ($p = 0.01$). Besides this, early onset of cannabis use (≤18 years), younger age at onset of 1 st episode, positive family history of psychiatric illness, being unmarried and lower socio-economic status were associated with poor prognosis. Abstinence later in the course of illness did not improve outcome significantly.

28. Rates and Predictors of Conversion to Schizophrenia or Bipolar Disorder Following Substance-Induced Psychosis

Starzer MSK et al. AJP in Advance (doi: 10.1176/appi.ajp.2017.17020223)

Substance-induced psychosis is strongly associated with the development of severe mental illness, and a long follow-up period is needed to identify the majority of cases.The highest conversion rate (47.4%) was found for cannabis-induced psychosis. Young age was associated with a higher risk of conversion to schizophrenia; the risk was highest for those in the range of 16–25 years.

29. Cannabis use disorder and suicide attempts in Iraq/Afghanistan-era Veterans

Kimbrel NA et al. Journal of Psychiatric Research 2017;89: 1-5

The objective of the present research was to examine the association between lifetime cannabis use disorder (CUD), current suicidal ideation, and lifetime history of suicide attempts in a large and diverse sample of Iraq/Afghanistan-era veterans (N= 3233) using a battery of well-validated instruments. As expected, CUD was associated with both current suicidal ideation (OR= 1.683, $p = 0.008$) and lifetime suicide attempts (OR = 2.306, $p < 0.0001$), even after accounting for the effects of sex, posttraumatic stress disorder, depression, alcohol use disorder, non-cannabis drug use disorder, history of childhood sexual abuse, and combat exposure. Thus, the findings from the present study suggest that CUD may be a unique predictor of suicide attempts among Iraq/Afghanistan-era veterans; however, a significant limitation of the present study was its cross-sectional design. Prospective research aimed at understanding the complex relationship between CUD, mental health problems, and suicidal behavior among veterans is clearly needed at the present time.

30. Long Lasting Effects of Chronic Heavy Cannabis Abuse

Nestoros JN et al. The American Journal on Addictions 2017;26:335-342

We provide evidence that chronic and heavy cannabis abuse results in long-lasting brain dysfunction in all users and in long-lasting schizophrenia-like psychotic symptoms in more than half of all users. These findings suggest a reevaluation of the current classification of cannabis as a “soft narcotic” which erroneously, therefore, is typically considered harmless.

31. U.S. cannabis legalization and use of vaping and edible products among youth

Borodovsky JT et al. Drug Alcohol Depend. 2017; 177: 299–306.

This study examined relations among specific provisions of LCL and cannabis vaping and use of edibles in youth ages 14–18. Consistent with our previous study of adult cannabis users recruited via Facebook, the present analyses indicated that longer LCL duration and higher dispensary density were related to a higher likelihood of lifetime vaping and edible use. The current study extended those findings by showing that provisions for recreational cannabis use and for permitting home cultivation were also related to a higher likelihood of lifetime vaping and edible use. Some of these increased likelihoods were substantial. For example, living in a high dispensary density state doubled the likelihood of trying vaping and tripled the likelihood of trying edibles.

32. The association between regular marijuana use and adult mental health outcomes

Guttmannova K et al. Drug and Alcohol Dependence 2017;179:109–116

Objective: The present study is a prospective examination of the relationship between regular marijuana use from adolescence through young adulthood and mental health outcomes at age 33. Methods: Data came from a gender-balanced, ethnically diverse longitudinal panel of 808 participants from Seattle, Washington. Outcomes included symptom counts for six mental health disorders. Regular marijuana use was tracked during adolescence and young adulthood. Regression analyses controlled for demographics and early environment, behaviors, and individual risk factors. Results: Nonusers of marijuana reported fewer symptoms of alcohol use disorder, nicotine dependence, and generalized anxiety disorder than any category of marijuana users. More persistent regular marijuana use in young adulthood was positively related to more symptoms of cannabis use disorder, alcohol use disorder, and nicotine dependence at age 33. Conclusions: Findings highlight the importance of avoiding regular marijuana use, especially chronic use in young adulthood. Comprehensive prevention and intervention efforts focusing on marijuana and other substance use might be particularly important in the context of recent legalization of recreational marijuana use in Washington and other U.S. states.

33. Patterns of marijuana use among psychiatry patients with depression and its impact on recovery

Bahorik AL et al. Journal of Affective Disorders 2017;213:168–171

Participants were 307 psychiatry outpatients with depression; assessed at baseline, 3-, and 6-months on symptom (PHQ-9 and GAD-7), functioning (SF-12) and past-month marijuana use

for a substance use intervention trial. Longitudinal growth models examined patterns and predictors of marijuana use and its impact on symptom and functional outcomes.
Results: A considerable number of (40.7%; n=125) patients used marijuana within 30-days of baseline. Over 6-months, marijuana use decreased (B=−1.20, p < .001), but patterns varied by demographic and clinical characteristics. Depression (B=0.03, p < .001) symptoms contributed to increased marijuana use over the follow-up, and those aged 50+(B=0.44, p < .001) increased their marijuana use compared to the youngest age group. Marijuana use worsened depression (B=1.24, p < .001) and anxiety (B=0.80, p=.025) symptoms; marijuana use led to poorer mental health (B=−2.03, p=.010) functioning. Medical marijuana (26.8%; n=33) was associated with poorer physical health (B=−3.35, p=.044) functioning.

34. Changes in cannabis potency and first-time admissions to drug treatment: a 16-year study in the Netherlands

Freeman TP et al. Psychological Medicine 2017 doi.org/10.1017/S0033291717003877

In this 16-year observational study, we found positive time-dependent associations between changes in cannabis potency and first-time cannabis admissions to drug treatment. These associations are biologically plausible, but their strength after adjustment suggests that other factors are also important

35. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis

Murray RM et al. World Psychiatry 2016;15:195–204

Epidemiological evidence demonstrates that cannabis use is associated with an increased risk of psychotic outcomes, and confirms a dose response relationship between the level of use and the risk of later psychosis. High-potency cannabis and synthetic cannabinoids carry the greatest risk.

36. Association of cannabis use with hospital admission and antipsychotic treatment failure in first episode psychosis: an observational study

Patel R et al. BMJ Open 2016;6:e009888. doi:10.1136/bmjopen-2015-009888

Cannabis use in patients with first episode psychosis (FEP) was associated with an increased likelihood of hospital admission. This was linked to the prescription of several different antipsychotic drugs, indicating clinical judgement of antipsychotic treatment failure. Together, this suggests that cannabis use might be associated with worse clinical outcomes in psychosis by contributing towards failure of antipsychotic treatment.

37. Limitations to the Dutch cannabis toleration policy Assumptions underlying the reclassification of cannabis above 15% THC

Van Laar M et al. International Journal of Drug Policy 2016;34:58–64

The purpose of this measure was twofold: to reduce public health risks and to reduce illegal cultivation and export of cannabis by increasing punishment. This paper focuses on the public health aspects and describes the (explicit and implicit) assumptions underlying this ‘15% THC

measure', as well as to what extent these are supported by scientific research. Based on scientific literature and other sources of information,we conclude that the 15% measure can provide in theory a slight health benefit for specific groups of cannabis users (i.e., frequent users preferring strong cannabis, purchasing from coffee shops, using 'steady quantities' and not changing their smoking behaviour), but certainly not for all cannabis users. These gains should be weighed against the investment in enforcement and the risk of unintended (adverse) effects. Given the many assumptions and uncertainty about the nature and extent of the expected buying and smoking behaviour changes, the measure is a political choice and based on thin evidence.

38. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study

DiForti M. et al. Lancet Psychiatry 2015 http://dx.doi.org/10.1016/S2215-0366(14)00117-5

The association between cannabis use and increased risk of developing schizophrenia-like psychosis has been consistently reported by prospective epidemiological studies.2,3 Our previous study was the first to show that use of high-potency (skunk-like) cannabis (>15% THC) carries the highest risk for psychotic disorders.8 In the present larger sample analysis, we replicated our previous report and showed that the highest probability to suffer a psychotic disorder is in those who are daily users of high potency cannabis. Indeed, skunk use appears to contribute to 24% of cases of first episode psychosis in south London. Our findings show the importance of raising awareness among young people of the risks associated with the use of high-potency cannabis. The need for such public education is emphasised by the worldwide trend of liberalisation of the legal constraints on cannabis and the fact that high potency varieties are becoming much more widely available. Finally, in both primary care and mental health services, a simple yes-or-no question of whether people use skunk might be more useful to identify those at increased risk to develop psychosis because of their cannabis use.

39. Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study

Schoeler T et al. Lancet Psychiatry 2016; 3: 947–53

Continued cannabis use (at least monthly use) after the onset of psychosis, especially use of high-potency cannabis, is associated with a significantly worse outcome in individuals with first episode psychosis. In our study, outcomes were better in those who used cannabis in smaller doses (reduced frequency, lower potency, and shorter duration of continuation) after onset, which suggests that interventions should aim to reduce frequency of use or shift to less potent forms of cannabis when complete cessation of cannabis use might not be a realistic goal.

40. Daily Use, Especially of High-Potency Cannabis, Drives the Earlier Onset of Psychosis in Cannabis Users

Di Forti M et al. Schizophrenia Bulletin vol. 40 no. 6 pp. 1509–1517, 2014

We confirm an association between cannabis use and earlier age onset psychosis (AOP) and further show this to be independent of gender. Moreover, daily cannabis use and the use of high-potency cannabis are independently associated with a significantly higher hazard to make contact with services for psychosis at any given time. Finally, a younger age at first cannabis

use (≤15 years) is associated with a younger AOP only in those who had used cannabis daily. All these findings support a true effect of cannabis use on AOP, which is dose dependent, similar to its effect on risk of developing a psychotic disorder.

41. Examining the profile of high-potency cannabis and its association with severity of cannabis dependence

Freeman TP, Winstock AR. Psychological Medicine 2015; 45: 3181–3189

High-potency cannabis use is associated with an increased severity of dependence, especially in young people. Its profile is strongly defined by negative effects (memory, paranoia), but also positive characteristics (best high, preferred type), which may be important when considering clinical or public health interventions focusing on cannabis potency.

42. Young adult sequelae of adolescent cannabis use: an integrative analysis

Silins E et al. Lancet Psychiatry 2014;1:286–293

We recorded clear and consistent associations and dose-response relations between the frequency of adolescent cannabis use and all adverse young adult outcomes. After covariate adjustment, compared with individuals who had never used cannabis, those who were daily users before age 17 years had clear reductions in the odds of highschool completion (adjusted odds ratio 0·37, 95% CI 0·20–0·66) and degree attainment (0·38, 0·22–0·66), and substantially increased odds of later cannabis dependence (17·95, 9·44–34·12), use of other illicit drugs (7·80, 4·46–13·63), and suicide attempt (6·83, 2·04–22·90).

43. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research (2017) National Academies of Sciences,Engineering, Medicine

PDF available at http://nap.edu/24625

44. Cannabinoids for Medical Use A Systema*tic Review and Meta-analysis*

Whiting PF et al. JAMA. 2015;313(24):2456-2473

Randomized clinical trials of cannabinoids for the following indications:nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, or Tourette syndrome. A total of 79 trials (6462 participants) were included; 4 were judged at low risk of bias. Most trials showed improvement in symptoms associated with cannabinoids but these associations did not reach statistical significance in all trials. There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs.

45. Benefits and harms of medical cannabis: a scoping review of systematic reviews

Pratt M et al. Systematic Reviews (2019) 8:320 https://doi.org/10.1186/s13643-019-1243-x

After screening 1975 citations, 72 systematic reviews were included. The reviews covered many conditions, the most common being pain management. Several reviews focused on management of pain as a symptom of conditions such as multiple sclerosis (MS), injury, and cancer. After pain, the most common symptoms treated were spasticity in MS, movement disturbances, nausea/vomiting, and mental health symptoms. Results from the included reviews were mixed, with most reporting an inability to draw conclusions due to inconsistent findings and a lack of rigorous evidence. Mild harms were frequently reported, and it is possible the harms of cannabis-based medicines may outweigh benefits.

46. Exploring cannabis concentrates on the legal market: User profiles, product strength, and health-related outcomes

Bidwell LC et al. Addictive Behaviors Reports 2018;8:102-106.

Background: Concentrated cannabis products are increasingly available and used, particularly in states with legal cannabis, but little is known about the profiles and characteristics of concentrate users. We aimed to characterize user profiles of cannabis users living in states with legal medical or recreational cannabis who reported using concentrates to those who do not use concentrates. Methods: An anonymous online survey was advertised in California, Colorado, Nevada, Oregon, and Washington. We compared respondents who endorsed frequent concentrate use (FC; N = 67) (i.e. 4 days/week) with cannabis users who never use concentrates (NC; N = 64), and with those who smoke/vaporize cannabis flower frequently but never or very rarely use concentrates (FF; N = 60), on measures related to cannabis use patterns and cannabinoid product strength, other substance use, and occupational functioning and health. Results: FC endorsed more symptoms of cannabis use disorder as compared to non-concentrate users ($p < 0.05$), but were similar to FF and NC on other health and occupational outcomes. FC also differed from FF and NC in that they tended to use cannabis that was higher in THC ($p < 0.0005$), even when using non-concentrated forms of cannabis ($p < 0.005$). Over half of FC users reported typically using concentrates of at least 80% THC, and 21% endorsed use of (non-concentrated) dry cannabis flower containing at least 30% THC. Conclusions: Concentrate users endorsed higher symptoms of cannabis use disorder and use higher strength cannabis even when using non-concentrated forms. Frequent use of concentrates may be associated with additional risks over and above frequent use of flower forms.

47. Acute Effects of Cannabis Concentrate on Motor Control and Speed: Smartphone-Based Mobile Assessment

Hitchcock LN et al. Frontiers in Psychiatry 2021 https://doi.org/10.3389/fpsyt.2020.623672

Use of cannabis concentrates in frequent users impairs movement speed and balance similarly in men and women. The motor impairment is largely uncorrelated with the change in THC plasma levels. These results warrant further refinement of cannabis impairment testing and encourage caution related to use of cannabis concentrates in work and driving settings.

48.Acute effects of naturalistic THC vs. CBD use on recognition memory: a preliminary study **Curran T et al. Journal of Cannabis Research 2020 2:28**

Thirty-two regular cannabis users consumed cannabis of differing THC and CBD levels purchased from a dispensary and were assessed via blood draw and a verbal recognition memory test both before (pretest) and after (posttest) ad libitum home administration in a mobile laboratory. Memory accuracy decreased as post-use THC blood levels increased (n = 29), whereas performance showed no relationship to CBD blood levels. When controlling for post-use THC blood levels as a covariate, participants using primarily THC-based strains showed significantly worse memory accuracy post-use, whereas subjects using strains containing both THC and CBD showed no differences between pre- and post-use memory performance. Using a brief and sensitive verbal recognition task, our study demonstrated that naturalistic, acute THC use impairs memory in a dose dependent manner, whereas the combination of CBD and THC was not associated with impairment.

49.Association between Friends' Use of Nicotine and Cannabis and Intake of Both Substances among Adolescents

Herold R et al. Int. J. Environ. Res. Public Health 2021, 18, 695

Over one-third of the 517 surveyed adolescents reported using tobacco and one-third reported using cannabis. A significant relationship between friends' substance use and self-use was found. For both tobacco and cannabis, over 90% ($p < 0.01$) of participants with urinary biomarker levels above cutoff had friends who used the respective substance. Friends' nicotine and friends' cannabis use were each independently associated with urinary biomarker levels for those substances (for nicotine, beta = 88.29, $p = 0.03$; for cannabis, beta = 163.58, $p = 0.03$). Friends' use of nicotine and cannabis is associated with adolescents' intake, as well as the physiological exposure to those substances. These findings underscore the importance of including peer influence in the discussion with adolescents about tobacco and cannabis use.

50. .When Cannabis Use Goes Wrong: Mental Health Side Effects of Cannabis Use That Present to Emergency Services

Crocker CE et al. Frontiers in Psychiatry 2021doi: 10.3389/fpsyt.2021.640222

The situation in Colorado is also interesting from an epidemiological point of view as the past month cannabis use level among native Coloradans has remained constant since recreational legalization but healthcare utilization associated with adverse events due to cannabis has increased (38, 75). Some authors have noted that this may be related to the current market forces being focused on sales with ever increasing concentrations of THC in cannabis products (38). This may suggest a cumulative dose dependency for at least certain types of adverse events associated with cannabis use as has been suggested by others for the development of psychosis (28, 29, 76). The lack of research in these areas is not surprising given the challenges of doing research in urgent care and across disciplines to obtain outcomes for longer term psychiatric care. This lack of information further impacts clinical care as if we knew the frequency of conversion from a severe adverse mental health event related to anxiety symptoms or depressive symptoms with cannabis use to a diagnosed disorder requiring ongoing care, clinical guidelines could be developed. As we move to greater cannabis use with greater acceptance of the product, the ED may be one of the sentinel locations to monitor any

emerging mental health trends. There are also opportunities for public education that may be possible in the ED setting. The effects we present here are, we suspect, more commonly associated with higher (often defined as 12% and greater) THC concentration strains of cannabis with little to no cannabidiol in the material as these are the most commonly sold strains in the marketplace in legalized settings (78, 79). The sale of these higher THC strains is based on consumer preference (80). However, there is evidence that consumers do not understand the significance of the percentages of THC and CBD in sales materials in the legal marketplace (81).

51. Recreational Marijuana Legalization and Use Among California Adolescents: Findings From a Statewide Survey

Paschall MJ et al. J. Stud. Alcohol Drugs 2021; 82: 103–111

We found no overall statistically significant association between RML and frequency of marijuana use among youth who reported any past-30-day use. However, marked increases in marijuana use frequency were observed in 2018–2019 across almost all demographic subgroups. This may reflect the recent substantial increases in vaping of tobacco and marijuana products among adolescents in the United States (Miech et al., 2019b). Our findings also indicate differential effects of RML on marijuana use prevalence among demographic subgroups of adolescents in California, notably having greater effects for those groups with historically lower prevalence rates of marijuana use. For example, stronger associations between RML and lifetime and past-30-day marijuana use were observed among females relative to males, and past-30-day marijuana prevalence use rates have converged in these two subgroups since 2010.Similarly, stronger RML effects on marijuana use were observed among non-Hispanic/Latinx relative to Hispanic/Latinx students, and marijuana use prevalence rates have converged in these two subgroups. Stronger associations between RML and marijuana use were also observed among White youth relative to African American and American Indian/Alaska Native youth, although somewhat higher prevalence rates persisted for these two groups

52. Association Between Recreational Marijuana Legalization in the United States and Changes in Marijuana Use and Cannabis Use Disorder From 2008 to 2016

Cerda M et al. JAMA Psychiatry 2020; 77(2):165-171.

Key Points Question How did marijuana use and cannabis use disorder change during 2008 to 2016 after the legalization of recreational marijuana in the United States? Findings In this multilevel, difference-in-difference survey study with 505 796 respondents comparing marijuana use before and after the legalization of recreational marijuana in the United States, the proportion of respondents aged 12 to 17 years reporting cannabis use disorder increased from 2.18% to 2.72%, while the proportion of respondents 26 years or older reporting frequent marijuana use increased from 2.13% to 2.62% and those with cannabis use disorder, from 0.90% to 1.23%. Meaning This study’s findings suggest that possible increases in the risk for cannabis use disorder among adolescent users and increases in frequent use and cannabis use disorder among adults after legalization of recreational marijuana use may raise public health concerns and warrant ongoing study.

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

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

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

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

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

Introduction

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

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

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

Methods

Search strategy and selection criteria

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

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

See Online for appendix

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

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

Data analysis

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

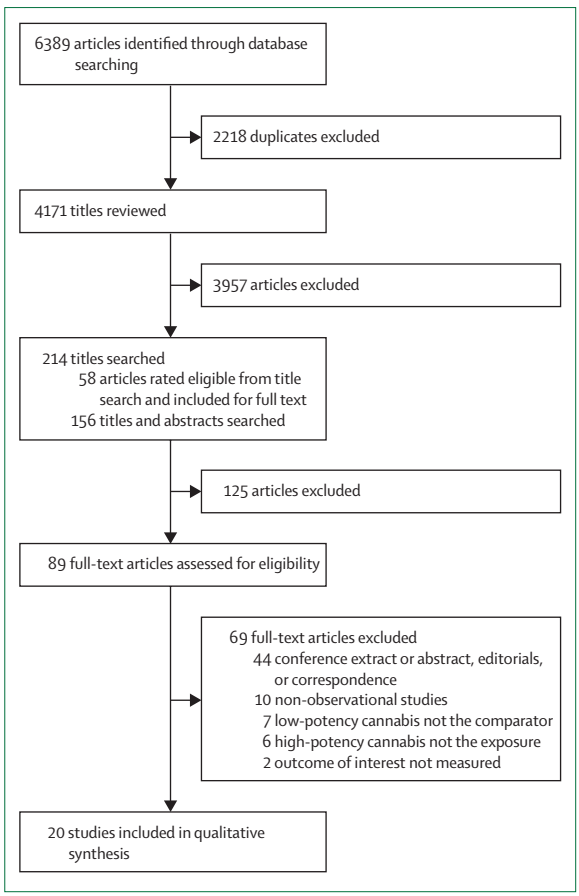

Figure: **PRISMA flowchart outlining the study selection process**

Results

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

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

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

(Table 1 continues on next page)

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

(Table 1 continues on next page)

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

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

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

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

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

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

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

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

(Table 2 continues on next page)

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

b=unstandardised regression coefficient.

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

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

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

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

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

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

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

(Table 3 continues on next page)

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

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

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

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

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

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

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

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

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

(Table 4 continues on next page)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

Contributors

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

Declaration of interests

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

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References

1 UNODC. World Drug Report 2021. United Nations, 2021. https://www.unodc.org/unodc/en/data-and-analysis/wdr2021.html (accessed Sept 7, 2021).

2 Hanuš LO, Meyer SM, Muñoz E, Taglialatela-Scafati O, Appendino G. Phytocannabinoids: a unified critical inventory. *Nat Prod Rep* 2016; **33:** 1357–92.

3 Curran HV, Freeman TP, Mokrysz C, Lewis DA, Morgan CJA, Parsons LH. Keep off the grass? Cannabis, cognition and addiction. *Nat Rev Neurosci* 2016; **17:** 293–306.

4 Curran HV, Brignell C, Fletcher S, Middleton P, Henry J. Cognitive and subjective dose-response effects of acute oral Δ 9-tetrahydrocannabinol (THC) in infrequent cannabis users. *Psychopharmacology* 2002; **164:** 61–70.

5 D'Souza DC, Perry E, MacDougall L, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* 2004; **29:** 1558–72.

6 Freeman TP, Craft S, Wilson J, et al. Changes in delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations in cannabis over time: systematic review and meta-analysis. *Addiction* 2021; **116:** 1000–10.

7 Chandra S, Radwan MM, Majumdar CG, Church JC, Freeman TP, ElSohly MA. New trends in cannabis potency in USA and Europe during the last decade (2008–2017). *Eur Arch Psychiatry Clin Neurosci* 2019; **269:** 5–15.

8 Smart R, Caulkins JP, Kilmer B, Davenport S, Midgette G. Variation in cannabis potency and prices in a newly legal market: evidence from 30 million cannabis sales in Washington state. *Addiction* 2017; **112:** 2167–77.

9 Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophr Bull* 2016; **42:** 1262–69.

10 Lev-Ran S, Roerecke M, Le Foll B, George TP, McKenzie K, Rehm J. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. *Psychol Med* 2014; **44:** 797–810.

11 Xue S, Husain MI, Zhao H, Ravindran AV. Cannabis use and prospective long-term association with anxiety: a systematic review and meta-analysis of longitudinal studies: Usage du cannabis et association prospective à long terme avec l'anxiété: une revue systématique et une méta-analyse d'études longitudinales. *Can J Psychiatry* 2021; **66:** 126–38.

12 Leung J, Chan GCK, Hides L, Hall WD. What is the prevalence and risk of cannabis use disorders among people who use cannabis? A systematic review and meta-analysis. *Addict Behav* 2020; **109:** 106479.

13 Di Forti M, Marconi A, Carra E, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *Lancet Psychiatry* 2015; **2:** 233–38.

14 Freeman TP, Winstock AR. Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. *Psychol Med* 2015; **45:** 3181–89.

15 Chan GCK, Hall W, Freeman TP, Ferris J, Kelly AB, Winstock A. User characteristics and effect profile of butane hash oil: an extremely high-potency cannabis concentrate. *Drug Alcohol Depend* 2017; **178:** 32–38.

16 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372:** n71.

17 Mateen FJ, Oh J, Tergas AI, Bhayani NH, Kamdar BB. Titles versus titles and abstracts for initial screening of articles for systematic reviews. *Clin Epidemiol* 2013; **5:** 89–95.

18 Higgins JPT, Thomas J, Chandler J, et al, eds. Cochrane handbook for systematic reviews of interventions. Chichester: John Wiley & Sons, 2019.

19 Di Forti M, Morgan C, Dazzan P, et al. High-potency cannabis and the risk of psychosis. *Br J Psychiatry* 2009; **195:** 488–91.

20 Di Forti M, Sallis H, Allegri F, et al. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophr Bull* 2014; **40:** 1509–17.

21 Sideli L, Fisher HL, Murray RM, et al. Interaction between cannabis consumption and childhood abuse in psychotic disorders: preliminary findings on the role of different patterns of cannabis use. *Early Interv Psychiatry* 2018; **12:** 135–42.

22 Di Forti M, Quattrone D, Freeman TP, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *Lancet Psychiatry* 2019; **6:** 427–36.

23 Quattrone D, Ferraro L, Tripoli G, et al. Daily use of high-potency cannabis is associated with more positive symptoms in first-episode psychosis patients: the EU-GEI case-control study. *Psychol Med* 2020; **51:** 1–9.

24 Schoeler T, Petros N, Di Forti M, et al. Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study. *Lancet Psychiatry* 2016; **3:** 947–53.

25 Prince MA, Conner BT. Examining links between cannabis potency and mental and physical health outcomes. *Behav Res Ther* 2019; **115:** 111–20.

26 Matsumoto T, Kawabata T, Okita K, et al. Risk factors for the onset of dependence and chronic psychosis due to cannabis use: survey of patients with cannabis-related psychiatric disorders. *Neuropsychopharmacol Rep* 2020; **40:** 332–41.

27 Hines LA, Freeman TP, Gage SH, et al. Association of high-potency cannabis use with mental health and substance use in adolescence. *JAMA Psychiatry* 2020; **77:** 1044–51.

28 Okey SA, Meier MH. A within-person comparison of the subjective effects of higher vs. lower-potency cannabis. *Drug Alcohol Depend* 2020; **216:** 108225.

29 Bidwell LC, YorkWilliams SL, Mueller RL, Bryan AD, Hutchison KE. Exploring cannabis concentrates on the legal market: user profiles, product strength, and health-related outcomes. *Addict Behav Rep* 2018; **8:** 102–06.

30 Craft S, Winstock A, Ferris J, Mackie C, Lynskey MT, Freeman TP. Characterising heterogeneity in the use of different cannabis products: latent class analysis with 55 000 people who use cannabis and associations with severity of cannabis dependence. *Psychol Med* 2020; **50:** 2364–73.

31 Brunt TM, van Genugten M, Höner-Snoeken K, van de Velde MJ, Niesink RJM. Therapeutic satisfaction and subjective effects of different strains of pharmaceutical-grade cannabis. *J Clin Psychopharmacol* 2014; **34:** 344–49.

32 Wan BA, Diaz P, Chan S, et al. Efficacy of different varieties of medical cannabis in relieving symptoms. *J Pain Manag* 2017; **10:** 375–83.

33 Cuttler C, Spradlin A, McLaughlin RJ. A naturalistic examination of the perceived effects of cannabis on negative affect. *J Affect Disord* 2018; **235:** 198–205.

34 Stith SS, Li X, Diviant JP, et al. The effectiveness of inhaled Cannabis flower for the treatment of agitation/irritability, anxiety, and common stress. *J Cannabis Res* 2020; **2:** 47.

35 Li X, Diviant JP, Stith SS, et al. The effectiveness of *Cannabis* flower for immediate relief from symptoms of depression. *Yale J Biol Med* 2020; **93:** 251–64.

36 Tanda G, Munzar P, Goldberg SR. Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. *Nat Neurosci* 2000; **3:** 1073–74.

37 Justinova Z, Tanda G, Redhi GH, Goldberg SR. Self-administration of delta9-tetrahydrocannabinol (THC) by drug naive squirrel monkeys. *Psychopharmacology* 2003; **169:** 135–40.

38 Freeman TP, van der Pol P, Kuijpers W, et al. Changes in cannabis potency and first-time admissions to drug treatment: a 16-year study in the Netherlands. *Psychol Med* 2018; **48:** 2346–52.

39 Freeman TP, Morgan CJ, Hindocha C, Schafer G, Das RK, Curran HV. Just say 'know': how do cannabinoid concentrations influence users' estimates of cannabis potency and the amount they roll in joints? *Addiction* 2014; **109:** 1686–94.

40 van der Pol P, Liebregts N, de Graaf R, Korf DJ, van den Brink W, van Laar M. Validation of self-reported cannabis dose and potency: an ecological study. *Addiction* 2013; **108:** 1801–08.

41 Leung J, Stjepanovic D, Dawson D, Hall WD. Do cannabis users reduce their THC dosages when using more potent cannabis products? A review. *Front Psychiatry* 2021; published online Feb 18. https://doi.org/10.3389/fpsyt.2021.630602.

42 Lorenzetti V, Chandni H, Petrilli K, et al. The International Cannabis Toolkit (iCannToolkit): a multidisciplinary expert consensus on minimum standards for measuring cannabis use. *Addiction* 2021; **117:** 1510–17.

43 Freeman TP, Lorenzetti V. 'Standard THC units': a proposal to standardize dose across all cannabis products and methods of administration. *Addiction* 2020; **115:** 1207–16.

44 Freeman AM, Petrilli K, Lees R, et al. How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (THC) in humans? A systematic review. *Neurosci Biobehav Rev* 2019; **107:** 696–712.

45 Fischer B, Russell C, Sabioni P, et al. Lower-risk cannabis use guidelines: a comprehensive update of evidence and recommendations. *Am J Public Health* 2017; **107:** e1–12.

United States marijuana legalization and opioid mortality epidemic during 2010–2020 and pandemic implications

Archie Bleyer, Brian Barnes, Kenneth Finn

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Abstract: Background: The hypothesis that marijuana availability reduces opioid mortality merits more complete testing, especially in a country with the world's highest opioid death rate and 2nd highest cannabis-use-disorder prevalence.

Methods: The United States opioid mortality rate was compared in states and District of Columbia that had implemented marijuana legalization with states that had not, by applying joinpoint methodology to Centers for Disease Control and Prevention data. Variables included race/ethnicity and fentanyl-type opioids (fentanyls).

Results: After the same rates during 2010–2012, the opioid mortality rate increased more rapidly in marijuana-legalizing than non-legalizing jurisdictions (2010–2020 annual pairwise comparison $p = 0.003$ for all opioids and $p = 0.0004$ for fentanyls). During the past decade, all four major race/ethnicities in the U.S. had evidence for a statistically-significant greater increase in opioid mortality rates in legalizing than non-legalizing jurisdictions. Among legalizing jurisdictions, the greatest mortality rate increase for all opioids was in non-Hispanic blacks (27%/year, $p = 0.0001$) and for fentanyls in Hispanics (45%/year, $p = 0.0000008$). The greatest annual opioid mortality increase occurred in 2020, the first year of the COVID-19 pandemic, with non-Hispanic blacks having the greatest increase in legalizing vs. non-legalizing opioid-death-rate difference, from 32% higher in legalizing jurisdictions in 2019 to more than double in 2020.

Conclusions: Instead of supporting the marijuana protection hypothesis, ecologic associations at the national level suggest that marijuana legalization has contributed to the U.S.'s opioid epidemic in all major races/ethnicities, and especially in blacks. If so, the increased use of marijuana during the 2020–2022 pandemic may thereby worsen the country's opioid crisis.

Keywords: Marijuana protection hypothesis ■ U.S. opioid mortality epidemic ■ Marijuana legalization ■ Race/ethnicity ■ COVID-19 pandemic

Author affiliations: Archie Bleyer Oregon Health and Science University, 541-610-4782 2884 NW Horizon Dr. Bend, Portland, OR 97703, United States, University of Texas McGovern Medical School, Houston, TX, United States; Brian Barnes St. Charles Healthcare System, Bend, OR, United States, Integral and Transpersonal Psychology, California Institute of Integral Studies, San Francisco, CA, United States; Kenneth Finn Springs Rehabilitation, Colorado Springs, CO, United States

Corresponding author at: Oregon Health and Science University, 541-610-4782 2884 NW Horizon Dr. Bend, Portland, OR 97703, United States.email: ableyer@gmail.com

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INTRODUCTION

The United States (U.S.) has, by far, the world's highest opioid death rate and, as of 2019, was 2nd among all countries and territories in cannabis-use-disorder prevalence (Fig. A.1).[1] The country just set a record for overdose deaths during a 12-month period, more than 100,000 and nearly twice the prior year[2] and of which 70−80% are opioid deaths. Are these dire statistics related, and if so, how?

Three early reports based on a limited number of states in the U.S. presented data supporting the marijuana-protection hypothesis: *availability of marijuana reduces deaths from opioids*.[3–5] A report in 2018 concluded that medical cannabis legalization was associated with a 30% reduction in Schedule III opioid Medicaid prescriptions, no change in Schedule II opioid prescriptions, and an estimate that, if all the states had legalized medical cannabis by 2014, Medicaid annual spending on opioid prescriptions would be reduced by 17.8 million dollars.[6] Another report in 2018 attributed reductions in opioid prescribing in the Medicare Part D population to medicinal cannabis laws, and especially in states that permit dispensaries.[7] A subsequent review concluded that these data were compelling and warranted further exploration of cannabis as an adjunct or alternative treatment for opioid use disorder.[8] The marijuana industry's campaign to advertise legalization then included reduction in opioid mortality as an advantage (Supplemental Fig. A.2). Most recently, the number of marijuana storefront dispensaries per county in states and the District of Columbia (D.C.) that legalized marijuana was found to be inversely correlated with the county's opioid-related mortality rate.[9] The more prevalent the marijuana dispensaries, the lower the opioid death rate.

Other studies have not supported the hypothesis. An initial reduction in opioid mortality after medicinal legalization was found to have reversed to an increase that exceeded the pre-legalization opioid death rate and was greater in legalizing than non-legalizing states.[10] Another analysis found little evidence of an association between medical marijuana law enactment and nonmedical prescription opioid use or prescription opioid misuse.[11] A study of Colorado data did not find evidence that recreational legalization attenuated the state's increasing opioid death rate.[12] In a national epidemiologic survey of

the U.S., nonmedical prescription opioid use increased 5.8-fold (95%CI=4.2–7.9) and opioid use disorder increased 7.9-fold (95%CI=5.0–12.3) within 3 years of using cannabis.[13] In a 4-year prospective-cohort study of 1514 patients with chronic non-cancer pain, those who used cannabis daily or near-daily used more opioids than those who did not.[14] In an individual-level analysis of a nationally representative sample, medical cannabis use was positively associated with greater use and misuse of prescription opioids.[15] Among college students, marijuana users were 12 times more likely to use opioids than non-users ($p < 0.02$) and the level of marijuana use was associated with greater likelihood of using opioids ($p < 0.02$).[16] Among pregnant women, the rate of opioid-related treatment admissions was 2.5-fold in states that legalized medicinal marijuana.[17] Both of two large U.S. studies of driving-while-intoxicated arrests showed that drivers testing positive for marijuana also tested positive for opioids more than those testing negative for marijuana.[18] Self-reported marijuana use during injury recovery was associated with an increased amount and duration of opioid use.[19] And for alcohol, when recreational marijuana was legalized in Canada and alcohol-related vehicle accidents were expected to decrease, there was no evidence for this effect in British Columbia.[20] In Norway and Israel, patients on opioids who were provided cannabis prescriptions had some subsequent decrease in opioid use, but overall the reductions were marginal.[21,22] Reviews of randomized trials have concluded that for acute pain cannabinoids were no better than placebo[23] and for chronic pain only marginally better than conventional pain management with pharmacotherapy, physical therapy, or a combination of these.[24] In the most recent report, a state-by-state analysis comparing 2006–2011 with 2000–2005 found no overall association between state medical cannabis laws and the rate of opioid overdose.[25]

To more adequately test the *marijuana-protection hypothesis* with more recent data, we evaluated all 50 states and D.C. during the last decade (2010–2020) by comparing opioid mortality rates in jurisdictions states that had or had not by the start of 2020 legalized marijuana for all opioids and the fentanyl group of synthetic opioids, and recreational marijuana legalization. We also analyzed race/ethnicity, which had not, to our knowledge, previously been analyzed with respect to marijuana legalization *per se*. The COVID-19 pandemic that began in March 2020 significantly altered prior opioid overdose and mortality trends and is therefore separately and provisionally analyzed.

METHODS

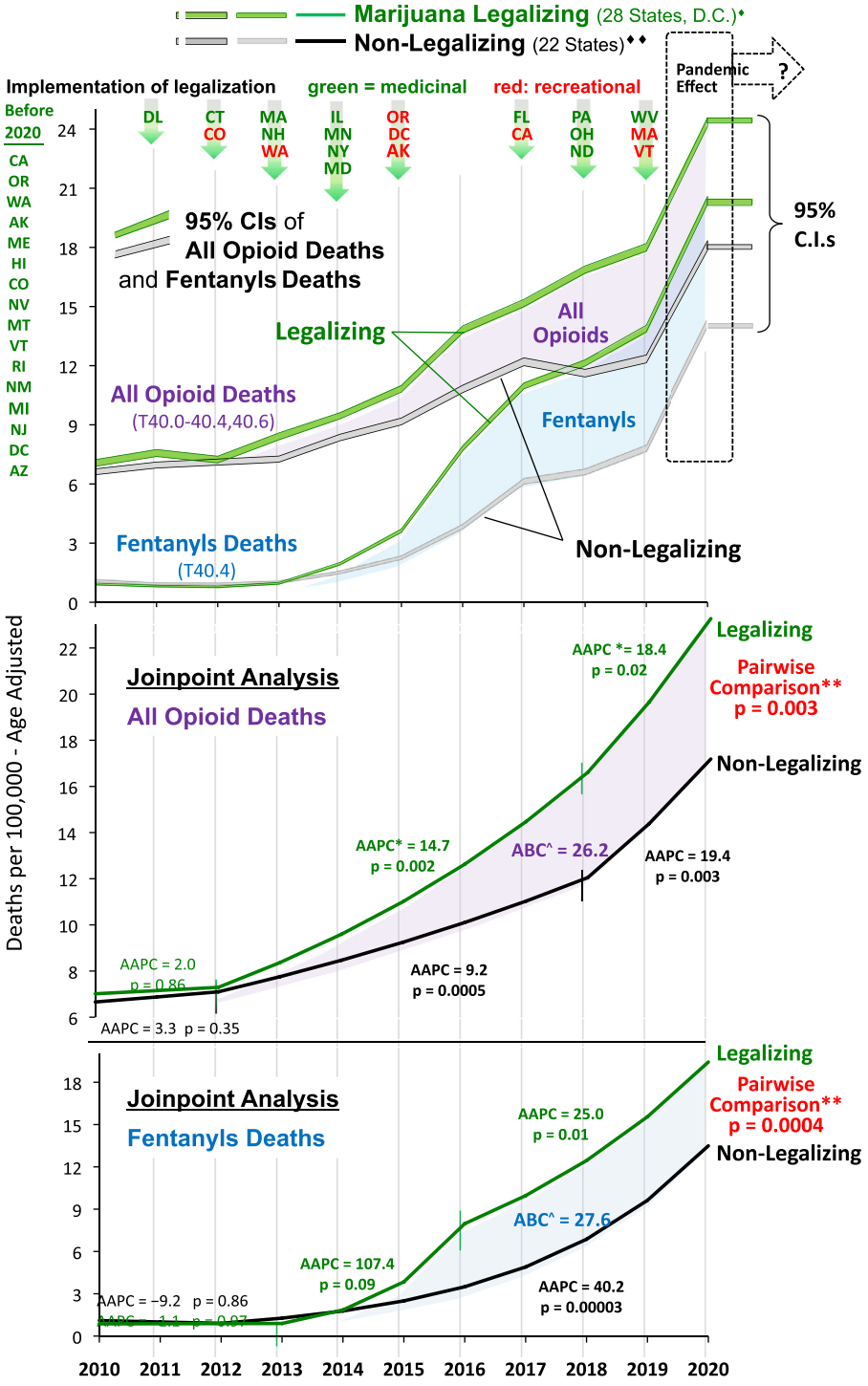
Age-adjusted opioid death data in the U.S. were obtained from CDC WONDER.[26] Trend analysis was performed with Joinpoint Regression Program version 4.9.0.0,[27] applying weighted least squares, logarithmic transformation, and standard errors provided by the Program. The Joinpoint Regression Program identifies when a trend changes to another trend, the average annual percent change (AAPC) and p-values for each trend detected, and relative comparison of concomitant trends via pairwise comparison with either parallel or non-parallel methodology for which we selected the latter. Our primary comparisons and most subtype comparisons were of trends that were not significantly different in the initial years (2010–2012) and hence difference-in-difference method was not necessary and for which we also quantitated the difference between joinpoint-derived regression curves from the area between the curves (ABC).

International Classification of Disease (ICD) codes for accidental poisoning (X40-X44), intentional self-poisoning (X60-X64), and other poisoning (Y10-Y14) were used in conjunction with following opioid T-Codes: T40.0 opium, T40.1 heroin, T40.2 other opioids, T40.3 methadone, T40.4 fentanyl and its semisynthetic derivatives (hereafter referred to as *fentanyls*), T40.6 other synthetic narcotics.[28] These categories include morphine, hydromorphone, oxycodone, fentanyl, semisynthetic fentanyl moieties, heroin, opium, codeine, meperidine, methadone, propoxyphene, tramadol, and other/unspecified narcotics. Because of the dramatic increase in fentanyls deaths since 2014, this category (T40.6) was also separately analyzed.

Supplemental Table A.1 lists each state and D.C. by whether and when marijuana legalization for medicinal or recreational use was implemented. The legalization implementation dates before 2015 are those published by Powell et al.[4] Those after 2015 are either from Powell et al.,[4] Martins et al.,[29] or additional information an indicated in Supplemental Table A.1.[30–34]

As of the start of 2020, 29 jurisdictions (28 states and D.C.) had implemented marijuana legalization (the Legalizing Group), as shown at the top of Fig. 1 and listed in Supplemental Table A.1, and 22 states that had not (Non-Legalizing Group), as delineated in Supplemental Table A.1.[30–34] Georgia, North Carolina, South Carolina, Texas and Wisconsin were included in the non-legalizing group since they legalized only CBD oil for medicinal use and primarily for epilepsy. Arkansas was not included in the Legalizing Group with the assumption that medicinal licenses were not statewide until 2020 (Supplemental Table A.1). Including Arkansas in the Legalizing Group

Fig. 1. 95% CIs (top panel) and Joinpoint/AAPC* Analysis (middle and bottom panels) of Annual Opioid Death Rates, 2010–2020, of Cumulative Aggregate of Marijuana Legalizing Jurisdictions (green data)^ and of Non-Legalizing Jurisdictions (black data)^^, U.S., by All Opioids and Fentanyl.
* AAPC - average annual percent change ** non-parallel, joinpoint analysis
♦ 28 states and D.C., in temporal order of legislation implementation: CA-California, OR-Oregon, WA-Washington, AK-Alaska, ME-Maine, HI-Hawaii, CO–Colorado, NV-Nevada, MT-Montana, VT-Vermont, RI-Rhode Island, NM-New Mexico, MI-Michigan, NJ-New Jersey, DC-D.C., AZ-Arizona, DL-Delaware, CT-Connecticut, MA-Massachusetts, NH–New Hampshire, IL-Illinois, MN-Minnesota, NY-New York, MD-Maryland, FL-Florida, PA-Pennsylvania, OH–Ohio, ND-North Dakota, WV-West Virginia
♦♦ 22 remaining states
^ AUC - area between the curves, in deaths per 100,000
Data Source: CDC WONDER.[26]



did not alter the results (Supplemental Figure A.3). Using year of legalization instead of year of implementation of legalization accentuated the difference in the all-opioids results and did not significantly alter the fentanyls results (Supplemental Figure A.4). Difference-in-difference methodology was unnecessary to compare subsequent trends since the rates in the two groups were nearly identical for the initial three years of comparison. Also, joinpoint methodology has both parallel and non-parallel pairwise comparison capability.

THEORY/CALCULATION

To more adequately test the marijuana-protection hypothesis, we evaluated all 50 states and D.C. during the last decade (2010–2020) by comparing opioid mortality rates in 22 states that by start of 2020 had not legalized marijuana with a cumulative aggregate of 28 states and D.C. that had. Variables included race/ethnicity and the fentanyl category of synthetic opioids, the latter since they account for most of the recent increase in opioid mortality. Recreational marijuana legalization was assessed in five evaluable states and D.C. The COVID-19 pandemic that began in March 2020 significantly altered prior opioid overdose and mortality trends and is therefore separately and provisionally analyzed.

RESULTS AND DISCUSSION

Al opioids and fentanyls comparisons

During 2010–2012, the annual opioid death rates were similar in the Legalizing and Non-Legalizing Groups, with overlapping 95%confidence intervals (CIs) in 2010 and 2012 (Fig. 1 top panel) and similar non-statistically significant trends (AAPC=2.0, $p = 0.86$ and AAPC=3.3, $p = 0.35$, respectively) (Fig. 1 middle panel). Thereafter, the annual opioid death rate increased in both groups, continuously more rapidly during 2012–2020 in the Legalizing Group whereas the increase in the Non-Legalizing Group slowed and stabilized during 2017–2018 before increasing again during 2019–2020 (Fig. 1 top panel). Joinpoint analysis identified a faster rate of increase in the opioid death in the Legalizing Group, with AAPCs of 14.7 ($p = 0.002$) vs. 9.2 ($p = 0.0005$) during 2012–2018 and an overall 2010–2020 non-parallel pairwise comparisons of $p = 0.003$ (Fig. 1 middle panel). Over the entire 2010–2020 decade, the mean rate in the Legalizing and Non-Legalizing Groups increased 16.8 (227%) and 11.1 (160%) deaths per 100,000 per year, respectively, and the Legalizing vs. Non-Legalizing ABC was 26.2 and 27.6 deaths per100,000 for all opioids and fentanyls, respectively (Fig. 1 middle and bottom panels).

The initial greater increase in the Legalizing Group occurred before the fentanyls epidemic. By 2016, however, the opioid death rate increase was primarily due to fentanyls, especially in the Legalizing Group (Fig. 1 top panel). During 2020, the first year of the pandemic, the opioid death rate accelerated in both Legalizing and Non-Legalizing Groups, due nearly entirely to fentanyls deaths (Fig. 1 top panel). Over the entire 2010–2020 decade, the fentanyls death rate increase was significantly greater in the Legalizing Group (joinpoint non-parallel pairwise comparison $p = 0.0004$) (Fig. 1 bottom panel).

Race/ethnicity trends

Each of the four most common categories of race/ethnicity in the U.S. had evidence for a statistically-significant greater increase in opioid mortality rates during 2010–2020 in the marijuana Legalizing than Non-Legalizing Groups, as measured by annual pairwise comparisons (Fig. 2). In the Legalizing Group, the fastest mortality rate increase for all opioids occurred in non-Hispanic blacks (AAPC=27.0, $p = 0.0001$), whereas for fentanyls it was in Hispanics (AAPC=45.0, $p = 0.0000008$). Non-Hispanic blacks had the greatest absolute differences (ABC=52.2 deaths/100,000) (Fig. 2). Non-Hispanic whites had the greatest statistically-significant differential rate increase between legalizing and non-legalizing jurisdictions, for both all-opioid and fentanyls mortality (annual pairwise comparisons of $p = 0.0002$ and $p = 0.0001$, respectively) (Fig. 2). For all opioids, Asians had no difference in rate increases between legalizing and non-legalizing jurisdictions but for fentanyls they had a distinctly greater increase in legalizing than non-legalizing jurisdictions (pairwise comparison $p = 0.0009$) (Fig. 2).

In terms of year-to-year changes in the annual death rate opioid death rate, it increased steadily overall and in each racial/ethnic population until 2016 after which it declined for 2 years until 2019, the year before the pandemic, mainly due to fentanyls (Fig. 3). Non-Hispanic blacks had the greatest single-year mortality increase prior to the pandemic, both for all opioids and fentanyls (Fig. 3) and by 2019 had the highest death rates for both all opioids and fentanyls (Fig. 4 middle panel). In 1999, Hispanics had the greatest difference between legalizing and non-legalizing jurisdictions, 165% higher in the Legalizing Group for all opioids and 249% higher for fentanyls (Fig. 4 bottom panel).

Fig. 2. Joinpoint/AAPC* Analysis of Pre-Pandemic Annual All Opioid (solid curves) and Fentanyls (dashed curves) Death Rates, 2010–2019, of Legalizing Aggregate (green data) and Non-Legalizing Jurisdictions (black data), U.S., by Race/Ethnicity.
Left Panels: All-Opioid Death Rates; Right Panels: Fentanyls Death Rates
* AAPC - average annual percent change ** non-parallel, joinpoint analysis
^ AUC - area between the curves, in deaths per 100,000
Data Source: CDC WONDER.[26]

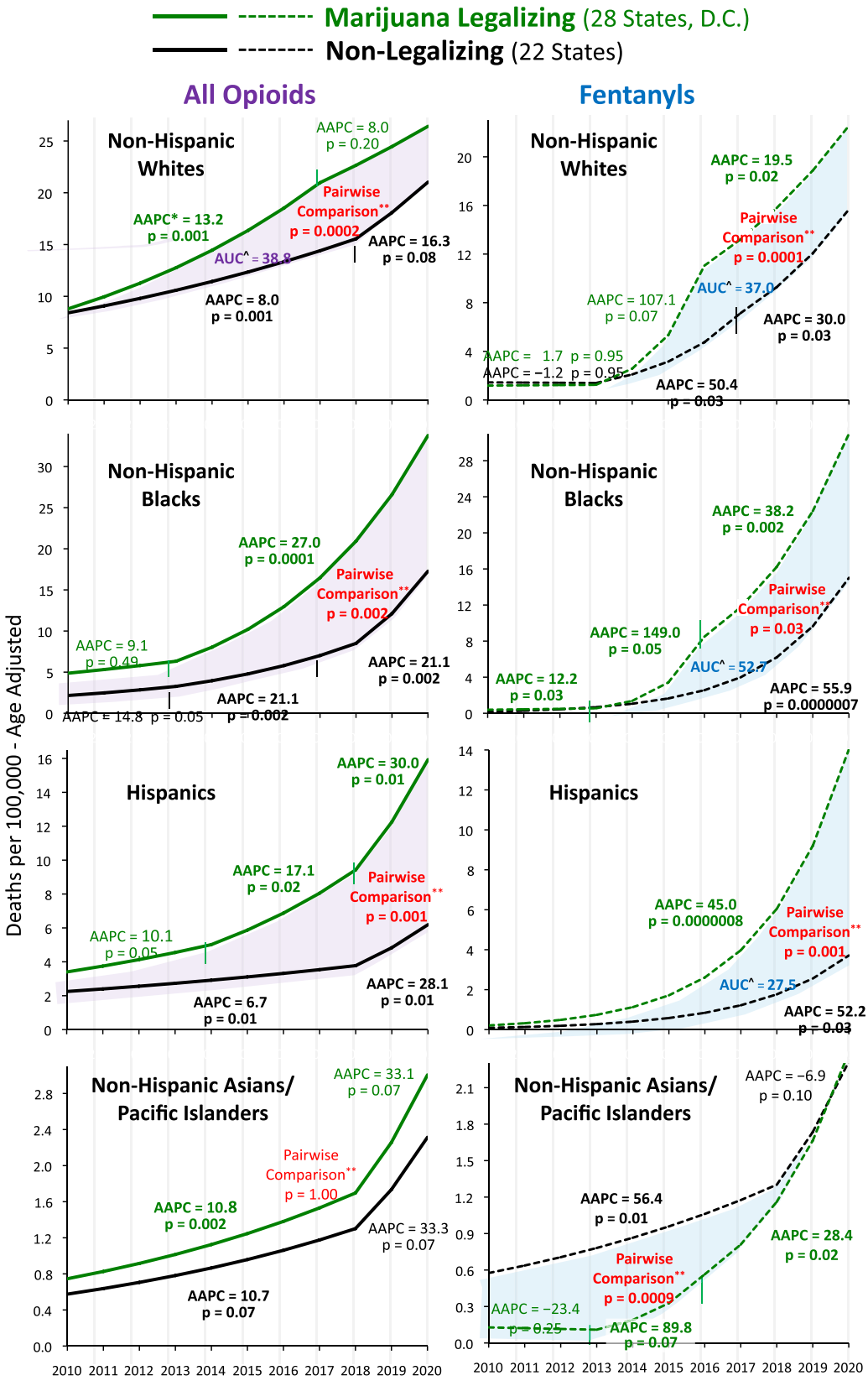


Fig. 3. Annual Change (from year before) in Opioid Death Rate, 2010–2020, U.S., Overall and by Race/Ethnicity and by Portion due to Fentanyls (blue zones).
* Labeled percentages are increases in all opioid deaths from year before
Data Source: CDC WONDER.[26]

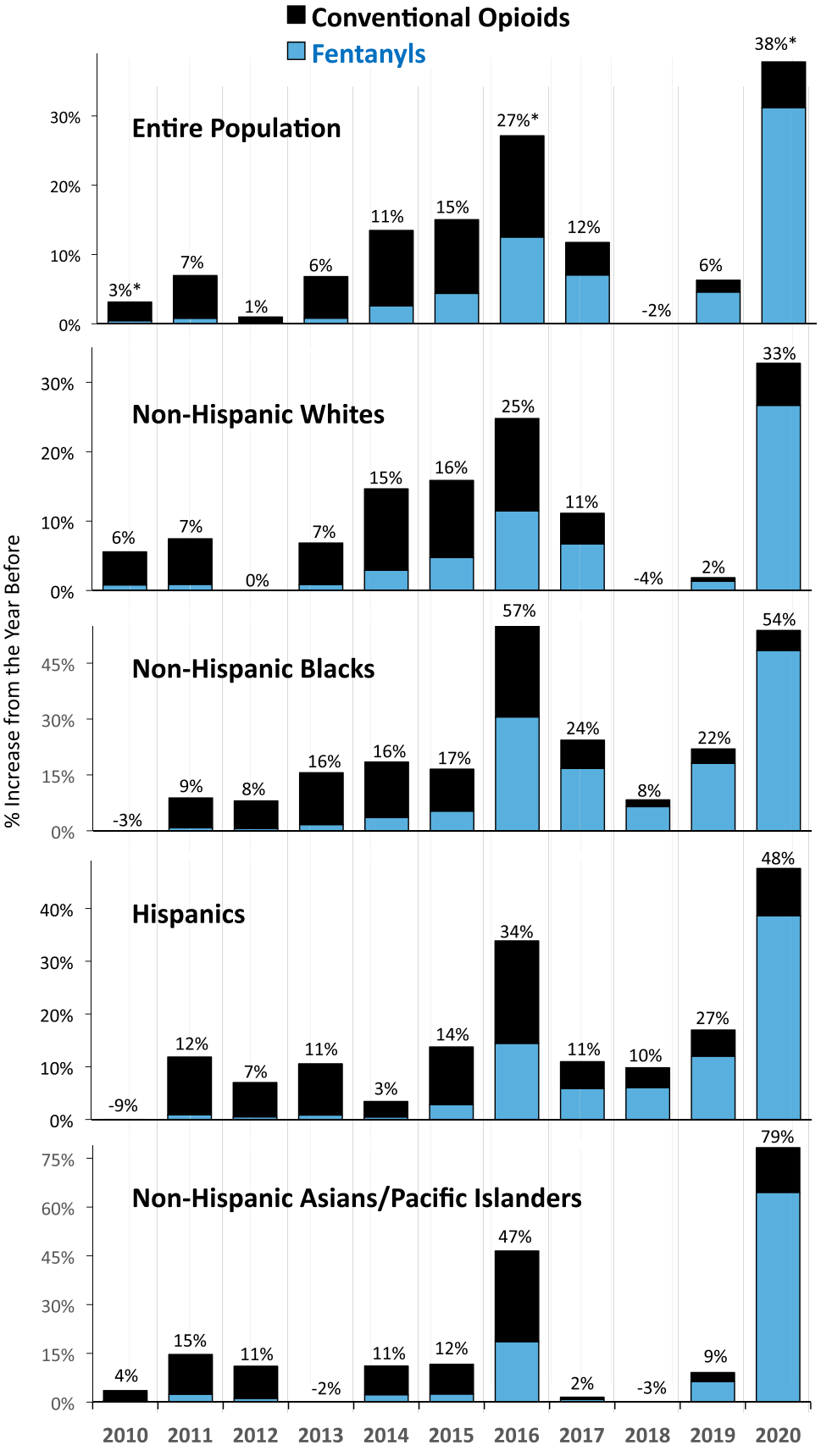
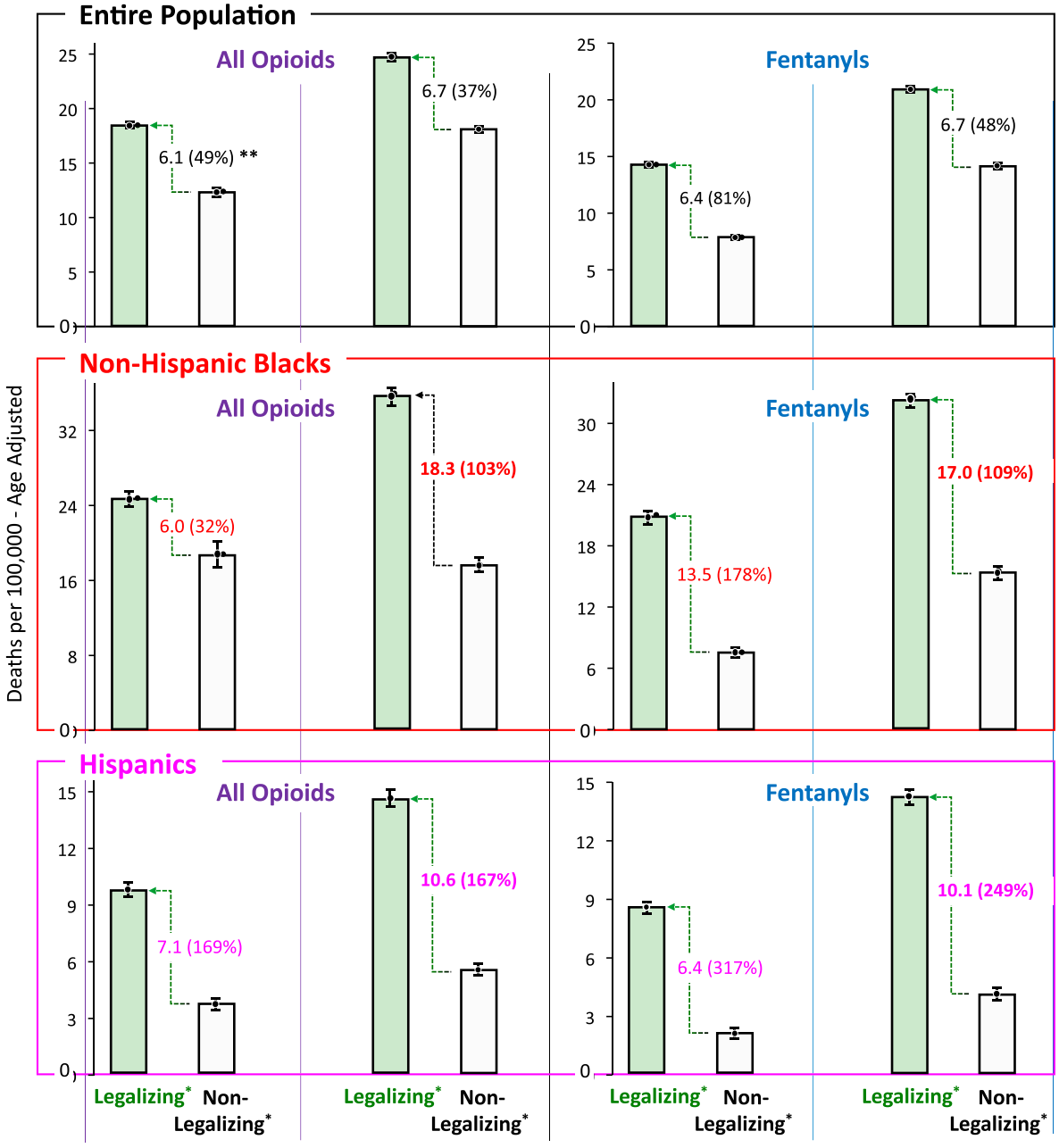


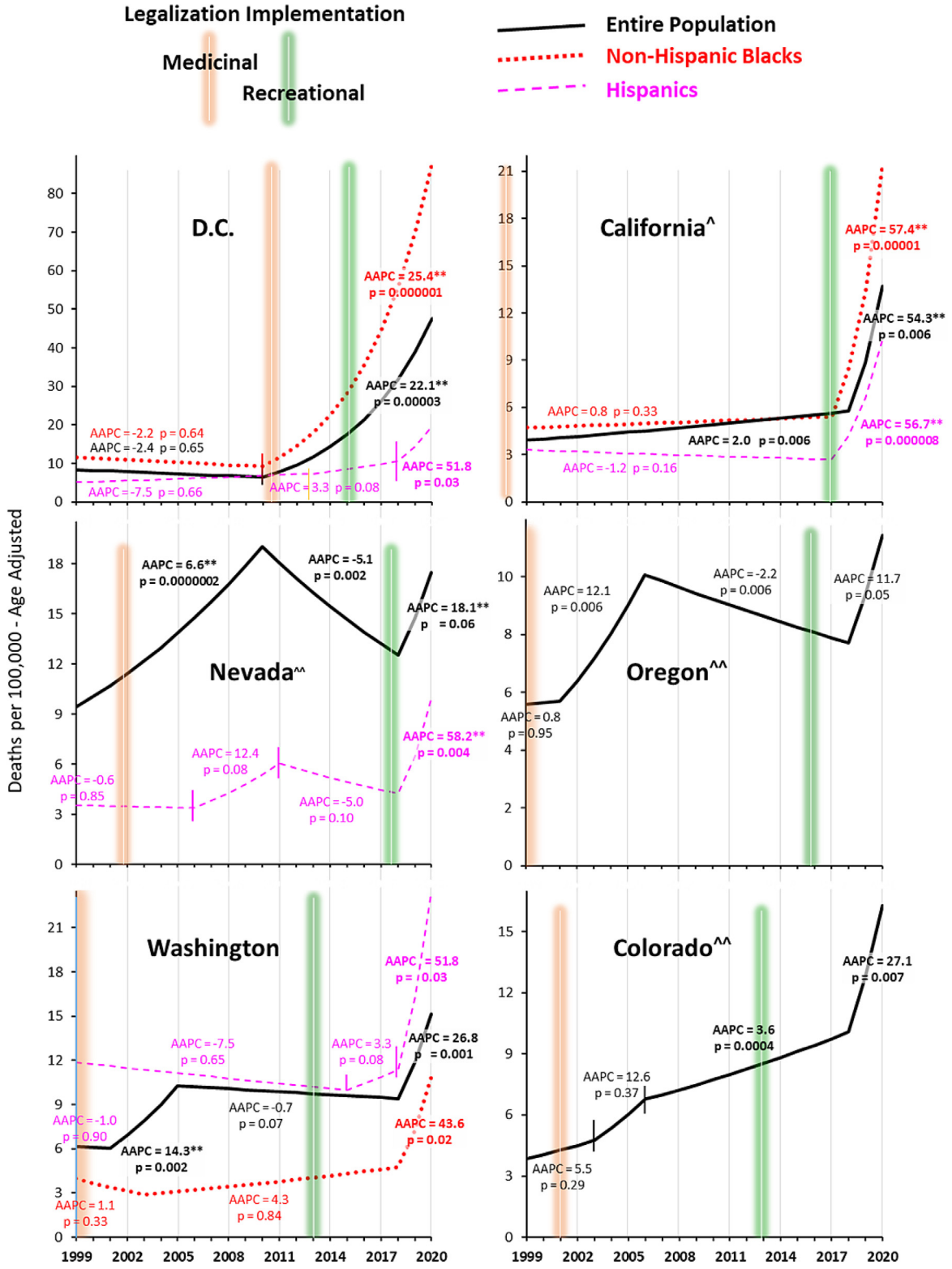
Fig. 4. All Opioid and Fentanyls Death Rate Means & 95% C.I.s among Entire Population, Non-Hispanic Blacks and Hispanics, 2019 and 2020, by Jurisdiction Marijuana Legalization Implementation Status.
* 29 legalizing and 22 non-legalizing jurisdictions as of January 1, 2020
** Absolute difference and % greater the legalizing mean was compared to the non-legalizing mean.
Data Source: CDC WONDER.[26]



Recreational legalization

Fig. 5 shows the 6 jurisdictions that legalized recreational use prior to 2017 and are evaluable for comparison of their pre-recreational-legalization opioid death rate trend after recreational legalization implementation and before the pandemic. D.C. had a reversal of what was a slightly decreasing rate prior to legalization to an exponentially increasing rate that began within 1 year after medicinal legalization implementation was even more rapid after recreational legalization. California also had an exponential increase in its opioid trend within 1 year after recreational legalization. Nevada, Oregon, and Washington had a reversal of a previous decreasing death rate within 1, 3 and 5 years after recreational legalization. Colorado had an increase 6 years after statewide recreational use began.

Fig. 5. Joinpoint/AAPC* Analysis of Annual All-Opioid Death Rate, 1999–2020, in Jurisdictions that Implemented Recreational Legalization of Marijuana before 2019.
* AAPC – Average annual percent change **Exponential increase
^ California legalized medicinal use in 1996
^^ Race/ethnicity evaluation limited by population size
Data Source: CDC WONDER.[26]



Non-Hispanic blacks in California had an exponential opioid death rate increase that began within 1 year of recreational legalization (AAPC=57.4, $p = 0.00001$) (Fig. 5). The non-Hispanic black rate in the Nation's capital became the highest in the country in 2019 and 2nd highest in 2020. Hispanics had a reversal of a previous decreasing death rate within 1 year after recreational legalization in In California and Nevada and within 3 years in Washington (Fig. 5). None of the jurisdictions had evidence for a decrease in, or even a slowing of, their pre-recreational implementation trend after recreational implementation, either overall or in the evaluable Hispanic and non-Hispanic black trends.

Initial impact of COVID-19 pandemic

During the first year of the COVID-19 pandemic, 2020, the overall opioid death rate in the U.S. increased 38% from the previous year, the greatest annual increase since at least 1999 when the metric was first tracked and 39% greater than the greatest prior annual increase since 1999, in 2016 (Fig. 3 top panel). Since 1999, the U.S. went from its least year of annual opioid mortality increase, 2018, to its worst increase, in 2020, in just 2 years (Fig. 3). Asians/Pacific Islanders had the greatest increase from 2019 to 2020, 79%, and non-Hispanics had the second greatest increase, 54%, followed by Hispanics, 45% (Fig. 3). Fentanyls accounted for more of the pandemic increases in non-Hispanic blacks than in any of the other race/ethnicities (Fig. 3).

In terms of the marijuana legalization status, the increase in both all opioid and fentanyls death rate from 2019 to 2020 was greater in the Legalizing Group for the entire population and for each of the race/ethnicities (Fig. 4). The greatest differential from 2019 to 2020 was in non-Hispanic blacks, from 6 deaths/100,000 (32%) higher in the Legalizing Group in 1999 for all opioids to more than double (18.3 deaths per 100,000 (103%) in 2020 (Fig. 4 middle panel). Asians had the greatest relative increase from 2019 to 2020 (Fig. 3 bottom panel) but the least difference between Legalizing and Non-Legalizing Groups.

Summary

As analyzed, the U.S. data we investigated do not support the *marijuana protection hypothesis*. Undoubtedly, marijuana can help some avoid opioid addiction and overdosing, but at the population level this benefit is not apparent in the U.S. We found no evidence for a reduction in either all opioids or fentanyls death rate in any of the four most common race/ethnicities during the last decade among marijuana legalizing jurisdictions, whether after medicinal or recreational legalization. On the contrary, our results indicate that marijuana legalization is associated with worsening of opioid mortality, whether it was primarily due to conventional opioids, during 2013–2015, or to fentanyls, during 2015–2020.

Gateway potential and biologic mechanisms

The critical issue then is whether the association of opioid mortality with marijuana legalization is causal or unrelated, and if causal, how much of the opioid mortality increase is due to marijuana legalization. Several causal mechanisms can be considered. Biologically, a gateway explanation for the marijuana-opioid connection is plausible since cannabinoids act in part via opioid receptors[35] and increase dopamine concentrations similarly to that caused by opioids.[36,37] Behaviorally and socially, marijuana may be a conduit to the use and eventual abuse of opioids and other addicting substances.[38–44] A national study of 43,093 cannabis user in the U.S. found that 10%, 20%, and 30% of them had progressed to illicit drug use within 3, 5 and 7 years, respectively, of first exposure to cannabis.[42] A study of 580 youth followed from ages 6 to 26 found that adolescent-onset marijuana use was associated with opioid misuse in young adulthood, including adjustment for socioecological factors associated with opioid misuse.[43] Cannabis use disorder in 21,040 youth aged 10–24 years was linked to a 2.4 (95% CI = 1.39-4.16) higher risk of unintentional overdose death within one year after cannabis disorder diagnosis.[44]

Marijuana's euphoric effect may promote opioid use, including other types such as fentanyls. In a study of U.S. adults with non-medical opioid abuse, opioid use was found to be approximately doubled on days when marijuana was used.[45] Because in the study this relationship did not appear to depend on pain severity, the authors suggested that marijuana was not used as a substitute for illegal opioids.[45] Nonetheless, marijuana use was associated with greater illicit opioid use. Also, to the extent that marijuana may ameliorate opioid withdrawal symptoms, users may abuse more opioids since they are not reminded of their addiction situation.

Marijuana's addiction potential is becoming more problematic,[46] as indicated by the increase in cannabis use disorder prevalence, and especially in the U.S. (Supplemental Fig. A.1). Deaths from marijuana are being increasingly reported, as reported in death certificates reviewed by the CDC. In the U.S., the rate has increased to >1000 deaths per year, and the greatest increase in the rate has been among non-Hispanic blacks (Supplemental Fig. A.5).

Legalizing jurisdictions may also have a culturally greater affinity for substance abuse and be more vulnerable to gateway mechanisms. As noted in Canada, mari-

juana may lead to premature withdrawal from opioid addiction treatment programs.[47] Although legalization is expected to decrease illicit activity, the black market may paradoxically benefit from access to more abundant hemp and marijuana crops, providing lower prices, and delivering marijuana to users instead of them having to travel to licensed dispensaries.[48] And, increasingly, because of decreasing wholesale prices of recreational marijuana as legal marketers have proliferated are now partnering with black market operatives to "subsidize our white market with our black market".[49]

Other studies have documented increases in overdose deaths before and during the pandemic in Hispanic and black Americans.[50–52] These reports do not specifically mention a possible association with marijuana legalization, but each recommends more research to understand contributing causes.

To the extent that the opioid epidemic may have become worse because of marijuana legalization, it is likely that the opioid mortality acceleration is due more to other factors such as the increasing availability of and lower cost of fentanyls and other non-prescriptions opioids, the increasing despair of Americans that began before the pandemic and has become worse during it, and the drug culture of the U.S. in general. Also decreased availability of prescription narcotics, as has been accomplished by the medical and pharmacy profession, has increased the demand for and use of black market narcotics. Nonetheless, general legalization of a psychoactive substance increases the drug culture of the society in which it is made available, analogous to the U.S. alcohol post-prohibition history.

Conventional opioids and fentanyls comparisons

The association of marijuana legalization and opioid mortality appears applicable to conventional opioid epidemic before widespread fentanyls' availability and to the subsequent fentanyls epidemic. To the extent that the preceding conventional-opioid phase of the opioid epidemic increased opioid addiction, the subsequent increased availability and lower cost of fentanyls may have been facilitated by marijuana legalization. Since most jurisdictions that legalized marijuana had previously decriminalized it, the increased freedom to use previously illicit substances may have also promoted the fentanyl black market. In any event, the opioid morality increase was greater in legalizing than non-legalizing jurisdictions during both the pre-fentanyls and fentanyls eras. As to race/ethnicity differences, fentanyls have affected Hispanics and black Americans more than other races/ethnicities, as cited in the Introduction, and the combination of opioids with either cocaine or methamphetamine and other stimulant drugs has been reported to have increased more in non-Hispanic blacks and cocaine/opioid overdose mortality more in Hispanic and Asian Americans.[53]

Initial pandemic impact

According to preliminary data from the CDC based on data available for analysis on January 2, 2022,[54] the U.S. had the greatest recorded annual increase in opioid mortality rate during the first year of the pandemic and it further increased 20+% from June 2020 to June 2021.[55] Our results quantitate the increase in 2020 at 38%, and comparable overall in both legalizing and non-legalizing jurisdictions. Among Hispanics and non-Hispanic blacks, however, the absolute and relative differences between the higher rate in the legalizing than non-legalizing jurisdictions worsened, both for all opioids and for fentanyls. The 2020 rates are stated by the CDC to be under-reported due to incomplete data[55,56] and hence the actual 2020 increases are probably even greater. Meanwhile, marijuana legalization in the U.S. continues to expand and marijuana sales have skyrocketed during the COVID-19 pandemic.[57]

Limitations

Our investigation has several limitations. Most importantly, the ecological design does not establish attribution or causation. Factors other than marijuana legalization may have resulted in the marijuana legalizing jurisdictions having a higher opioid death rate. Legalizing jurisdictions that are more willing to enable cannabis use may be culturally and psychosocially different from those that are not, in ways that enable opioid abuse such as differences in socioeconomic status, race/ethnicity, or medical and psychiatric diagnoses that may have caused more opioid deaths in legalizing jurisdictions. The economic issue is particularly concerning, given how opioid use disorder is considered as a "disease of despair" brought about by economic hardship. On the other hand, the 2020 gross domestic product per capita in the legalizing states we analyzed was greater than in the non-legalizing states, with means (95% CI) of $65,584 ($63,139-$68,029) and $56,023 ($54,252-$57,794), retrospectively ($p = 0.02$) (Supplemental Table A.2).[58] With only six evaluable recreational-legalizing jurisdictions, potential differences in the impact of medicinal and recreational legalization could not be quantitated, albeit in the U.S. the degree of overlap between medicinal and recreational cannabis users has been estimated to be nearly 90%.[59]

On the other hand, ecologic associations have been used to support most of the studies that we have cited, including one that theoretically contradicts our results with the

county-level analysis cited in the Introduction. In it, the authors found that the number of marijuana storefront dispensaries during 2014–2017 was inversely correlated with opioid mortality rate during 2014–2018 jurisdictions that by 2017 had legalized marijuana.[9] The authors did not, however, adjust dispensary store number for population size and thereby likely represented disproportionate usage by more populous counties and by relatively small factions of the community of marijuana users. Also, the impact of legalization *per se* was not directly assessed since jurisdictions that legalized toward the end of the surveillance interval were included. Also, counties in legalizing jurisdictions were not compared with counties in non-legalizing jurisdictions. In a secondary analysis that included the rest of the U.S. that had not legalized marijuana, nearly all of the inverse correlations of dispensaries with opioid death rates were weaker or statistically insignificant. The authors also acknowledged that the source of dispensary information they selected (Weedmaps) had multiple limitations.

Strengths

The current investigation also has several advantages over prior reports. It adds 9, 6, 4, 2 and 1 additional follow-up years to the prior studies.[3,4,5,12,11, respectively] Compared to the most recently reported state-level analysis[25] that presented 2000–2011 data, we included more recent data, up to 2019 and preliminary data for 2020. In comparison to a report that showed a reversal of initial benefit to worsening opioid mortality,[10] our analysis adds two more years of data and D.C., and further strengthens the reversal observation. It also differs in that our control group was states that had not legalized marijuana whereas their control group began with all states and excluded those that legalized when they did. Our analysis of their data shows a divergence in the opioid death rates during 2012–2017 that is similar to what we observed during those years (Fig. 1). Also, we included separate analyses of the T40.4 category of fentanyl and semi-synthetic analogues and we included heroin and opium that were either not assessed[3,4,11,12] or specified[5,12] in prior studies.

Comparison with other conclusions

The National Academy of Sciences,[60] International Association for the Study of Pain,[61] and other experts[62–64] have concluded that jurisdiction regulations that allow medical cannabis as an opioid substitute for chronic pain or addiction have at best equivocal evidence regarding safety, efficacy, and comparative effectiveness, and substantial evidence that substituting opioid addiction treatments with cannabis is potentially harmful.

IMPLICATIONS

Opioid mortality trends in the United States, a world leader in both opioid mortality and cannabis use disorder, do not support the hypothesis that marijuana availability reduces opioid mortality. During the past decade, the country's opioid mortality trends in marijuana legalizing and non-legalizing jurisdictions suggest the opposite. Non-Hispanic blacks and Hispanics in particular need assistance in reversing trends that may have been facilitated by marijuana legalization. Worsening of its opioid mortality epidemic during the first year of the COVID-19 pandemic, especially deaths from fentanyls and including prescription semi-synthetic opioids,[2] and its potential causal relationship with the country's increased marijuana legalization, availability and utilization merits in-depth research. Until then, recommendations to legalize marijuana should not be based on attenuating the opioid crisis, and jurisdictions and other countries considering legalization should be prepared to provide more drug overdose prevention.

DECLARATION OF COMPETING INTEREST

All authors have no interests to disclose.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jnma.2022.03.004.

REFERENCES

1. Institute for Health Metrics and Evaluation (IHME). *GBDCompareDataVisualization* Seattle, WA: IHME, University of Washington; 2020 Available from *http://vizhub.healthdata.org/gbd-compare* Accessed December 5, 2021).
2. Drug overdose deaths in the U.S. top 100,000 annually. National Center for health statistics, centers for disease control and prevention. https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm. Accessed February 16, 2022.
3. 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. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/1898878. doi:101001/jamainternmed20144005.
4. Powell D, Pacula RL, Jacobson M. Do medical marijuana laws reduce addictions and deaths related to pain killers? *J Health Econ*. 2018;58(March):29–42 PMID: 29408153.
5. Livingston MD, Barnett TE, Delcher C, Wagenaar AC. Recreational cannabis legalization and opioid-related deaths in Colorado, 20002015. *Amer J Public Health*. 2017;107(11, November 17):1827–1829.

6. Liang D, Bao Y, Wallace M, Grant I, Shi Y. Medical cannabis legalization and opioid prescriptions: evidence on US Medicaid enrollees during 1993–2014. *Addiction*. 2018;113(11):2060–2070 Nov. doi:10.1111/add.14382.

7. Bradford AC, Bradford WD, Abraham A, Adams GB. Association Between US state medical cannabis laws and opioid prescribing in the Medicare part D population. *JAMA Intern Med*. 2018;178(5):667–672. doi:10.1001/jamainternmed.2018.0266.

8. Wiese B, Wilson-Poe AR. Emerging evidence for cannabis' role in opioid use disorder. *Cannabis Cannabinoid Res*. 2018;3(1):179–189 Sep 1. doi:10.1089/can.2018.0022.

9. Hsu G, Kovács B. Association between county level cannabis dispensary counts and opioid related mortality rates in the United States: panel data study. *BMJ*. 2021;372:m4957. doi:10.1136/bmj.m4957.

10. Shover CL, Davis CS, Gordon SC, Humphreys K. Association between medical cannabis laws and opioid overdose mortality has reversed over time. *Proc Natl Acad Sci U S A*.. 2019;116(26):12624–12626 Jun 25.

11. Segura LE, Mauro CM, Levy NS, et al. Association of US medical marijuana laws with nonmedical prescription opioid use and prescription opioid use disorder. *JAMA Netw Open*. 2019;2(7):e197216 Published 2019 Jul 3. doi:10.1001/jamanetworkopen.2019.7216.

12. Alcocer JJ. Exploring the effect of Colorado's recreational marijuana policy on opioid overdose rates. *Public Health*. 2020;185:8–14. doi:10.1016/j.puhe.2020.04.007.

13. Olfson M, Wall MM, Liu SM, Blanco C. Cannabis use and risk of prescription opioid use disorder in the United States. *Am J Psychiatry*. 2018;175(1):47–53 Jan 1.

14. Campbell G, Hall WD, Peacock A, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. *Lancet Public Health*. 2018;3:e341–e350 (July).

15. Caputi TL, Humphreys K. Medical marijuana users are more likely to use prescription drugs medically and non-medically. *J Addict Med*. 2018;12(4):295–299. doi:10.1097/ADM.

16. Palfai TP, Tahaney KD, Winter MR. Is marijuana use associated with health promotion behaviors among college students? Health-promoting and health-risk behaviors among students identified through screening in a university student health services center. *J Drug Issues*. 2016;46(1):41–50.

17. Meinhofer A, Witman A, Murphy SM, Bao Y. Medical marijuana laws are associated with increases in substance use treatment admissions by pregnant women. *Addiction*. 2019;114(9):1593–1601. doi:10.1111/add.14661.

18. Li G, Chihuri S. Is marijuana use associated with decreased use of prescription opioids? Toxicological findings from two US national samples of drivers. *Subst Abuse Treat Prev Policy*. 2020;15(1):12 Published 2020 Feb 17. doi:10.1186/s13011-020-00257-7.

19. Bhashyam AR, Heng M, Harris MB, Vrahas MS, Weaver MJ. Self-reported marijuana use is associated with increased use of prescription opioids following traumatic musculoskeletal injury. *J Bone Joint Surg*. 2018;100(24):2095–2102 (Dec 19).

20. Brubacher JR, Chan HC, Erdelyi S, Staples JA, Asbridge M, Mann RE. Cannabis legalization and detection of tetrahydrocannabinol in injured drivers. *N Engl J Med*. 2022;386:148–156. doi:10.1056/NEJMsa2109371.

21. Bramness JG, Hjellvik V, Stubhaug A, Skurtveit S. Possible opioid-saving effect of cannabis-based medicine using individual-based data from the Norwegian Prescription Database. *Basic Clin Pharmacol Toxicol*. 2021 Sep 24Epub ahead of print. PMID: 34559439. doi:10.1111/bcpt.13660.

22. Sznitman S, Mabouk C, Said Z, Vulfsons S. Opioid and healthcare service use in medical cannabis patients with chronic pain: a prospective study. *BMJ Support Palliat Care*. 2021 Sep 14:bmjspcare-2020-002661Epub ahead of print. PMID: 34521640. doi:10.1136/bmjspcare-2020-002661.

23. Stevens AJ, Higgins MD. A systematic review of the analgesic efficacy of cannabinoid medications in the management of acute pain. *Acta Anaesthesiol Scand*. 2017;61(3):268–280 Mar. doi:10.1111/aas.12851.

24. Meng H, Johnston B, Englesakis M, Moulin DE, Bhatia A. Selective cannabinoids for chronic neuropathic pain: a systematic review and meta-analysis. *Anesth Analg*. 2017;125(5):1638–1652 Nov. doi:10.1213/ANE.0000000000002110.

25. Kim JH, Martins SS, Shmulewitz D, Hasin D. Association between fatal opioid overdose and state medical cannabis laws in US national survey data, 2000-2011. *Int J Drug Policy*. 2022;99:103449 (January)ISSN 0955-3959. doi:10.1016/j.drugpo.2021.103449.

26. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2020 on CDC WONDER Online Database, released in 2021. Data are from the Multiple Cause of Death Files, 1999-2020, as compiled from data provided by the 57 vital statistics jurisdictions through the vital statistics cooperative program. Accessed at http://wonder.cdc.gov/mcd-icd10.html on Feb 5, 2022.

27. Joinpoint Regression Program, Version 4.9.0.0. March 2021; statistical research and applications branch, national cancer institute. Statistical research and applications branch, National Cancer Institute. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med. 2000;19:335-351 (correction: 2001;20:655).

28. 2018/2019 ICD-10-CM Diagnosis Code T40.6. https://www.icd10data.com/ICD10CM/Codes/S00-T88/T36-T50/T40-/T40.6. Accessed October 20, 2018.

29. Martins SS, Segura LE, Levy NS, et al. Racial and ethnic differences in cannabis use following legalization in US states with medical cannabis laws. *JAMA Netw Open*. 2021;4(9):e2127002. doi:10.1001/jamanetworkopen.2021.27002.

30. Office of Marijuana Policy. State of maine office of administrative and financial services. https://www.maine.gov/dafs/omp/adult-use. Accessed December 6, 2021.

31. Cannabis in [State name]. https://en.wikipedia.org/wiki/Cannabis_in_[state name]. Accessed December 6, 2021.

32. A look back at four years of recreational marijuana in Massachusetts. *Boston Bus J*. 2021. https://www.bizjournals.com/boston/news/2020/10/23/an-industry-grows-a-look-back-on-four-years-of-re.html. Accessed December 6.

33. Low THC oil - FAQ for general public georgia department of public health. https://dph.georgia.gov/low-thc-oil-registry/low-thc-oil-registry-faq/low-thc-oil-faq-general-public. Accessed December 6, 2021.

34. Medical marijuana. Department of agriculture & forestry, state of Louisiana. https://www.ldaf.state.la.us/medical-marijuana/. Accessed December 6, 2021.

35. Scavone JL, Sterling RC, Van Bockstaele EJ. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. *Neuroscience*. 2013;248:637–654. doi:10.1016/j.neuroscience.2013.04.034.

36. Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ1 opioid receptor mechanism. *Science*. 1997;276(5321):2048–2050.

37. Ashton CH. Pharmacology and effects of cannabis: a brief review. *Br J Psychiatry*. 2001;178 101 106. doi:10.1192/bjp.178.2.101.

38. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med*. 2014;370(23):2219–2227.

39. Lynskey MT, Heath AC, Bucholz KK, et al. Escalation of drug use in early-onset cannabis users vs co-twin controls. *JAMA*. 2003;289(4):427–433.

40. Yamaguchi K, Kandel DB. Patterns of drug use from adolescence to young adulthood, III: predictors of progression. *Am J Public Health*. 1984;74(7):673–681.

41. Fergusson DM, Horwood LJ. Early onset cannabis use and psychosocial adjustment in young adults. *Addiction*. 1997;92(3):279–296.

42. Secades-Villa R, Garcia-Rodríguez O, Jin CJ, Wang JS, Blanco C. Probability and predictors of the cannabis gateway effect: a national study. *Int J Drug Policy*. 2015 Feb;26(2):135–142. doi:10.1016/j.drugpo.2014.07.011.

43. Reboussina BA, Rabinowitz JA, Thrulb J, Maher B, Greenc KM, Ialongob S. Trajectories of cannabis use and risk for opioid misuse in a young adult urban cohort. *Drug Alcohol Depend*. 2020;215(Oct 1):108182. doi:10.1016/j.drugalcdep.2020.108182.

44. Fontanella CA, Steelesmith DL, Brock G, Bridge JA, Campo JV, Fristad MA. Association of cannabis use with self-harm and mortality risk among youths with mood disorders. *JAMA Pediatr*. 2021:e205494 Jan 19. doi:10.1001/jamapediatrics.2020.5494.

45. Gorfinkel LR, Stohl M, Greenstein E, Aharonovich E, Olfson M, Hasin D. Is Cannabis being used as a substitute for non-medical opioids by adults with problem substance use in the United States? A within-person analysis. *Addiction*. 2020;116(5):1113–1121. doi:10.1111/add.15228.

46. D'Souza DC, DiForti M, Ganesh S, et al. Consensus paper of the WFSBP task force on cannabis, cannabinoids and psychosis. *World J Biol Psychiatry*. 2022 Mar 22:1–24 Epub ahead of print. doi:10.1080/15622975.2022.2038797.

47. Franklyn AM, Eibl JK, Gauthier GJ, Marsh DC. *The Impact of Cannabis Use On Patients Enrolled in Opioid Agonist Therapy in Ontario, Canada*. PLOS; 2017 November 8 *https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0187633* .

48. Jensen EL, Roussell A. Field observations of the developing legal recreational cannabis economy in Washington State. *Int J Drug Policy*. 2016;33 Jul96 101.

49. Blood MR. *Double Dealing: Legal, Illicit Blur in California pot Market*. Associated Press; 2022 January 16 *https://apnews.com/article/business-california-los-angeles-marijuana-congress-c237d1bd1f7cb14faa8d32b930d860ad* Accessed January 23, 2022.

50. Friedman JR, Hansen H. Evaluation of increases in drug overdose mortality rates in the US by race and ethnicity before and during the COVID-19 pandemic. *JAMA Psychiatry*. 2022:e220004 Mar 2Epub ahead of print. doi:10.1001/jamapsychiatry.2022.0004.

51. Friedman J, Mann NC, Hansen H, et al. Racial/ethnic, social, and geographic trends in overdose-associated cardiac arrests observed by US emergency medical services during the COVID-19 pandemic. *JAMA Psychiatry*. 2021;78(8):886–895 Aug 1. doi:10.1001/jamapsychiatry.2021.0967.

52. Hoopsick RA, Homish GG, Leonard KE. Differences in opioid overdose mortality rates among middle-aged adults by race/ethnicity and sex, 1999–2018. *Public Health Rep*. 2021;136(2):192–200 Mar-AprEpub 2020 Nov 19. doi:10.1177/0033354920968806.

53. Townsend T, Kline D, Rivera-Aguirre A, et al. Racial/ethnic and geographic trends in combined stimulant/opioid overdoses, 2007–2019. *Am J Epidemiol*. 2022:kwab290 Feb 8Epub ahead of print. doi:10.1093/aje/kwab290.

54. Emergency Preparedness and Response. Centers for disease control and prevention health alert network (HAN) advisory. https://emergency.cdc.gov/han/2020/han00438.asp. Accessed May 10, 2021.

55. National Vital Statistics System, Centers for Disease Control and Prevention, 2022. *12 Month-ending Provisional Number of Drug Overdose Deaths, National Vital Statistics System*. CDC; 2022 *https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm* Accessed January 17, 2022.

56. National Vital Statistics System, Centers for Disease Control and Prevention. 2021. *12 Month-ending Provisional Number of Drug Overdose Deaths by Drug or Drug Class, National Vital Statistics System*. CDC; 2021 *https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm#dashboard* Accessed December 31, 2021.

57. Mukherjee S. *The Pandemic Created the American cannabis consumer, Who's Not Going Away*. Fortune; 2021 *https://fortune.com/2021/04/20/420-cannabis-consumer-customer-weed-smokers-pot-users-thc-legal-marijuana-industry/* Accessed May 10.

58. U.S. States and territories by GDP per capita. https://en.wikipedia.org/wiki/List_of_U.S._states_and_territories_by_GDP_per_capita. Accessed March 29, 2022.

59. Pacula RL, Powell D, Heaton P, Sevigny EL. Assessing the effects of medical marijuana laws on marijuana use: the devil is in the details. *J Policy Anal Manage*. 2015;34(1):7–31 Winter.

60. . *The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research*. National Academy of Sciences; 2017 *https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state* Accessed December 31, 2020.

61. International association for the study of pain presidential task force on cannabis and cannabinoid analgesia position statement. *Pain*. 2021 Mar 16Epub ahead of print. PMID: 33729207. doi:10.1097/j.pain.0000000000002265.

62. Humphreys K, Saitz R. Should physicians recommend replacing opioids with cannabis? *JAMA*. 2019;321(7):639–640. doi:10.1001/jamanetworkopen.2020.10001.

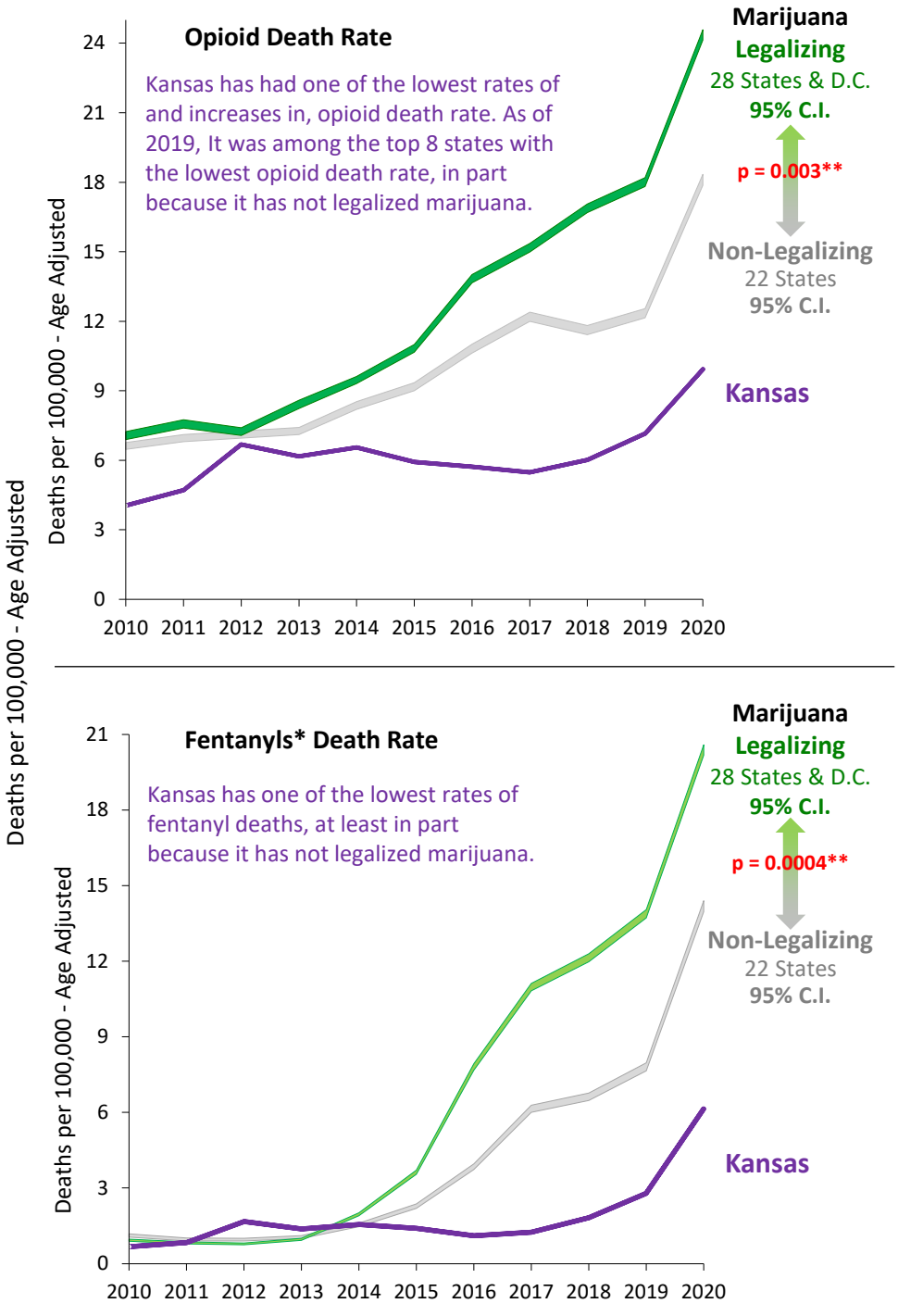
63. Suzuki J, Weiss RD. Cannabinoids for the treatment of opioid use disorder. *J Addiction Med*. 2020 September 08Volume Publish Ahead of Print - Issue -. doi:10.1097/ADM.0000000000000711.

64. Faculty of pain medicine, Australian and New Zealand college of anaesthetists. https://www.choosingwisely.org.au/recommendations/fpm6. Accessed May 21, 2021.

Annual Opioid and Fentanyls Death Rate, 2010-2020

Comparison of Kansas with 95% Confidence Intervals of Marijuana Legalizing (28 States + D.C.)^ and Non-Legalizing (22 States) Jurisdictions, U.S.

Composite data: Bleyer A, Barnes B, Finn K. *J Natl Med Assoc*. 2022:Online 22 April 2022.
https://www.sciencedirect.com/science/article/abs/pii/S0027968422000529?dgcid=author



^cumulative aggregate *including semi-synthetics **joinpoint pairwise comparison

Opioid* Death Rate, 2019, by State & D.C.