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Review

Methodological challenges and actionable recommendations in studying the health effects of high-concentration THC products

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Abstract

In conducting a scoping review on the health effects of high-concentration cannabis products, we have uncovered pervasive methodological shortcomings within the cannabis literature. This review begins by defining the "causal effect" of interest for public health and delineating the desirable features of study design that can address crucial questions pertaining to public health and policy. We further delve into the methodological complexities inherent in studying the health effects of high-concentration cannabis products, describing challenges associated with the measurement of exposures and outcomes, confounding, selection bias, and the generalizability of findings. We introduce causal inference methods to mitigate potential biases in observational cannabis use studies. We identify specific areas that necessitate further development and investigation to deepen our understanding of this topic. Finally, this review extends actionable recommendations, serving as a roadmap for upcoming research initiatives in this domain.

Key words: cannabis; high-concentration; methodological challenges.

Introduction

Cannabis use has been common in the United States for the last half-century, even though cannabis was placed in Schedule I of the Controlled Substance Act in 1970.[1] Since 1996, states have moved to legalize some uses of cannabis; in 1996, California was the first to legalize medical cannabis, and Colorado was the first to permit recreational cannabis sale in 2014. As of August 2024, 38 states, 4 US territories, and the District of Columbia allow access to medical cannabis, while recreational cannabis use is legal in 24 states, 3 US territories, and the District of Columbia.[2] In addition, 27 states and the District of Columbia have decriminalized the possession of small amounts of cannabis.[2] With these broad contextual changes, demand and consumption of cannabis products are likely to increase, and there is also a strong time trend of increasing concentration of delta-9-tetrahydrocannabinol (THC) in these products.[3,4] Consequently, there is an ever-stronger imperative for research on potential risks and benefits of cannabis as the marketplace changes.

In response to the passage of House Bill 21-1317 during the 2021 session of the Colorado General Assembly, the Colorado School of Public Health was tasked with conducting a thorough review of the health effects associated with "high-potency marijuana and THC concentrates" and producing an education campaign for the public.[5] This legislative mandate prompted the completion of a scoping review by the Colorado School of Public Health aimed at characterizing the literature on the health implications—both beneficial and adverse—of high-concentration cannabis products on health outcomes among users.[6] For the purpose of inclusivity, high-concentration cannabis products were defined in the scoping review as those with a THC concentration exceeding 5 mg of THC or 10% THC, or products described as "high-potency concentrate," "shatter," or "dab" even when specific concentration levels were not provided. It is important to note that we were not tasked with evaluating policy measures or their impact, nor with examining the full panorama of factors such as product design that may affect health at the individual level or user patterns at the population level. Here, we address contemporary methodological challenges in conducting research on cannabis based on the 452 studies included in the scoping review. We systematically describe methodological shortcomings, propose solutions, and offer recommendations for research on high-concentration THC products, with a focus on consequences for the health of individuals. Although the legislature allocated funding to the Colorado School of Public Health through House Bill 21-1317 for the initial review, it had no role in the design, execution, analysis,

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or interpretation of the scoping review, nor in the drafting of or decision to publish this manuscript. Additionally, the Colorado School of Public Health was not involved in writing the legislation.

What are the research questions related to cannabis use and its legalization?

There has long been concern about the medical and public health consequences of using cannabis, centered on youth and the long-term implications for physical and mental health. However, investigation has been constrained by federal restrictions on the use of cannabis in research and the limitations of observational studies. Consequently, no certain answer can be given to the first-order question—*what are the health consequences of cannabis use throughout an individual's life course?* Now, there are additional questions raised by the changing legal access to cannabis products including, *what are the public health implications of allowing legal access to medical and recreational cannabis at the population level?* And yet, an additional question has become salient as the products available in the marketplace have changed with a rise in the concentration of THC in cannabis flower and other products—*what are the public health consequences, both at the individual and population levels, of these newer products with higher concentrations of THC than were previously available?* We suggest that each of these questions needs to be addressed with some urgency, given the changing picture of legal cannabis access and the increasing concentration of THC in cannabis products. Here, we propose specific research approaches to addressing these 3 questions, attempting to bring greater conceptual clarity to research on potential harms and benefits of high-concentration cannabis use for individuals at this critical point in the evolution of cannabis products.

How do we answer the research questions?

The concept of counterfactual and target trial

A starting point for conceptualizing an ideal study design is to define one or more questions of interest and then consider how to achieve the unbiased measurement and quantification of the effects associated with the exposure(s) of interest (eg, the increased risk of a first episode of psychosis associated with high-concentration cannabis use in individuals). Measuring an effect requires a study design that compares what happens in units of analysis with the exposure of interest with what happens in units of analysis with another exposure or no exposure (eg, cannabis users vs nonusers, states with cannabis liberalization vs states without), the 2 groups being otherwise similar in all respects. Implicit to this comparison of risks in exposed and nonexposed is the notion of the counterfactual. For example, to infer causal effects on individuals, contrary to the reality that some individuals are cannabis users, we want to surmise what would have happened to them had they not been cannabis users. Likewise, if we are interested in the causal effects of health policy at the population level, we need to consider what the health outcomes of the population would have been in the absence of the policy. This hypothetical comparator is referred to as a "counterfactual" in the terminology of causal inference (ie, it is counter to the facts) (Table 1).[7,8]

One certain way to achieve comparability of exposed and nonexposed is to randomize units of analysis (individuals or populations) to be exposed or nonexposed (ie, to conduct a randomized trial). Such trials may not be feasible nor ethical for potentially harmful exposures. However, one helpful way to articulate the causal effect of interest is to envision a hypothetical "target trial" that is free of the "real-world" constraints involved in attempting to estimate the effect using observational epidemiology.[9] For example, a study that randomizes cannabis users to high-concentration vs low-concentration THC cannabis use may not be feasible but would arguably provide the most valid evidence on positive and negative health effects associated with high-concentration THC exposure at the individual level. The causal effect on individuals estimated by such a trial defines the result that would be seen (other than the impact of sampling variation) in the absence of bias.

For each of the 3 questions, Table 1 lists the counterfactual and the associated target trial. Research approaches to answering these questions involve a mix of designs (Table 1). For the first and most general question, the full gamut of experimental and observational research is relevant. The research needs to yield evidence relevant to today's products and how they are being used, posing an ongoing challenge to the research community. For the second question, assessing the consequences of legalization, evidence will primarily come from designs based on the spatial and temporal contrasts afforded by the staggered implementation of legalization across the country and perhaps internationally. The third question calls for research that is linked to the changing marketplace and the generation of complementary evidence from experimental and observational studies. Given the dynamicity of the marketplace and of use patterns, longitudinal data are needed to track patterns of use and their health implications. To be informative, studies should collect data over a long enough period and with sufficient frequency to capture the health consequences of cannabis use at this very dynamic juncture. Cross-sectional studies alone will not be sufficient.

Examples from tobacco control

To sharpen the exposition of the 3 questions and the approaches to answering them, we offer examples from tobacco control; a parallel scenario in that reliance on observational data was necessary, given the impossibility of individual-level randomized trials of cigarette smoking other than for cessation. Regulations were put in place over time, and the nature of tobacco products in the marketplace was dynamic. Since the start of the 20th century epidemic of tobacco use, the range of products has constantly changed with increasing heterogeneity of cigarettes (filters, lower-yield products, flavorings, and brands) and other types of products (small and flavored cigars, electronic cigarettes, and heat-not-burn products). The product design and packaging have also evolved, becoming more sophisticated and visually appealing to attract consumers. The range of products has challenged the surveillance systems that track use of tobacco products and the conduct of research on the health risks of using tobacco products. In recent years, the pace of change in tobacco products in the marketplace has accelerated, further complicating characterization of the risks of the many products available.

National-level surveillance has long been in place that covers youth and adult populations using tobacco products.[10] It is at sufficient granularity to support analyses at the state, potentially municipal, and individual levels that address the impact of policy measures. For example, these data collection systems, augmented by biomarkers of tobacco exposure, have been invaluable in tracking the consequences of policies directed at eliminating exposures to secondhand smoke. However, these population-based surveys have been challenged by the quickly changing marketplace of electronic products, which is evolving at a pace that cannot be matched by changes in the surveillance systems.

Table 1. Research questions, counterfactuals, and preferred study designs.

Research question	Target trial and *counterfactuals*	Main outcomes of interest	Study designs or features that could address the research questions
1. What are the health effects of *using* cannabis?	Randomize cannabis naïve individuals to cannabis use or *no-cannabis* use	Health outcomes[a]	Randomized controlled trials (RCTs); observational designs (eg, cohort study, case control study)
2. What are the effects of *legalization* of medical and/or recreational cannabis?	Randomize groups of individuals (eg, cities, counties, states) to legalization or *no legalization of cannabis*	User patterns[b] Health outcomes[a]	Observational designs (eg, interrupted time series, difference-in-difference approach, regression discontinuity)
3a. What are the health effects of *using* high-concentration THC products?	Randomize cannabis users to high-concentration THC products or *THC products not considered as high concentration*	Health outcomes[a]	RCTs and observational designs
3b. What are the effects of *availability* of high-concentration THC products?	Randomize groups of cannabis users (eg, cities, counties, states) to having access to high-concentration THC products or *not having access to high-concentration THC products*	User patterns[b] Health outcomes[a]	Cluster RCTs; cohort designs with staggered entries; population-level observational designs

Italicized text, counterfactuals.
[a] Measured at the individual level
[b] Measured at the population level

Cohort studies represent another approach to tracking use of tobacco products and the associated health consequences over time. To that end, the US Food and Drug Administration (FDA) in collaboration with the National Institutes of Health (NIH) established the Population Assessment of Tobacco and Health (PATH) Study, which began data collection in 2013.[11] The PATH study population of about 46 000 is followed-up annually with collection of information on use of tobacco products and health indicators. With this design, changes in use of tobacco products are tracked over time so that temporal use profiles can be characterized. To date, the initial PATH cohort has been replenished on one occasion to remain informative for younger ages.

Population-level interventions have also been implemented and evaluated. The Community Intervention Trial for Smoking Cessation (COMMIT) was a community-based intervention study involving 11 matched pairs of communities.[12-15] One community in each pair was randomized to receive a comprehensive set of interventions. The American Stop Smoking Intervention Study (ASSIST) was a state-level tobacco control project with 17 nonrandomly selected states and a comparison group of the remaining states.[16-19] The intervention states were tasked with implementing an array of policy measures. The evaluation was complicated by the nonrandom assignment to intervention but did show an effect on several outcome measures.

These examples are representative of approaches used to assess the impact of tobacco control policies. The 2014 50th anniversary report of the Surgeon General on Smoking and Health provides a comprehensive review of the very large body of literature on tobacco control interventions and their consequences.[20] Evaluation of tobacco control measures was facilitated by the rich surveillance data and the close linkage of smoking to several specific health outcomes (eg, lung cancer) that could be tracked. Heterogeneity of tobacco control measures across states and municipalities made population-level studies feasible and informative. Policy-tracking databases were a further asset; for example, the American NonSmokers' Rights Foundation maintains a database on state and local tobacco-related ordinances and regulations in the United States.[21] There was also interest in the economic benefits of tobacco control because of the costs of the morbidity and mortality caused by tobacco products. Most critically, following investment by individual states, substantial funding was provided by the National Cancer Institute for advancing and assessing tobacco control policy.

Critical lessons from tobacco control include the need for harmonized and dynamic surveillance systems on products and how they are used and by whom; tracking the policy landscape with sufficient detail to support research; and methodological rigor in policy research. By comparison with the support available for evaluation of tobacco control over the previous decades, specific and adequate funding sources for cannabis policy research are generally unavailable. There is also the need of standardized characterization of product use, along with the ability to modify assessment tools to reflect the changing marketplace.

What are the barriers to answering the research questions for cannabis?

Drawing examples from the recently completed scoping review, we aim to delve deeper into the methodological complexities in assessing the potential health and policy implications of the increased THC concentrations in cannabis products.[22] The concentration of THC in recreational cannabis has reached as high as 70%-90% in certain concentrated products in the United States and worldwide.[23] For comparison, cannabis flower currently has an average of 20% THC.[24] High-concentration THC may be associated with adverse health effects.[25-27] However, the state of the literature (452 studies in total, including 225 observational studies, 142 randomized trials, 51 case reports, and 34 case series) on these now widely available high-concentration THC products has numerous deficiencies, and as a result, many unknowns remain concerning risks and benefits and policy options.[22] While we place emphasis on the third question, specifically regarding the health consequences for individuals, the methodological issues covered also pertain to the first 2 questions.

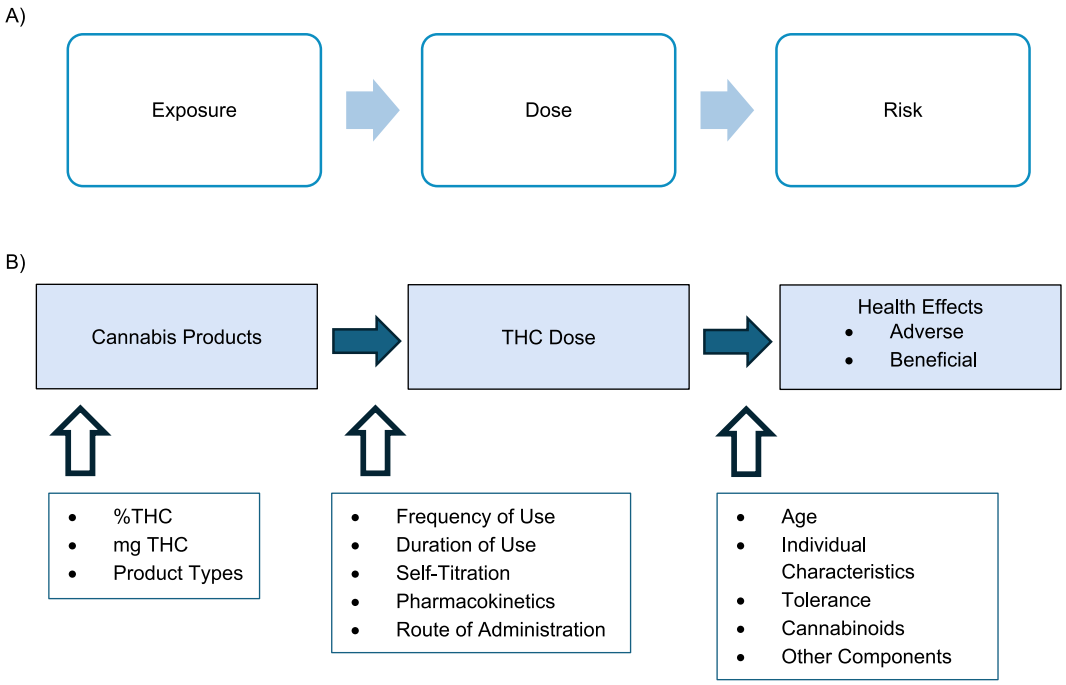

Figure 1. (A) A paradigm involving exposure, does, and risk for environmental exposures. (B) A paradigm illustrating how cannabis products are linked to health effects.

General considerations

The associations estimated by observational studies usually deviate from the causal effect due to imperfect measurement tools for exposures and outcomes, as well as residual confounding and selection bias that are unlikely to be fully corrected by design or analysis. Such observational studies may nonetheless provide useful evidence of an effect of the exposure on the outcome of interest. For example, the estimated magnitude of effect may be sufficiently large that there is clear evidence of an important effect, given the plausible amount of bias. Alternatively, the predicted direction of bias may be towards the null, so we can be confident that the effect is at least as large as that estimate.[28] The assessment of the utility of observational studies should therefore consider risk of *material bias* (rather than risk of any bias), interpreted as bias sufficient to affect the direction of the estimated effect or to threaten the ability to draw a correct conclusion from the study in relation to the exposure-outcome association being studied.[29,30]

A second consideration is related to the ability of a study to provide useful information about the effect of exposure on outcome, even when the study is free from bias (for example, whether the study examines an appropriate range of exposure levels and has sufficient follow-up for effects on outcomes to be observed).[4,31,32] Finally, drawing conclusions about the effect of exposure on outcomes will require triangulating results from different types of studies and also considering other types of relevant evidence including animal and mechanistic studies.

A third consideration is the inevitable lag between when a study is launched and when findings are reported. For exposures that are temporally dynamic, as with cannabis products at present, the generalizability of findings on previously available products to those available at the time of publication may be uncertain. The resulting uncertainty as to generalizability may be a barrier in using the findings for decision-making.

Exposure definition and measurement

The relationship between THC concentration and health effects is complex and influenced by modifying factors related to how products are used, along with the tolerance of the individual using the product. Generally, in conceptualizing how environmental exposures (consider cannabis and high-concentration THC products as such) may increase risk for various health effects, whether harmful or beneficial, a paradigm involving exposure, dose, and risk is often applied (Figure 1A). Exposure constitutes the contact of the agent with people; dose is the amount of the agent that enters the body; and risk is the probability that an event will occur (and is assumed to vary along a dose–response relationship). In a relevant example, we are all exposed to ambient or outdoor air pollution (the exposure, referring to what is in the air) and we inhale air pollutants, such as small particles, into our lungs (the dose, referring to what is taken into the body), leading to increased risk for various adverse health consequences, such as worsening of asthma and even increased risk for dying. In this example, exposure is the product of concentration of the pollution with the time of exposure, and dose is the amount (weight) of material entering the body.

In Figure 1B, we generalize this paradigm to THC products and capture the complexities of estimating THC dose. The cannabis product now constitutes exposure, while dose refers to the amount of THC entering the body by any route. Risk refers to the likelihood of occurrence of potential outcomes related to exposure and the attendant doses in individuals. There is some dose–response relationship between dose and risk that may take various forms depending on the health outcome. The characteristics and the THC concentration of the product are critical to determining THC dose, as are the frequency of use and the duration of use, depending on the time span over which the dose is to be estimated (ie, shorter- or longer-term). When comparing similar use patterns and characteristics with 2 different strength products, certainly the higher concentration

product will lead to a higher THC dose. However, many factors impact the dose reaching receptors in the brain. Patterns of use (infrequent or chronic) will significantly impact dose and affect risks for short-term and long-term health outcomes in individuals. Differences in bioavailability and pharmacokinetics between routes of exposure (eg, inhalation or ingestion) will also affect systemic absorption, dose, and ultimately health outcomes. For instance, inhalation leads to rapid onset of effects due to direct absorption into the bloodstream through the lungs, whereas ingestion results in slower onset and potentially different metabolites due to processing through the digestive system and liver. The dose of THC that reaches the receptors in the brain will vary with the way that an individual reacts to the product and particularly how the THC is distributed and metabolized (ie, the pharmacokinetics). Finally, if cannabis is used in combination with other addictive substances, such as alcohol and opioids, drug interactions can alter the way THC and other cannabinoids are metabolized, absorbed, and distributed in the body.[27,33]

As implied by Figure 1B, the effects on individual health will vary with the characteristics of the person using the product and the tolerance of the individual. These factors need to be considered in the context of the purpose for which the product is used, particularly recreational or medicinal. An individual's tolerance to the effects of THC, similar to other drugs and substances, can change the amount, frequency, and duration used by an individual. In an experienced user, tolerance can lead to increased frequency of use, or use of higher concentration products to obtain the same pharmacological effects compared to a naïve user.[34] Similar doses in an individual naïve to cannabis use can lead to stronger effects or undesired adverse effects.[35] People who use cannabis may also self-titrate to the desired intake based on the concentration or product used.[36-38]

The lack of sufficient ascertainment and control over these factors presents a serious obstacle in observational epidemiology. Incomplete, invalid, and imprecise ascertainment of the duration, frequency, modality, and chronicity of use constitutes one of the main challenges to understand consequences of high-concentration THC for individual health. Most observational studies of individuals depend on self-reporting to assess cannabis exposure.[27] When relying on self-reporting of cannabis exposure, the investigators may not be able to capture nuances about participants' cannabis exposure; and cannabis users may be unable to accurately report their consumption.[39-41] Cultural attitudes towards cannabis use, stigma, and legal repercussions may vary among racial and ethnic groups, influencing how individuals report their cannabis use.[42,43] For instance, individuals from minority groups might underreport usage due to fear of legal consequences or social stigma, particularly in communities with a history of disproportionate law enforcement. Additionally, socioeconomic factors like income, education, and access to healthcare can also affect self-reporting accuracy.

We found that there is no universal definition for occasional, regular, and heavy use of cannabis. Regular, chronic, and/or heavy use are terms that are variously used in the literature, which can include reference to frequency of use (eg, daily or near daily), a pattern of use over time (eg, at least a year, or several years), and/or an amount used at each occurrence.[44-48] Some studies use these terms without providing precise definitions of the pattern of use.[49] Definitions can vary for occasional use, ranging from once a month to once a week. Definitions of regular use extend from several times weekly to once daily. Heavy use can refer to daily or more often, or the amount used on each occasion. The chronicity of use, or age of initiation, can also impact overall dose exposure. There has been no standardization of such categories to date.

Knowing the delivered exposure dose based on the cannabis products used is difficult. In places where cannabis has not been legalized, there is no routine testing of cannabis products to determine concentration of THC in the flower or the product used. Often high-concentration products are identified by slang names such as "skunk" and "hashish" which can have different meanings throughout the world.[50] In US states that have legalized either medical or recreational cannabis, testing is typically mandated to confirm the THC concentration in the product.[51] Although the regulations call for standardization of testing, there is evidence of substantial variability in testing results among different facilities.[52] A study in Colorado tested 23 cannabis products from 10 dispensaries. It demonstrated that in 70% of samples tested, the concentrations were more than 15% lower than reported on the label.[53]

Researchers in the state of Washington have attempted to develop a comprehensive tool to measure cannabis consumption. Their inventory is a 6-factor structure measuring daily sessions, frequency, age of onset, marijuana quantity, cannabis concentrate quantity, and edibles quantity.[54] Similar scores and inventories can help standardize usage characteristics among cannabis users to determine the levels of cannabis dose that may impact an individual's physical or mental health. Lorenzetti et al developed an expert consensus on minimum standards for measuring cannabis use.[47] They proposed 3 tiers for universal measures. The first tier includes questions on "ever use of cannabis, last use, and frequency of use in the past month." The second tier quantifies additional aspects of use taking into context the goals of determining cannabis use (research, hospital, or school use) and local legal status. The final tier comprises biologic measures of cannabinoid use, using various matrices and measuring cannabinoids and respective metabolites. The tiered measurement approach mirrors standard practice such as with tobacco for which instruments are available with varying intensity of detail and for which biomarkers are available that cover short-term to longer-term time windows.[20] Depending on the exposure and outcome, these individual-level measures may be translated to population metrics of use such as prevalence, incidence, and changes over time.

Interpretation of cannabis biomarker data can also be difficult. Measurement of THC metabolites in urine is the most commonly used biomarker test for cannabis exposure. However, urine biomarkers can represent both acute and chronic use and are not accurate for determining patterns of use, levels of intoxication, or physical effects.[55] THC metabolites in blood can help determine both recent and longer-term use. However, the parent compound (THC) and its metabolites will rise and fall at different times depending on route of use (ingestion vs inhalation), with concentrations also dependent on the frequency of overall and the timing of last use.[56] Furthermore, a blood draw is an invasive method and impractical when studying large populations; interpretation of the levels is highly dependent on the tolerance of the individual.[55,57-59]

Finally, the cannabis plant can contain about 100 different cannabinoids besides THC, and other constituents and contaminants may be relevant to particular health outcomes. Several commercially available products contain different mixtures and fractions of the various cannabinoids and constituents, some combining THC with cannabidiol (CBD). A recent study demonstrated that high doses of oral CBD can inhibit the

metabolism of THC, resulting in a stronger drug effect from THC.[60] Understanding how the various cannabinoids and other constituents interact, perhaps magnifying or attenuating effects, may need to be considered for some research questions.

Historically, cannabis for research purposes in the United States was primarily available through the National Institute on Drug Abuse (NIDA) Drug Supply Program due to its classification as a Schedule I drug (the reclassification of cannabis to a Schedule III drug is currently in progress).[61] More diverse products have become accessible for research purposes through recently authorized growers regulated by the Drug Enforcement Administration (DEA).[62] Despite this progress, the range of cannabis products studied in the literature has remained narrow, featuring concentrations lower than what people can purchase at their local dispensaries or from the illegal market.[63] Furthermore, researchers planning to administer cannabis in their research need to navigate a complex and lengthy approval process, which entails obtaining approval from multiple federal agencies, including the DEA and the FDA. Researchers also face limitations on the types of participants they can recruit for cannabis studies.[64,65] In December 2022, President Biden signed into law H.R. 8454, Medical Marijuana and Cannabidiol Research Expansion Act, allowing companies to apply to become "bulk manufacturers" and offer diverse products for research purposes that the DEA can distribute to NIDA and other approved institutions.[66] As of April 2024, there were 8 suppliers listed.[62] While this may be a step forward for researchers, due to the prevailing policy restrictions, the assessment of high-concentration THC will depend on observational data.

Recommendation 1: Future studies should (1) explicitly define the causal effect of interest on individuals' health outcomes, including the specification of exposure and dose; (2) apply validated and standardized tools and instruments to measure exposure and dose *per* the causal effect of interest. These approaches need to be modified in a timely way so that the data collected for research reflect actual patterns of use. Only by means of a strict and careful evaluation of exposures will we be able to associate high-concentration THC, either *availability* or *actual use*, with health outcomes consistently across studies with minimal bias and establish dose–response relationships or thresholds relevant to risks for harmful effects.

Confounding

Generally, a confounding factor is a variable associated with the exposure and causally with the outcome, leading to a distorted or spurious association between exposure and outcome. Unlike randomized trials, the ability to control and adequately adjust for confounding in observational epidemiology may be limited. The challenge of controlling confounding arises because potential confounders may not be identified; they may not be accurately measured; and the method or model used to adjust for confounding may be mis-specified. Additionally, integrating epidemiologic theories of population health and health inequity is crucial for constructing causal frameworks and sorting out confounding, modifying, and mediating factors. This approach can explore social factors in theory-based frameworks and use of multilevel models to estimate causal effects at both individual and population levels.[67,68] There are numerous factors that may be relevant and considered for incorporation in models including demographic characteristics (eg, age, sex, comorbidity), socioeconomic, behavioral factors, personal traits (eg, sensation seeking, risk taking), and genetic predisposition for addiction. Additionally, observational studies of cannabis use may be complicated by polysubstance use of other substances such as alcohol, opioids, and tobacco.

Associations between cannabis use and mental health, psychosocial, and substance use dependence outcomes have most commonly been addressed in cohort studies. Such studies often have limited measures of social and environmental context, and of individual characteristics. For example, a cohort study of adolescents examined associations between various tobacco products used and later initiation of cannabis use.[69] The authors adjusted for parent and peer tobacco use, and individual factors (eg, depression, impulsivity), yet many potential confounding factors remained unmeasured (eg, parent or peer cannabis use).

Usual approaches to address confounding, such as matching and multivariable regression analysis, rely on the assumption that the full set of confounders is known and validly measured.[70] This assumption is often unrealistic, necessitating the utilization of more sophisticated analytical approaches (see Analytical considerations).

Another related problem is ecological fallacy—a potential error in research that occurs when inferences or conclusions about individuals are made based solely on group-level data.[71,72] It arises when associations observed at the population or group level are wrongly assumed to hold true for individuals within those groups. For instance, consider a study investigating the relationship between the density of cannabis dispensaries and the incidence of mental health disorders across different regions. Researchers collect data on the density of dispensaries and mental health disorder diagnoses at the population level and observe a strong positive association between the 2 variables. The conclusion that dispensary density is a *direct cause* of mental health disorders may suffer from the ecological fallacy because other factors, such as the individual characteristics (genetic or family history, substance abuse and addition, traumatic life events), social and environmental influences, and availability of mental health services are not considered, resulting in confounding. The converse problem, known as atomistic fallacy, occurs when conclusions about group-level phenomena are drawn from individual-level data, potentially leading to erroneous inferences about the relationships within the population.

Recommendation 2: Future studies should employ rigorous experimental and observational designs to reduce the threats to internal validity introduced by confounding. Studies should consider possible causal relationships (for example through causal diagrams), identify potential confounders, and incorporate accurate measurement of these confounders. Modern causal inference methods offer a design and analytical approach to minimize the impact of confounding (see Analytical considerations). To prevent ecological fallacy, it is crucial to consider the interplay of drivers of use and outcome to identify relevant confounding factors when drawing conclusions from group-level data. Likewise, to prevent atomistic fallacy, causes of state- or other population-level outcomes should not be inferred from individual level associations.

Selection bias

Selection bias arises when the process of selecting participants for a study (or participants leaving a study) affects the estimated risk for the occurrence of the outcome in relationship to exposure. Suppose we are interested in the long-term effects of cannabis use on cognitive function in adults. Researchers recruit participants who have a history of long-term cannabis use from an addiction and mental health rehabilitation center. The nonexposed group consists of people who have never used cannabis or any other illicit drugs. In this scenario, selection bias is present because the

participants recruited from the addiction and mental health rehabilitation center have a higher likelihood of experiencing cognitive impairments compared with the general population of long-term cannabis users, overestimating the true effect. In this hypothetical study, selection bias can also occur when participants recruited from the addiction and mental health rehabilitation center are more likely to be lost to follow-up compared with the nonexposed group because of the severity of their conditions or personal circumstances related to their ongoing mental health problems.

Recommendation 3: To mitigate the influence of selection bias in observational cannabis research, it is crucial to select a study population that closely represents the target population and to have an understanding of factors placing people in the study population. Researchers should establish clear and well-defined eligibility criteria and provide a comprehensive description of the recruitment process and participants, enabling users of the information to assess the extent of potential selection bias. Additionally, in cohort studies, efforts should be made to minimize attrition and loss to follow-up by implementing robust tracking systems and providing appropriate incentives for participation. Meeting this recommendation will be challenging, given the difficulties of identifying definable populations of cannabis users. One approach would be to select participants from existing cohorts who are cannabis users with sampling of nonusers. This approach would remain affected by any selection bias arising from the original cohort selection.

Measurement of the outcomes

The potential for outcome measurement error to bias associations between exposures and outcomes depends on the appropriateness of the method for measuring the outcome: whether ascertainment of the outcome differs between exposure groups; the data collection method and whether the outcome assessment approach is blinded to the exposure status; and whether the assessment of outcome is likely to be influenced by knowledge of exposure. For instance, in the case of high-concentration THC exposure and psychotic episodes, an increased frequency of such episodes may lead to more hospital visits and subsequent diagnoses of other health problems, creating a spurious association. Moreover, poor interviewing techniques, participant recall or reporting, and other factors affecting the accuracy of outcome measurement can further distort the association with the exposure.

Lack of common outcome definitions and methods for assessment in studies of cannabis is another concern. In the scoping review, we found substantial variability in the level of specification for outcomes.[22] To completely define an "outcome," a common system including domain (eg, anxiety), specific measurement (eg, Beck anxiety inventory), specific metric (eg, change from baseline), method of aggregation (eg, mean), and time points (eg, at 3-month follow-up) should be considered.[73] When we examined a subset of 20 studies investigating whether there is any dose–response relationship between THC concentration and anxiety, we identified numerous and differing types of measurements. These included general mental health instruments assessing anxiety as a subdomain (such as the Profile of Mood States and the Brief Psychiatric Rating Scale), instruments specifically designed for anxiety (such as the Generalized Anxiety Disorder 7-item, a 10-point anxiety severity scale, and Beck anxiety inventory), chart review for ICD-9/ICD-10 codes, individual self-reported anxiety, and interview-based assessments using the Clinical Interview Schedule (administered by clinicians) or the Clinical Interview Schedule-revised (administered by laypersons) based on the DSM-IV criteria for generalized anxiety disorder. Some studies utilized multiple measurement tools, each with different metrics (such as change from baseline or value at a follow-up time point), methods of aggregation (continuous or categorical), and assessment time points. Lack of consistency and standardization in outcome definition and measurement across studies hinders the ability to combine data in meta-analysis.

The heterogeneous approaches to outcome definition and assessment are not unique to cannabis research.[74-82] Core outcome sets (COSs) are widely recognized as an integral part of the solution to the current problems with outcomes in studies. A COS is an agreed-upon *minimum* set of outcomes (usually 5-7), typically agreed by a community of stakeholders, that will be measured and reported in research in a given disease area.[83,84] The existence of an agreed-upon COS recognizes that certain outcomes are important, valid, and relevant to the community's knowledge; facilitates consistency in outcomes across studies; and facilitates incorporation of critical outcomes from *all relevant studies* in evidence syntheses. The Core Outcome Measures in Effectiveness Trials (COMET) Initiative, launched in 2010, is a global effort across all areas of healthcare that brings together those developing and applying COSs.[85]

Recommendation 4: Researchers should implement COSs in future cannabis studies. By adopting a COS, researchers can establish a standardized set of outcomes that should be consistently measured and reported across studies. This will enhance the comparability and interpretability of findings, allowing for meaningful synthesis of data through meta-analyses and systematic reviews.

Analytical considerations

Recent advancements in the design and analysis of observational epidemiology enhance the potential to derive more meaningful insights and to draw more robust conclusions regarding the effects of high-concentration THC products. To maintain the desirable attributes of randomized trials within observational analyses, one approach is to carefully structure them in a manner that explicitly replicates a hypothetical "target trial."[86] The initial step involves formulating a causal question that precisely defines the effect of exposure on the outcome (also see The concept of counterfactual and target trial). This causal question is articulated in the form of a protocol for a hypothetical randomized trial that would provide the desired answer. This protocol outlines crucial elements defining the causal estimands, such as eligibility criteria, treatment strategies, treatment assignment, follow-up duration, outcomes, and causal contrasts. The protocol serves as the focal point for investigating the intended causal inference. The second step is explicit emulation of the protocol's components using observational data. This involves identifying eligible study participants, "assigning" them to a treatment strategy (or exposure) compatible with their data, following them up from assignment (time zero) until the occurrence of the outcome or the completion of the follow-up period. The analysis conducted mirrors that of the corresponding target trial, with adjustments made for baseline confounders in an attempt to emulate random treatment assignment.

The goal of target trial emulation is to avoid critical design and analysis errors that can lead to incorrect causal conclusions. For instance, in the well-known Women's Health Initiative randomized trial, estrogen plus progestin hormone therapy was found to increase the risk of coronary heart disease in postmenopausal women compared with a placebo.[87] However, observational analyses failed to detect this heightened risk and pointed to a protective effect.[88-90] This bias in the observational estimate likely

stemmed from comparing long-term hormone therapy users (current users) with nonusers, rather than conducting a proper comparison from the time of hormone therapy initiation. The observational analysis unintentionally disregarded early coronary events and introduced selection bias by initiating the follow-up period for current users long after therapy commencement. Consequently, the population of current users was partially depleted of women who were susceptible to heart disease. By emulating a target trial, eliminating this bias, the effect estimates were found to be consistent.[91] It is worth noting that while target trial emulation offers the potential for more valid causal conclusions, its implementation may be constrained by the nonavailability of necessary data. It also cannot rectify measurement errors in exposures and outcomes as previously discussed.

Advanced design and analytical methods such as propensity scores, instrumental variables, interrupted time series, difference-in-difference, and regression discontinuity approaches, when applied properly, can facilitate causal inference despite lack of randomization. The propensity score method is a statistical technique that helps researchers make fair comparisons between 2 groups in a study, even when they may have different prognostic characteristics. The estimated "propensity score" captures likelihood of being in a particular group based on these characteristics. Once the scores are calculated, researchers can match or group individuals with similar scores from each group, making the comparison fairer (reducing selection bias). The instrumental variable approach works by finding an "instrument" that affects the exposure but is unrelated to the outcome, helping isolate the true causal relationship. As an example, higher cigarette taxes were used as an instrument to study the effect of smoking during pregnancy on birth outcomes.[92] Interrupted time series compares outcomes over time before and after an interruption (eg, legalization of cannabis). The postinterruption outcome time trend is compared with what the counterfactual trend would have been in the absence of the interruption. Difference-in-difference approach compares changes in outcomes over time between 2 groups: one that is exposed and another that is not. By analyzing the differences in outcomes before and after the exposure and comparing those differences between the 2 groups, the causal impact of the exposure is estimated. As an example, researchers used this approach to study the effect of increasing the minimal legal age for cannabis from 18 to 21 years in Quebec, Canada.[93] Regression discontinuity design compares what happens to individuals just above and just below a certain cutoff point. For example, this approach was used to estimate changes in prostate-specific antigen at the time of prostate cancer diagnosis after Medicaid expansion in young men.[82]

Recommendation 5: Researchers should consider and leverage advanced causal inference design and analytical approaches to addressing potential biases in observational studies of cannabis use. It would be beneficial to delineate the causal pathways. By incorporating these techniques, researchers can enhance the validity and robustness of their findings, leading to more accurate conclusions about the impact of exposures, interventions, or policies.

Generalizability

Generalizability refers to the extent to which the findings and conclusions drawn from a specific study can be applied and extrapolated to the broader population or other settings beyond the study's sample. Of necessity, many cannabis studies rely on nonrandom sampling methods, such as convenience sampling or self-selection, and on voluntary participation of necessity. Cannabis use has historically been stigmatized and subject to legal restrictions in many jurisdictions. This legacy may discourage certain groups from participating in research, particularly heavy, chronic, or young users and those groups who suffered legal consequence in the past. The availability and accessibility of cannabis also varies across different locations and time periods. Historically, cannabis dispensaries in Colorado have disproportionately targeted disadvantaged neighborhoods.[94] Geographical proximity to dispensaries have been associated with increased frequency of use and negative health outcomes.[95,96] We could not find updated data on dispensary locations for Colorado, one of the first states to legalize cannabis a decade ago, nor for other states. As the cannabis industry evolves and matures, it will be crucial to gather contemporary data on location of dispensaries and sales of high-concentration THC products to better understand market trends and their potential impact in possibly targeted neighborhoods. Such analyses have been critical in tobacco control for understanding how the tobacco industry targeted various groups.[97]

In addition, many studies recruit participants and gather data through approaches that are targeted to individuals who use cannabis for specific reasons or therapeutic purposes. Consequently, the user populations captured in studies may not represent the entire spectrum of cannabis users nor even those in a particular class of users. As a result, researchers must be cautious in interpreting and extrapolating these findings beyond the study's sample, acknowledging the potential limitations in generalizability.

Recommendation 6: To enhance the generalizability of cannabis research, researchers should strive to ensure more representative and diverse samples from the target populations. Efforts should be made to encourage participation from underrepresented groups by employing inclusive recruitment strategies and addressing the stigma associated with cannabis use. Additionally, researchers should consider conducting multisite studies across different locations and time periods to account for variations in cannabis accessibility, usage patterns, and regulatory environments, ultimately increasing the external validity and broader applicability of the research findings.

In conclusion, this review has considered the most serious methodological challenges associated with studying the health effects of high-concentration THC products. We provide this review having become concerned about the quality of the literature by the findings of our scoping review.[22] By outlining the desirable features of study design that can enhance scientific advancements in addressing crucial public health and policy questions, we hope to advance research in the complex landscape of this field. Moreover, we have identified specific areas that require further development and investigation to deepen our understanding of this topic. Finally, this review has offered recommendations to guide future research endeavors in this domain. By considering our guidance, researchers can strive towards generating comprehensive and credible evidence that informs public health initiatives and policy decisions regarding high-concentration THC products and use. Such evidence is urgently needed.

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Conflict of interest

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Data availability

Not applicable

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