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GUIDELINES FOR PUBLIC HEALTH AND SAFETY METRICS TO EVALUATE THE POTENTIAL HARMS AND BENEFITS OF CANNABIS REGULATION IN CANADA

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LIST OF ABBREVIATIONS

ACMPR: Access to Cannabis for Medical Purposes Regulations

AUD: Alcohol use disorder

CBD: Cannabidiol

CCDSS: Canadian Chronic Disease Surveillance System

CCHS: Canadian Community Health Survey

CCS: Canadian Cannabis Survey

COPD: Chronic obstructive pulmonary disorder

CSTADS: Canadian Students Tobacco Alcohol and Drugs Survey

CTADS: Canadian Tobacco Alcohol and Drugs Survey

CTUMS: Canadian Tobacco Use Monitoring Survey

CVSD: Canadian Vital Statistics: Deaths

CUD: Cannabis use disorder

DAD: Discharge Abstract Database

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (Version 4)

FARS: Fatal Accident Reporting System

HMD: Hospital Mortality Database

HMHDB: Hospital Mental Health Database

IQ: Intelligence quotient

MI: Myocardial infarction

NACRS: National Ambulatory Care Reporting System

NTIP: National Treatment Indicators Project

NFD: National Fatality Database

OUD: Opioid use disorder

RSF: Road Safety Monitor

THC: Tetrahydrocannabinol

TIRF: Traffic Injury Research Foundation

UCRS: Uniform Crime Reporting Survey

UNGASS: United Nations General Assembly Special Session

EXECUTIVE SUMMARY

Recently, global drug policy experts issued a high-profile call for governments to prioritize health, peace and security, development, and human rights in evaluating global drug policy. Canada will soon be the first major industrialized to implement a legal framework for the production, sale, and use of cannabis by adults for medical and non-medical purposes. Unlike some United States jurisdictions that have introduced commercialized approaches to cannabis legalization, the Canadian government intends to keep public health as a central principle of its legal framework. Accordingly, consensus regarding ways to measure the public health and safety impact of the policy reform will need to be achieved across the scientific community, various health stakeholders, and levels of government. This report contributes to this objective by establishing guidelines for a balanced evaluation of the public health and safety risks and benefits of cannabis legalization in Canada.

Through an academic search of the literature and consultations with a team of cannabis-focused clinical and public health scientists from across Canada, the monitoring of 28 broad priority indicator areas was recommended to establish the public health and safety impacts of cannabis legalization in Canada:

Public Safety

- Cannabis-impaired driving
- Cannabis-related motor vehicle injuries and fatalities
- All-cause motor vehicle injuries and fatalities
- Alcohol-impaired driving
- Alcohol-related motor vehicle injuries and fatalities
- Dating and intimate partner violence
- Cannabis-related workplace injuries overall and across work sectors
- Violent and property crime

Cannabis Use Trends

- Cannabis use initiation among youth
- Cannabis use rates among youth
- Cannabis use disorder
- Unregulated cannabis product use
- Cannabis use among expectant and breastfeeding mothers
- Trends in cannabis use products and practices
- Cannabis-related health care utilization
- Cannabis-related poison center calls
- Cannabis-attributable burden of disease

Other Substance Use Trends

- Medical and non-medical opioid use and use disorders
- Fatal and non-fatal drug overdoses
- Illicit stimulant use and use disorders
- Alcohol use and use disorders
- Tobacco use and use disorders

Cardio-Respiratory Health

- Respiratory problems including COPD and lung cancer
- Cardiovascular problems including MI, cardiac arrest, and ischemic stroke

Mental Health and Cognition

- Psychosis and psychotic disorders
- Depression and anxiety
- Attempted and completed suicide
- Cognitive functioning and educational achievement among youth

Wherever available, preliminary evidence of the potential changes in the recommended indicators was summarized from research conducted in other North American jurisdictions with legal non-medical and/or medical cannabis regulatory frameworks (e.g., Colorado, Washington). A review of this research highlights potential public health and safety challenges associated with legalization (e.g., cannabis-related hospital admissions), but low consensus overall that a legal cannabis framework would exacerbate harms to public health and safety. Furthermore, this review outlined an emerging body of evidence to support the possibility of potential benefits to public health and safety (e.g., possible reductions in opioid use and overdose).

Determining the net effect of cannabis legalization on the public health and safety of Canadians requires a system of metrics that balances consideration for potential harms with potential benefits. The proposed guidelines should be incorporated across Canada (and other jurisdictions similarly looking to implement a public health framework for the legalization of non-medical cannabis) to support an evidence-informed public health and safety evaluation that seeks to minimize the harms and maximize the benefits of cannabis regulation.

INTRODUCTION

Criminal prohibitions on possession, sale and use remain the dominant policy response to illicit drug use worldwide. This is despite an increasing scientific consensus that such policies are ineffective, exacerbate existing social and economic inequities, contribute to unintended consequences and, in some settings, are linked to serious violations of legal norms and human rights.[1-3] Public health and drug policy experts have long argued that enforcement has not succeeded in deterring cannabis use, while the health and social harms that result from such a regulatory approach are disproportionately high relative to the health risks of cannabis use, especially given that cannabis use is common in industrialized countries.[4] Accordingly, several reform efforts, such as reducing criminal penalties or decriminalizing personal possession, have been implemented in jurisdictions throughout industrialized countries without resulting in any major spikes in usage.[4] One consequence of the prohibitionist approach to drugs has been the prioritization of measures of drug supply and demand over measures of public health or human rights in drug policy evaluations.[5] In the wake of the recent United Nations General Assembly Special Session (UNGASS) on the World Drug Problem in 2016, leading drug policy researchers issued a high-profile call for governments to implement an expanded system of metrics for drug policy evaluation based on health, peace and security, development and human rights.[6,7]

The UNGASS meetings coincided with the first steps of the Canadian federal government's effort to replace cannabis prohibition with a regulatory framework to legalize the production, sale, and non-medical use of cannabis by adults. In a speech to UNGASS delegates, Canada's then-Minister of Health, Jane Philpott, announced the Canadian government's intent to "legalize

and strictly regulate" cannabis with the hopes of reducing youth usage rates and curbing the income of organized crime.[8] Approximately one year later (April 13, 2017), the governing Liberal party tabled the first reading of Bill C-45,[9] otherwise known as the *Cannabis Act,* with the objective of implementing the legal framework nation-wide by July 2018.[10] Canada will be the first major industrialized country to introduce a regulatory framework for cannabis. In doing so, it will effectively introduce a population-level natural experiment with relevance beyond the country's borders. In contrast to the more commercialization-driven approaches to non-medical cannabis regulation undertaken in certain jurisdictions throughout the United States (e.g., Washington, Colorado),[11] the Canadian government has promised to build a public health-based framework of cannabis regulation.[12] The perceived public health and safety successes and failures of Canada's cannabis legalization framework will depend on the ongoing assessment of a set of indicators deemed relevant by the scientific community, health stakeholders, and various levels of government. This presents a valuable opportunity to prioritize a new system of metrics to evaluate the overall impact of policies governing psychoactive substances.

To date, a small number of perceived harms to the health and safety of Canadians have dominated public discourse around cannabis regulation. For example, concerns about cannabis-impaired driving and adolescent/youth use were raised numerous times by members of Canada's opposition Conservative party during the bill's readings,[13] and these issues have been discussed extensively in the Canadian media.[14,15] The design and implementation of distinct provincial and territorial legal frameworks around distribution (e.g., private vs. government retail,[16] minimum age requirements)[17] has received substantial attention, along with prevention and detection of impaired driving.[18] Inevitably, the development of a comprehensive monitoring and evaluation

system is necessary to move away from speculation towards evidence-informed decisions about the impact of cannabis regulation on Canadians' health and safety.

In this paper, we propose a comprehensive set of population indicators to yield a balanced evaluation of the public health and safety risks and benefits of cannabis legalization in Canada.

METRICS & PRELIMINARY EVIDENCE

A set of metrics was developed (methodological details provided as a Supplementary File) and organized into five broad themes: Public safety; Cannabis use trends; Other substance use trends; Cardiovascular and respiratory health; and Mental health and cognition. In Tables 1-5, each indicator is listed alongside a brief rationale for its inclusion and a summary of findings from jurisdictions that have legalized non-medical and/or medical cannabis. Wherever possible, existing Canadian data sources from which measures might be ascertained pre- and post-legalization are also provided.

Public safety

Eight indicators were identified pertaining to cannabis-impaired driving, alcohol-impaired driving, motor vehicle injuries and fatalities (overall, cannabis-related, alcohol-related), dating and intimate partner violence, workplace safety, and crime.

Data from Colorado[19] and Washington[20] show that the proportion of fatally injured drivers with a blood tetrahydrocannabinol (THC) concentration >1 ng/mL increased after legalization. In Washington, the proportion of THC-positive blood samples from drivers suspected of impaired driving increased significantly from an average of 19.1% in 2009-2012 to 24.9% in 2013 (the year after legalization).[21] Although these findings suggest that cannabis legalization may have resulted in an increase in the prevalence of cannabis use among Washington's driving population, they cannot infer a direct role of cannabis intoxication in driving problems. A significant limitation of these studies is the inability to assess the level of driver impairment, as the complex pharmacokinetics of cannabinoids pose a challenge to establishing a universally accepted and scientifically valid standard of cannabis impairment.[22]

Measures of overall traffic injuries and fatalities, rather than rates of putative driver impairment, may provide a more meaningful criterion for evaluating the consequences of changes to cannabis regulation. A recent study analyzed fatal accident reporting system (FARS) data in Washington and Colorado and did not find that rates of motor vehicle crash fatalities changed significantly after non-medical cannabis legalization compared to eight control states.[23] Two other studies used FARS data to examine changes in motor vehicle crash fatalities before and after medical cannabis legalization in US states, and found that medical cannabis legalization was associated with significant reductions in motor vehicle fatalities, most prominently among young adults.[24,25] The findings were suggestive of an underlying substitution effect given high rates of binge drinking within this age demographic. Furthermore, two studies observed significant reductions in alcohol-related motor vehicle fatalities after the passage of state medical cannabis laws;[24,26] however, one study noted that the effect was reduced if the state law allowed for dispensaries.[26]

The role of cannabis in dating and intimate partner violence is not yet well understood,[27] but given the robust association between alcohol use and violence in intimate relationships[28] it would be of interest to examine whether rates of this prevalent form of violence are altered in the wake of cannabis legalization as a result of possible cannabis substitution. No preliminary evidence was identified for this outcome, or for indicators of cannabis-related workplace safety.

Overall, preliminary research did not support the notion that cannabis legalization would lead to increases in crime. In terms of medical cannabis laws, three studies did not find a significant effect,[29-33] and two studies found that medical cannabis legalization was associated with significant reductions in violent and property crime.[31,33] Most recently, a study examined crime rates along the Washington-Oregon border before and after non-medical cannabis legalization in Washington and observed significant post-legalization drops in rape and property crime in counties along the Washington border relative to counties in the Oregon border.[32] Studies examining the effect of cannabis retail outlet density on crime rates in geographical proximity were mixed, with one study noting significant decreases[29] and other noting no effect on crime in the surrounding areas.[34,35]

Cannabis use trends

Nine areas of interest were identified and correspond to cannabis use initiation; usage trends among youth; cannabis use disorder (CUD); unregulated cannabis use (particularly among youth); changes in cannabis use practices (e.g., products, dosing, potency, method of

consumption); cannabis use among expectant and breastfeeding mothers; cannabis-related healthcare utilization; unintentional pediatric cannabis exposures; and cannabis-attributable burden of disease (Table 2).

Although national epidemiological surveys in the US have not detected significant changes in the prevalence of cannabis use following non-medical cannabis legalization in relevant states,[36,37] studies accounting for simultaneous changes in a control group provide a better indication of the impact of legalization. An analysis of 8th, 10th, and 12th grade students in Washington and Colorado against students from non-legalized states demonstrates significant increases in previous 30-day use among 8th and 10th grade students in Washington only (by 2.0% and 4.1%, respectively).[38] In Oregon, the frequency of previous 30-day use was estimated to increase after legalization among students transitioning from 8th to 9th grade, relative to students in these years before legalization; however, legalization was not observed to lead to an increase in the proportion of new cannabis initiates in this age group.[39] Studies among university students (many of whom would be the age of majority under Canadian law) estimate post-legalization increases in the prevalence and frequency of cannabis use among students in Washington,[40] and only among binge drinking students in Oregon.[41] A recent meta-analysis of studies exploring the effect of medical cannabis legalization on pre-post changes in cannabis use among adolescents estimated a non-significant pooled effect, with none of the 11 included studies detecting a significant relative change.[42] Findings included here should be considered against the limitations inherent in survey-based analyses, which may result in the under-reporting of stigmatized and criminalized behaviours.[43]

In Washington and Colorado, treatment admissions for CUD had been decreasing ahead of legalization and are continuing to decrease,[44] but there has not been a statistical analysis to determine the impact of legalization on these trends. Studies examining population survey data have observed significant associations between medical cannabis legalization and increased prevalence of DSM-IV cannabis abuse and dependence among adults,[45,46] but not youth.[46] Studies examining changes in treatment admissions for CUD after medical cannabis law implementation have been inconsistent, with significant increases noted in one study,[45] and significant decreases noted in another.[47] Pacula and colleagues highlight the importance of accounting for different policy dimensions, showing that legally sanctioned dispensaries were associated with significant increases in CUD treatment admissions, despite an overall negative effect of medical cannabis legalization on CUD treatment admissions.[47]

Considering the potential social (e.g., criminalization)[48] and health harms (e.g., due to unknown purity, dose, potential toxins/contaminants)[49] associated with the use of unregulated cannabis, a metric was included to monitor for use of unregulated cannabis products among Canadians – especially among minors, who will be prohibited from engaging in the regulated market. No preliminary research was identified in this area. Monitoring the characteristics of cannabis used including the amount, strain, potency, and route of administration will play an important role in addressing possible links to acute and chronic cannabis-related harms. For example, the use of cannabis with a lower relative concentration of THC or higher concentrations of CBD may reduce risk of dependence[50] and psychosis-like symptoms[51] – although existing research on cannabinoid ratios and psychosis is limited. In addition, vapourizing cannabis and consuming edible preparations of cannabis are comparably safer modes of administration with respect to

respiratory effects,[52] although it should be noted that edibles and concentrates will not be covered in the first round of Canada's policy change.[53] In cross-sectional studies of cannabis-using youth[54] and adults[55] in the US recruited through social media, users in states with regulated medical cannabis were more likely to engage in vapourizing and edible cannabis consumption; however, these studies do not show whether changes in smoking occurred alongside initiating alternative modes of consumption. The extent to which individuals use cannabis in accordance with recently-released Canadian guidelines for lower-risk non-medical cannabis consumption,[56] and whether compliance with these recommendations leads to lower rates of acute and chronic cannabis-related harms, will require attention.

As outlined by the government taskforce on cannabis legalization,[57] expectant and new mothers and their newborn babies represent important risk groups to monitor for changes after legalization. There is growing concern that cannabis exposure *in utero* or through breast milk could be linked with adverse perinatal outcomes (e.g., stillbirth, preterm birth, low birth weight) and poorer neurodevelopmental outcome, but studies exploring these links are mixed.[58] No preliminary research was identified on changes in cannabis use among pregnant women (or potentially related adverse outcomes in children) resulting from a legalized framework.

Although there are no documented cases of fatal overdose as a direct result of natural cannabis consumption,[59] cannabis use in high doses can cause transient acute harms, such as tachycardia, cannabis-induced psychosis, and paranoia.[60] The occurrence of acute harms among first-time, new, and infrequent users should be a target of analysis, since these individuals may be particularly susceptible to negative reactions from lower doses.[60] Although Shi found that the

implementation a state medical cannabis policy did not increase hospitalizations related to cannabis abuse or dependence significantly more than other states from 1997-2014,[61] increases in acute cannabis intoxication have emerged as a concern in states that have legalized non-medical cannabis.[62] Hospital and poison center data from Colorado point to significant post-legalization increases in pediatric (<9 years) emergency room visits, hospitalizations, and poison center calls related to acute cannabis intoxication following non-medical cannabis legalization.[63,64] Adults also experienced significant increases in cannabis-related ER visits and hospitalizations in the state following legalization,[63,65] but these changes have not been compared against a control. The majority of adverse events in Colorado were among visitors to the state,[66] and many pediatric exposures were linked to the consumption of candy edibles.[64]

Cannabis is estimated to account for 55,813 years of Canadian life lost due to disability,[67] and this burden of disease could increase if legalization leads to an increase in the prevalence or frequency of cannabis use among Canadians.[67] Considering the substantially lower burden of disease attributable to cannabis compared to opioids, tobacco, and alcohol,[67,68] it will also be important to monitor changes in the cannabis-attributable burden of disease against potential shifts in the burden of disease attributable to these other substances, in case of substitution or complementary effects. No preliminary research estimating changes in the burden of disease attributable to cannabis after medical or non-medical cannabis legalization was identified.

Other substance use trends

The five indicator areas of interest identified under this theme are concerned with the potential for cannabis to complement, exacerbate, or substitute the use of other substances, specifically: medical and non-medical opioid use (including pharmaceutical and non-pharmaceutical) and related overdoses; illicit stimulant use; alcohol use; and tobacco use (Table 3).

As many North American jurisdictions are responding to ongoing opioid-related public health crises marked by unprecedented rates of overdose mortality, a growing number of studies are assessing the potential for cannabis to be used as a so-called substitute for opioids. There is some evidence that the passage of medical cannabis laws is associated with reductions in broad (i.e., combined pharmaceutical and illicit) opioid use[69] and use disorders.[61] One study noted that the implementation of state medical cannabis laws with provisions for dispensaries was associated with significant reductions in treatment admissions for opioid use disorder (OUD), but the overall passage of any medical cannabis law did not have a significant effect.[70] In terms of pharmaceutical opioids, two studies did not detect a significant change in medical use of pharmaceutical opioids (as indicated through distribution to the medical market)[70] or self-reported non-medical pharmaceutical opioid use associated with medical cannabis legalization.[46,70] One study found that heroin treatment admissions were reduced significantly relative to control states after the passage of state medical cannabis laws.[71]

Studies of non-fatal and fatal opioid overdose offer some support to the notion that cannabis legalization promotes reductions in opioid use. Bachhuber and colleagues reported a significant 25% reduced rate of opioid overdose deaths relative to control states after the passage of medical cannabis laws,[72] and a more recent analysis also estimates a significant 25% reduction – but only

for states with legal and operational dispensaries (otherwise, the broad passage of a medical cannabis law was not significantly associated with reduced opioid-related fatalities).[70] Shi examined data from 27 states and noted significant reductions in hospitalizations for OUD (23%) and opioid overdose (13%) associated with medical cannabis legalization.[61] Finally, a recent study evaluated the short-term impact of non-medical cannabis legalization on opioid-related fatalities in Colorado and demonstrated a modest yet significant reduction relative to two control states.[73]

In a study of students at Washington State University, there were no marked post-legalization changes in the self-reported use of illicit drugs (including stimulants and opioids), alcohol, or tobacco, despite significant increases in cannabis use.[40] The passage of a state medical cannabis law was not significantly associated with changes in cocaine use among adults or youth.[46] Another US state-level analysis found no significant change in cocaine-related treatment admissions after medical cannabis legalization.[71] Although treatment admissions for AUD continue to decrease in Washington and Colorado,[44] the extent to which this has been influenced by cannabis legalization has not been explored. In addition to reductions in alcohol-related motor vehicle accidents (see Table 1), alcohol sales were estimated to reduce significantly compared to control states after the passage of medical cannabis laws.[24,74] One study also noted simultaneous underlying reductions in self-reported alcohol use frequencies in several age groups.[24] In contrast, another study observed significant increases in the frequency of binge drinking and likelihood of cannabis and alcohol co-consumption among adults, but not youth, after medical cannabis legalization.[46] Pacula and colleagues estimated that the passage of a state medical cannabis law was associated with reductions in adult alcohol consumption;[26] however, they

noted important differences according to policy dimensions, including a positive effect for states with laws allowing for cannabis dispensaries.[26] Cross-sectional research shows that states with medical cannabis laws have significantly elevated rates of cannabis and tobacco co-use,[75] but a longitudinal analysis is required to determine whether the passage of medical cannabis laws had any effect on this finding.

Cardiovascular and respiratory health

Two broad indicator categories identified under this theme relate to acute and chronic cardiovascular and respiratory harms that have been cited as potential concerns of cannabis smoking or cannabis use more generally (Table 4).

As smoking is the most common mode of cannabis administration,[76] and cannabis is frequently consumed as a cannabis-tobacco mixture in certain regions in Canada (e.g., Ontario),[77] there are concerns regarding a potentially increased risk of respiratory problems including lung cancer. In this regard, the above-listed recommendations to observe shifts in alternative modes of administration as well as changes in prevalence of tobacco use are particularly pertinent. Cardiovascular health remains an important consideration due to mounting concerns of cannabis as a potential trigger for cardiovascular problems, including myocardial infarction (MI),[78] even among young people.[79] No research has been identified from US jurisdictions examining changes to respiratory and cardiovascular problems such as lung cancer, stroke, or MI, after cannabis regulation. More time will be needed to establish the impact on these longer-term health outcomes.

Mental health and cognition

Four indicator areas of interest were identified from commonly cited mental health and cognitive concerns related to cannabis. These include psychosis and schizophrenia; anxiety and depression; suicide; and cognitive and educational performance among youth (Table 5).

Causal links between cannabis and schizophrenia continue to be contested in the scientific literature,[80] and despite the fact that cannabis-related psychotic outbreaks are often raised as a concern of cannabis legalization,[81] no studies were identified that examined changes in rates of schizophrenia or psychosis in relation to cannabis policy. Given the potential severity of this outcome, especially as it relates to the health of young people, it should be given high priority in the wake of legalization. Similarly, no studies of the effect of cannabis legalization on rates of anxiety, depression or depressive symptoms were identified.

Although research has not shown that the use of cannabis causes suicide, modest links between chronic cannabis use and suicide/suicidal behaviour have been described in the literature.[82] Suicide rates per annum have been increasing gradually in Alaska, Washington, Colorado, and Oregon over the past decade (i.e., beginning before legalization),[44] and these trends have not been statistically analyzed against trends in non-legalized states. In Colorado, no significant association was detected between the number of medical cannabis registrants and the rate of completed suicide.[83] A longitudinal study compared suicide rates in states that legalized medical cannabis to control states, and found no statistical association between medical cannabis

legalization and suicide overall; however, among men aged 20-39 years old, legalization was associated with a significant reduction in suicide.[84]

High-frequency cannabis use during adolescent years has been linked to negative cognitive outcomes (e.g., reduced IQ)[85] in later life. However, it should be noted that several more recent studies have not found an association between cannabis and IQ after controlling for social and environmental factors such as poverty and neighbourhood disadvantage,[86-88] and social/behavioural outcomes (e.g., high school non-completion).[89] No research exploring whether measures of cognitive function, including IQ, changed after cannabis regulation was identified. In terms of academic performance, standardized test scores to measure reading proficiency among 8th and 10th grade students in Washington were not observed to change following legalization,[44] but the effect of cannabis legalization on these measures has not been formally assessed against a control group. One study found that longer exposure to state medical cannabis laws was associated with significantly increased odds of high school and college non-completion.[90]

DISCUSSION

Balancing the benefits and harms of legal cannabis on public health and safety will require rigorous monitoring of Canada's new regulatory framework. Five key areas of interest comprising of 28 indicators were recommended as a guideline to address the level of public harm and benefit that may directly or indirectly result from cannabis legalization.

A review of preliminary research yielded little consensus of negative short-term policy effects on public health and safety. For example, increases in youth cannabis use and CUD are frequently cited amongst policymakers and the public as concerns of non-medical cannabis legalization;[91] however, among youth in Washington and Colorado, cannabis use was only observed to increase in two of the six student groups under observation post-legalization,[38] while studies of the impact of medical cannabis regulation have shown mixed effects on youth (see Table 2). Increases in adverse exposures to cannabis, including unintentional ingestion among young children (via poison centre calls and hospital contact) were observed following non-medical legalization in Colorado.[63-65] However, the population-level impact remains low. For example, in the first six months after retail legalization, there was total of 10 cannabis-related hospitalizations of children aged <9, representing roughly 0.03% of all hospitalizations in that age group.[63] Potential changes to patient reporting behaviours and clinician assessment practices after legalization should also be taken into consideration. For example, concerns of child protective involvement may no longer act as a barrier to parents seeking help for pediatric exposures under a legal framework.[63,92] Preliminary evidence of the impact of cannabis legalization was not identified for a number of indicators including cannabis use during pregnancy; workplace injury resulting from cannabis impairment; short- and long-term respiratory and cardiovascular problems; and depression, anxiety, and psychosis.

The current recommendations for indicators to monitor for potential risks to public health and safety are in line with a recent report released by Public Safety Canada.[93] Beyond these shared recommendations, the current review suggests that monitoring several additional indicators for potential benefits would produce a more balanced evaluation of the public health and safety

impacts. Preliminary evidence was identified from US jurisdictions to support the possibility that a policy reform of this magnitude may spur unanticipated benefits including possible reductions in opioid use[69] and use disorders,[61,70,71] opioid-related overdose,[72,73] and alcohol-related motor vehicle fatalities.[24,25] Although this trend towards improvement in opioid indicators was prominent, it was not consistent across studies, with two studies noting no significant reduction in self-reported non-medical pharmaceutical opioid use after medical cannabis legalization.[46,70] Furthermore, since much of this evidence is based on medical cannabis legalization, its relevance to non-medical cannabis regulation remains limited. Yet, considering the substantial estimated overlap between medical and non-medical users[94] and given that many jurisdictions across Canada are responding to public health emergencies involving unprecedented rates of fatal overdoses from opioids (e.g., pharmaceutical opioids, heroin, fentanyl, and fentanyl derivatives),[95,96] monitoring these indicators will be critical to understanding the impact of cannabis regulation within the current public health climate. The recommendation of indicators related to potential public health benefits under a legalized framework is supported by an open letter signed by cannabis researchers across Canada urging the federal government to prioritize research to maximize the public health benefits of cannabis regulation along with research to minimize the potential harms.[97]

In developing these guidelines, the importance of establishing baseline measures to monitor for changes after the policy takes effect was taken into consideration. Wherever available, examples of potentially relevant national-level data were suggested for each indicator. There are several notable limitations associated with relying solely on these data sources such as self-reported measures, exclusion of key population groups, and measurement or reporting differences across

provincial and territorial jurisdictions. There is also a clear need for analysis of detailed original data from longitudinal studies of specific sub-populations at elevated risk of harm from changes in drug markets (e.g., youth, racial and ethnic minorities, people who use illicit drugs). Establishing a system to track cannabis from production to sale will further provide a new and legitimate way to observe trends in regulated product use, which will deeply enhance the understanding of outcomes with respect to regulatory details (e.g., price, purity, dosage).

Despite that approximately one in eight Canadians over 15 (and one in three aged 18-24) use cannabis under current prohibitive laws,[98] details on cannabis use (e.g., usage during pregnancy, impaired driving) are not well captured through existing epidemiological surveys. New cannabis surveys launched by Health Canada[99] and Statistics Canada[100] should take into account these existing knowledge gaps. Past and current clinical studies tend to assess cannabis exposure through regularity of use (e.g., daily, weekly, monthly), quantity of use (e.g., "joint"-years: one joint per day for one year = 1 joint-year, or measures in grams/day), or potency (usually measured as %THC dry weight of herbal cannabis). However, these measures do not capture variability in cannabis modes of administration (smoked, vapourized, oral, topical) or reasons for use (the spectrum from medical to non-medical) and do not translate into meaningful risk measures (e.g., alcohol: units per week; opioids: morphine daily equivalents). There is a need for a global consensus on standardized cannabis use measures (e.g., standard joint unit)[101] for inclusion in future epidemiological and clinical assessment tools in order to fully describe, evaluate, and compare associations between cannabis and different outcomes.[102] In anticipation of cannabis regulation, Statistics Canada plans to re-assess its national surveys (e.g., CTADS), and has acknowledged the need to develop measures for standard units in the future.[37]

Considering that the preliminary evidence reviewed here examined how recommended health and safety indicators changed in the wake of a major policy reform, most studies were ecological in nature and are subject to common limitations such as a reduced ability to measure and control for certain individual-level factors or important state-level differences. Furthermore, the public health and safety impacts of changing the legal status of cannabis will largely depend on how cannabis is regulated federally (e.g., marketing) and across provincial/territorial jurisdictions (e.g., retail sales, public consumption, age of access). The regulatory landscapes from which preliminary findings were drawn have a high degree of heterogeneity (see, for example Powell et al., 2018,[70] and Pacula et al., 2013),[26] and will not necessarily match proposed provincial/territorial, and federal legislations.[103] This evidence is included to broadly inform possible short-term outcomes of cannabis policy reform associated with a range of regulatory models, and individual studies should be interpreted within their regulatory-specific contexts. Considering that progress in cannabis health research has been stunted through decades of prohibition, a legal framework will likely spur new public health and safety areas of interest. The recommended indicators will be subject to ongoing modification as cannabis becomes more openly used, discussed, and studied.

Although beyond the primary scope of this paper, several issues rooted in the social dimensions of health, human rights, social justice, and equality will require additional consideration in the overall evaluation of the policy change. For example, just over half of police-reported drug offences in Canada are for cannabis possession, and among minors (12-17 years old), cannabis possession accounts for 81% of drug offences.[104] Given the range of social and economic harms

(e.g., reduced educational attainment, employment, housing opportunities) associated with exposure to the criminal justice system (e.g., arrest, incarceration, holding a criminal record), potential reductions in the criminalization of Canadians for non-violent cannabis offences could have wide reaching societal benefits for Canadians.[105] Criminalization is particularly pertinent to the health of marginalized populations (e.g., people who inject drugs, street-involved youth) as it exacerbates existing social and health disparities,[106] and many racial and ethnic minority groups have suffered disproportionately under current cannabis laws in Canada[107] and the US.[108] Further, selling cannabis is a common income generating strategy for marginalized and street-based drug users with little access to the licit economy.[109,110] In Washington[111] and Colorado,[112] legalization of non-medical cannabis was followed by substantial (i.e., >80%) decreases in cannabis possession charges and cannabis-related convictions. In Colorado, juveniles (i.e., 10-17 years old) were the only age group in which cannabis arrests were observed to increase (by approximately 5% after legalization).[112] It was found that white juveniles experienced a decline by 8%, whereas arrests among Hispanic and African-American juveniles increased by 29% and 58%, respectively.[112] These discrepancies in social benefits across age and ethnic/racial strata demonstrate a clear need to monitor changes across minority populations to prevent ongoing discrimination after regulation. It should also be noted that, although population-level rates of cannabis-related offenses are expected to decrease under a legal framework, clauses of the *Cannabis Act* are set to impose enhanced criminal penalties on individuals continuing to produce, distribute, sell or use cannabis outside the legal regime.[9,113] The regulatory structure of the cannabis production and retail industry (e.g., corporatization vs. small businesses) is likely to play a large role in influencing these upstream societal factors through changes to the distribution of wealth.

CONCLUSIONS

The unprecedented transition from cannabis prohibition to regulation in Canada will provide a valuable opportunity to study the health impacts of cannabis use and cannabis regulation on an individual- and the population-level. Under the themes of public safety, cannabis use trends, other substance use trends, cardiovascular and respiratory health, and mental health and cognition, 28 key population indicator areas of interest were prioritized to establish the public health and safety impact. Preliminary and short-term evidence on these indicators from nearby jurisdictions that have regulated medical or non-medical cannabis provides some insight into possible harms (e.g., potential increases in the occurrence of cannabis-related hospitalizations) and benefits (e.g., potential decreases in opioid use and overdose) to the Canadian public. However, generalizability of these outcomes to the Canadians population is limited by the high degree of policy variability across jurisdictions with medical or non-medical cannabis laws. Considering the Canadian government's commitment to a regulatory cannabis framework driven by public health and supported by scientific evidence, this review underscores the importance of considering both the public health risks and benefits in preparing a truly comprehensive public health monitoring and evaluation system.

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CONTRIBUTIONS

The idea for this paper was conceived by TK, M-JM and SL. M-JM and SL designed the study. SL developed the search and conducted the review. SL and MJ-M wrote the initial draft. TK, DW, RH-S, BF, GT, ZW, MAW, and EW conducted critical revisions of the draft. All authors contributed to and agreed on the proposed set of indicators, and approved the final manuscript draft.

POTENTIAL CONFLICTS OF INTEREST

The University of British Columbia has received unstructured funding to support MJ-M from NG Biomed, Ltd., an applicant to the Canadian federal government for a license to produce medical cannabis. ZW is Coordinating Principal Investigator on a clinical trial sponsored by Tilray, a licensed producer of medical cannabis. MAW is a consultant to CHI, CannaRoyalty and Zynerba and has received a grant to his institution for clinical research from CanniMed.

Table 1. Suggested public health indicators for the evaluation of cannabis regulation in Canada: Individual and public safety

Indicator(s)	Relevance to cannabis regulation	Preliminary evidence	Existing data source(s)
1. Prevalence and frequency of **cannabis-impaired driving** overall and across risk demographics	In placebo-controlled simulated driving studies, cannabis impairment is associated with slower driving, greater headway, and slower reaction time.[114-117] Driving after using cannabis is associated with an estimated 22-36% increased risk of a motor vehicle crash.[118]	**Non-medical cannabis legalization:** In the year following cannabis legalization in Washington, the proportion of suspected impaired driving cases that tested positive for THC increased significantly from the four-year period before legalization.[119]*	Canadian Tobacco Alcohol and Drugs Survey (CTADS); Canadian Student Tobacco Alcohol and Drugs Survey (CSTADS); Canadian Cannabis Survey (CCS); National Cannabis Survey (NCS) Road Safety Monitor (RSM) via Traffic Injury Research Foundation (TIRF)
2. Number and incidence of **cannabis-related motor vehicle crash injuries and fatalities** overall and across risk demographics		**Non-medical cannabis legalization:** The proportion of fatally injured drivers who tested positive for THC (≥1 ng/mL) increased after legalization in Washington[20] and Colorado,[19]* however it is not possible to determine the extent to which these deaths were cannabis-related.	National Fatality Database (NFD) via TIRF; Uniform Crime Reporting Survey (UCRS; not drug-specific)
3. Number and incidence of **all-cause motor vehicle crash injuries and fatalities** overall and across risk demographics	Since a universally accepted and scientifically valid standard of impairment for cannabis has not been established,[22] measures of overall road safety should be examined, as they would be expected to increase if cannabis-related motor vehicle accidents increase.	**Non-medical cannabis legalization:** Compared to eight control states that did not legalize non-medical cannabis, Washington and Colorado did not experience significantly different changes in the rate of motor vehicle crash fatalities up to three years after legalization.[23] **Medical cannabis legalization**: Medical cannabis legalization was associated with reductions in overall rates of motor vehicle fatalities compared to states that did not legalize cannabis; the effect was mostly accounted for by significant immediate and sustained reductions among those aged 25-44.[25] Another study estimated that medical cannabis legalization was associated with an 8-11% reduction in overall traffic fatalities in the year following legalization, with largest reductions observed among young adults (20-39 years).[24]	National Collision Database (Transport Canada); NFD via TIRF
4. Prevalence and frequency of **alcohol-impaired driving** overall and across risk demographics	Increased access to and use of cannabis may substitute excessive alcohol intake,[120] as has been documented among medical cannabis patients[121] However, some research also supports concurrent use with alcohol.[120] Concurrent consumption of cannabis and alcohol increases the risk of motor vehicle accident beyond consumption of either alone.[122]	**Medical cannabis legalization:** A US study found that medical cannabis legalization was associated with a 13% reduction in motor vehicle fatalities involving alcohol.[24] A second study noted similar findings, but the effect was reduced in states with legal medical cannabis dispensaries.[26]	CTADS; CSTADS; Canadian Community Health Survey (CCHS); RSM
5. Number and incidence of **alcohol-related motor vehicle injuries and fatalities** overall and across risk demographics			NFD via TIRF; UCRS
6. Prevalence of **dating and intimate partner violence**	Given that alcohol is a widely reported predictor of intimate partner violence,[28,123] and studies have generally not found an association between cannabis and dating or intimate partner violence,[124] rates of intimate partner violence should be monitored for potential cannabis substitution effects.	Not found	UCRS

7. Number of and **cannabis-related workplace injuries** overall and across work sectors	Cannabis legalization poses questions around cannabis in the workplace, including potential increases in prevalence of cannabis impairment in the workplace and cannabis-related workplace injuries.[125]	Not found	Not found
8. Rate of **violent and property crime**, particularly in areas surrounding cannabis production and retail sites	Removing organized crime from involvement in the cannabis market is a primary objective of regulating cannabis in Canada[126] Some studies have linked cannabis use to increased likelihood of violent behaviour,[127] but the causal nature of this association remains unclear. There are also fears of heightened criminal activity, as some cannabis dispensaries have been the target of violent robberies across different Canadian cities.[128]	**Non-medical cannabis legalization:** In Washington, violent crime decreased by 10% and burglaries decreased by 6% from pre- to post-legalization (2011 to 2014).[111]* Washington counties along the Washington-Oregon border experienced significant reductions in rape (15-30%) and property crime (10-20%) following legalization, relative to counties on the Oregon side of the border (before Oregon's legalization took effect).[31] In Denver, Colorado, one study found that cannabis retail outlet openings were associated with significant reductions in crime (particularly violent crime) in the surrounding area,[29] while another did not record a significant association between density of retail outlets and surrounding area crime.[34] **Medical cannabis legalization:** Two studies found no significant impact of medical cannabis legalization on overall rates of violent and property crime,[30,129] although one study noted a significant 20% reduction in California.[30] An analysis conducted in Long Beach, California demonstrated that the density of retail cannabis outlets was not significantly associated with increased crime in the surrounding area (although increases were detected in adjacent areas).[35] Another study noted significant reductions in violent and property crime following the passage of a state medical cannabis law.[33] A recent study found that medical cannabis legalization was significantly associated with reductions in violent crime in states bordering Mexico but not in inland states, suggesting an impact on reducing crime involving Mexican drug trafficking.[32]	UCRS
Note: *Indicates that the reported change in number/proportion/rate was not analyzed against a control group or adjusted for any potential confounding factors			

Table 2. Suggested public health indicators for the evaluation of cannabis regulation in Canada: Cannabis use trends

Indicator(s)	Relevance to cannabis regulation	Preliminary evidence	Existing data source(s)
1. Incidence and average age of **cannabis use initiation among youth**	The human brain continues to develop throughout adolescent years and into young adulthood.[130] The use of cannabis in adolescence and earlier onset of adolescent cannabis use has been associated with adverse cognitive and mental health outcomes in some studies but not in others (see Table 5 below). Preventing youth cannabis use and delaying onset of use are clear priorities of the Canadian cannabis legislation.[57]	**Non-medical cannabis legalization:** In Oregon, legalization was not associated with increased initiation rates among a sample of students transitioning from 8th to 9th grade.[39] **Medical cannabis legalization:** The implementation of state medical cannabis laws was associated with a 5% increase in the probability of initiating cannabis among individuals aged 12-20 relative to control states.[46]	CTADS; CSTADS; CCS
2. Prevalence and frequency of recent (e.g., past-month, past-year) **cannabis use among youth**		**Non-medical cannabis legalization:** Overall, the prevalence of cannabis use (past 30-day or past year) among adolescents (12-17) did not change significantly from pre- to post-legalization in Colorado, Washington, Alaska, Oregon, or Washington DC.[36,37]* Compared to control states, prevalence of past 30-day use was increased in the 3-year period post-legalization among 8th and 10th but not 12th graders in Washington, but did not increase among students in Colorado.[38] Oregon students who transitioned from 8th to 9th grade during legalization experienced significantly greater increases in the frequency, but not prevalence, of past 30-day cannabis use compared to the pre-legalization cohort.[39] After legalization in Washington, past 30-day use and frequency of use among university students, including underage students, were estimated to increase significantly more than expected from national usage trends.[40] Among university students in Oregon, legalization was not observed to affect overall rates of past 30-day use compared to control universities; however, past 30-day use increased significantly more than controls among students who engaged in binge drinking.[41] **Medical cannabis legalization:** A meta-analysis of 11 US studies did not find evidence that medical cannabis legalization is associated with changes in overall prevalence of adolescent cannabis use.[42] Of the 7 included studies that also examined frequency of use,[26,46,47,131-134] Two found a positive association with medical cannabis legalization.[47,134]	CSTADS; CCHS; CCS; NCS
3. Prevalence of **cannabis use disorder** (CUD) overall, among cannabis users, and across risk demographics (e.g., youth)	The lifetime risk of cannabis dependence among users is approximately 9%, and has been estimated at 18% among adolescent initiates.[60] Past-year prevalence of CUD (abuse and dependence) is roughly 30% among current adult (≥18 years) users,[135] 20% among youth (12-17 years) users, and 2-3% overall across adults and youth.[135,136] There are concerns that increased social acceptability of and legal access to cannabis may lead to increased prevalence of CUDs by way of increased prevalence of use and frequency of use among current users.	**Non-medical cannabis legalization:** In Washington and Colorado, annual treatment admissions for cannabis began decreasing ahead of legalization and continued to decrease after legalization.[44]* **Medical cannabis legalization:** Some studies have found evidence that the implementation of state medical cannabis laws is associated with increased use of cannabis and prevalence of DSM-IV cannabis abuse/dependence among adults[46,137], but not among youth.[46] Using administrative data for CUD treatment admissions in US states, one study estimated that medical cannabis legalization was associated with a significant 10-20% increase in CUD admissions.[45] A more recent analysis using the same data source found medical cannabis legalization to be significantly associated with a 14% reduction in CUD treatment admissions relative to control states.[47] Separation of legalized states by medical cannabis law provisions revealed that dispensary provisions were associated with significant increases in CUD treatment admissions.[47] These findings also held for individuals under the age of 21.[47]	National Treatment Indicators Project (NTIP; Publicly funded treatment services only); CTADS (screens for high-risk use but not CUD)

4. Prevalence of **unregulated cannabis product use**, particularly among youth	Under a legalized framework, those who continue to engage in the unregulated cannabis market will be subject to criminal penalties.[9] An estimated 1 in 5 youth between ages 15 and 17 currently use cannabis,[98] and will be prohibited from accessing cannabis through the regulated system. Usage of unregulated and untested products may carry a higher risks of adverse effects and other health problems due to unknown purity and dosage, toxic contaminants (e.g., yeast, mould, bacteria), etc.[49]	Not found	CCS; NCS
5. Trends in cannabis use **products and practices** (e.g., potency, dosing, method of consumption)	Regulating the production, sale, and use of cannabis will allow for increased control over and knowledge of product characteristics (e.g., composition, potency, dosing, purity) and increased variety of cannabis-based products and accessories. These changes may promote alternative forms of use including lower-risk practices (e.g., transitions from smoked cannabis to vapourized cannabis or edibles, controlling dosing by selecting products with lower THC or THC/CBD ratios, etc.)[138]	**Medical cannabis legalization:** Among cannabis-using adults and youth (aged 15-18), those who live in a state with a medical or non-medical cannabis law were significantly more likely to report vapourizing or consuming edible forms of cannabis.[54,55] Cannabis-using youth in legalized states had a younger age of initiating these modes of administration (by 1.7 months for vapourizing, and 2.3 months for edibles) than cannabis-using youth who lived in states without legalized medical or non-medical cannabis.[54] These studies did not examine changes in usage practices relative to legalization.	CCS; NCS
6. Prevalence and frequency of cannabis use among **expectant and breastfeeding mothers**	Children whose mothers used cannabis during pregnancy have been outlined as a vulnerable group by the government task force on cannabis legalization.[57] Findings from studies exploring the cannabis-associated risk of certain perinatal outcomes including stillbirth and pre-term birth have been mixed, and much of the research has been confounded by tobacco and other substance use as well as socio-structural exposures.[58] There are also concerns of poorer mental development and cognitive functioning among infants exposed to cannabis in-utero, based on animal studies and a small number of human studies.[58]	Not found	Not found
7. Prevalence of cannabis-related **health care utilization** (e.g., ER visits, hospitalizations) overall and across demographics (e.g., infants, young children)	Acute cannabis intoxication can lead to adverse physical (e.g., dizziness, nausea and vomiting, increased heart rate, increased blood pressure and psychological effects (e.g., anxiety and paranoia).[139,140] There is concern that expanding access to cannabis will lead to unintentional exposures among children (e.g., via consumption of edible products).[62]	**Non-medical cannabis legalization:** In Colorado, hospitalizations for likely cannabis exposure among children aged <9 increased significantly by 2.5 times in the six-month period after retail cannabis legalization.[63] * At 21 months post-legalization, the rate was no longer significantly different from the pre-legalization period.[65]* No significant increase was detected in ER visits from cannabis exposure in this age group after six[65]* or 21 months.[65]* Cannabis-related ER visits and hospitalizations among those aged >9 increased significantly in Colorado from the four-year period before retail cannabis legalization to 21 months post-legalization.[65]* **Medical cannabis legalization:** An analysis of 27 US states did not find a significant effect of medical cannabis law implementation on the rate of hospitalizations involving cannabis abuse or dependence.[61] In Colorado, cannabis-related hospitalizations (including among children) increased significantly in the four-year period after medical cannabis commercialization.[63]*	Discharge Abstract Database (DAD); Hospital Morbidity Database (HMD) National Ambulatory Care Reporting System (NACRS)

8. Number of poison centre calls related to **cannabis intoxication**		**Non-medical cannabis legalization:** In Colorado, the overall number of poison centre calls for cannabis exposure increased significantly by 139% from 2010 to 2014, but remained stable in 2016.[65] In Washington, the average number of calls in the three-year post-legalization period increased by 70%.[141]* Between 2009-2015, the number of poison control centre calls related to paediatric (0-9 years) cannabis exposure in Colorado increased significantly by 34% per year on average, which was significantly higher than the average US rate increase (19% per year).[64] **Medical cannabis legalization:** In Colorado, the overall number of poison centre calls for cannabis exposure increased from 44 in 2009 (the year of medical cannabis commercialization) to 95 in 2010.[63]*	Data collected at the provincial-level (no national database)
9. Cannabis-attributable **burden of disease** via measures of health-adjusted quality of life (e.g., DALY, QALY, YLL)	The cannabis-attributable burden of disease in Canada in 2012 was estimated to include 55,813 years of life lost due to disability (mainly caused by CUD).[67] Although the burden of disease attributable to cannabis is comparatively lower than that for alcohol, tobacco, or opioids,[67,68] if the prevalence of use (or frequency of use among users) increases after legalization, the cannabis-attributable burden of disease is estimated to increase.[67]	Not found	Estimated using data sources for several outcomes
Note: *Indicates that the reported change in number/proportion/rate was not analyzed against a control group or adjusted for any potential confounding factors			

Table 3. Suggested public health indicators for the evaluation of cannabis regulation in Canada: Other substance use trends

Indicator(s)	Relevance to cannabis regulation	Preliminary evidence	Existing data source(s)
1. Prevalence and frequency of medical and non-medical **opioid use** and prevalence of **opioid use disorder (OUD)** overall and across risk demographics.	Cannabis is increasingly being explored as an effective alternative to opioid therapy among individuals with chronic non-cancer pain.[142] However, problematic use of pharmaceutical opioids and cannabis has also been documented among pain patients in some settings,[143] and concerns remain within the public discourse that cannabis may be a gateway to higher-risk drug use including opioids.[144]	**Medical cannabis legalization:** All opioids: Analysis of blood samples from driver fatalities over time suggests that the passage of medical cannabis laws was not associated with reductions in opioid use relative to control states; however, a significant reduction was recorded in drivers aged 21-40.[69] Hospitalizations for opioid abuse or dependence were estimated to decrease significantly by 23% relative to control states after the passage of medical cannabis laws.[61] Another study found no overall significant change in treatment admissions for OUD in legalized states relative to control states, but noted significant reductions in states with legal and operational dispensaries.[70] Medical use of pharmaceutical opioids: Medical use of pharmaceutical opioids, as indicated by state pharmaceutical opioid analgesic distribution, was not observed to change significantly relative to control states after medical cannabis legalization.[70] Non-medical use of pharmaceutical opioids: Two studies found no statistical effect of medical cannabis legalization on self-reported non-medical use of pharmaceutical opioids.[46,70] Heroin: Treatment admissions for heroin OUD decreased by an estimated 13-24% relative to control states after the passage of state medical cannabis laws.[71]	CTADS (non-medical); CSTADS (non-medical); National Prescription Drug Utilization Information System (medical); NTIP
2. Incidence of **fatal and non-fatal drug overdose**, including opioid-related overdoses	Many jurisdictions across Canada are responding to unprecedented rates of opioid-related overdoses due, in part, to high rates of opioid prescribing for non-cancer pain,[145,146] but cannabis has the potential to substitute for opioids (see above).	**Non-medical cannabis legalization:** Recreational cannabis legalization in Colorado was associated with an estimated 6.5% reduction in opioid-related fatalities in the short-term.[73] **Medical cannabis legalization:** Fatal overdose: Opioid-related fatal overdoses were estimated to be 25% lower in US states that legalized medical cannabis, compared to states without medical cannabis laws.[72] A more recent study that added three years to the analysis and used a slightly different modelling approach did not detect a significant reduction in opioid-related deaths relative to control states after medical cannabis legalization overall; however, the adoption of medical cannabis laws allowing for operational dispensaries was significantly associated with a 25% reduction in opioid-related deaths.[70] Non-fatal overdose: Hospitalizations from opioid overdose were significantly reduced by 13% relative to control states after the passage of state medical cannabis laws. There did not appear to be an increased effect for dispensary states.[61]	Canadian Vital Statistics - Deaths (CVSD; fatal overdoses); DAD (non-fatal); NACRS (non-fatal); HMD (non-fatal)
3. Prevalence of illicit **stimulant use** (e.g., cocaine, crack-cocaine, methamphetamine) and **stimulant use disorders** overall and across risk demographics	In addition to the potential substitute for opioids, research among medical cannabis patients and people who use illicit drugs also points to the potential for cannabis to be used as a substitute for other drugs including illicit stimulant.[147-149] By contrast, despite a lack of causal evidence supporting the so-called gateway hypothesis,[150],there is concern amongst the public that cannabis regulation will lead to increases in use of higher risk drugs.[144]	**Non-medical cannabis legalization:** Past 30-day use of illicit drugs (including stimulants) was not observed to change significantly alongside post-legalization increases in cannabis use among students at Washington State University.[40] **Medical cannabis legalization:** The implementation of state medical cannabis laws was not observed to have a significant effect on rates of cocaine (or heroin) use among adults or youth.[46] Another study did not find that medical cannabis legalization in US states was associated with significant changes in treatment admissions for cocaine.[71]	CTADS; CSTADS; CCHS; NTIP

4. Prevalence and frequency of **alcohol use** and prevalence of **alcohol use disorders (AUD)** overall and across risk demographics (e.g., youth and young adults)	Alcohol is generally considered more harmful than cannabis in the public health literature.[151] A legal framework for cannabis has the potential to support increased substitution of alcohol for cannabis or increased co-use use of these substances (see Table 1).	**Non-medical cannabis legalization:** In Washington and Colorado, annual treatment admissions for AUD had been decreasing ahead of legalization, and this trend has continued post-legalization.[44]* Past 30-day alcohol consumption was not observed to change significantly alongside post-legalization increases in cannabis use among students at Washington State University.[40] **Medical cannabis legalization:** In two studies, medical cannabis legalization was associated with significant reductions in alcohol sales compared to control states.[24,74] In one study, this finding was further supported by significant reductions in the frequency of alcohol use among most age groups following legalization.[24] One study found that the passage of state medical cannabis laws was significantly associated with increased self-reported binge drinking days and cannabis/alcohol co-consumption among adults (>21), but not with alcohol usage trends among youth (aged 12-20) or rates of AUD in either age group.[46] Another analysis found that the overall passage of a state medical cannabis law was associated with a reduction in the prevalence alcohol use among adults but not among youth (<21 year).[26] A further examination of distinct policy features revealed that: in general, provisions for home cultivation and dispensaries were associated with increased alcohol use; patient registries were associated with decreased alcohol use; and dispensaries were associated with increases in AUD treatment admissions.[26]	CTADS; CSTADS; CCHS; NTIP
5. Prevalence and frequency of **tobacco use** and prevalence of **tobacco use disorder** overall and across risk demographics (e.g., youth)	Cigarette use is a risk factor for several negative health outcomes including lung cancer and cardiovascular disease.[112] Cannabis use increases the likelihood of nicotine dependence in adolescents and adults who smoke.[75,152] Although tobacco use appears to be decreasing among cannabis users,[153] there is concern within the tobacco public health community that cannabis legalization may re-normalize smoking, which could encourage initiation of cigarettes.[77]	**Non-medical cannabis legalization:** Past 30-day tobacco use was not observed to change significantly alongside post-legalization increases in cannabis use among students at Washington State University.[40] **Medical cannabis legalization:** The overall prevalence of tobacco and cannabis co-use was estimated to be higher in states with medical cannabis laws compared to those without, but a longitudinal comparison of changes in tobacco and cannabis co-use is needed to establish the effect of legalization.[75]	Canadian Tobacco Use Monitoring Survey (CTUMS); CTADS; CSTADS; CCHS
Note: *Indicates that the reported change in number/proportion/rate was not analyzed against a control group or adjusted for any potential confounding factors			

Table 4. Suggested public health indicators for the evaluation of cannabis regulation in Canada: Cardiovascular and respiratory health

Indicator(s)	Relevance to cannabis regulation	Preliminary evidence	Existing data source(s)
1. Incidence and prevalence of **respiratory problems** including chronic obstructive pulmonary disorder (COPD) and lung cancer	Smoked cannabis has been linked with respiratory problems including chronic bronchitis symptoms and airway inflammation.[154] Evidence of an association between cannabis use and lung cancer has been inconsistent, with some studies finding a weak dose-dependent association,[155,156] and others finding no association.[157] This research has often been subject to confounding by co-occurring tobacco use.[158]	Not found	Canadian Chronic Disease Surveillance System (CCDSS); Canadian Cancer Registry
2. Incidence of **cardiovascular problems** including myocardial infarction, cardiac arrest and ischemic stroke	Some studies have linked cannabis use with ischemic stroke,[159,160] while two recently published prospective studies did not find a cumulative effect of cannabis use on ischemic stroke.[161,162] Alongside discussions of legalization, concerns have been raised about increasing cannabis-related MIs, including among young people.[79] Based on the results of one case-crossover study,[163] cannabis was added to a list of potential triggers of myocardial infarction.[78] However, a recently published prospective study did not identify an independent association between cumulative cannabis use and coronary heart disease or deaths related to cardiovascular disease.[162]	Not found	CCDSS

Table 5. Suggested public health indicators for the evaluation of cannabis regulation in Canada: Mental health and cognition

Indicator(s)	Relevance to cannabis regulation	Preliminary evidence	Existing data source(s)
1. Incidence and prevalence of **psychosis and psychotic disorders** (e.g., schizophrenia) overall and across risk demographics (e.g., youth).	Psychosis has been the topic of many discussions around cannabis regulation in Canada (e.g., see Kohut, 2016).[81] Cannabis use (particularly early onset, high frequency, high potency and/or synthetic cannabis) has been linked to exacerbations of symptoms of schizophrenia among those who may be predisposed.[164-166] However, the causal nature of this association continues to be debated in the scientific literature.[80]	Not found	Hospital Mental Health Database (HMHDB)
2. Prevalence of **depression and anxiety** overall and across risk demographics	Cannabis has been linked to anxiety,[167] depression and suicidal ideation.[168] However, studies have been met with various methodological limitations,[168] and causality has been difficult to establish.	Not found	CCDSS; CCHS; HMHDB
3. Incidence of **attempted and completed suicide** overall and across risk demographics (e.g. young adult males)		**Non-medical cannabis legalization:** Annual rates of suicide have been increasing slightly in Alaska, Washington, Colorado, and Oregon over the past decade, including since legalization.[44]* **Medical cannabis legalization:** The number of medical cannabis registrants was not correlated with rates of completed suicide in Colorado, after controlling for other risk factors.[83] Analysis of US state-level data from 1997-2007 show that legalization of medical cannabis was not statistically associated with suicide overall; however, legalization was associated with significant reductions in suicide among men aged 20-29 (-10·8%) and 30-39 (-9·4%) relative to control states.[84]	CCHS; HMHDB; CVSD
4. Level of **cognitive functioning and educational achievement** (e.g., rate of high school completion) among youth	Cannabis use among youth has been linked with poorer educational achievement, including lower rates of high school completion.[169] Some studies have linked early onset, high-frequency cannabis use with negative cognitive impacts (e.g., lower IQ),[85] however more recent studies have failed to confirm such an association after accounting for environmental factors including socioeconomic status.[86-88]	**Non-medical cannabis legalization:** Standardized test scores measuring reading proficiency among 8th and 10th graders in Washington remained stable following legalization.[44]* **Medical cannabis legalization:** Exposure to US state medical cannabis legalization among youth aged 14-18 was not associated with increased likelihood of high-school non-completion overall.[90] However, exposure to medical cannabis legalization was significantly associated with increased odds of failing to receive a high school diploma or GED despite completion of 12th grade; college non-enrolment; and college non-completion. In all analyses, there was a dose-response association with number of years exposed to medical cannabis laws.[90]	Pan-Canadian Assessment Program; Census; Labour Force Survey

Note: *Indicates that the reported change in number/proportion/rate was not analyzed against a control group or adjusted for any potential confounding factors

SUPPLEMENTARY MATERIALS

Strategy for metric selection and preliminary evidence generation

Metrics Selection

A search was conducted to identify public health and safety issues of potential interest/concern related to cannabis policy. Five scientific databases (Medline, Embase, Academic Search Complete, CINAHL, and Web of Science) were searched using search terms including "cannabis use", "cannabis policy", and "health/public health" (and synonyms). The search was limited to peer-reviewed articles published in the previous five years (i.e., 2012-2017) to cover current research questions involving cannabis, and was restricted to English language academic commentaries, reviews, and original research involving human subjects.

Since the aim was to outline indicators that would be relevant to public health and safety under Canada's impending legislation regulating *Cannabis sativa*, any health issues discussed in relation to synthetic cannabinoids (e.g., "spice" or "K2") or isolated cannabinoids (e.g., cannabidiol [CBD] alone) were not considered relevant for the purpose of this paper. Previously published literature quantifying the population health impact of cannabis use on key public health outcomes including accident/injury, cannabis use disorders, mental health, and lung cancer,[170] as well as literature describing common public health objectives of regulatory approaches to cannabis[171] were used to guide the understanding of public health relevance. For example, articles discussing cannabis in the clinical management of health problems (e.g., pain, HIV/AIDS, kidney disease) were not considered relevant for public health metric development.

Articles underwent a title screen and were removed from consideration if outside the scope of public health and safety in the context of cannabis use or cannabis policy. Abstracts of the remaining articles were screened and either removed if not relevant, or assigned a topic category (e.g., "motor vehicle accidents", "workplace injuries"). These topic categories were used to guide the development of the proposed set of indicators, and were further organized into broad

themes based on shared characteristics (e.g., "public safety"). The primary author (SL) conducted the search, article screens, and indicator identification. All co-authors were invited to review and revise the list of indicators and suggest any additional potentially relevant indicators for consideration. Any co-author disagreements were discussed with the primary author until a consensus was reached. All authors approved the final set of indicators.

Preliminary evidence generation

Wherever possible, preliminary evidence of the short-term impact of cannabis regulation on each proposed indicator was drawn from North American jurisdictions that have legalized medical or non-medical cannabis (e.g., Washington, Colorado) up until March 1, 2018. To do this, the primary author hand-searched reference lists from relevant articles identified in the initial database search, and conducted a series of indicator-specific academic and non-academic database searches to identify scientific and grey (e.g., media coverage of breaking peer-reviewed studies, government reports) literature, respectively.

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