Testimony of Maine Public Health Association in Opposition to:
LD 1952: An Act to Allow On-site Cannabis Consumption

Joint Standing Committee on Veterans and Legal Affairs
State House, Room 437
Wednesday, January 24, 2024

Good morning, Senator Hickman, Representative Supica, and distinguished members of the Joint Standing Committee on Veterans and Legal Affairs. My name is Rebecca Boulos. I am a resident of South Portland and executive director of Maine Public Health Association.

MPHA is the state's oldest, largest, and most diverse association for public health professionals. We represent more than 700 individual members and 60 organizations across the state. The mission of MPHA is to improve and sustain the health and well-being of all people in Maine through health promotion, disease prevention, and the advancement of health equity. As a statewide nonprofit association, we advocate, act, and advise on critical public health challenges, aiming to improve the policies, systems, and environments that underlie health inequities – but which also have potential to improve health outcomes for all people in Maine. We are not tied to a national agenda, which means we are responsive to the needs of Maine's communities, and we take that responsibility seriously.

MPHA is in opposition to LD 1952: "An Act to Allow On-site Cannabis Consumption." This bill would allow for the consumption of cannabis and cannabis products in the venue where the products were purchased.

We have previously shared our concerns about accuracy in cannabis testing, specifically edible cannabis products. Studies from Washington State show clear and systematic differences within results provided by cannabis testing facilities, even when controlling for confounding factors.[1] A 2019 audit of Oregon's testing system found that the state's testing program "cannot ensure that test results are reliable and products are safe" and "[l]imited authority, inadequate staffing, and inefficient processes reduce OHA's ability to ensure Oregon marijuana labs consistently operate under accreditation standards and industry pressures may affect lab practices and the accuracy of results."

In addition to variability in the accuracy of product testing, there is variability in the time it takes to feel the drug's effects. A team of international researchers prepared a summary of research and an accompanying list of recommendations for lower-risk cannabis use (see attached). Per their findings: "Inhalation use generally may impair essential driving skills for about 6-8 hours; use of edibles can produce impairment for 8-12 hours." The evidence to support those findings was graded as "Substantial to Moderate."[2] Given these data, we remain concerned about consumers leaving the venue "under the influence" without realizing it. Furthermore, there is no established maximum allowable limit for driving while under the influence of cannabis. While we have a nationally recognized maximum blood alcohol concentration (a BAC of 0.08) and concrete ways for law enforcement to assess drivers under the influence of alcohol (breathalyzer tests), no comparable standard or test exists for cannabis use.

Moreover, at a fundamental level, we have concerns about the health impacts of smoking cannabis and second-hand cannabis smoke exposure. Indeed, there are carcinogens in cannabis smoke; these pose health risks to the person smoking and to others in proximity. According to the U.S. CDC, "smoked marijuana delivers THC and other cannabinoids to the body, but it also delivers harmful substances, including many of the same toxins and carcinogens (cancer-causing chemicals) found in tobacco smoke, which are harmful to the lungs and cardiovascular system." These toxins include mercury, ammonia, cyanide, lead, and formaldehyde, as well as hazardous fine particles. If smoking were allowed, then staff and other consumers would be exposed to these substances.

In 2003, Maine became the fifth state in the country to pass comprehensive smoke-free laws, including prohibiting smoking in bars and lounges; that was the right decision then, and continues to be now. We are strongly opposed to any efforts to roll back Maine's strong smoke-free laws.

Over the past few years, policymakers have passed legislation that has increased access to more potent cannabis products, including through off-premises sales and home delivery (even in municipalities that have opted out), and increasing the allowable THC in a product. In 2020, in Maine, there were 5,632 cannabis-related emergency department visits, representing a 21% increase from 2019.[3] Rates were disproportionately higher for males and for people ages 18 to 25 years old. Included with our testimony are example edible cannabis products currently for sale in Maine. You can see how much THC is included in these multi-serving, but seemingly single-serving, products. If products like these were for sale at a social club, it's easy to see how individuals could unintentionally overconsume, and then either need medical attention or drive impaired – increasing the risks to public health and safety.

The public safety and regulatory infrastructure are simply not ready to allow on-site cannabis consumption. Allowing on-site consumption of cannabis without concurrent investments in improved product testing, enforcement support, and consumer education threatens public health and safety.

Given these public health concerns, we are in opposition to this bill. Thank you for considering our testimony.

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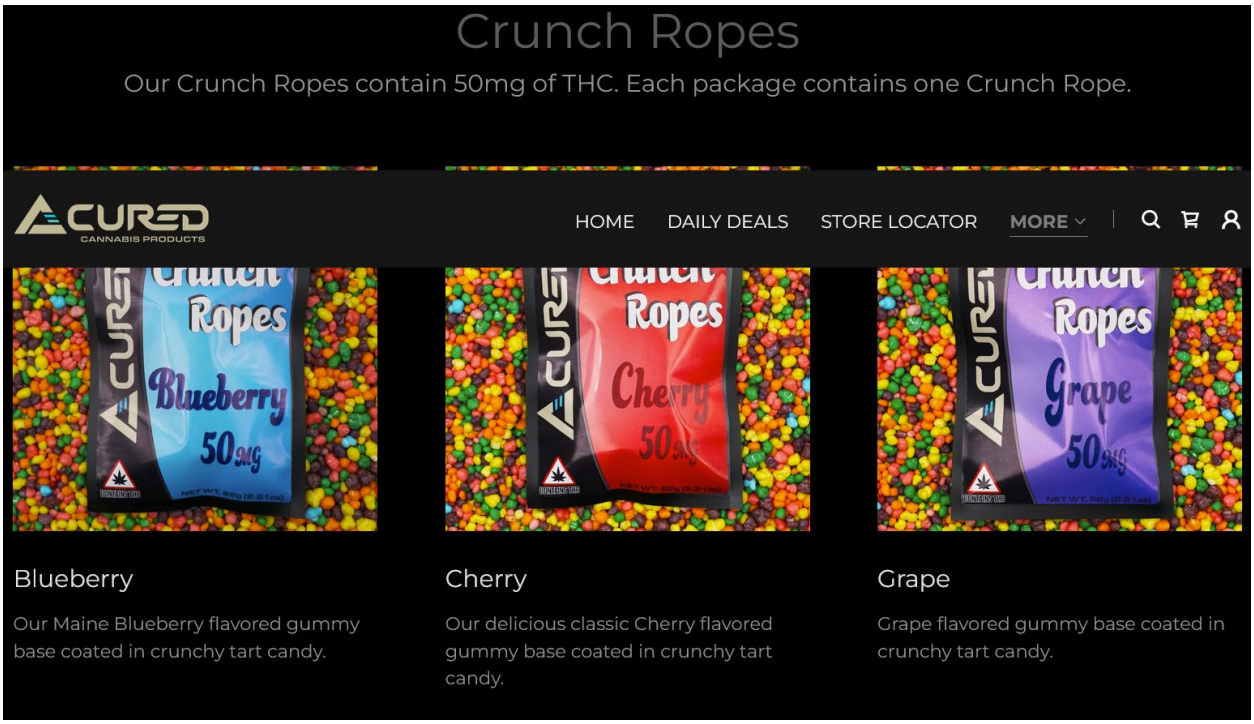
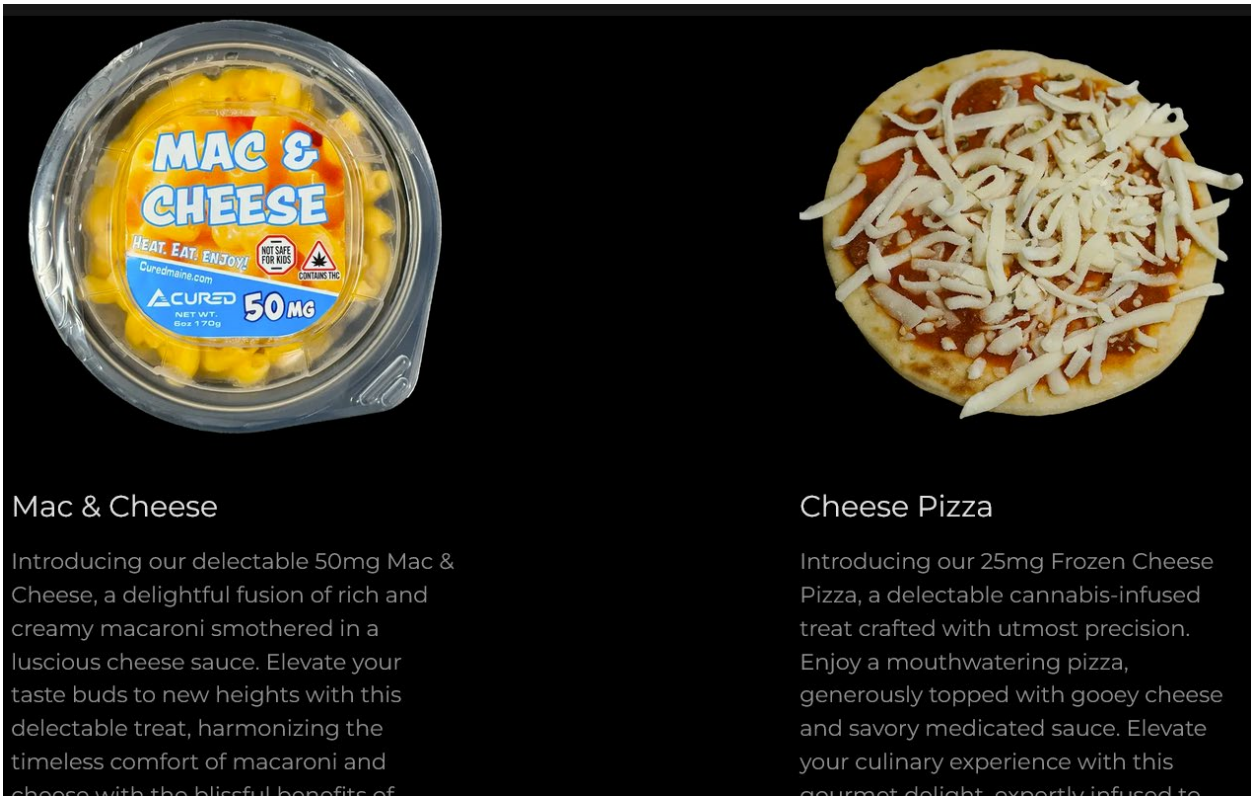
[1] Jikomes, N., Zoorob, M. The cannabinoid content of legal cannabis in Washington State varies systematically across testing facilities and popular consumer products. *Scientific Report.* 8: 4519 (2018).
[2] Fischer B, Robinson T, Bullen C, Curran V, Jutras-Aswad D, Medina-Mora ME, Pacula RL, Rehm J, Room R, van den Brink W, Hall W. Lower-Risk Cannabis Use Guidelines (LRCUG) for reducing health harms from non-medical cannabis use: A comprehensive evidence and recommendations update. *Int J Drug Policy*. 2022 Jan;99:103381.
[3] Cannabis Use Dashboard. Maine State Epidemiological Outcomes Workgroup.

Edible Cannabis Product Examples from a Company in Maine





Edible Cannabis Product Examples from a Company in Maine

Ramen - Beef

Our mouthwatering 25mg Beef Ramen is the perfect fusion of comfort food and cannabis goodness! This delectable package of ramen soup is not your average fix; it's a tantalizing blend of beefy flavors with just the right amount of cannabis-infused magic. With every savory slurp, you'll experience the

Ramen - Chicken

Elevate your taste buds and experience pure culinary delight like never before! This heavenly bowl of noodles combines the comforting flavors of succulent chicken with the perfect balance of cannabis-infused broth. Each serving contains precisely 25mg of high-quality cannabis, ensuring a

Mug Cakes - White Rainbow Chip

Our 100mg Mug Cakes in a sweet & fun white cake with rainbow chips, thoughtfully crafted to elevate your cannabis experience. Indulge in the

Crunchy Munchies - Cookies & Cream

Chex base coated in a medicated cookies & cream mix.
Each Crunchy Munchy contains 6mg of THC.

Edible Cannabis Product Examples from a Company in Maine

Peanut Butter Cups

Our delicious, hand made peanut butter cups are a quick, easy and yummy way to medicate. Each cup contains 25mg of THC.

Gingerbread Cookie

Sold Out Until Next Winter

Our 100mg Gingerbread Cookie is a delightful experience from start to finish. Picture this: a beautiful gingerbread cookie, generously coated with velvety white icing that glistens

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Review

Lower-Risk Cannabis Use Guidelines (LRCUG) for reducing health harms from non-medical cannabis use: A comprehensive evidence and recommendations update

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ABSTRACT

Background: Cannabis use is common, especially among young people, and is associated with risks for various health harms. Some jurisdictions have recently moved to legalization/regulation pursuing public health goals. Evidence-based 'Lower Risk Cannabis Use Guidelines' (LRCUG) and recommendations were previously developed to reduce modifiable risk factors of cannabis-related adverse health outcomes; related evidence has evolved substantially since. We aimed to review new scientific evidence and to develop comprehensively up-to-date LRCUG, including their recommendations, on this evidence basis.

Methods: Targeted searches for literature (since 2016) on main risk factors for cannabis-related adverse health outcomes modifiable by the user-individual were conducted. Topical areas were informed by previous LRCUG content and expanded upon current evidence. Searches preferentially focused on systematic reviews, supplemented by key individual studies. The review results were evidence-graded, topically organized and narratively summarized; recommendations were developed through an iterative scientific expert consensus development process.

Results: A substantial body of modifiable risk factors for cannabis use-related health harms were identified with varying evidence quality. Twelve substantive recommendation clusters and three precautionary statements were developed. In general, current evidence suggests that individuals can substantially reduce their risk for adverse health outcomes if they delay the onset of cannabis use until after adolescence, avoid the use of high-potency

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(THC) cannabis products and high-frequency/-intensity of use, and refrain from smoking-routes for administration. While young people are particularly vulnerable to cannabis-related harms, other sub-groups (e.g., pregnant women, drivers, older adults, those with co-morbidities) are advised to exercise particular caution with use-related risks. Legal/regulated cannabis products should be used where possible.

Conclusions: Cannabis use can result in adverse health outcomes, mostly among sub-groups with higher-risk use. Reducing the risk factors identified can help to reduce health harms from use. The LRCUG offer one targeted intervention component within a comprehensive public health approach for cannabis use. They require effective audience-tailoring and dissemination, regular updating as new evidence become available, and should be evaluated for their impact.

Introduction

Cannabis is commonly used for non-medical purposes throughout the world, where it remains illegal in most countries while undergoing legal status changes in selected others. In 2018, the prevalence of past-year cannabis use among 15-64 year-olds was estimated to be 3.8% (2.7%-4.9%), or about 200 million people who use cannabis (PWUC) globally (Degenhardt, Ferrari, & Hall, 2017). Regional use is highest in North America, Oceania, and West Africa, with a past-year prevalence of 10-25%, followed by Europe and other regions. Moreover, and important for potential life-course outcomes, cannabis use is most common among adolescents and young adults (e.g., 15 – 25 years). In this group, past-year prevalence is 25% or higher in high-use regions, often greater than tobacco use (Carliner, Brown, Sarvet, & Hasin, 2017; ESPAD Group, 2016; United Nations Office on Drugs and Crime, 2020).

An extensive body of literature documents the association of cannabis use with an increased risk for a variety of acute and long-term health harms (Cohen, Weizman, & Weinstein, 2019; Hall et al., 2019; Hoch, Friemel, & Schneider, 2019; Memedovich, Dowsett, Spackman, Noseworthy, & Clement, 2018; National Academies of Sciences Engineering and Medicine, 2017; World Health Organization, 2016). These include: acute intoxication with impaired cognitive, memory and psychomotor skills; increased involvement in motor-vehicle crashes and related injury and deaths; impaired neurocognitive and psychosocial functioning; mental health problems (e.g., psychosis and schizophrenia, depression and suicidal behaviors); cannabis use disorder/dependence; and select respiratory, reproductive, cardiovascular, gastro-intestinal conditions (Cohen et al., 2019; Hall et al., 2019; Hoch et al., 2019; Memedovich et al., 2018; National Academies of Sciences Engineering and Medicine, 2017; Patel, Khan, & Hamid, 2020; World Health Organization, 2016). Some of these associations are stronger than others, and causality is not always firmly established.

Reflecting the social epidemiology and specific vulnerabilities of this phenomenon, cannabis use-related problems are disproportionately concentrated in young adult males. However, the overall probabilities of cannabis-related harms need to be put into perspective. The vast majority of PWUC do not experience severe problems from their use, even with long-term exposure (Boden, Dhakal, Foulds, & Horwood, 2020; Budney, Sofis, & Borodovsky, 2019; Hall, 2015; Hasin, 2018). The most serious problems arise in a sub-group of high-risk (e.g., intensive) users, where up to half are estimated to develop cannabis use disorder (CUD) (Budney et al., 2019; Hasin, Shmulewitz, & Sarvet, 2019; Huestis, 2015; Leung, Chan, Hides, & Hall, 2020). In addition, about 15-30% of PWUC drive under the influence of cannabis, with roughly 20% of cannabis-related traffic injuries being fatal (compared to 40% or more related to alcohol) (Azofeifa, Rexach-Guzman, Hagemeyer, Rudd, & Sauber-Schatz, 2019; Robertson, Mainegra Hing, Pashley, Brown, & Vanlaar, 2017; Wadsworth & Hammond, 2019). Furthermore, it is estimated that only about 2% or less of PWUC experience a severe cannabis-induced mental health problem (e.g., psychosis, schizophrenia) (Curran et al., 2016; Hall & Degenhardt, 2008, Hall & Degenhardt, 2010). The population-based probabilities of PWUC experiencing many of the other identified cannabis-associated adverse health outcomes (e.g., cardiovascular, reproductive, pulmonary problems) are even smaller. In addition, except for cannabis-related motor-vehicle-crash (MVC) fatalities, cannabis use makes virtually no direct contribution to mortality (especially when compared to the high mortality rates for alcohol and tobacco) (Calabria, Degenhardt, Hall, & Lynskey, 2010; Degenhardt et al., 2018; Drummer, Gerostamoulos, & Woodford, 2019; Hall, 2017). Recent national and global estimates have identified cannabis-impaired driving and related injuries/death – which may include non-using others - and CUD as leading contributors to the cannabis-related disease burden (Degenhardt et al., 2013; Degenhardt et al., 2017; Imtiaz et al., 2016). While the estimated contribution of cannabis to disease burden is not insubstantial, it is far smaller than that for alcohol or tobacco.

In many jurisdictions, longstanding laws prohibiting non-medical cannabis use under penalties have been liberalized in recent years. This has, partly, been because cannabis has limited adverse health consequences and partly because of the excess of personal and societal costs of criminal penalties for cannabis use (Decorte, Lenton, & Wilkins, 2020). The most liberal policies have included the legalization and regulation of non-medical cannabis use and supply to adults in Uruguay (2013), Canada (2018), Mexico (2021), and in a growing number (currently 15) of state jurisdictions in the United States (US), initially including Colorado and Washington (2012 onward). These legalization regimes, however, feature rather heterogeneous regulatory frameworks (Decorte et al., 2020; Hall & Lynskey, 2020; Hall et al., 2019). In addition, other jurisdictions have been contemplating legalization reforms.

Commonly, the case for cannabis legalization is made to improve public health and safety outcomes (Decorte et al., 2020; Fischer, Daldegan-Bueno, & Boden, 2020; Rehm & Fischer, 2015). Specifically, it is assumed that under legalization, the distribution of cannabis products will shift from criminal to legal markets allowing better regulation of cannabis products and targeted interventions to minimize adverse cannabis-related health and social outcomes from – now legal - use (Fischer, Daldegan-Bueno, et al., 2020; Rehm & Fischer, 2015; Room, Fischer, Hall, Lenton, & Reuter, 2010). While mostly US-dominated, evidence suggests that legalization has reduced some social harms (e.g., decreasing arrests of PWUC, illicit cannabis markets) (Armstrong, 2021; Caulkins et al., 2019; Firth, Maher, Dilley, Darnell, & Lovrich, 2019; Fischer, Bullen, Elder, & Fidalgo, 2020; Plunk, Peglow, Harrell, & Grucza, 2019). The evidence on public health impacts is mixed. Specifically, data have suggested select increases in the prevalence and intensity (e.g., frequency/potency of products) of use among adults (but not among adolescents), hospitalizations, and cannabis-related MVCs, mostly by comparison to non-legalized settings (Cerda et al., 2020; Hall & Lynskey, 2020; Hall et al., 2019; Hammond, Chaney, Hendrickson, & Sharma, 2020; Smart & Pacula, 2019). The effects of legalization on CUD or treatment seeking has been mixed, while attitudes towards risks of cannabis use have softened in several sub-groups (Carliner et al., 2017; Hasin, 2018; Smart & Pacula, 2019; Wen, Hockenberry, & Druss, 2019).

The success of cannabis legalization as a policy experiment that benefits public health and safety outcomes therefore remains uncer-

tain. However, these desired beneficial outcomes will require PWUC, especially the disproportionately large number of young users, to have guidance on how to reduce key risk-behaviours that contribute to adverse health outcomes and related disease burden (Carliner et al., 2017; Curran et al., 2016; Degenhardt et al., 2017; Lorenzetti, Hoch, & Hall, 2020; Miech, Johnston, & O'Malley, 2017; Volkow et al., 2016). To that general end, international expert teams had previously (e.g., 2011, 2017) tabled evidence-based 'Lower-Risk Cannabis Use Guidelines' (LRCUG) including targeted recommendations for PWUC, with the principal aim of identifying use behaviour-related risk factors modifiable by the user-individual that will aid to reduce risks of adverse health outcomes from non-medical (as distinct from medical/therapeutic) cannabis use (Fischer et al., 2011, 2017).

The LRCUG are based on concepts of health behavior change and similar guidance-oriented interventions implemented in other areas of population health (e.g., low-risk drinking guidelines, sexual health, nutrition) (Holmes, Angus, Meier, Buykx, & Brennan, 2019; Kushi et al., 2012; Satcher, Hook, & Coleman, 2015). They represent a targeted prevention tool to complement universal prevention and treatment (e.g., for CUD) measures on the intervention continuum (Halladay et al., 2019; Jutras-Aswad et al., 2019; Lee et al., 2019; Norberg, Kezelman, & Lim-Howe, 2013). The LRCUG' previous iterations were endorsed by leading government agencies and health/addiction stakeholder organizations in Canada and internationally to encourage their widespread utilization to reduce cannabis-related health harms among PWUC. They were communicated and distributed widely in different formats customised to different target audiences (e.g., health professionals, general and sub-groups of PWUC) (Government of Canada, 2020).

The body of scientific evidence on cannabis use and its health outcomes has evolved substantially since the most recent version of the LRCUG. Given these developments, and the building momentum towards cannabis policy liberalization, we undertook a comprehensive review of new scientific evidence to inform an update and refinement of the LRCUG and their recommendations.

Methods

Scope and approach

A comprehensively scoped, targeted review of recent literature focused on identifying new evidence on modifiable risk factors for cannabis use-associated behaviors, and related adverse health outcomes was conducted. Topic areas for risk factors were initially informed by the previous LRCUG' content (Fischer et al., 2011; Fischer et al., 2017) and iteratively developed and expanded on the basis of emerging data and information from recent literature reviews informing the present work. The assembled evidence was used as the empirical foundation to develop the LRCUG' recommendations to guide appropriate choices of PWUC or use behaviors to reduce the risks of cannabis use-related health harms.

Search strategy

Literature searches were conducted using the Embase, Medline, CINAHL, PsycInfo, the Cochrane Library, and Web of Science databases. Initial search strategies were developed for use in Embase and modified for other databases. Medical Subject Headings (MeSH; e.g., Cannabis, Cannabis Addiction, Cannabis Use) were used where applicable and combined with appropriate keywords for each risk factor topic. An example of the Embase search strategy used (for the topic of 'age-of-onset') can be found in [Supplement 1]. Searches principally focussed on recent systematic or other comprehensive reviews, or other topically pertinent, high-quality studies. Subject areas where systematic review evidence was limited or absent were supplemented by reviewing individual studies identified through targeted or secondary searches, Google Scholar, and manual searches of reference lists. Given that this review was not conceptualized as a systematic review, in addition to the multiple risk factor topics involved, this paper does not present a routinised system for reporting systematic reviews (e.g., PRISMA) (Ferrari, 2015).

Inclusion/exclusion criteria

Specific inclusion and exclusion criteria were developed for each topical area, but general selection criteria applied to all topics. In general, we included English language, peer-reviewed journal reviews and individual studies that contained data on behavior-based and -modifiable risk factors for adverse health outcomes associated with cannabis use. As this effort was principally approached as a review and update focusing on new evidence and insights following previously published LRCUG content, we only included literature published in 2016 or later that had not been included in the most recent (2017) iteration of the LRCUG. Given our primary focus on modifiable risks of adverse health outcomes among PWUC non-medically, we did not include in our scope studies whose main focus was on the medical benefits of cannabis, use of synthetic cannabinoids, social/legal harms, or risks-to-others.

Evidence presentation

Literature and data results were topically organized by risk-factor and narratively and qualitatively summarized as the empirical basis for the development of the recommendations (see below). Topical evidence review sections on individual risk factors, overall, are ordered in a generally sequential order (e.g., use initiation, use-related patterns and practices, particular risk conditions) as related to use. Intrinsically, they are generally structured by evidence standard (e.g., systematic reviews, other reviews, individual studies), from biological to behavioral and psychosocial evidence, and/or sub-topical risk groups or factors (or combinations thereof).

Grading of the evidence

Towards recommendations development, the quality of review evidence assembled was assessed using the same grading criteria as used in the previous iteration of the LRCUG, as presented below (Fischer et al., 2017; National Academies of Sciences Engineering and Medicine, 2017). Where evidence content for recommendations spanned across quality ranges, multiple grades were given. These grades were finalized through the project's consensus development process among co-authors and are included with the recommendations.

1. *Conclusive:* Evidence is based on many supportive, good quality studies, with no credible opposing findings, and firm conclusions can be made.
2. *Substantial:* Evidence is based on supportive findings from good quality studies, with few or no opposing findings.
3. *Moderate:* Evidence is based on supportive findings from several fair/good quality studies, with few or no opposing findings.
4. *Limited*: Evidence is based on findings from fair quality studies or mixed findings, with most favoring the same conclusion.
5. *No or Insufficient:* Evidence is based on a single poor-quality study, mixed findings, or non-existent.

In general, consistent findings from systematic reviews/meta-analyses or large-scale randomized controlled trials were required for higher (e.g., 'conclusive' or 'substantial') ratings, whereas data from observational or similar studies were assessed as 'moderate' or 'limited' quality of evidence.

Recommendations development process

The topical evidence summaries and evidence grading were used as the empirical foundation to develop the recommendations for related risk-factors. This occurred through a combination process of reviewing

and updating recommendations informed by previous LRCUG content and the creation of *de novo* recommendations, all based on the new evidence identified and reviewed (Fischer et al., 2011; Fischer et al., 2017; Schunemann et al., 2017). Initial drafts of the recommendations were generated by the lead authors (BF, WH, TR). Co-authors provided iterative rounds of substantive comments and input for development and revisions of the recommendations towards their final content. This process was repeated until a consensus was reached on the full set of recommendations by all authors.

Management of conflicts

Following similar conflict-of-interest management principles in other health guideline development areas (Boyd et al., 2012; Schunemann et al., 2019), the study excluded authors who had received any financial contributions (including research funding) or held financial interest in private/for-profit (medical or non-medical) cannabis-related entities or products in the last two years.

Results

In the following, summary reviews on current evidence related to individual risk factor topics for cannabis use-related adverse outcomes are narratively presented (see the Methods section for general organizational principles). The corresponding LRCUG recommendations, developed by expert consensus based on this evidence, are presented in TEXTBOX 1. (See Supplemental materials for other language versions of the Recommendations.)

Textbox 1. The LRCUG' Recommendations

General Precaution A: ***People who use cannabis (PWUC) need to know that there is no universally safe level of cannabis use; thus, the only reliable way to avoid any risk for harm from using cannabis is to abstain from its use.*** Those who use cannabis should be aware that certain ways of using cannabis increase risks of a variety of acute and long-term adverse health and psychosocial outcomes. The likelihood and potential severity of these adverse outcomes will furthermore depend on the characteristics of the user-individual and the circumstances in which use occurs. Consequently, reducing relevant risk-factors can help reduce the likelihood of such harms for the person engaging in cannabis use.

[*Evidence Grade: Conclusive*]

Recommendation #1: ***The initiation of cannabis use should be delayed until after late adolescence, or the completion of puberty, to reduce development-related vulnerabilities for harm.*** While data are mixed, young PWUC may be more vulnerable to adverse effects from cannabis use because of ongoing neurological, mental, and psycho-social development. Early initiation of cannabis use (i.e., that beginning before late adolescence or the completion of puberty) is associated with adverse health and psycho-social effects, especially in those who engage in intensive use (e.g., high-frequency use of potent cannabis products) and have other vulnerabilities. In general, the later in young adult life cannabis use is initiated, the lower the risks of adverse effects on general health and wellbeing.

[*Evidence Grade: Moderate*]

Recommendation #2: ***PWUC should use 'low-potency' cannabis products, i.e., cannabis products with ideally lower total THC content, or a high CBD/THC content ratio.*** The higher the total or relative THC-content of cannabis that is used, the greater the risks of acute and chronic adverse mental or physical health outcomes. If possible, PWUC should select cannabis products that provide reliable information on their composition and potency, so that they can better regulate their cannabis exposure and related risks. While CBD attenuates some of THC's adverse effects on mental and cognitive-behavioral outcomes and use of cannabis with high CBD content should be preferred, CBD use does not attenuate all of THC's adverse outcomes. Rather, CBD may contribute to some (e.g., driving performance-relevant) impairment effects on its own and its use requires corresponding caution.

[*Evidence Grade: Substantial to Moderate*]

Recommendation #3: ***All main available modes-of-use options come with some risk for harm; PWUC should refrain from cannabis 'smoking' and employ alternative routes-of-use for pulmonary health protection.*** Routes and modes of use significantly influence the acute effects of cannabis and the risks of some adverse outcomes. In general, cannabis inhalation (whether by smoking or vaping) produces similar, rapid onset and dynamics of psychoactive effects. Cannabis smoking can harm the respiratory system; this is particularly the case when tobacco is added. Vaping/vaporizing of cannabis substantially reduces the levels of toxin exposure compared with smoking but may involve other harmful contaminants. Inhalation of high-potency cannabis extracts ('dabbing') can produce acutely adverse psychoactive and other physiological effects. The oral ingestion of cannabis products (e.g., edibles or drinkables) results in more delayed onset and extends the duration of psychoactive (e.g., impairment) effects. This can lead to over-consumption and effects that are more intense than intended. Overall, there is no categorically 'safe' route of use for cannabis and each route option brings some level of distinct risks that needs to be taken into account for use.

[*Evidence: Substantial to Moderate*]

Recommendation #4: ***If use occurs by inhalation, PWUC should avoid "deep inhalation", prolonged breath-holding, or similar inhalation practices.*** These practices may be used by some PWUC with the aim of increasing absorption of THC and related psychoactive effects. However, they also increase the intake of toxic content material and the risk of harm to the pulmonary system.

[*Evidence Grade: Limited*]

Recommendation #5: ***PWUC should refrain from frequent (e.g., daily or near-daily) or intensive (e.g., binging) cannabis use, and instead limit themselves to less frequent or occasional use.*** Frequent or intensive use patterns are strongly associated with a multiplicity of severe adverse outcomes in mental and physical health (e.g., including neuro-cognitive deficits and dependence) and psycho-social domains. This is especially the case for intensive use beginning at a young age and sustained ('chronic') use over long periods of time. Ideally, PWUC should limit their cannabis consumption to occasional or infrequent use (e.g., use only on 1 or 2 days per week, on weekends only) and avoid repeated, intensive 'binge' use throughout the day or night over extended time-periods.

[*Evidence Grade: Substantial*]

Recommendation #6: ***Where circumstances allow, PWUC should use legal and quality-controlled cannabis products and use devices.*** Illegal cannabis products are not regulated for quality and safety, and are typically not labelled for their THC and other content, and so may increase risks of adverse experiences and health problems. Legally regulated cannabis products are more predictable in their composition and potency, especially when there is product content labelling, and presumably safer because of their regulated production and other quality standards that minimize the contaminants that they may contain.

[*Evidence grade: Limited*]

Recommendation #7: ***PWUC who experience impaired cognitive performance should consider temporarily suspending or substantially reducing the intensity (e.g., frequency/potency) of their cannabis use.*** Intensive cannabis use can impair neurocognitive function and produce other adverse health outcomes with ongoing use. There is some evidence that these adverse effects may at least partially reverse after relatively short periods (e.g., several days to weeks) of abstinence or very substantial reductions in the intensity of cannabis use. Individuals with intensive cannabis use experiencing adverse cognitive effects should thus consider temporarily suspending or substantially reducing the intensity of

their use and see if such a step helps improve their cognitive performance.

[*Evidence: Limited*]

Recommendation #8: ***PWUC should avoid driving a motor-vehicle or operating machinery while under the influence of cannabis because of acute impairment and elevated risk of crash involvement, including injury or death; however, the severity and duration of impairment vary depending on multiple factors.*** Operating a motor-vehicle or other machinery while under the influence of cannabis and related impairment approximately doubles the risk of MVC-involvement that may result in injury or death. The extent and duration of impairment and risk for harm substantially depends on the type and mode of cannabis consumption, and the user-individual's characteristics. In general, the more cannabis is used and the greater its potency (THC), the more severe the impairment. Individuals with infrequent use may experience more acute impairment, but impairment may last longer in individuals with frequent use. Inhalation use generally may impair essential driving skills for about 6 – 8 hours; use of edibles can produce impairment for 8 - 12 hours, but these times can vary from one use context to another. During these impairment periods, driving or similar risk activities should be avoided. CBD does not reliably attenuate THC-related impairments for driving, and may of itself contribute to select driving-relevant deficits; its presence in cannabis used therefore should not be mis-interpreted for categorical protection and requires its own precautions. Co-use of alcohol with cannabis furthermore increases multifold driving impairment and should be avoided.

[*Evidence Grade: Substantial to Moderate*]

Recommendation #9: ***It is prudent for people who intend to procreate and for women who are pregnant or breastfeeding to abstain from cannabis use towards reducing possible risks for reproduction and of health harm to offspring, respectively.*** There is some evidence that especially intensive cannabis use may somewhat compromise reproductive abilities for women and men. Cannabis use, especially during pregnancy, may adversely affect some pre- and post-natal health outcomes in offspring. Cannabinoids may also be passed on to infants via breastmilk. The magnitude of any of these adverse effects from these exposures on conception, the fetus or infant development is likely small but it is generally prudent for those intending to reproduce, and for women who are pregnant or breastfeeding, to abstain from cannabis use during these particular periods of risk.

[*Evidence Grade: Limited*]

Recommendation #10: ***PWUC should exercise general caution in combining other psychoactive substances with cannabis use.*** The concurrent use of cannabis and other psychoactive substances or psychotropic medications can amplify the risks of some harms to health. For example, the frequent use of cannabis and tobacco and/or alcohol can magnify risks for a variety of adverse outcomes (e.g., dependence, pulmonary or reproductive health, besides acute impairment from alcohol). Cannabinoids can also influence metabolic processes in ways that adversely interact with a variety of medications (e.g., protease inhibitors, psychotropics). Consequently, co-use of cannabis and other drugs should be minimized and occur based on expert (e.g., medical) advice.

[*Evidence Grade: Moderate to Limited*]

Recommendation #11: ***Some specific groups of people are at elevated risk for cannabis use-related health problems because of biological pre-dispositions or co-morbidities. They should accordingly (and possibly on medical advice as required) avoid or adjust their cannabis use.*** Higher risks for harm extend to individuals with a genetic predisposition (e.g., a first-degree family or personal history) for, or an active psychosis, mood (e.g., depressive) disorder, or substance use disorder. Individuals with pre-existing cardio-vascular risks may be at increased risk of acute harm especially if they inhale high-potency products. Older-age PWUC may be at increased risk for some adverse outcomes (e.g., cognitive, metabolic, cardio-vascular problems; falls/injuries) because of general ageing-related deficits, other co-morbid chronic diseases, and/or the (e.g., medical) use of other psychotropic drugs. They should exercise caution by using lower cannabis doses and acting on medical advice. Female PWUC may be at risk of developing cannabis use-related problems (e.g., dependence) more quickly or more severely than men.

[*Evidence Grade: Moderate to Limited]*

Recommendation #12: ***The combination of risk-factors for adverse health outcomes from cannabis use further amplifies the likelihood of experiencing severe harms and should be avoided.*** Research on the combinations of cannabis-related risk behaviors is limited but it is plausible that the more risk factors one has the greater the risk and severity of adverse outcomes from using cannabis. Overall, the strongest evidence suggests that combining frequent, intensive use of high-potency cannabis products, especially at a young age (e.g., adolescence), substantially increases the risk of key acute or chronic adverse outcomes and harms (e.g., mental health, neuro-cognition, dependence). PWUC should generally be aware that there are multiple possible risk-factors or -behaviors that determine their odds of experiencing adverse health outcomes from cannabis use, and that they should aim to avoid as many of these as possible to lower their risk for experiencing acute or chronic harm. This general awareness about risk factors should be a principal aim for education and prevention.

[*Evidence Grade: Substantial to Limited*]

General Precaution B: ***Frequent cannabis use, and especially intensive use over longer periods, can lead to a 'cannabis use disorder' (CUD) or cannabis dependence, that may require treatment.*** CUD is characterized by symptoms such as cannabis craving, withdrawal, neglect of essential obligations, and limited capacity to control or reduce cannabis use. These symptoms may entail or overlap with some of the cannabis use-related risk behaviors described above. PWUC experiencing CUD symptoms, and particularly if their own attempts to control or substantially reduce their cannabis use fail, should seek professional assessment and care that may need to involve treatment.

[*Evidence Grade: Substantial*]

General Precaution C: ***PWUC should exercise social consideration and responsibility in avoiding cannabis use that may result in harm-to-others.*** Cannabis use, like alcohol and tobacco use, can cause harm-to-others, including non-users. This may arise from use-related impaired judgment or control; the harmful consequences of impaired driving; or second-hand exposure to cannabis smoke and its hazardous by-products (e.g., toxins), especially when use occurs indoors. Some cannabis-related harm-to-others can particularly affect vulnerable young people or minors. PWUC should generally exercise social consideration by protecting others from exposure to risks for harm from their cannabis use, regardless of whether such use is legal or not.

[*Evidence Grade: Substantial to Limited*]

Age of use onset

Cannabis use is often initiated in adolescence and use is most common among young adults. Its main psychotropic effects – as documented per seminal reviews - occur through the central nervous system's (including the brain's) endocannabinoid system (ECS), which undergoes major neurodevelopment during this transition period. This renders young, and especially adolescents' neurological systems, vulnerable to adverse effects from exogenous cannabinoid exposure (Curran et al., 2016; Ramaekers, Mason, Kloft, & Theunissen, 2021). Some (animal and human) evidence suggest that the neurobiological effects of cannabis use are similar in adult and adolescent PWUC. Extensive data, however, suggest that those initiating use by their mid-teens are at higher risk of transitioning to regular (i.e., frequent) use and experiencing more persistent adverse outcomes than older PWUC, such as possible alterations in brain structure and functioning, although confounding conditions may contribute

and causality is not consistently clear (Chye, Christensen, & Yucel, 2020; Levine, Clemenza, Rynn, & Lieberman, 2017; Sagar & Gruber, 2018).

Systematic and other reviews of human neuroimaging studies suggest that adolescent cannabis use is associated with structural brain alterations expressed in reduced volumes in the hippocampus and orbitofrontal cortex, thicker cerebral cortices, and decreased integrity of prefrontal and medial temporal brain regions (Jacobus, Courtney, Hodgdon, & Baca, 2019; Lorenzetti et al., 2016; Lorenzetti, Chye, Silva, Solowij, & Roberts, 2019). Functional brain imaging studies among adolescent PWUC show alterations in frontal and parietal brain regions related to inhibition, reward, and memory (Blest-Hopley, Giampietro, & Bhattacharyya, 2018, 2019; Bloomfield et al., 2019). Despite these alterations, adolescents with cannabis use do not consistently show impaired performance in functional magnetic resonance imaging (fMRI) tasks, suggesting the possible employment of compensatory cognitive resources to offset performance decrements (Lorenzetti et al., 2016; Lorenzetti et al., 2020).

In adult PWUC, evidence shows inconsistent associations between age-of-onset of use and brain functioning metrics (Chye et al., 2020). A systematic review detected a small overall reduction in cognitive functioning in youth-aged persons with frequent cannabis use but no variation with age or age-of-onset of use (Scott et al., 2018). A subsequent study involving persons aged 14-21 with frequent and occasional use found similar brain metrics among both adolescent and young adult cannabis using and non-using individuals (Scott et al., 2019), whereas other studies have have not identified long-term effects of adolescent cannabis use on neuropsychological or executive functions (Meier, Schriber, Beardslee, Hanson, & Pardini, 2019; Zehra et al., 2018). Systematic and other reviews have found both more severe and persistent executive functioning impairment among (mostly “heavy”) adolescent compared with adult PWUC (Gorey, Kuhns, Smaragdi, Kroon, & Cousijn, 2019; Levine et al., 2017).

Mental health outcomes of adolescent PWUC may also be affected by cannabis use. A systematic review found associations between adolescent (<18 years) cannabis use and the development of depression (OR:1.37, 95%CI:1.16-1.62), suicidal ideation (OR:1.50, 95%CI:1.11-2.03), and suicide attempts (OR:3.46, 95%CI:1.53-7.84) in young adulthood (Gobbi et al., 2019). A systematic review found adolescent (frequent) PWUC at the highest risk of suicidal behaviours (Schmidt, Tseng, Phan, Fong, & Tsuang, 2020). Earlier age-of-initiation was associated with a higher risk for psychosis in all but one study and with increased symptoms of depression or anxiety by age 25 in a systematic review (Hosseini & Oremus, 2019). A prospective longitudinal study found cannabis initiation before age 18 was associated with a higher risk for major depressive disorder (MDD), especially in individuals with higher-frequency (OR:8.83, 95% CI:1.29-70.79) compared with lower-frequency early-onset use (OR:2.41, 95%CI:1.22-4.76) (Schoeler et al., 2018). It is unclear, however, to which extent use and mental health disorders are causal, as they may be multi-directional and are likely to co-occur because the prevalence of mental health problems and cannabis use are both high in adolescence (Cancilliere, Yusufov, & Weyandt, 2018).

In an age-stratified placebo-controlled, double-blind cross-over trial involving exposure to equivalent doses of cannabis, adults showed greater impairment and intoxication, while adolescents showed impaired inhibitory processes and increased desire for cannabis use, suggesting differential age-based neuro-behavioral response profiles to use (Mokrysz, Freeman, Korkki, Griffiths, & Curran, 2016; Ramaekers et al., 2021). Some evidence from prospective longitudinal studies suggests that adolescent (mostly frequent) PWUC have lower or declining IQs than non-using peers, but the possible role of confounders is unclear (Gonzalez, Pacheco-Colon, Duperrouzel, & Hawes, 2017; Lorenzetti et al., 2020; Power et al., 2021). Adolescent PWUC have shown lower educational attainment, more substance use/problems, and higher levels of antisocial behavior and other health problems in later adult life (Lorenzetti et al., 2020; Meier et al., 2019). In the US population, PWUC aged 15–19 years had a significantly higher risk of developing CUD than those aged 20 and older (Feingold, Livne, Rehm, & Lev-Ran, 2020). In a study of cannabis-related driving skills among individuals with intensive recreational use, significant impairment was concentrated among those indicating early-onset use (Dahlgren et al., 2020).

Overall, it is unclear whether early-onset cannabis use has an independent effect on adverse outcomes from cannabis use, and the magnitude of any effects on brain functioning (Cancilliere et al., 2018; Scott et al., 2018). Most adverse effects observed in individuals reporting early-onset use appear to involve frequent and/or high-potency cannabis use as relevant factors (Blithikioti et al., 2019; Bloomfield et al., 2019; Kroon, Kuhns, Hoch, & Cousijn, 2020), and young people with poorer cognitive functioning are more likely to transition to frequent cannabis use patterns (Lorenzetti et al., 2020; Zehra et al., 2018). While assessments of early-onset related impairments typically focus on nominal ages (e.g., 16 years), neurological vulnerabilities can vary between youth of the same age. Therefore, it would be better to apply “adolescent pubertal markers” that more accurately index the stage of brain development (Curran et al., 2016; Sagar & Gruber, 2018). A systematic review failed to find evidence of the effects of cannabis use specifically on pubertal outcomes themselves (Sims et al., 2018).

Frequency of use

Many reviews on the adverse health effects of cannabis use have selectively focused on outcomes among those with intensive or chronic cannabis use only. Moreover, definitions of intensive use have varied, but it is commonly defined as ‘daily/near-daily’ use. On this basis, there is substantial evidence that frequent cannabis use, also when directly compared with less frequent (e.g., occasional) use, represents and functions as a strong predictor of adverse health outcomes (Cohen et al., 2019; Curran et al., 2016; Sagar & Gruber, 2018, 2019; Steeger et al., 2021).

A systematic review including multiple meta-analyses of the associations between cannabis use and brain volume found that frequent cannabis use was associated with significantly smaller volumes in the hippocampus (involved in motivation, learning, memory), orbitofrontal cortex (involved in emotion and memory) and lateral regions than in controls (Lorenzetti et al., 2019). While acute tetrahydrocannabinol (THC) exposure leads to acute increases in cerebral blood flow (CBF) in multiple brain regions, chronic (frequent) cannabis use results in an overall reduction in CBF, especially in the prefrontal cortex, in a dose-dependent manner (Ogunbiyi, Hindocha, Freeman, & Bloomfield, 2020). Other reviews have confirmed deficits are more common in persons with intensive cannabis use than controls in both brain structure (hippocampus volume, gray matter density) and neurocognitive performance (memory, executive control, reward, and memory processing systems) (Bloomfield et al., 2019; Nader & Sanchez, 2018).

A systematic review and meta-analyses found a significant association between frequent, heavy cannabis use and deficits in cognitive functioning in adolescents and young adults (<26 years) (Scott et al., 2018). Another systematic review of studies on cerebellar structure and functioning found that deficits in behavioral performance (e.g., memory, learning, decision-making) were associated with chronic (frequent) cannabis use (Blithikioti et al., 2019). Another comprehensive review identified strong associations between intensive cannabis use and short-term impairments in cognition (learning/memory, attention, craving), with mixed evidence for long-term effects, and symptoms of depression, anxiety, and psychosis (Kroon et al., 2020).

Systematic reviews have found stronger associations between adverse outcomes and heavy/chronic rather than less intensive cannabis use for psychotic symptoms, suicide-related behaviors, depression,

and dependence (Memedovich et al., 2018; van der Steur, Batalla, & Bossong, 2020). Other systematic reviews and meta-analyses have confirmed a relationship between frequency of cannabis use and the risk of psychosis and dependence (Hasan et al., 2020; Kraan, Velthorst, Koenders, & Zwaart, 2016). In a US-based study, cannabis use frequency was associated with psychosis and depression symptoms among a youth cohort and with mental health symptoms in the general population at later ages (18 to 65) (Leadbeater, Ames, & Linden-Carmichael, 2019). A multi-country modelling study on first-episode psychosis (FEP) found a linear relationship between symptom dimensions (paranoia, hallucinations) and cannabis exposure, with the highest scores observed in individuals with daily use of high-potency cannabis (B=0.35; 95% CI 0.14–0.56) (Di Forti et al., 2019). In a retrospective cohort study of monozygotic twins, the twin who used cannabis more frequently was more likely to report a MDD (OR:1.98, 95%CI: 1.11–3.53) or suicidal ideation (OR:2.47, 95%CI: 1.19–5.10) (Agrawal et al., 2017). Among US adults (2008-2016), daily cannabis use was significantly more common among those with past-month serious psychological distress (SPD; 8.07%), compared to those without past-month SPD (2.66%) (Weinberger et al., 2019). Systematic reviews have found associations between frequent (e.g., daily) cannabis use and hyperemesis syndrome (e.g., cyclic vomiting), especially among young individuals reporting cannabis use, though co-occurring mental health problems appear common (Sorensen, DeSanto, Borglet, Phillips, & Monte, 2017; Zhu, Gonsalves, Issenman, & Kam, 2020).

In a meta-analytic review, the risk for CUD was 33% in persons with daily and near-daily cannabis use compared to 12% in those with any lifetime use (Leung et al., 2020). Among the US general adult population (2012–2013 NESARCIII), cannabis-use quantity (OR=1.98 (95%CI, 1.64;2.39), p<0.001) and frequency (OR=1.78 (95%CI, 1.62;1.96), p<0.001), but not age-of-onset, predicted CUD and other cannabis-related problems among those individuals with past-year use (Callaghan, Sanches, & Kish, 2020). In a comprehensive systematic review, daily cannabis use predicted an elevated risk of cannabis withdrawal syndrome (CWS) in different populations of PWUC (Bahji, Stephenson, Tyo, Hawken, & Seitz, 2020). In several multi-variate analyses-based studies, high-frequency cannabis use predicted multiple adverse consequences, including dependence and impaired driving (Erin Goodman, Leos-Toro, & Hammond, 2019; Gunn, Aston, Sokolovsky, White, & Jackson, 2020; Krauss, Rajbhandari, Sowles, Spitznagel, & Cavazos-Rehg, 2017).

A US-based sample showed that frequency of cannabis use was associated with poorer mental/physical health and reduced health-related quality-of-life (Liao et al., 2019). In a secondary analysis of a randomized controlled trial (RCT) assessing pharmacotherapy for CUD, larger reductions in cannabis use frequency after treatment were associated with greater improvements in quality-of-life (Brezing et al., 2018). Comprehensive reviews have concluded that the greatest psychosocial functioning deficits (e.g., in adulthood) were observed among individuals reporting chronic/frequent cannabis use; these effects may arise regardless of whether the onset of use occurred in adolescence or adulthood (Castellanos-Ryan, Morin, Rioux, London-Nadeau, & Leblond, 2021; Meier, 2021). Among PWUC in the US' general adult population who reported driving under the influence of cannabis (29.5% [95%CI=28.6-30.3]; 2016-2018), the predicted probabilities of cannabis-impaired driving were highest for those with more frequent use, with 57% predicted probability for those with daily use (Salas-Wright, Cano, Hai, Oh, & Vaughn, 2021).

Overall, frequent and intensive cannabis use strongly and consistently predicts long-term adverse outcomes from cannabis use after controlling for at least some of the other risk factors (Curran et al., 2016; Ganzer, Broning, Kraft, Sack, & Thomasius, 2016; Scott et al., 2018). However, there is a general need for better measures of the overall 'magnitude' of cannabis exposure that consider and integrate cannabis use frequency, amounts, and potency to better estimate associations with these adverse outcomes (Sagar & Gruber, 2018).

Cannabis potency and composition

Cannabis products have further diversified in their pharmacological characteristics, including composition or amounts of the major cannabinoids THC and cannabidiol (CBD). There is substantial evidence of a dose-response relationship between THC-amount/potency and acute adverse (e.g., neurocognitive) effects and some evidence for long-term effects (Ramaekers et al., 2021). Reviews generally suggest more extensive white matter/brain alterations among PWUC consuming high- as opposed to lower-potency cannabis products (with the latter usually defined as <10-15% THC content). Exposure to cannabis products with higher THC potency is generally associated with acutely impaired cognition, memory problems, and increased symptoms and severity of CUD (Craft et al., 2020; Hindley et al., 2020; Murray, Quigley, Quattrone, Englund, & Di Forti, 2016; Sagar & Gruber, 2018, 2019). Systematic reviews have confirmed a dose-response relationship between frequent use of high-potency cannabis and psychotic symptoms and disorders, although questions remain about causality (Di Forti et al., 2019; Hasan et al., 2020; Sommer & van den Brink, 2019; van der Steur et al., 2020). High-potency cannabis use is associated with significantly higher anxiety or depression outcomes in youth, and adolescents using high potency cannabis are less likely than older individuals to titrate their cannabis dose, and so increase their risk of cannabis dependence or other harms (Wilson, Freeman, & Mackie, 2019).

In a pharmacodynamic study of edible cannabis product use, low THC (10mg) doses produced moderate subjective (e.g., feeling 'high', paranoia, restlessness) but not cognitive or psychomotor impairment effects. High doses (25-50mg) produced more marked subjective effects and impairment (Schlienz et al., 2020). Among youth aged PWUC in the US, the risk of progressing from cannabis use initiation to CUD significantly increased for each percentage increase in the national average THC level of cannabis observed. Those initiating cannabis use at a national THC content average of 12.3% had a 2.6 times higher risk of CUD incidence than those initiating use at a 4.9% THC content average (Arterberry, Treloar Padovano, Foster, Zucker, & Hicks, 2019). In the Netherlands, an increase in THC potency levels of cannabis sold (years 2000 to 2015) was significantly associated with rising admissions to cannabis treatment, and admissions dropped when the average THC content declined (Freeman et al., 2018).

Cannabis extracts/concentrates typically contain extremely high THC concentrations (e.g., 70-90% or more compared to <10-25% in cannabis flower), and their inhalation can rapidly deliver an exceptionally high dose of THC into the body. Concentrate use is generally associated with higher THC exposure and blood-THC levels, stronger neuro-behavioral intoxication and impairments, higher levels of dependence, and depression and anxiety in cohort studies, although select acute impairments from concentrate use may be moderated by tolerance or THC-saturation effects among user-individuals (Bidwell et al., 2020; Bidwell, Martin-Willett, & Karoly, 2021; Meier, 2017; Sagar & Gruber, 2018, 2019). Samples of individuals using cannabis flower (~20% THC) and concentrate (~75% THC) products reported significant associations between cannabis potency used and multiple negative physical and mental health outcomes (Prince & Conner, 2019). Among a large sample of adolescents, experimental cannabis use involving concentrates predicted subsequent progression to frequent use compared to other cannabis product types (Barrington-Trimis et al., 2020).

CBD is a common non-intoxicating cannabinoid constituent of cannabis. It has demonstrated neuroprotective, anti-inflammatory, and anxiolytic effects in laboratory studies and attenuates some of the neurocognitive and behavioral effects of THC, with few and mostly mild adverse effects of itself (Bonaccorso, Ricciardi, Zangani, Chiappini, & Schifano, 2019; Dos Santos et al., 2020; Englund, Freeman, Murray, & McGuire, 2017; Solowij et al., 2019). In clinical trials for CUD, CBD-based pharmacotherapies have somewhat reduced cannabis use frequency, craving and withdrawal symptoms (Batalla, Janssen, Gangadin, & Bossong, 2019; Freeman et al., 2020;

Sholler, Schoene, & Spindle, 2020). Consequently, the use of cannabis with high CBD-to-THC ratios has been suggested as a way to reduce adverse outcomes of cannabis use (Englund et al., 2017; Solowij et al., 2019). A systematic review found that CBD attenuates some of THC's acute psychoactive effects, such as intensity of psychosis/anxiety symptoms and emotional/reward processing. However, it does not consistently affect memory and cognitive functions or the level of intoxication produced by THC (Freeman et al., 2019). Other studies have found inconsistent evidence on whether combined CBD and THC use attenuates memory impairment and hippocampal volume changes, suggesting that extremely high doses of CBD are required for attenuation (Ramaekers et al., 2021; Sagar & Gruber, 2018). In a systematic review, only one of four studies found that CBD produced a significant reduction in THC-induced psychiatric symptoms (Hindley et al., 2020). Studies of the effects of CBD vary in methodology, dosing, and routes of administration (Iffland & Grotenhermen, 2017; Larsen & Shahinas, 2020). Questions remain about CBD-related dose/effect relationships and whether its protective effects differ between individuals reporting frequent and infrequent cannabis use (Colizzi & Bhattacharyya, 2018; Freeman et al., 2019; Larsen & Shahinas, 2020).

Overall, CBD may attenuate some of THC's acute deleterious effects, but this may largely be limited to exceptionally CBD-rich cannabis products, and it may not reliably protect against the cognitive and psychomotor impairments produced by THC (Cohen et al., 2019; Freeman et al., 2019; Ramaekers et al., 2021). These limitations for attenuating effect, in particular, seem to be the case with the majority of cannabis products on the non-medical market that typically contain relatively low levels or dosages of CBD. Notably, CBD by itself may actually produce or exacerbate selected impairment deficits, as may be particularly important for driving impairments and possible MVC involvement (Arkell et al., 2019; Boggs, Nguyen, Morgenson, Taffe, & Ranganathan, 2018; Chesney et al., 2020). Importantly, there are currently no empirically defined standards or risk thresholds for cannabis (e.g., THC content) potency serving to reliably reduce adverse health outcomes (Freeman & Lorenzetti, 2020; Wilson et al., 2019).

A systematic review also suggests that many, especially un-regulated cannabis products contain toxic contaminants such as microbes (e.g., moulds), heavy metals, pesticides, and residual solvents. Their direct human impact has not been assessed but they may increase the risks of infections, carcinogenicity, and adverse reproductive effects, with the magnitude and route of exposure likely to influence outcomes (Dryburgh et al., 2018). Unregulated illegal cannabis products also come without reliable information on product potency or composition, so PWUC should prefer legal and regulated cannabis products where these are available, as these can be presumed to be safer in regards to production and content quality and allow them to better self-regulate their use and thus protect their health (Corroon, MacKay, & Dolphin, 2020; Hammond, 2021; Leos-Toro, Fong, Meyer, & Hammond, 2020; Pusiak, Cox, & Harris, 2021).

Modes of use

Modes of cannabis administration have diversified in recent years, especially in jurisdictions where cannabis is legal for non-medical use. While there are indications for differential or moderating mode-of-use-based effects on health outcomes, there is very little comparative evidence on the health outcomes of these different cannabis administration modes (Prince & Conner, 2019; Russell, Rueda, Room, Tyndall, & Fischer, 2018; Steeger et al., 2021; Streck, Hughes, Klemperer, Howard, & Budney, 2019). The most popular cannabis use modes include smoking cannabis plant material (with or without tobacco), vaping/vaporizing electronically ('flower') heated herbal or liquid/extract, and orally ingesting cannabis 'edible' and 'drinkable' products (Russell et al., 2018; Spindle, Bonn-Miller, & Vandrey, 2019).

Cannabis smoking produces a relatively rapid onset (within 5-10 minutes) and peak of psychoactive effects. Acute effects may last 2-6 hours but residual effects (e.g. on memory) may last for 24 hours or multiple days (Peters & Chien, 2018; Ramaekers et al., 2021; Solowij et al., 2019). A meta-analysis demonstrated that smoking cannabis alone was associated with significantly increased risk of cough, sputum production, wheezing, and dyspnea (Ghasemiesfe et al., 2018). Cannabis continues to be commonly smoked in combination with tobacco in many settings, which makes it difficult to assess the respiratory health effects of cannabis smoking alone. Co-use of cannabis and tobacco does, however, increase risks of adverse respiratory health outcomes that may be exacerbated by intensive inhalation (e.g., 'deep inhalation' or breath holding) practices (Bisconti et al., 2019; Mishra, Patel, & Khaja, 2017; Russell et al., 2018). Cannabis smoking can produce both bronchodilation and bronchoconstriction. Chronic cannabis smoking (without tobacco co-use) increases the risk of chronic bronchitis, airway inflammation, bullous lung disease and pneumothorax, but it remains uncertain if it increases the risk of chronic obstructive pulmonary disease or lung cancer (Ghasemiesfe, Barrow, Leonard, Keyhani, & Korenstein, 2019; Tashkin & Roth, 2019). Of different use modes available, cannabis smoking also features the highest environmental (second-hand) smoke exposure and emission rate, resulting in possible toxin exposure and related adverse effects to others (Chu, Kaufman, & Chaiton, 2019; Zhao, Cheng, Ott, Wallace, & Hildemann, 2020).

Cannabis vaporizing/vaping (e.g., with a vaporizer or vape pen/e-device) has become an increasingly popular use method, especially among younger individuals, because of perceived possible health advantages (Aston, Farris, Metrik, & Rosen, 2019; Spindle et al., 2019). Vaping can involve different cannabis products, namely herbal/flower products, liquids as well as (high potency) cannabis concentrates. The vaporization process heats but aerosolizes (rather than burns) the cannabis product into a vapour, which then is inhaled and absorbed through the respiratory system (Bidwell et al., 2021; Chadi, Minato, & Stanwick, 2020). While cannabis smoking and vaporizing provide for generally similar cannabinoid delivery dynamics, vaporization is a more 'efficient' (partly due to higher bio-absorption) mode of administration for THC and produces higher peak THC-levels (Newmeyer et al., 2016; Ramaekers et al., 2021; Solowij, 2018). A placebo-controlled cross-over trial on the effects of smoked and vaporized (herbal) cannabis at different dose-levels (10mg and 25mg THC) among individuals with infrequent use found dose-response relationships for subjective and cardiovascular effects and for cognitive and psychomotor impairment, with vaporization producing greater pharmacodynamic effects and higher blood-cannabinoid concentrations (Spindle et al., 2018). It is uncertain, however, whether this holds true for more frequent use patterns. In another pharmacokinetic study, no major differences were observed in cannabinoid blood concentrations between individuals who smoked and vaped occasionally, but individuals with frequent use achieved higher concentrations from smoking, possibly through reverse titration (Newmeyer et al., 2016). A study assessing subjective effects from different use modes found the least positive and negative effects reported to be associated with vaporization (Boisvert et al., 2020).

Since the combustion process is avoided, cannabis vaporization reduces the formation of pyrolytic toxic compounds, including carbon monoxide and carcinogens (Bidwell et al., 2021; Newmeyer, Swortwood, Abulseoud, & Huestis, 2017; Solowij, 2018; Spindle et al., 2019). Individuals using cannabis by vaporization have reported fewer respiratory problem symptoms than smokers, but long-term effects remain unclear (Bidwell et al., 2021; Tashkin & Roth, 2019). Consequently, vaporization – at least in some forms - has been suggested as a 'safer' inhalation mode than smoking for cannabis use at least for pulmonary health. Overall, this further depends on the type of cannabis product used; for example, the use of high-potency extracts is associated with higher levels of acute and long-term (e.g., mental health) effects (Chadi et al., 2020; Spindle et al., 2019). Furthermore, many cannabis extract products have been found to contain contaminants, for example pesticides, residual solvents, heavy metals or bacteria and fungi (Bidwell et al., 2021; Spindle et al., 2019). Further concerns are that cannabis vap-

ing products include toxins (acetyls, aldehydes) from flavouring agents and can cause bronchiolitis. A recent outbreak of acute lung injuries among young adults in the US, including some deaths, was linked to the vaping of counterfeit cannabis oil cartridges adulterated with vitamin-E acetate, an inflammatory irritant (Cherian, Kumar, & Estrada, 2020; Hall, Gartner, & Bonevski, 2021).

Cannabis ingestion (e.g., of 'edibles' or beverage products) has become common because it eliminates the respiratory risks of inhalation use and produces more prolonged and potentially intense psychoactive effects than other modes of use (Doran & Papadopoulos, 2019; Russell et al. 2018). While studies suggest that individuals using cannabis 'edibles' initiate use at a younger age, consume overall larger quantities of cannabis and drive more often after use, consumption of edibles occurs less commonly than other use modes (Doran & Papadopoulos, 2019; Friese, Slater, & Battle, 2017; Goodman, Wadsworth, Leos-Toro, Hammond, & International Cannabis Policy Study, 2020; Krauss et al., 2017). Ingestion of cannabis products has been observed to be increasing especially among older adult users (Subbaraman & Kerr, 2021). 'Edible' products are available in different compositions, usually with lower THC doses. They exert slower, although variable, bio-absorption and related effect dynamics that delay the onset of psychoactive effects (e.g., to 1-2 hours or more after use) yet produce a substantially longer duration of impairment (e.g., 6-12 hours or more) than cannabis inhalation use (Peters & Chien, 2018; Poyatos et al., 2020; Ramaekers et al., 2021; Russell et al., 2018). 'Edible' use can lead to sleepiness, nausea, anxiety and hallucinations, with some individuals reporting they are unable to perform normal tasks (Doran & Papadopoulos, 2019). While their use allows to avoid inhalation-related adverse consequences, their particular (delayed) pharmacodynamics make cannabis edibles more difficult for dose titration and increase the risks of unexpected levels of intoxication, including overdose experiences, especially in individuals with infrequent or those inexperienced in cannabis use (Hammond, 2021). Adolescents report more negative effects from 'edibles' use than from smoking or vaping cannabis products, suggesting the need for caution in their intake and use (Boisvert et al., 2020).

A placebo-controlled crossover study involving individuals with infrequent use given cannabis 'edibles' at different doses (10-50mg) found dose-dependent acute impairments in attention, memory and psychomotor performance. Perceptible drug effect onset occurred 30-60 minutes after intake, peaked at 2-5 hours, and lasted eight hours or more (Schlienz et al., 2020). While the cognitive impairments observed were comparable to similar doses of inhaled (e.g., smoked or vaped) cannabis the THC-blood concentrations observed were lower than peak concentrations reported in other studies on cannabis inhalation (Spindle et al., 2020). On this basis, individuals with 'edibles' use could have been under existing limits for THC blood level for cannabis-impaired driving, despite their marked impairment being comparable to that from smoking or vaping THC.

Furthermore, extending the evidence on the role of different use modes for cannabinoids, the pharmaco-dynamic (e.g., onset of) effect patterns of CBD itself have been observed to be similar to those for THC-products, yet generally also vary depending on the use mode/route employed (Bruni et al., 2018; Larsen & Shahinas, 2020). Moreover, a recent study reported students using cannabis products in multi-modal ways were at greater risk of cannabis-related problems, dependence, and alcohol co-use than those individuals with single-mode use (Swan, Ferro, & Thompson, 2021).

Tolerance & effect reversal

Systematic reviews suggest that individuals reporting frequent use of cannabis may develop tolerance to the acute effects of THC, especially its effects on memory, executive functioning, and psychomotor impairments, which are less pronounced in individuals with frequent than those with non-frequent use (Colizzi & Bhattacharyya, 2018; Curran et al., 2016; Freeman et al., 2021; Ramaekers et al., 2021). Tolerance is generally evident in a blunting effect on impairment, rather than its avoidance; it appears to be a result of neuroadaptation, a downregulation of cannabinoid receptors in response to frequent THC exposure (Colizzi & Bhattacharyya, 2018; Curran et al., 2016; Ramaekers et al., 2021). A recent meta-analysis confirmed a moderating effect of frequent cannabis use on the subjective impairment and psychosis-like effects of THC (Freeman et al., 2021). A double-blind, randomized, placebo-controlled study of the acute effects of cannabis use on neuro-behavioral functioning found that in subjects with occasional use, cannabis-induced alterations in brain functioning were associated with increased subjective intoxication and decreased behavioral performance; conversely, neuroadaptive processes were observed as facilitating reduced responses in individuals with chronic use (Mason et al., 2021). Other studies suggest that acute tolerance may be limited to persons with extremely high-intensity patterns of cannabis use (Freeman et al., 2021; Ramaekers, Mason, & Theunissen, 2020; Ramaekers et al., 2016). Individuals engaging in frequent (e.g., daily) cannabis use may also develop tolerance to the protective effects of CBD (Wilson et al., 2019). Tolerance may lead to increased cannabis intake in order to achieve the desired level of intoxication, thereby increasing the risk of adverse effects.

Some adverse neuro-cognitive effects of cannabis on memory, learning and mental state may reverse after a period of abstinence or substantial reductions in use (Kroon et al., 2020; Sorkhou, Bedder, & George, 2021; Zehra et al., 2018). Reversible downregulation of brain functioning has been reported in animal and human studies, with structural levels returning to those of healthy controls within a few weeks, or even days, of non-exposure (Blest-Hopley et al., 2019; Curran et al., 2016; Lovell, Akhurst, Padgett, Garry, & Matthews, 2020; Ogunbiyi et al., 2020; Ramaekers et al., 2021). A recent systematic review concluded that abstinence from cannabis use for periods of >72 hours diminished the neurocognitive deficits found in adolescent and young adult PWUC (Scott et al., 2018). Other studies have found reversals in key cognitive deficits but observed residual effects on higher-order cognitive functions and related brain networks (Hurd et al., 2019; Blest-Hopley et al., 2019). Overall, conditions and measures of related studies vary considerably (Sagar & Gruber, 2018). In a sample of young (18–25 years) cannabis-using women, reductions in cannabis use frequency at 3- and 6-months post-baseline were associated with significant reductions in depressive symptoms, with the largest changes for more severe depressive symptoms at baseline (Moitra, Anderson, & Stein, 2016). Furthermore, abstaining or reducing the amount of cannabis smoked can reduce respiratory problem symptoms (Ghasemiesfe et al., 2019; Tashkin & Roth, 2019).

Driving

Key reviews have documented moderately but significantly increased associations (e.g., ORs 1.5–2.5) between driving under the influence of cannabis and user-drivers' involvement in MVCs that cause injury or death (Bondallaz et al., 2016; Drummer et al., 2020; Hostiuc, Moldoveanu, Negoi, & Drima, 2018; Preuss et al., 2021). Risk ratios may be higher if evidence is limited to drivers with acute impairments in relevant cognitive and psychomotor control functions (Gjerde & Morland, 2016). Similar risk associations have been confirmed for motorcycle crashes and occupational injuries (Asgarian, Namdari, & Soori, 2020; Biasutti, Leffers, & Callaghan, 2020). Using cannabis together with alcohol increases multifold the impairment of driving-relevant performance skills and MVC involvement risk (e.g., 5- to 10-fold) (Bondallaz et al., 2016; Brubacher et al., 2019; Chihuri, Li, & Chen, 2017; Fares et al., 2021; Woo, Willits, Stohr, Hemmens, & Hoff, 2019).

Driving simulator and on-road performance studies confirm that acute cannabis use impairs driving-related reaction, tracking, and psychomotor control, including among youth drivers as a particular high-risk group for driving-related adverse events (Alvarez et al., 2021;

Bondallaz et al., 2016; Micallef et al., 2018). While cannabis-using individuals appear to compensate for some cannabis-related impairing effects at low doses, impairment is estimated to begin at around 5ng/ml THC-blood concentration and to increase with the amount and potency of the cannabis consumed, although probably not linearly (Brubacher et al., 2019; Doroudgar et al., 2018). Importantly, THC-related impairments may persist for several hours after acute intoxication, depending on the specific characteristics of use and the user-individual (Bondallaz et al., 2016).

The distinct pharmacokinetics of different routes of cannabis administration differentially affect driving-related impairment dynamics. The impairment patterns arising from cannabis smoking and vaping/vaporization are similar, with a relatively rapid onset of effects. These effects typically subside within timeframes of 6- to 8-hours after use but may persist for longer, especially in those people using frequently. Ingestion of edibles produces a slower onset of psychoactive effects and longer durations of impairment that may persist for 8-12 hours (or longer in some cases) (McCartney, Arkell, Irwin, & McGregor, 2021; Newmeyer et al., 2016; Spindle et al., 2018). Therefore, different routes of use vary in the periods of time required for driving-related impairment to resolve.

Characteristics of cannabis used, patterns of use and individual-user characteristics furthermore substantially affect impairment dynamics. The use of higher potency (THC) products generally leads to greater impairment of driving-relevant skills (Bidwell et al., 2021; Eadie et al., 2021). A study comparing simulated driving performance after smoking cannabis in young adults found greater acute impairment that lasted longer in individuals with occasional use, while THC blood concentrations remained higher for longer in individuals with chronic use (Hartley et al., 2019). Similarly, a simulated driving study among younger-age individuals with intensive cannabis use who were not acutely intoxicated found significant impairment (resulting in crashes, speed, lateral movement deviations) compared to non-using controls (Dahlgren et al., 2020). Other studies with mainly young, occasional cannabis smokers demonstrated dose-dependent impairments in driving performance 5-6 hours after use but no consistent longer-term residual effects (Brands et al., 2019; Doroudgar et al., 2018; Tank et al., 2019). Overall, the evidence suggests that THC produces more pronounced acute impairment in individuals with infrequent use and may involve partial tolerance or compensation in more frequent users, despite higher THC blood concentrations (Bondallaz et al., 2016; Karoly, Milburn, et al., 2020; McCartney et al., 2021; Peng, Desapriya, Chan, & J, 2020; Ramaekers, 2018). These overall dynamics make it both difficult to clearly define time-windows for sufficiently compensated impairment for driving following cannabis use and for user-individuals to reliably self-assess their cannabis-related impairment before driving. In a US-based survey of individuals reporting high-potency cannabis use, about 50% believed that it was risky to drive after using concentrates and most did not drive; however, the other 50% felt comfortable driving immediately or shortly after use (Cavazos-Rehg, Krauss, Sowles, Zewdie, & Bierut, 2018).

CBD does not appear to consistently attenuate THC-related cognitive or psychomotor impairments relevant for driving; conversely, select data even suggest that CBD may potentiate THC's cognitive and behavioral effects relevant for driving (Arkell et al., 2019; Arkell et al., 2020; Ramaekers et al., 2021). In a randomized crossover study of subjects with occasional cannabis use vaporizing THC-dominant, THC- and CBD-equivalent, and placebo cannabis, subjective drug and cognitive effects were similar for THC-dominant products, but the peak plasma THC-concentrations were higher after exposure to THC-/CBD-equivalent cannabis, suggesting that CBD-rich cannabis had no less impairing effects on driving than THC-dominant cannabis (Arkell et al., 2019). In a subsequent, similar study by the same authors, driving-related impairments were found for vaporized THC-dominant and THC/CBD-equivalent cannabis but no differences for CBD-dominant cannabis exposure compared with placebo (Arkell et al., 2020). The effects of CBD alone on cognitive or psychomotor impairment and driving performance are insufficiently studied and assumed to be limited; they, however, can involve some impairment effects that may undermine driving performance towards increased MVC risk (Chesney et al., 2020; Dos Santos et al., 2020; Iffland & Grotenhermen, 2017; McCartney et al., 2020).

Reproduction, pregnancy, breastfeeding

As with alcohol, cannabis use may have adverse effects on the reproductive health of both sexes. A systematic review has shown that males with chronic, intensive cannabis use had significantly lower sperm counts than those who used less often, suggesting dose-dependent effects (Payne, Mazur, Hotaling, & Pastuszak, 2019). Cannabis use also negatively affects sperm morphology, motility, viability, and fertilization capacity (Payne et al., 2019; Rajanahally et al., 2019). Animal and human studies have found that CBD exposure reduces mammalian testis size, spermatogenesis, fertilization rates, and concentrations of reproductive hormones, and chronic doses impair sexual function (Carvalho, Andersen, & Mazaro-Costa, 2020). The evidence on the impacts of cannabis use on male sex hormones is inconclusive (Payne et al., 2019; Rajanahally et al., 2019). A systematic review and meta-analysis found men reporting cannabis use were twice as likely as controls (OR 2.34, 95% CI:1.04-5.97) to report erectile dysfunction (Pizzol et al., 2019). Animal and human studies indicate that cannabinoids may adversely affect female sexual desire and receptivity at high doses, but enhance desire or show no effect at lower doses (Lynn, Gee, Zhang, & Pfaus, 2020). Furthermore, cannabis exposure reduces female fertility by reducing estrogen and progesterone levels, producing anovulatory menstrual cycles, and increasing the follicular phase length of reproductive cycles (Brents, 2016; Dubovis & Muneyyirci-Delale, 2020).

In addition to ordinary use, some women use cannabis during pregnancy to self-treat pregnancy-related nausea (Volkow, Compton, & Wargo, 2017; Young-Wolff et al., 2019). Evidence on the possible adverse impacts of maternal cannabis use on fetal development and neonatal outcomes is inconsistent. Several systematic reviews/meta-analyses and observational studies suggest a dose-dependent association with elevated rates of pre-term birth, lower birthweight, placement in neonatal intensive care units, and lowered Apgar scores (Bailey, Wood, & Shah, 2020; Gabrhelik et al., 2020; Grzeskowiak et al., 2020; Gunn et al., 2016; Ko et al., 2018; Metz & Borgelt, 2018; Volkow et al., 2017). In one study, mothers identified with pre-natal CUD had higher odds of their infant's death within one-year of birth (Shi, Zhu, & Liang, 2021). Results, however, are conflicting, with some studies finding weak associations for physiological outcomes (Metz et al., 2017). A review and large population-based analysis both found that cannabis use was not associated with adverse neonatal outcomes after adjusting for confounders (Conner et al., 2016; Ko et al., 2018). Some reviews have suggested a possible relationship between prenatal cannabis exposure and neurocognitive and psychiatric consequences, such as anxiety, depression, and attention deficit hyperactivity disorder (ADHD) in the offspring's later (e.g., adult) life, while others have not found such evidence (Hurd et al., 2019; Roncero et al., 2020; Torres, Medina-Kirchner, O'Malley, & Hart, 2020). Pre-clinical data suggest possible (dose response-based) teratological genotoxicity for congenital defects from cannabinoid exposure (Reece & Hulse, 2016). A review of neurodevelopmental data in humans and animals concluded that prenatal THC-exposure may lead to subtle but persistent changes in psychological and cognitive health (Grant, Petroff, Isoherranen, Stella, & Burbacher, 2018). However, a meta-analysis did not find significant associations between maternal cannabis use and neurological or conduct disorders among offspring (Ruisch, Dietrich, Glennon, Buitelaar, & Hoekstra, 2018). In the large-scale Adolescent Cognitive Brain Development (ABCD) study, cannabis exposure after maternal knowledge of pregnancy was associated with increased psychotic-like experiences and with select psycho-behavioral and social (but not physiological) problems in offspring; these problems persisted after controlling for confounders (Paul et al., 2021).

Some lactating women use cannabis while breastfeeding (Brown et al., 2016). A mass-spectroscopy-based study of breastfeeding women using an average amount of (high-THC) cannabis detected THC in breastmilk at low concentrations for several hours after use. Breastfed infants were estimated to have ingested 2.5% of the maternal THC dose (Baker et al., 2018). An analysis of human milk samples from cannabis-using breastfeeding women found measurable levels of THC in a majority and CBD in about 10% of the samples (Bertrand, Hanan, Honerkamp-Smith, Best, & Chambers, 2018; Ryan et al., 2018). While cannabinoids may transfer through breastmilk, there is currently no concrete evidence on the potential health impacts on the exposed infants (Baker et al., 2018).

Interactions with other psychoactive substances

Cannabis is often used with other recreational and prescribed psychoactive substances. The co-use of cannabis and tobacco smoked together continues to be common; this behavior may facilitate exposure to tobacco-only use but also produces multidirectional effects on neurobiological and behavioral outcomes (Jayakumar et al., 2021; Lemyre, Poliakova, & Belanger, 2019). THC increases self-administration of nicotine in animals, suggesting increases in its rewarding effects (Curran et al., 2016). CBD reduces increased attentional bias towards cigarettes in humans who use both drugs, suggesting it may have anti-nicotine addictive properties (Hindocha et al., 2018). Adolescents who co-use tobacco and cannabis report more problems with and dependence on both drugs, consume more alcohol, and experience stronger withdrawal symptoms than those individuals with singular drug use (Lemyre et al., 2019; Schlienz & Lee, 2018). In large samples of young adults, co-users of cannabis and tobacco reported more intensive use and poorer physical and behavioral functioning than those without co-use (Tucker et al., 2019); similarly, among adults, cannabis use has been significantly associated with the initiation of cigarette smoking, smoking persistence, and relapse after cessation (Jayakumar et al., 2021; Weinberger et al., 2020). Cannabis and tobacco smoking also pose additive risk for toxicant exposure (Meier & Hatsukami, 2016) and psychotic symptoms (Curran et al., 2016; Englund et al., 2017). Maternal tobacco co-use has been identified as a confounder for the possible effects of cannabis use on adverse neonatal outcomes, for example birthweight or gestational age (Dubovis & Muneyyirci-Delale, 2020; Ko et al., 2018; Shi et al., 2021), and predicts future use of cannabis and tobacco by offspring (De Genna, Richardson, Goldschmidt, Day, & Cornelius, 2018).

The concurrent use of cannabis and alcohol can have complex effects (Karoly, Ross, et al., 2020). Individuals reporting daily cannabis use who also used alcohol did not differ in brain structure from matched individuals with alcohol-only use; however alcohol co-use is a potential confounder in studies of long-term cannabis-related cognitive function (Curran et al., 2016). Concurrent adolescent cannabis and alcohol use may be associated with better neurophysiological and structural brain outcomes than alcohol-only use, but data are limited and effect dynamics uncertain (Karoly, Ross, et al., 2020). It is possible that THC exposure may acutely increase the rewarding effects of alcohol and produce quicker and more marked intoxication, and thus lower alcohol use. Co-using individuals may use both drugs more frequently, increasing the risks of co-morbid substance use and mental health problems, and poorer treatment outcomes than those not using both drugs (Karoly, Ross, et al., 2020; Schlienz & Lee, 2018; Yurasek, Aston, & Metrik, 2017). Comprehensive reviews suggest that frequent cannabis and alcohol co-use by adolescents is associated with greater neuropsychological impairments, adverse health and psycho-social outcomes, such as poorer academic performance and impaired driving. Concurrent use of cannabis and alcohol increases acute impairment, and increases the risk of MVC involvement and other injuries (Bondallaz et al., 2016). Concomitant use of alcohol and/or tobacco with cannabis increases the risks of adverse cardiovascular events, including stroke (Singh et al., 2018).

Interactions between cannabis and other psychotropic drugs, for example, psychostimulants, may negatively influence physical and mental health outcomes (Bahdila et al., 2020; Timko, Han, Woodhead, Shelley, & Cucciare, 2018). As specifically relevant for prescription drugs, cannabinoids can inhibit the liver and other enzymatic systems, increasing the plasma levels and hence the toxicity of other psychotropic drugs via adverse drug-drug interactions (Hudson & Hudson, 2021; Iffland & Grotenhermen, 2017; MacCallum & Russo, 2018; Sagar & Gruber, 2018). Conversely, there may be some health-protective effects (e.g., for opioids) for individuals with high-risk use (Hutchison, Hagerty, Galinkin, Bryan, & Bidwell, 2019; Reddon et al., 2020), but research in this area is underdeveloped. Both THC and CBD can produce drug-drug interactions and related adverse events, such as impaired neurological and cardiovascular functioning and infections (Memedovich et al., 2018). They both can interact with tricyclic antidepressants, central nervous system depressants, protease inhibitors, and warfarin therapy (Brown, 2020; MacCallum & Russo, 2018; Memedovich et al., 2018).

Special risk factors/groups

Cardiovascular risks

Some reviews have found cannabis smoking to be associated with adverse cardiovascular outcomes such as acute myocardial infarction (AMI), arrhythmias, and ischemic attack (stroke), while other reviews have questioned the strength of the evidence (Cohen et al., 2019; Memedovich et al., 2018; Ravi, Ghasemiesfe, Korenstein, Cascino, & Keyhani, 2018; Yang, Odom, Patel, Loustalot, & Coleman King, 2021). A systematic review found that the association with using large doses of THC was stronger for ischemic stroke than for other cardiovascular outcomes (Jouanjus, Raymond, Lapeyre-Mestre, & Wolff, 2017). Case studies have reported temporal relationships between cannabis smoking and adverse cardiovascular events, but the confounding role of tobacco and alcohol is unclear (Jouanjus et al., 2017). While the evidence for cannabis-related cardiovascular outcomes is limited, it appears that THC exposure can exert substantial stress on the cardiovascular system, especially in individuals with novice or occasional use and consequentially limited tolerance to its effects (Drummer et al., 2019). Systematic reviews have documented acute dose-response effects of cannabis use on tachycardia (>100 heartbeats/minute) in young subjects without cardiovascular deficits (Ghasemiesfe, Ravi, Casino, Korenstein, & Keyhani, 2020; Richards et al., 2020). Similarly, cannabis smoking has been suggested as a trigger for AMI in young individuals immediately after use (Patel et al., 2020; Ravi et al., 2018). Furthermore, risks for adverse acute cardiovascular events appear to be dose-dependent, and higher in individuals with frequent use of high THC-potency cannabis (Cohen et al., 2019; Pacher, Steffens, Hasko, Schindler, & Kunos, 2018; Yang et al., 2021) as well as in older PWUC and in individuals with pre-existing cardiovascular conditions (Ravi et al., 2018; Richards et al., 2020).

Genetic/shared vulnerabilities

It is estimated that approximately half or more of the risks of developing substance use disorders (SUDs) is related to genetic susceptibility/heritability (Demontis et al., 2019). These effects are partly explained by the additive effects of common variants on neurotransmission pathways and other physiological processes that are partially shared between substances (Gurriaran et al., 2019; Prom-Wormley, Ebejer, Dick, & Bowers, 2017). Comprehensive studies suggest a possible role of specific genetic predispositions for cannabis use problems, adverse psychiatric outcomes, and other substance use disorders (Hurd et al., 2019). Large genome-wide studies of cannabis dependence have identified independent regions with genome-significant polymorphisms (Agrawal et al., 2018; Demontis et al., 2019; Ferland & Hurd, 2020). In a large genome-wide association study, eight independently associated polymorphisms explained a substantial amount of the variance in associations between cannabis use and risks of other SUDs and schizophrenia

(Pasman et al., 2019). Small but significant associations were found between polygenic risk scores for multiple SUDs and select mental health disorders, some indicating that those with a genetic risk for schizophrenia were more vulnerable to CUD than persons pre-disposed for other psychiatric conditions (Gurriaran et al., 2019; Sherva et al., 2016) . Overall, data suggest that individuals with an immediate or familial history of SUD or schizophrenia and depression are at elevated risk of developing chronic cannabis-related problems. Given the limitations of genetic risk diagnosis, such histories may serve as the best general indicators of increased risk. In those affected by mental health problems (e.g., psychosis or depression) the prevalence of cannabis use is commonly elevated and associated with increased disease severity, progression or outcome severity (Hamilton, 2017; Hanna, Perez, & Ghose, 2017; Lowe, Sasiadek, Coles, & George, 2019; Schoeler et al., 2017). The cause-and-effect dynamics involved between cannabis use, SUD, and mental health problems are complex, including possibly bi-directional relationships. The effects of cannabis may vary in response to other causes, and its use among those with mental health problems may also be a form of self-medication.

Sex/gender

Cannabis use has traditionally been twice as common in men as women, but the sex ratio of PWUC has substantially narrowed in more recent birth cohorts in many contexts (Chapman et al., 2017). Fewer women than men, however, engage in intensive cannabis use, and some sex-based and suggestive gender differences in outcomes have been found, although the data may primarily reflect differential exposure levels (Brabete, Greaves, Hemsing, & Stinson, 2020; Greaves & Hemsing, 2020). There are sex-related biological differences in the ECS and its role in the metabolic and endocrine systems, which may produce sex-based differences in the effects of cannabis on brain structures and functions and on mental health outcomes (Bidwell et al., 2021; Ramaekers et al., 2021). Male PWUC develop CUD more often and typically express more problem symptoms than females. A series of double-blind, placebo-controlled pharmacodynamic studies comparing the effects of vaporized and oral cannabis use at different doses by sex found overall dose-related increases in subjective drug effects and cognitive/psychomotor performance, heart rate, and blood-cannabinoid concentrations in female PWUC. Females exhibited greater peak-THC concentrations in blood and subjective effects as well as ratings of “anxious/nervous,” “heart racing,” and “restless” than males, suggesting differential effect profiles (Sholler, Strickland, Spindle, Weerts, & Vandrey, 2020). Women seem to experience greater and more prolonged sedation and psychomotor impairment from cannabis that also may increase their risks of MVC involvement (Greaves & Hemsing, 2020). Female PWUC may have a higher prevalence of anxiety symptoms or disorder and an earlier onset of schizophrenia, although studies of depression outcomes are mixed (Calakos, Bhatt, Foster, & Cosgrove, 2017). Women engaging in cannabis use, overall, may show a ‘telescoping effect’ in which they may more quickly transition from use initiation to CUD or other problems, although these dynamics may also include gendered differentials in social responses; furthermore, some studies suggest that women may experience more severe dependence and withdrawal symptoms (Bidwell et al., 2021; Calakos et al., 2017; Cooper & Craft, 2018; Schlienz, Budney, Lee, & Vandrey, 2017). Male PWUC have been found to have twice the prevalence of cannabis-impaired driving as females (Lloyd, Lopez-Quintero, & Striley, 2020).

Older adults

Cannabis use is increasing among older adults in North America but there are only very limited data on health outcomes in this specific age group (Sagar & Gruber, 2019). Human and animal data on ECS upregulation suggest that some age-related decrements may be balanced by neuro-protective effects or improved cognitive function in older PWUC. Reviews have found limited evidence for adverse effects on neuro-cognitive functioning (Hudson & Hudson, 2021; Sagar & Gruber, 2019; Scott, Brennan, & Benitez, 2019; Weinstein & Sznitman, 2020). Systematic reviews of mental and cognitive health among older adult PWUC (with and without neurocognitive disorders) found only modest reductions in cognitive performance, and were concentrated in individuals with intensive and higher-dose use (E. P. Scott et al., 2019; Vacaflor, Beauchet, Jarvis, Schavietto, & Rej, 2020). A structural MRI study of frequent older-adult PWUC and non-using controls (mean age >65) did not find any inter-group differences in in the brain’s total volumes of gray or white matter. User-individuals, however, showed greater regional volumes in the left putamen, lingual cortex, and rostral middle frontal cortex. There were no differences in cognitive performance indicators, suggesting minimal impact on brain structure and function (Thayer, York-Williams, Hutchison, & Bryan, 2019). Adverse impacts of cannabis use in older-age PWUC may be influenced by or arise from interactions with independently existing age-related deficits. For example, cannabis-related impairment of cognitive and executive functions and reaction/memory may amplify age-related declines in these abilities (Hudson & Hudson, 2021; E. P. Scott et al., 2019). Furthermore, slowed metabolism/liver function and interactions with commonly used psychotropic medications may increase cannabis-related intoxication and impairment, and thereby magnify the risks of falls and injuries, including as related to driving and crash involvement (Choi, Dinitto, & Arndt, 2019; Han, Le, Funk-White & Palamer, 2021; Hudson & Hudson, 2021; Sagar & Gruber, 2018, 2019). A recent, large-scale US-based case-control relative risk study (n=2839 crashes and 6238 controls) found no overall association between cannabis use and risk of MVC involvement; however, significant interaction effects between age and THC emerged at age 64, resulting in significantly increasing risk of crash involvement for older THC-exposed drivers (Johnson, Mechtler, Ali, Swedler, & Kelley-Baker, 2021). There is some evidence of declines in lung function associated with cannabis smoking and potentially elevated risk of cardiovascular problems in older-age PWUC (Ghasemiesfe et al., 2020; Tashkin & Roth, 2019). Some of these older age-specific risks may be attenuated by the use of low-potency cannabis, titration of doses, and other intake precautions (MacCallum & Russo, 2018).

Combinations of risks

Individuals with combinations of the risk factors identified above are likely to be at markedly elevated risk of experiencing cannabis-related adverse health outcomes. The combination of greatest concern is the high-frequency use of high-potency cannabis products, especially when initiated at and sustained from a young (e.g., adolescent) age. This pattern predicts increased risks of multiple adverse mental and physical outcomes, including neuro-cognitive, psychosis and cardiovascular problems (Arterberry et al., 2019; Gorey et al., 2019; Kraan et al., 2016; Sorkhou et al., 2021). An analysis of a sample of patients with first-episode-psychosis found that those who continued daily use of high-potency cannabis (compared to those who less frequently used lower-potency cannabis or abstained from use) had an increased risk of relapse (OR:3.28; 95%CI:1.22–9.18), shorter time-to-relapse (b−0.22; 95%CI:−0.40 – 0.04), and required more psychiatric care (OR:3.16; 95%CI:1.26–8.09) after the initial episode (Schoeler et al., 2016). Similarly, adolescent-aged individuals with high-potency cannabis use were more likely to engage in daily use (OR:4.38; 95%CI:2.89-6.63) and report cannabis-related problems (AOR:4.08; 95%CI: 1.41-11.81) and anxiety disorders (AOR:1.92; 95%CI:1.11-3.32) than lower-risk controls (Hines et al., 2020). In a systematic review, adolescent cannabis use increased the risk for psychosis (RR=1.71; 95%CI:1.47-2.00); this association was significantly moderated by (early) age of onset and frequent cannabis use, concurrent use of other substances, and genetic risks, among other factors (Kiburi, Molebatsi, Ntlantsana, & Lynskey, 2021).

As noted above, the evidence is mixed on whether an early age-of-onset independently increases the risks of major adverse outcomes. It may be that individuals who report early age of onset of use more

often engage in intensive cannabis use, commonly involving higher-potency cannabis, that adversely affects their developmental and physiological vulnerabilities and increases their risks of neuro-cognitive impairment, poor mental health, and cannabis dependence (Curran et al., 2016; Ganzer et al., 2016; Prince & Conner, 2019). A systematic review, however, found stronger evidence for the role of cannabis use intensity and potency than age-of-onset in predicting psychosis outcomes (van der Steur et al., 2020). Studies of brain structure and functioning and neurocognitive impairments in young individuals with cannabis use found deficits associated with frequency of use and possibly the potency of cannabis used (Burggren, Shirazi, Ginder, & London, 2019; Jacobus et al., 2019; Lorenzetti et al., 2019). Adolescent onset of frequent cannabis use has been found to predict the highest risk of suicidal behaviors (Schmidt et al., 2020). Elsewhere it has been emphasized that the earlier the onset of use and the more intensive the use, the greater the risk of adverse health and psychosocial outcomes later in life (Castellanos-Ryan et al., 2021; Levine et al., 2017). Notably, while cannabis use was generally associated with MDD among US adolescents, individuals reporting frequent use had a significantly lower prevalence of lifetime and past-year MDD than those with less frequent use (Gukasyan & Strain, 2020).

Other risk-combinations that may be relevant are understudied. For example, sex, age-of-onset and mode of use have shown associations with cannabis-related problem severity among different populations of PWUC, and their combination may differentially contribute to risk for adverse health outcomes (Mader, Smith, Afzal, Szeto, & Winters, 2019; Prince & Conner, 2019; Steeger et al., 2021). Combined use of cannabis with alcohol and/or tobacco increases the risk of acute and chronic adverse outcomes, such as dependence, cardiovascular problems (ischaemic stroke/attacks), and potential neonatal deficits related to use during pregnancy (Dubovis & Muneyyirci-Delale, 2020; Kroon et al., 2020; Ravi et al., 2018). Similarly, frequent cannabis use among adolescents/young adults predicts an increased risk of alcohol use disorder, nicotine dependence, and CUD in mid-adulthood (Guttmannova et al., 2017).

Discussion

While cannabis control regimes are liberalizing in many settings, evidence on the adverse health outcomes of cannabis use and related risk factors has substantially grown, but findings are mixed for some outcomes. Systematic reviews and seminal studies have expanded and enhanced the knowledge bases related to some of the earlier findings, and so allow for the strengthening of confidence in the LRCUG recommendations on risk factors and ways to reduce adverse outcomes from use. The evidence has suggested some important additions and refinements. Notably, the role of 'early-age-onset' (e.g., use beginning in adolescence) as an independent determinant of adverse outcomes has become less clear, particularly with regards to neuro-cognitive effects. Current evidence suggests increased importance of frequency of use and the potency of cannabis used, the adverse impacts of which may increase if cannabis use is also initiated at a young age (Castellanos-Ryan et al., 2021; Curran et al., 2016; Lorenzetti et al., 2020; Scott et al., 2018; van der Steur et al., 2020).

There are other major areas where evidence gaps or limitations remain. For example, comprehensive evidence is lacking on the comparative health risks of the increasingly diversified routes of cannabis administration. There is also no robust evidence to quantify thresholds for cannabis (THC) potency or THC/CBD ratios that may allow consumers to reliably reduce risks of adverse outcomes. The same is true of recommendations for driving-related risks. These require qualifications in light of the multiple factors that influence impairment.

There is a need to define and quantify cannabis use in multi-factorial ways that ideally take account of the frequency, amount, and potency of cannabis used for measuring the 'magnitude' of use. Overall evidence on direct and causal associations between cannabis use and – much-debated – adverse outcomes, for example, mental health or reproductive harms, are limited or mixed. There is minimal evidence on the risk of cannabis use among older-aged PWUC, a growing group of user-individuals especially in settings that have liberalized cannabis use. All of these limitations add to the complexity of defining and guiding individuals to adopt 'lower-risk' patterns of cannabis use as clearly as possible while not being overly precise or pretending to universality (Holmes et al., 2019).

While a basic start has been made on defining cannabis consumption units (Freeman & Lorenzetti, 2020), we are currently unable to quantify 'risk-thresholds' for harms in the way that has been done for 'low-risk drinking'. This reflects the complexity of cannabis as a pharmacological product and of the factors influencing risks, the legal status of cannabis, the marked heterogeneity and limitations of operational definitions of use, and the limited quality of data on adverse outcomes from cannabis use (Connor & Hall, 2018; Shield et al., 2017; Wood et al., 2018). For these reasons, the present LRCUG explicitly focus on 'lower-risk' (as opposed to 'low-risk') cannabis use, and the recommendations are mostly qualitative rather than quantitative. It should be a principal future aim of cannabis health research to generate the evidence needed to define threshold levels for at least the major adverse outcomes associated with cannabis use (Campeny et al., 2020). While most cannabis use involvement occurs without major consequential problems, substantive sub-groups – an estimated 25 to 30% of PWUC – experience adverse outcomes that substantially burden cannabis-related public health outcomes (Boden et al., 2020; Budney et al., 2019; Callaghan et al., 2019; Caulkins, Pardo, & Kilmer, 2020; Chan & Hall, 2020; Leung, Hall, & Degenhardt, 2020).

In summary, current evidence suggests that a substantial extent of the principal long-term adverse health effects of cannabis use can be reduced, considering the main individual risk factors, if: the initiation of use is delayed until after puberty; the frequency of use is 'occasional' rather than frequent (e.g., daily); THC-potency of cannabis used is kept low; and use occurs in ways other than smoking. These recommendations need to be qualified for persons with increased pre-existing risks (e.g., genetic or familial risks or pertinent co-morbidities) for select adverse outcomes. It deserves note that possible acute harms of cannabis use, such as injury or even death (e.g. from cannabis-impaired driving or cardio-vascular incidents) occur infrequently but may arise from single-use episodes (Cherpitel, Ye, & Poznyak, 2018; Drummer et al., 2019).

Some caveats

The LRCUG require some important qualifications. First, they have been developed chiefly for non-medical cannabis use (i.e., use that is principally for recreational purposes). This differs from the use of or exposure to cannabinoids that is mainly for medicinal reasons, for which there is good evidence of therapeutic benefit for selected (e.g., pain and various neurological) conditions (Hauser et al., 2018; Pratt et al., 2019; Stockings et al., 2018). Survey data suggest that as many as two in five PWUC report their consumption to be for medical purposes, although this includes extensive self-medication practices (including for disease categories where there is little or no evidence on safety and efficacy), whereas rates of prescribed medical cannabis use are much lower (Fischer, Lee, O'Keefe-Markman, & Hall, 2020; Lin, Ilgen, Jannausch, & Bohnert, 2016). In the case of PWUC for medical purposes, some of the LRCUG recommendations may conflict with therapeutic use needs or practices, while some risks for harm identified (e.g., with regard to risks for driving) may still apply and so should be considered.

Second, PWUC can only act on some of the LRCUG recommendations if there are legal markets and complementary regulatory provisions that aim and aid to reduce risks, such as labelling of THC-strength and other product composition and availability restrictions (Barry & Glantz, 2018). Other recommendations are based solely on scientific evidence and geared towards improving health outcomes regardless of applicable laws or regulations for use, such as those concerning age-of-onset and

driving under the influence of cannabis use (Fischer, Daldegan-Bueno, et al., 2020; Hosseini & Oremus, 2019).

Third, a considerable number of PWUC, and especially those with frequent use over long periods of time may meet at least some criteria of CUD, characterized by craving, withdrawal symptoms, compulsive use, and neglect of obligations (Budney et al., 2019; Kroon et al., 2020; Leung et al., 2020). Recent estimates suggest that 60-80% of cannabis is consumed by 10-20% of individuals with high-frequency use, many of whom likely meet criteria for CUD (Callaghan et al., 2019; Caulkins et al., 2020; Chan & Hall, 2020). It is unrealistic to expect these user-individuals to be helped principally by information-based behavior change advice such as the LRCUG. Neither are the LRCUG intended as a diagnostic tool for CUD, but they may allow some PWUC to recognize the presence of problems related to their cannabis use. It is crucial for PWUC experiencing persistent severe problems associated with their use, including potential CUD symptoms to seek professional assessment and assistance, which may need to include treatment (Copeland & Pokorski, 2016; Gates, Sabioni, Copeland, Le Foll, & Gowing, 2016; Jutras-Aswad et al., 2019).

Fourth, the principal objective of the LRCUG is to reduce adverse effects on the health of users rather than the social or legal outcomes for users or their adverse effects on the health and welfare of others. Nonetheless, cannabis use is an activity common in 'social' contexts or interaction settings that, hence, may cause harm to others. The LRCUG recommendations as framed by public health principles, therefore, acknowledge in basic terms that individuals who choose to engage in cannabis use have a social responsibility to protect others from any adverse consequences of their use (Barry & Glantz, 2018; Hall et al., 2019; Karriker-Jaffe, Room, Giesbrecht, & Greenfield, 2018).

Use and dissemination of the LRCUG

There is limited and mixed evidence on the impact of educational/behavioral interventions like the LRCUG on population-level harms in other areas of health or substance use (Dunkley et al., 2014; Holmes et al., 2020; Jepson, Harris, Platt, & Tannahill, 2010). In recent assessments of population-level data in North America, sizable subgroups of PWUC did not adhere to key LRCUG recommendations, including the mode of cannabis use, use frequency, and driving under the influence (Goodman, Fischer, & Hammond, 2020; Lee, Lee, Goodman, Hammond, & Fischer, 2020). Recent data from jurisdictions where cannabis has been legalized suggest that selected higher-risk use behaviours persist or may even be increasing. The prevalence of these risk behaviors may be increasing in these contexts as a result of expanding availability and marketing of cannabis at the population level and the socio-cultural 'normalization' of use (Budney & Borodovsky, 2017; Hammond et al., 2020; Murray & Hall, 2020). Altogether, this suggests considerable room and potential for the LRCUG to provide and serve as an intervention tool that contributes to protecting and improving cannabis use-related public health especially in contexts of liberalized control.

The LRCUG may serve at least two didactic functions. One is to create general awareness among PWUC (and the population-at-large) that there are gradations of risk for adverse outcomes from cannabis use that are within the individual-user's control. They underscore the fact that PWUC can substantively reduce some of these risks by actively modifying use-related behaviors and choices, and adopting safer and responsible use practices. This may also help to shape emerging norms around cannabis use, especially in new contexts of legality (Blevins et al., 2018; Carliner et al., 2017; Roditis, Delucchi, Chang, & Halpern-Felsher, 2016). The second is to provide specific advice and guidance to PWUC on how to reduce cannabis-related risk of health problems. These efforts should ideally be linked with and reinforced by other targeted intervention efforts and programs, such as targeted prevention campaigns on specific risk factors of relevance.

Knowledge translation strategies are a key to the effective implementation, dissemination and uptake of the LRCUG. These may include endorsements by leading organizations and stakeholders and buy-in from science, health, and prevention experts that amplify their profile and credibility. The present LRCUG review and recommendations are principally science-based and geared towards related audiences. Differentiated and specifically tailored communication approaches will be required for different target audiences (Lustria et al., 2013; Noar, Benac, & Harris, 2007; Pope, Pelletier, & Guertin, 2018). These efforts may need to vary for different age, cultural or other specific groups and involve different communication styles and media formats. These 'knowledge translation' challenges are similar to those for other health interventions and need to be better understood and their effects evaluated (Krebs, Prochaska, & Rossi, 2010; Prochaska, Spring, & Nigg, 2008).

Conclusion

Overall, the present, evidence-based LRCUG offer a valuable - while naturally limited - education and guidance tool on cannabis use-related risk factors influencing adverse health outcomes, and ways to reduce these risks in the sizeable populations of PWUC. This is especially the case in, but not restricted to, settings where cannabis has been legalized and regulated, and where preventive information can be openly provided and disseminated to non-medical consumers open to reducing risks for related adverse health outcomes. The evidence base informing the recommendations at the LRCUG' core ought to be periodically updated as the scientific knowledge on cannabis-related health risks and harms continues to evolve. The LRCUG' impact on cannabis use-related knowledge, behaviors and health outcomes should also be assessed.

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Supplementary materials

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