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MINI REVIEW ARTICLE

Impact of Changing Cannabis Laws on Cannabis Use Disorders, Serious Mental Illness, and Mortality Outcomes in US Youth: A Narrative Review

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Abstract: Youth cannabis use is a major public health crisis. Cannabis laws carry significant health implications for American youth. Relaxing of these laws – through decriminalization, medical and recreational legalization – by a majority of states in the United States (US) over the past 25 years has dramatically shifted societal perceptions and adult use. How cannabis policy changes have affected the population-wide health of US youth and downstream public health implications of cannabis laws remain topics of significant debate. Cannabis is the most commonly used federally-illicit drug by US adolescents and the main drug for which US teens obtain substance use treatment. Adolescent cannabis use is associated with negative long-term consequences for mental health, risk-taking behaviors, and academic/job achievement. As of January 2023, 37 states and the District of Columbia (DC) have enacted medical cannabis laws; of these, 21 states and DC have recreational cannabis laws. Multiple studies have assessed the association between cannabis laws and youth cannabis use; results indicate mostly null effects for medical laws and mixed effects for recreational laws. Little is known about the effects of cannabis laws on mental health and mortality outcomes for American youth. Methodological limitations have made the interpretation of this literature difficult. This article presents a narrative review of current scientific literature investigating the impact of changing cannabis policies on cannabis and other drug use, mental health, and mortality outcomes in US youth. Implications are framed within a larger discussion on national trends in youth drug use, effects of adolescent cannabis exposure on health outcomes, and research-based policymaking.

Keywords: Cannabis laws. adolescent, young adult, serious mental illness, substance use, mortality.

1. INTRODUCTION

Over the past 25 years, the United States (US) has seen widespread changes in cannabis policies relating to the legal status of cannabis and other plant-based cannabinoid products for medical and recreational uses, resulting in shifting use patterns in Americans and a multi-billion-dollar US cannabis market (Hall, 2020). The downstream public health effects related to changing US cannabis laws are poorly understood and represent

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an area of intense investigation. These policy changes may positively impact health outcomes in some groups of Americans and negatively impact health outcomes in others. American youth represent a vulnerable group that may be at increased risk for experiencing net negative health outcomes related to shifting cannabis policies (Hammond, Chaney, Hendrickson, & Sharma, 2020). Concerns about youth as a vulnerable group in this era of cannabis legalization are based upon four lines of evidence showing that: (1) the brain undergoes significant developmental changes across adolescence and doesn't reach adult maturation until the mid-20s, (2) youth have high rates of cannabis use relative to other age groups, (3) there is developmental sensitivity to cannabis exposure (particularly to delta-9-tetrahydrocannabinol [delta-9-THC]) and (4) there is an increased risk for adverse health outcomes related to exposure during adolescence (Giedd, 2004; Gobbi *et al.*, 2019; Hammond, Mayes, & Potenza, 2014; K. Z. Peters, Zlebnik, & Cheer, 2021) Given this, if changing cannabis policies lead to population-level increases in use of cannabis or a shift to use of riskier cannabis products (*e.g.*, higher delta-9-THC potency products), then a greater proportion of American youth will experience adverse health outcomes related to cannabis exposure (Wilson, Freeman, & Mackie, 2019). In this regard, adolescents and young adults (AYA) with psychiatric conditions may be even more vulnerable to cannabis-related adverse health outcomes compared to their counterparts without psychiatric conditions (Hammond *et al.*, 2020). Changing cannabis policies may influence health outcomes for US youth indirectly, as well, by impacting healthcare utilization and treatment approaches for medical and psychiatric conditions. Healthcare practice in this era is changing as cannabinoid-based products, whose use requires limited physician monitoring, expand into the US healthcare domain (Sharma *et al.*, 2022). In this report, we present a narrative review of the current scientific literature investigating the impact of changing cannabis policies on cannabis and other drug use, addictive disorders, mental health, and mortality outcomes in US AYA. Methodologic strengths and limitations of the current literature are examined. Review results are framed within a larger discussion on national trends in youth drug use, effects of adolescent cannabis exposure on health outcomes, and research-based policymaking.

2. STATE AND FEDERAL CANNABIS POLICY LANDSCAPE IN THE UNITED STATES

State laws governing possession and sales of cannabis products have changed dramatically in the US over the last three decades, with minimal scientific evidence available to inform policymakers (Hall, 2020). Under the Controlled Substances Act (CSA), cannabis remains classified as a Schedule I drug, meaning that it is illegal under federal law, with highly limited exceptions for research. California became the first state to legalize cannabis for medical use in 1996. As of January 2023, 37 states and the District of Columbia (DC) have enacted medical cannabis laws (MCL) with varying degrees of restrictiveness (National Conference of State Legislatures, 2022). Colorado and Washington became the first two states to legalize cannabis for adult recreational use in 2012. As of January 2023, 21 states and DC have enacted recreational cannabis laws (RCL) (National Conference of State Legislatures, (National Conference of State Legislatures, 2022). The Marijuana Opportunity Reinvestment and Expungement Act (MORE Act) – which was passed by the US House of Representatives in April 2022 but is still awaiting a vote in the US Senate – would decriminalize cannabis. Individual US states have continued to pass laws loosening restrictions on cannabis access. In this era of rapidly changing cannabis policy, the health impacts of cannabis as a medical treatment and as a more accessible, quasi-legal recreational drug remain unclear.

3. CANNABIDIOL PRODUCTS

There has also been policy experimentation in the legal allowance of cannabidiol (CBD) and other related cannabis products. Federal

deregulation of hemp-derived cannabinoid products in the past five years has expanded the already growing US cannabinoid market and user base (Mead, 2019). Hemp is a cannabis sativa plant cultivar containing less than 0.3% delta-9-THC. With its passage in 2018, the Agriculture Improvement Act (US Farm Bill) legalized the production and sale of hemp-derived cannabinoid products throughout the US. It removed hemp-derived products from the US Drug Enforcement Administration's schedule of Controlled Substances. Some states – including Wisconsin and Texas – have also experimented with amending their analogous state law to allow cannabis products with high levels of CBD and low levels of THC (Texas State Legislature, 2019; Wisconsin State Legislature, 2017). As a result, hemp-derived cannabinoid products are now widely sold in the US as dietary/health supplements and cannabinoid infused food and cosmetic products, making up a billion-dollar market in its own right (Vandolah, Bauer, & Mauck, 2019). Most of these products are supplements containing cannabidiol (CBD), a non-psychoactive cannabinoid that has potential medicinal properties, but there is a growing market of hemp-derived delta-9-THC analogues, including delta-8 and delta-10, that are sold as "legal highs" and alternatives to dispensary sold cannabis. (U.S. Food & Drug Administration, 2022) While more research is needed, preliminary studies point to overlapping pharmacologic effects of delta-9-THC, delta-8-THC, and delta-10-THC, suggesting that use of hemp-derived delta-9-THC analogues may carry similar risk for adverse health outcomes to use of high delta-9-THC potency cannabis in youth (Livingston, Walker, Cannell, & Rossheim, 2022).

In terms of policy research, the impact of federal hemp deregulation is less well understood than that of state cannabis laws, with relatively few studies investigating downstream outcomes despite the dramatic expansion of the use of hemp-derived CBD products by Americans. A recent national survey found that over a quarter of US adults have tried hemp-derived CBD supplements in the past two years, with young adults representing the highest using age-group (20% past year CBD users) (Brenan, 2019; Gill, 2013). While a comprehensive review of CBD policy is beyond the scope of this review, it is essential to be aware that there is a parallel set of issues to be addressed in regard to CBD products and their regulation.

4. EPIDEMIOLOGY OF CANNABIS USE AMONG US ADOLESCENTS AND YOUNG ADULTS

Cannabis is the most commonly used psychoactive drug among US AYA and the most common drug problem reported by teens admitted for substance use disorder (SUD) treatment in the US. (Substance Abuse and Mental Health Services, 2022). According to the 2021 National Survey of Drug Use and Health (NSDUH), 10.5% of all US adolescents (2.7 million individuals aged 12 to 17) and 35.4% of US young adults (11.8 million individuals aged 18 to 25) reported using cannabis in the past year (Substance Abuse and Mental Health Services Administration, 2022). In 2020, among US high school students, 6.5% of 8^{th}, 16.6% of 10^{th}, and 21.1% of 12^{th} graders reported past month cannabis use; 11.4%, 28.0%, and 35.2%, respectively, reported past year use (Johnston *et al.*, 2021). Daily use of cannabis was reported by 1.1%, 4.4%, and 6.9% of US 8^{th}, 10^{th}, and 12^{th} graders respectively. Rates of past-year cannabis use by 19-22-year-old 'college-aged' young adults residing in the US have gradually increased over the past two decades, with 13.2% of non-college enrolled US young adults reporting daily use, representing the highest levels in the past three decades (Schulenberg *et al.*, 2018). These results indicate that cannabis use among AYA is prevalent in the US.

With the expansion in the number and types of novel cannabis products available for consumption (*e.g.*, vapes, concentrates, edibles), patterns of cannabis use among US adolescents have changed (Hammond, Chaney, Hendrickson, & Sharma, 2020). In this new era, most AYA cannabis users are poly-cannabis product users using multiple administration methods for consumption (Knapp *et al.*, 2019; Peters, Bae,

Barrington-Trimis, Jarvis, & Leventhal, 2018). In particular, vaping as a method of cannabis administration has increased among American youth. Current prevalence data from 2021 show that approximately 2.9% of 8th-grade students, 8.4% of 10th-grade students, and 12.4% of 12th-grade students reported past-month cannabis vaping (Johnston *et al.*, 2022). A recent meta-analysis of studies examining adolescent cannabis vaping prevalence rates in the US found that lifetime, past 12-month, and past 30-day cannabis vaping showed a two-to-seven-fold increase from 2013 to 2020 (Lim *et al.*, 2022). Additionally, use rates of cannabis concentrates (*e.g.*, dabs, wax, budder) that contain high levels of delta-9-THC are also increasing among US youth (Zhang, Zheng, Zeng, & Leischow, 2016).

5. EARLY-ONSET CANNABIS USE AND RISK OF DEVELOPING A CANNABIS USE DISORDER

Rates of current cannabis use among 12-17-year-olds increased from 2016 to 2019 by 21.7% and by 10.6% for 18-25-year-olds. In the same time period, rates of past year cannabis use disorder (CUD) diagnoses increased by 21.7% for 12-17-year-olds, and by 17.6% for 18 to 25-year-olds (Substance Abuse and Mental Health Administration, 2019). In 2021, 4.8% of all US adolescents (*N*=1.3 million) and 14.4% of US young adults (*N*=4.8 million) met DSM-5 criteria for the past year CUD (Substance Abuse and Mental Health Services Administration, 2022).

6. EARLY-ONSET CANNABIS USE AND RISK OF DEVELOPING A SERIOUS MENTAL ILLNESS (SMI) OR NON-CANNABIS SUBSTANCE USE DISORDER

Below, we review the literature examining associations between early-onset cannabis use during adolescence and risk for psychiatric disorders and non-cannabis substance use disorder (SUD) from longitudinal cohort studies, focusing on four diagnostic categories: psychotic, mood, anxiety, and non-cannabis SUD.

6.1. Psychotic Disorders

There is substantial and strong evidence of an association between cannabis use and the risk of developing psychosis and schizophrenia. Cannabis use during adolescence increases the risk of developing schizophrenia in young adulthood (Fridberg, Vollmer, O'Donnell, & Skosnik, 2011; Hall & Degenhardt, 2009; Moore *et al.*, 2007). In a 15-year follow-up study of 45,750 Swedish male conscripts, those who had tried cannabis at least once by age 18 were 2.4 times (95% CI 1.8-3.3) more likely to be diagnosed with schizophrenia than those who never used it (Andréasson, Allebeck, Engström, & Rydberg, 1987). Among adults diagnosed with psychotic disorders, early adolescent cannabis use is associated with poorer prognosis, including greater risk for and more frequent relapses, poorer treatment adherence, and increased hospitalizations (Levine, Clemenza, Rynn, & Lieberman, 2017). There is consistent evidence of a dose-response relationship between frequency, amount, duration, and potency of cannabis consumption and risk of developing psychosis (Di Forti *et al.*, 2014; Hall & Degenhardt, 2009). The first meta-analysis of six studies (Moore *et al.*, 2007) estimated that risk more than doubled among those with the most frequent cannabis use. A subsequent meta-analysis (Marconi, Di Forti, Lewis, Murray, & Vassos, 2016) found that in 10 studies, the odds ratio was 3.9 (95% CI 2.84-5.34) for risk of psychosis-related outcomes among the heaviest cannabis users compared to non-users. Higher potency types of cannabis, defined in these studies as cannabis products containing >10% delta-9-THC, also carry more risk than traditional lower potency products. Daily use of high-potency cannabis starting before age 15 poses a 5-to-6-fold greater risk of developing a psychotic disorder compared to non-use (Marconi, Di Forti, Lewis, Murray, & Vassos, 2016). While some variance in cannabis-psychosis relationships can be accounted for by genetics, shared latent vulnerability, and common risk factors, a significant portion cannot be attributed to these factors, and may be explained by cannabis

exposure (D'Souza, 2007). Given complex multifactorial pathways linking youth cannabis use and psychosis and difficulty disentangling these effects, an investigation into CL effects on psychotic outcomes is warranted. As CL is associated with increased availability of high-potency cannabis and more frequent cannabis use, these individual person-level factors additively increase the risk of psychosis (Quattrone *et al.*, 2021).

6.2. Mood Disorders

The majority of epidemiological studies have found that adolescent-onset cannabis use is associated with an increased risk of developing depressive disorders or symptoms in adulthood; earlier age of cannabis initiation during adolescence and more frequent use confer higher risk (Gobbi *et al.*, 2019; Lev-Ran *et al.*, 2014; Moore *et al.*, 2007; Silins *et al.*, 2014) However, some studies have not found an association between adolescent cannabis use and later depression diagnosis or symptom severity after controlling for multiple confounding factors (Scholes-Balog, Hemphill, Evans-Whipp, Toumbourou, & Patton, 2016). Bipolar disorder is less well studied. Of the few studies conducted to date, limited evidence suggests that cannabis use increases the likelihood of developing bipolar disorder (Di Forti *et al.*, 2014). Two systematic reviews (Gibbs *et al.*, 2015; Mammen *et al.*, 2018) found that continued cannabis use moderates the course of bipolar disorder by increasing the length of time to recovery, risk for relapse, and recurrence of manic episodes. Additionally, patients with comorbid CUD were more likely to have a rapid cycling course than non-users and cannabis users reported greater severity of manic/psychotic symptoms (Sideli, Quigley, La Cascia, & Murray, 2020).

6.3. Anxiety Disorders

Few studies have examined the association between cannabis use and anxiety disorders. Findings are mixed, depending upon whether anxiety symptoms or disorders were assessed, whether cannabis use or CUD was the key exposure or dependent variable and whether adjustments were made for demographic factors and psychiatric comorbidity. One systematic review and meta-analysis (Kedzior & Laeber, 2014) (articles published 1996-2013) identified five longitudinal studies, 4 of which used adolescent samples and examined prospective associations between cannabis use and the development of anxiety at follow-up. Results from this meta-analysis showed that cannabis use at baseline was prospectively associated with the development of anxiety at follow-up, even after adjusting for confounders (OR = 1.28, 95% CI = 1.06-1.54). In contrast, a more recent 2019 meta-analysis failed to find an association between adolescent cannabis use and later anxiety disorders (OR = 1.18, 95% CI 0.84-1.67) (Gobbi *et al.*, 2019). Further research is needed to examine the relationship between cannabis use and CUD and the development of anxiety symptoms and anxiety disorders in AYA.

6.4. Non-Cannabis Substance Use Disorders

Both cross-sectional and longitudinal studies have consistently found that early-onset cannabis use is associated with increased likelihood of developing non-cannabis SUDs (Coffey & Patton, 2016; Fergusson, Boden, & Horwood, 2015; Nocon, Wittchen, Pfister, Zimmermann, & Lieb, 2006; Silins *et al.*, 2017; Swift, Coffey, Carlin, Degenhardt, & Patton, 2008; Swift *et al.*, 2012). These studies support a gateway hypothesis that cannabis use often precedes the use of illicit drugs, including cocaine, opioids and stimulants (Hammond, Chaney, Hendrickson, & Sharma, 2020; Scholes-Balog, Hemphill, Evans-Whipp, Toumbourou, & Patton, 2016). Using a nationally representative sample of US adults 18 years or older, Blanco *et al.* found that earlier-onset adolescent cannabis use was associated with increased risk for SUD (OR= 6.2, 95% CI 4.1-9.4), alcohol use disorder (OR= 2.7, 95% CI 1.9-3.8), CUD (OR =9.5, 95% CI 6.4-14.1), and any other drug disorder (OR=2.6, 95% CI 1.6-4.4); with higher cannabis use frequency associated with greater risk.

6.5. Summary of SMI and Non-Cannabis SUD Associations

In summary, current evidence suggests that early-onset cannabis use during adolescence is associated with modest increases in the prevalence of psychotic, mood, and non-cannabis SUDs and poorer courses of psychosis and mood disorders in young people who have these disorders and continue to use cannabis. Some associations, particularly for psychosis and mood disorders, show dose-response relationships related to frequency, quantity, duration, age-of-onset, and delta-8-THC potency of cannabis use on outcomes. Associations for early-onset cannabis use as a risk factor for developing non-cannabis SUD are well supported, although the impact of premorbid factors in this relationship and continued cannabis use on non-cannabis SUD outcomes is under investigation. Associations between early-onset cannabis use and anxiety disorders are less consistent, especially when controlling for premorbid anxiety symptoms, suggesting more complicated bidirectional effects. The scientific evidence for these conclusions comes from > 10 longitudinal studies that have been conducted to examine associations between adolescent cannabis use and mental health outcomes. Most studies reported risk ratios or odds ratios, adjusting for sociodemographics and premorbid confounding variables, including severity of psychiatric symptoms (for the outcome of interest) prior to the onset of cannabis. The breadth of studies and consistency of findings for psychosis and, to a lesser extent, for depression and non-cannabis SUD outcomes is noteworthy, even when using different definitions, measurement tools, and samples. Still, there are some limitations of these studies related to cannabis use definitions, over reliance on self-report measures, generalizability of population source (*i.e.*, most samples are predominantly white and from Australian/New Zealand), and small sample sizes for some outcomes (*e.g.*, bipolar disorder). One notable limitation is that most of the studies included in this review captured adolescent cannabis use as an exposure 10-20 years ago. Cannabis has changed considerably since these studies were conducted. The average delta-9-THC potency of cannabis plant products has more than tripled in the past twenty years (Elsohly *et al.*, 2016). Additionally, recent technological advances in the cannabis market have led to novel product types (*e.g.*, concentrates and edibles) and more efficient delta-9-THC delivery methods (*e.g.*, vaping and dabbing) that are increasingly used by American youth, the majority of whom now identify as poly-cannabis product users (Hopfer, 2014; Peters *et al.*, 2018). Thus, current cannabis products may carry different risk for adverse outcomes to youth compared to cannabis from the past. Given the above limitations, there is a critical need for rigorous, population-based research into contemporary cannabis use associations in different youth populations, as is being done in the US with the Adolescent Brain Cognitive Development (ABCD) study, a longitudinal study that is following a nationally-representative sample of 10,000 US preadolescents over a 10-year period (Jernigan, Brown, & Coordinators, 2018).

7. ASSOCIATION BETWEEN CANNABIS USE, SUICIDE-RELATED OUTCOMES, AND ALL-CAUSE MORTALITY

7.1. Suicide-Related Outcomes (SRO)

Multiple longitudinal studies (described above) have also shown evidence for an association between early-onset cannabis use and SRO. Aggregating these data - three systematic reviews have examined the association between cannabis use and SROs (suicidal ideation, attempts, completed suicide) in youth and adults (Borges, Bagge, & Orozco, 2016; Gobbi *et al.*, 2019; Moore *et al.*, 2007). Results suggest that cannabis use is significantly associated with increased SROs and there is a dose-response effect, with heavy cannabis use being associated with a higher risk of suicidal ideation and attempts. In the most recent meta-analysis of 11 studies examining over 23,000 adolescents, those who used cannabis were at significantly increased risk for suicidal ideation (OR=1.50, 95% CI, 1.11-2.03) and suicide attempt (OR=3.46, 95% CI, 1.53-7.84) in young adulthood (Gobbi *et al.*, 2019).

7.2. All-Cause Mortality (ACM)

Very few cohort studies have examined the association between cannabis use and ACM (*i.e*., fatal motor vehicle crashes [MVC], cancers and other medical conditions, suicide, and homicide) in the general population (Calabria, Degenhardt, Hall, & Lynskey, 2010; National Academies of Sciences, Health and Medicine, 2017). Studies are difficult to compare due to differences in exposure and outcome measures and problems adjusting for other risk behaviors that track with cannabis use and are linked to higher mortality outcomes (*e.g*., tobacco smoking and alcohol consumption). Some studies examine low cannabis use frequency whereas others examine high-frequency cannabis use and CUD diagnostic status as exposure variables. Existing evidence suggests that cannabis use may be associated with an increased risk of ACM, particularly for individuals with CUD. Of six studies that examined the association between cannabis use and ACM, four found that cannabis use was associated with increased ACM risk (Andréasson & Allebeck, 1990; Arendt, Munk-Jørgensen, Sher, & Jensen, 2013; Fontanella *et al.*, 2021; Manrique-Garcia, Ponce De Leon, Dalman, Andréasson, & Allebeck, 2016; Muhuri & Gfroerer, 2011; Sidney, Beck, Tekawa, Quesenberry, & Friedman, 1997) Given the paucity and limitations of existing studies, there is clearly a need for more well-designed cohort studies that determine the relationship between cannabis use and ACM among large, representative populations. In addition to ACM, several studies have examined specific causes of death among cannabis users. Cannabis has been linked with increased risk of MVCs and overdose deaths (Calabria *et al.*, 2010; Darke & Duflou, 2008; Eksborg & Rajs, 2008; Gerberich *et al.*, 2003; Laumon, Gadegbeku, Martin, Biecheler, & SAM Group, 2005; Macdonald *et al.*, 2003) and is detected in the toxicology reports of homicide victims (or victims of violence-related deaths) at rates higher than what would be explainable by chance alone (Darke & Duflou, 2008; Macdonald *et al.*, 2003). In a meta-analysis of 21 case-control studies in 13 countries with a combined sample of 239,739 participants, driving under the influence of cannabis was associated with 20-30% higher odds of MVCs (Calabria *et al.*, 2010; Darke & Duflou, 2008; Eksborg & Rajs, 2008; Gerberich *et al.*, 2003; Laumon, Gadegbeku, Martin, Biecheler, & SAM Group, 2005). Cannabis use is also associated with an increased risk of overdose injuries or death among pediatric populations in US states where cannabis is legal (National Academies of Sciences, Health and Medicine, 2017).

7.3. Summary of SRO and ACM Associations

In summary, current evidence suggests that adolescent-onset cannabis use is associated with an increased risk for SRO and cannabis use is associated with increased ACM, particularly in individuals with a CUD. The scientific evidence for associations between adolescent cannabis use and SRO is stronger for suicidal ideation and attempts compared to suicide-related deaths, with data on the former outcomes coming from the same longitudinal cohort studies described in the mental health section (Gobbi *et al.*, 2019; Lev-Ran, *et al.*, 2014; Moore *et al.*, 2007; Sillins *et al.*, 2014). While there is a signal for a positive association between cannabis use and ACM and some evidence for associations between cannabis use and higher mortality related to MVC or violence victimization, these findings come from a small literature with methodologic limitations and should be interpreted cautiously. More research is needed to characterize the relationships between cannabis use and mortality risk in both adults and adolescents.

8. IMPACT OF CANNABIS LAWS ON CANNABIS USE AND CANNABIS-RELATED HEALTH OUTCOMES IN US YOUTH

Given evidence for developmental sensitivity related to cannabis exposure and that adolescent cannabis use increases the risk for adverse health outcomes, laws that influence youth cannabis use behaviors are important. State and federal policies that have the effect of increasing the prevalence of cannabis use and CUD during adolescence or

young adulthood may subsequently result in downstream negative health outcomes. In the sections that follow, we review studies examining the effects of MCL and RCL enactment on cannabis use and CUD; mental health, non-cannabis SUD, SRO, ACM, and healthcare utilization in US youth.

9. EFFECTS OF CANNABIS LAWS ON CANNABIS USE AND CANNABIS USE DISORDER

9.1. Medical Cannabis Laws

Given the rapid passage of MCL in the past 30 years, a number of studies have sought to examine the effects of MCL on cannabis use and, to a lesser extent, on CUD prevalence. Enactment of MCL is associated with increased prevalence of cannabis use, daily cannabis use, and CUDs in the US adult population and is particularly notable in adults ages 26 and older (Smart & Pacula, 2019). Results in AYA samples have been less consistent.

9.2. Focusing on Young Adults

Age-stratified subgroup analyses from adult MCL studies consistently show that 18-25-year-olds have the highest rates of past-month cannabis use, daily cannabis use, and CUD of any age-group (Harper, Strumpf, & Kaufman, 2012; Martins *et al.*, 2016; Williams, Santaella-Tenorio, Mauro, Levin, & Martins, 2017). In examining the effects of MCL in this population: Across studies, results show that 18-25-year-olds living in states that have ever enacted MCL have higher rates of past-month cannabis use and CUD. However, this is not the full story. Results from well-controlled studies using difference-in-difference analyses that are adjusted for state-level confounding variables have largely shown minimal effects of MCL enactment on past-month and past-year prevalence rates of cannabis use (Harper, Strumpf & Kaufman, 2012; Martins *et al.*, 2016; Williams, Santaella-Tenorio, Mauro, Levin, & Martins, 2017). One notable exception is a recent study by Mauro and colleagues that conducted age-by-sex subgroup MCL analyses focused on multiple cannabis-related outcomes and found that enactment of MCL was associated with increased rates of daily cannabis use among US males aged 18-25-years (Mauro *et al.*, 2019).

9.3. Focusing on Adolescents

More than ten studies have been published in the past 10 years examining the effects of MCL on cannabis use /CUD in adolescent samples. Similar to MCL studies in young adults, the majority of MCL studies in adolescent samples have shown null effects of MCL enactment on the prevalence of cannabis use in adolescents, although there are some notable exceptions, particularly in studies that have focused on non-prevalence-based cannabis-related outcomes. For example, Pacula *et al.,* 2015 used National Longitudinal Survey of Youth (NLYS) data from 1997-2005 to examine MCL effects on different cannabis-related outcomes and found that MCL enactment was associated with increased days of cannabis use in 12-20-year-old youth who had used cannabis in the past-year, but did not find evidence for an increase in past-month cannabis use following MCL enactment in 12-20-year-olds in general (Pacula, Powell, Heaton, & Sevigny, 2015). Another study by Wen and colleagues used 2004-2012 data and found that enactment of MCL was associated with an increase in the prevalence of 12-20-year-olds who initiated cannabis in the past-year (Wen, Hockenberry, & Cummings, 2015).

Aggregating results across studies through systematic review and meta-analysis can provide a good index of the strength of the science in this space, as long as there is sufficient number of non-overlapping studies for comparison. A 2014 meta-analysis aggregated results from AYA MCL studies and included data through 2014, at which time only 21 states had passed MCL (Sarvet *et al.*, 2018). That number has nearly doubled by 2023. An updated meta-analysis examining the effects of MCL on past-month cannabis use in AYA was recently conducted, identifying 19 published studies with 33 comparisons between states that passed and did not pass MCL (Pawar, Firmin, Wilens, & Hammond, 2022). The results from this updated 2023 meta-

analysis were consistent with the prior one, showing no significant association between MCL passage and change in past-month adolescent cannabis use (standardized mean difference, pooled estimate (95%CI)=-0.003(-0.009, 0.003)). Collectively, results from these overlapping sources indicate that, in contrast with adults, AYA living in states that passed MCL had higher rates of cannabis use prior to the passage of MCL, and passage of MCL has had minimal impact on past-month and past-year cannabis use rates, which have largely remained stable in the general population of US adolescents but has increased for US young adults and certain subgroups of US adolescents over the past decade. Of note, the stable rates of past-month and past-year cannabis use in the US adolescent population over the past decade represents an outlier when compared to alcohol, tobacco smoking, and other drug use rates, all of which have decreased significantly over the same time period (Hammond, Chaney, Hendrickson, & Sharma, 2020). This has led some researchers to posit that other societal factors including prevention and public health programming have led to a reduction in adolescent drug use across categories, and the absence of a decline in cannabis use in this population may reflect the effects of CL exerting opposite pressure on cannabis use behaviors resulting in them being unchanged (Hammond, Chaney, Hendrickson, & Sharma, 2020). Also, the number of states that have passed MCL from the time of the meta-analysis and 2023 has nearly doubled, indicating that the relationship between MCL and cannabis use /CUD warrants reexamination.

The inconsistency of results in the literature on MCL effects in AYA populations could be related to the methodological limitations of youth-focused studies. Most AYA MCL studies have focused on prevalence rates of cannabis use (past-month and past-year) as their primary outcomes of interest, with few examining other cannabis-related behaviors (Sarvet *et al.*, 2018). AYA MCL studies are also limited by the data sources from which they are collected and the years for which data are available. It is important to note that >95% of adolescent MCL studies have obtained their data from the same four datasets - two school-based surveys (Monitoring the Future and Youth Risk Behavior Survey [YRBS]) and two household surveys (NLSY and NSDUH). These surveys collect self-report data on substance use behaviors and perceptions in nationally-representative samples of adolescents largely over the same time periods (Smart & Pacula, 2019). Similar limitations are also present in the AYA RCL literature.

As noted above, most AYA studies investigating MCL effects have focused on past-year or past- month cannabis use outcomes. Consequently, little is known about the effects of MCL on CUD prevalence. Findings on the effects of MCL passed prior to 2010 (when 12 states had MCL) and treatment admissions for CUD are mixed. Some studies report a positive effect, while others find negative or no effects.(Chu, 2014; Anderson, Hansen, & Rees, 2015) Other studies have examined the effects of MCL using self-reported measures of CUD over a longer time period. They report MCLs are associated with an increased prevalence of CUD among adults, with some evidence of a lagged effect, as well as more pronounced effects in states that allowed dispensaries or collective cultivation.(Hasin *et al.*, 2017; Wen *et al.*, 2015) Given the dearth of studies on the effect of MCL on CUD in AYA, further study is warranted, particularly because more states have passed these laws, and attitudes towards cannabis have become more permissive and perception of risks related to the regular use of cannabis have decreased in adults and adolescents nationwide (Azofeifa *et al.*, 2016; Johnston *et al.*, 2021). Continued monitoring of adolescent cannabis use in MCL states is also critical due to the differential development of commercialized markets.

9.4. Recreational Cannabis Laws

Less is known about the association between RCL and cannabis use, and whether the impact of RCL differs from that of MCL with regard to cannabis use and CUD in AYA. There are fewer RCL studies and these studies have generally been less well-controlled, focusing on small clusters of states or lacking comparators. We identified 11 studies in the literature examining the effects of

RCL passage on CU/CUD outcomes in AYA samples. Results are mixed; studies show increased prevalence rates of past-month and past-year cannabis use in some states following RCL enactment (*e.g*., Washington and Oregon) but not in other states (*e.g*., Colorado) (Anderson, Hansen, Rees, & Sabia, 2019; Cerdá *et al.*, 2017; Kerr, Bae, & Koval, 2018; Kerr, Bae, Phibbs, & Kern, 2017; Miller, Rosenman, & Cowan, 2017) (Cerdá *et al.*, 2020) utilized the NSDUH dataset to examine the association between RCL passage and changes in self-reported cannabis use, frequent cannabis use, and CUD from 2010-to-2015. Respondents aged 12-17 years reported a 25% increase in CUD from 2.18% to 2.72%. Those aged 26 years or older reported a 23% increase in frequent cannabis use, from 2.13% to 2.62% and a 37% increase in CUD, from 0.90% to 1.23%. No associations were found among respondents 18-25 years of age. Another study found evidence for increased use of high potency cannabis products in RCL states compared to MCL states and states without CL (termed 'no-CL' states), and in MCL states compared to no-CL states (*i.e*., RCL>MCL>no-CL states) (Hasin *et al.*, 2021). An updated meta-analysis examining effects of RCL on past-month cannabis use in AYA was recently conducted identifying 11 published studies with 20 RCL *versus* no-CL comparisons (Pawar *et al.*, 2022). Results from this 2023 meta-analysis showed a modest positive association between RCL passage and change in past-month adolescent cannabis use (standardized mean difference, pooled estimate [95%CI]= 0.061[0.035, 0.088]).

While studies in the current literature have added to the knowledge base, they have tended to rely on data that cover a relatively short period of time following RCL enactment and have focused primarily on three RCL states (Washington, Colorado, and Oregon). As more states legalize cannabis for adult recreational use (currently, 21 states plus DC), further research is warranted to examine the long-terms effects of RCL on different cannabis-related outcomes across differing age groups.

10. THE ROLE OF SPECIFIC PROVISIONS IN THE LAW

Specific *MCL provisions* (*i.e*., specific regulations related to *barriers* to obtaining medical cannabis-such as diagnoses covered in the law, the *quantity* that can be purchased, and how *distribution* is managed *via* dispensaries or private cultivation) vary considerably in their *restrictiveness* from state to state (Chapman, Spetz, Lin, Chan, & Schmidt, 2016). Few studies examine the effects of specific MCL provisions or their degree of restrictiveness within states (Freisthler, Kepple, Sims, & Martin, 2013;Pacula *et al.*, 2000). This is problematic, as more loosely regulated MCLs with few restrictions and certain provisions (*e.g*., the greater number of MCL health indications, higher possession limits, ability to privately cultivate) may differentially impact down-stream health outcomes. Few studies have been conducted in this space and results to date have been mixed. For example, a recent study by Williams *et al.*, 2017 using NSDUH data from 2004-2013 to examine the impact of loosely regulated *versus* restrictive MCL on different cannabis-related outcomes across age-groups found that enactment of restrictive but not loosely-regulated MCL was associated with a decrease in heavy cannabis use in 12-17-year-old users (Williams, Santaella-Tenorio, Mauro, Levin & Martins, 2017). Another recent study using YRBS data showed that states that enacted MCL with higher possession limits (≥ 2.5 ounces) had higher rates of past-month cannabis use in adolescents (Johnson, Hodgkin, & Harris, 2017). Furthermore, while MCLs vary substantially across states and over time, most studies that examined the association between MCL and cannabis use relied on binary coding (MCL *vs*. no-CL), which does not permit examination of the laws' restrictiveness or permissiveness (Johnson *et al.*, 2018; Pacula *et al.*, 2015).

11. EFFECTS OF CANNABIS LAWS ON PREVALENCE OF SMI, NON-CANNABIS SUD, SRO, AND ACM

11.1. Effects of CL on SMI

Only one study has examined the association between cannabis laws (CL) and SMI prevalence,

focusing on specific CL provisions in an adult sample (Dutra, Parish, Gourdet, Wylie, & Wiley, 2018). Two specific CL provisions were examined: 1) "restrictive" (*i.e*., covering a narrow set of medical conditions) *versus* "liberal" (*i.e*., covering a broad set of medical conditions) CL; and 2) whether CL permits patients to petition their physician to approve medical cannabis use for specific medical conditions. Utilizing the 2008-2015 NSDUH dataset, results indicated that liberal CL is associated with a higher prevalence of SMI, with cannabis use partially accounting for this association.

11.2. Effects of CL on SRO

Two studies have sought to characterize the effects of CL on SRO, one focusing on MCL effects on SRO in adults and the other on MCL and RCL effects on SRO in AYA. These studies show divergent findings. For adults: Using data from the 1990-2007 National Vital Statistics System, Anderson *et al.* (Anderson, Rees, & Sabia, 2014) reported there was no significant association between MCL passage and suicide deaths in US adults; however, in analyses stratified by age and sex, legalization was associated with a 10.8% reduction in suicide for males aged 20-39 years (Dutra *et al.*, 2018). The authors hypothesized that this reduction in SRO in males 20-39 years might be on account of cannabis helping this subgroup of individuals cope with stressful life events. As mortality was only through 2007 and only in 12 states with MCL, these findings reflect early adoption of MCL and effects of RCL on suicide were not considered. For AYA: Hammond and colleagues recently completed a study examining associations between MCL, RCL, and SRO in AYA (aged 12-25 years) from 2000-2019, also using mortality data from the National Vital Statistics System (Hammond *et al.*, 2019). Results from this study showed that, after controlling for individual- and state-level covariates, MCL and RCL passage were both associated with increased SRO in female youth; and that youth aged 14-16 years in RCL states had increased SRO compared to those residing in MCL and no-CL states. The CL-by-sex result was restricted to female youth, and was seen across the age spectrum for both MCL and RCL passage, with each policy shift resulting in an approximately 10-15% increase in suicide deaths for impacted females between 2000 and 2019. Summarized findings are based upon two studies and should be interpreted cautiously. Additional research is needed to replicate findings and clarify potential mechanisms that might explain CL-SRO associations. Still, combined results from the adult and AYA studies suggest that there are complex relationships between CL and SRO that vary by age and sex, and indicate that AYA, in particular female youth, may represent vulnerable subgroups at increased risk for suicide related to MCL and RCL passage in the US.

11.3. Effects of CL on ACM

No studies have examined the effects of CL provisions on ACM. Focusing on specific causes of death, several studies have examined the impact of CL enactment on traffic fatalities (Anderson, Hansen, & Rees, 2013; Fink *et al.*, 2020; Santaella-Tenorio *et al.*, 2017). While MCLs are associated with increased driving under the influence of cannabis, MCLs are associated with reduced traffic fatalities (Anderson, Hansen, & Rees, 2013; Fink *et al.*, 2020; Santaella-Tenorio *et al.*, 2017). Study authors hypothesize that MCLs may reduce alcohol-impaired drivers by substituting cannabis for alcohol, resulting in reduced traffic accidents. In contrast, findings on the effects of RCLs and traffic fatalities are mixed; some studies find no association while others find increased fatalities (Aydelotte *et al.*, 2017; Hansen, Miller, & Webber, 2018; Lane & Hall, 2019; Santaella-Tenorio *et al.*, 2020). Given these mixed findings, further research is needed to clarify the influence of CL enactment on population-wide MVCs and traffic fatalities and to determine if variations in findings are the result of specific law types or provisions or reflect increased or decreased MVCs and fatalities in specific subgroups of the population.

12. DECREASING CUD TREATMENT UTILIZATION DURING THE ERA OF CL AND THE ROLE OF CANNABIS POLICY

Most AYA who experience drug-related problems or who meet criteria for CUD or non-cannabis SUD never receive treatment. In 2017,

while 1.1 million US adolescents met the criteria for a SUD, fewer than 1 in 10 received SUD treatment. This treatment gap appears to be widening for CUD specifically. National data on SUD treatment episodes from the Treatment Episode Dataset (TEDS) indicates that fewer adults and adolescents are seeking treatment for cannabis-related problems/CUD in the past decade compared to prior decades (Hammond, Chaney, Hendrickson, & Sharma, 2020; Sahlem, Tomko, Sherman, Gray, & McRae-Clark, 2018). For example, there was a 48% decrease in total number of cannabis-related SUD treatment admissions for 12-17-year-olds between 2005 and 2015 (Substance Abuse and Mental Health Services Administration, 2019). Researchers have hypothesized this reduction may result from reduced perceived risk or increased social acceptability of cannabis, both of which may be a byproduct of changing CL (Sahlem, Tomko, Sherman, Gray, & McRae-Clark, 2018). If the expansion of CL results in increased cannabis engagement and decreased CUD treatment utilization in US youth, this widening treatment gap could portend a future public health crisis.

12.1. Summary of CL Effects on Youth Cannabis Use and Cannabis-Related Health Outcomes

In summary, current evidence suggests that cannabis policies have complex and heterogenous effects on youth cannabis use that may differ across medical and recreational laws, with the effects of these policy changes on downstream health indices such as SMI, non-cannabis SUD, SRO, and ACM being unknown. Effects from MCL and, to a lesser extent, from RCL on cannabis use outcomes are the best studied. In aggregate, the CL literature shows that MCL passage has had limited impact on cannabis use but that RCL passage may result in increased cannabis use among US youth, although this requires further study, given fewer RCL studies to date. There is also early evidence that certain access-related provisions and implementation approaches (*e.g.*, lack of possession and purchase limits, higher density of dispensaries) are associated with increased cannabis use in youth populations. Data for RCL and MCL effects on downstream outcomes such as SMI, non-cannabis SUD, SRO, and mortality are sparse, difficult to interpret, and require further study. When a sufficient number of studies have been conducted, systematic review, quantitative summarization, and meta-analytic reporting will be needed to properly demonstrate the strength of the science related to these specific questions.

These summative results should be interpreted cautiously, given limitations in the current literature. Cannabis policy has varied substantially both across and within states, and there is not a well-established way of measuring either CL or their implementation. In recent years, some policy scientists have sought to develop taxonomies and standardized composite measures of variability/ heterogeneity in CL (Chapman, Spetz, Lin, Chan, & Schmidt, 2016)) (*e.g.*, the Chapman restrictiveness index). While these composite measures have shown promise, they require additional validation. Of note, these measures may not be developmentally sensitive, as they were not designed with the goal of detecting the effects of policy variability on downstream health outcomes in youth, and they exclude many youth-relevant provisions (*e.g.*, specific laws/provisions relating to how cannabis businesses can advertise their products) in their formulas. Given this, developmentally-informed variance measures are needed that take into consideration population and outcome characteristics, and incorporate provisions and policies that are most likely to impact youth health outcomes. In addition to measurement issues, there is simultaneously a lack of individual-level data that also contributes to the difficulty in evaluating the effects of policy changes. To date, many studies have investigated the effects of CL by assessing differences in states with legalized cannabis to those without *via* binary CL status categorization (*e.g.*, MCL=1 and no-CL=0) without taking into consideration the heterogeneity of specific provisions (conversely, see Johnson and Johnson, 2018) (Johnson, *et al.* 2018). Moreover, much of our knowledge of the impact of CL is derived from either MCL or the early days of RCL, making it difficult to account for ways in which the recreational cannabis

market has changed over time. Consequently, there is much we still do not know about long-term health outcomes associated with heavy cannabis use. The effects of pre-legalization public perception and demand, as well as the potential for retailers to downplay the harms associated with cannabis use, may complicate understanding the effects of policy changes on cannabis use and related health outcomes. Finally, there is a lack of research on the potential mechanisms through which changes in CL and resultant shifts in societal beliefs and drug and healthcare markets influence public health outcomes, particularly related to how youth decide to initiate cannabis and how various policy changes may influence these decisions.

13. IMPACT OF FEDERAL HEMP-DERIVED CANNABINOID POLICIES ON CANNABINOID PRODUCT USE AND HEALTH OUTCOMES IN US YOUTH

While a comprehensive investigation into the impact of US cannabinoid policies on the use of hemp-derived cannabinoid products and their associated health outcomes in US youth was beyond the scope of this narrative review, it remains an important focus of future inquiry. The interactive effects of federal hemp and state cannabis laws on American consumption of cannabis- and hemp-derived cannabinoid products also warrant additional study, particularly in light of the overlapping pharmacologic effects of delta-9-THC, delta-8-THC, and delta-10-THC. Hemp-derived delta-9-THC analogues may carry a similar risk for adverse health outcomes to the use of high delta-9-THC potency cannabis in youth (Livingston, Walker, Cannell, & Rossheim, 2022).

CONCLUSION

Given dramatic shifts in CL across the US in the past 25 years and the established associations between adolescent cannabis use and negative mental and physical health outcomes, it is critical to understand potential down-stream consequences related to MCL and RCL policy shifts on cannabis use, CUD, mental health and non-cannabis SUD outcomes in AYA (Hammond, Chaney, Hendrickson, & Sharma, 2020). CL appear to change adult rates of SUD and SMI treatment utilization (Sahlem, Tomko, Sherman, Gray, & McRae-Clark, 2018), but effects on treatment utilization rates in AYA are understudied (Hammond, Chaney, Hendrickson, & Sharma, 2020). Knowledge about the impact of cannabis policy on relevant AYA health indicators may inform current and future public health efforts and CL policy decisions. While effects of MCL and RCL on youth cannabis use have been investigated previously (Sarvet *et al.*, 2018), prior studies frequently utilize a categorical approach to measuring CL and have studied a product significantly less potent than what is currently available. The impact of CL on youth health outcomes likely varies in relation to different provision types and levels of restrictiveness (Chapman, Spetz, Lin, Chan & Schmidt, 2016). Furthermore, prior studies on CL effects in youth have focused almost exclusively on adolescent cannabis use as a primary outcome, ignoring relevant downstream cannabis-related outcomes of CUD, SMI, non-cannabis SUD, SRO, and ACM, which are associated not only with cannabis use *vs*. non-use in the population, but with age of cannabis onset, frequency, and THC potency of cannabis use (Smart & Pacula, 2019).

LIST OF ACRONYMS

ABCD	=	Adolescent Brain Cognitive Development Study
ACM	=	All-Causes Mortality
AYA	=	Adolescent and Young Adult
CBD	=	Cannabidiol
CI	=	Confidence Interval
CL	=	Cannabis Law
CSA	=	Controlled Substances Act
CUD	=	Cannabis Use Disorder

DC = District of Columbia

DSM = Diagnostic and Statistical Manual

MCL = Medical Cannabis Law

MVC = Motor Vehicle Crash

NSDUH = National Survey of Drug Use and Health

OR = Odds Ratio

RCL = Recreational Cannabis Law

SMI = Severe Mental Illness

SRO = Suicide-related Outcome

SUD = Substance Use Disorder

THC = Tetra-hydrocannabinol

US = United States

YRBS = Youth Risk Behavior Survey Study

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