# Cannabis Recreational Legalization and Prevalence of Simultaneous Cannabis and Alcohol Use in the United States



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**BACKGROUND:** Simultaneous cannabis/alcohol use, using both substances within a short time interval so that their effects overlap, has a greater risk of potential negative consequences than single-substance use and is more common in younger age. Relationships between recreational cannabis laws (RCLs) and changes in simultaneous cannabis/alcohol use prevalence remain untested.

**OBJECTIVE:** To examine trends in simultaneous cannabis/alcohol use from 2008 to 2019, and investigate associations between implementation of RCLs (i.e., presence of active legal dispensaries or legal home cultivation) and simultaneous cannabis/alcohol use in the United States (U.S.).

**DESIGN:** Repeated cross-sectional samples from the 2008–2019 U.S. National Survey on Drug Use and Health (NSDUH).

**PARTICIPANTS:** Respondents (51% female) aged 12 and older.

**INTERVENTIONS:** Changes in simultaneous cannabis/alcohol use before and after RCL implementation (controlling for medical cannabis law implementation) were compared in different age groups (12–20, 21–30, 31–40, 41–50, 51+), using adjusted multi-level logistic regression with state random intercepts and an RCL/age group interaction.

**MEASUREMENTS:** Self-reported simultaneous cannabis/alcohol use.

**RESULTS:** From 2008 to 2019, the overall prevalence of simultaneous cannabis/alcohol use declined among those aged 12–20 but increased in adults aged 21+. Model-based simultaneous cannabis/alcohol use prevalence increased after RCL implementation among respondents aged 21–30 years (+1.2%; aOR= 1.15 [95%CI = 1.04–1.27]), 31–40 years (+1.0; 1.15 [1.04–1.27]), and 41–50 years (+1.75; 1.63 [1.34–1.98]), but not in individuals aged <21 or 51+ years.

**CONCLUSIONS:** Implementation of recreational cannabis policies resulted in increased simultaneous use of cannabis and alcohol, supporting the complementarity hypothesis, but only among adults aged 21+. Efforts to minimize harms related to simultaneous cannabis/

alcohol use are critical, especially in states with RCLs. Future studies should investigate cultural norms, perceived harm, and motives related to simultaneous use.

KEY WORDS: recreational cannabis laws; simultaneous cannabis/alcohol use: cannabis use: alcohol use.

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## INTRODUCTION

Individuals using cannabis and alcohol represent several different patterns of consumption, including cannabis/ alcohol co-use (using both substances in a given period, for example, the same month, but not necessarily simultaneously) and simultaneous cannabis/alcohol use (using both substances within a short time interval so that their effects overlap). Both co-use and simultaneous use are associated with severe consequences in all age groups. 1-16 However, specific age groups seem to be more vulnerable to particular consequences. In adolescents, cannabis/ alcohol co-use is associated with disruptions in brain structure and function, cognitive development, poor cognition, limited educational achievement, and increased risk for psychiatric disorders.<sup>3-6</sup> In adults, cannabis/alcohol co-use is related to risky behaviors, 6, 7 heavy patterns of cannabis/alcohol use, 2, 9, 10 and alcohol use disorder. 2,11 Simultaneous cannabis/alcohol use is even more concerning than co-use as the combined effects of both substances can interfere with absorption, bioavailability, and subjective intoxication effects. 17-20 However, little is known about the trends of simultaneous use in adults in the United States (U.S.), where adult cannabis use<sup>21, 22</sup> and alcohol use<sup>23-25</sup> are increasing in a changing cannabis policy environment.

Cannabis legislation is an important environmental factor influencing cannabis supply, availability, risk perception, cannabis use, and simultaneous cannabis/alcohol use. <sup>26–31</sup>

Cannabis legalization is complex, involving multiple policy decisions, including regulations of supply chain and operation (e.g., government monopoly, profit retail sales, legal home cultivation, advertisement), types of products distributed, prices, and taxes.<sup>32, 33</sup> Permissive cannabis laws can increase cannabis use by two mechanisms: (1) increased availability and (2) decreased perceived risk.<sup>26, 28, 30, 34</sup> However, these mechanisms show different impacts across age groups.<sup>26, 28–31, 35–37</sup>

Shifts in cannabis legislation have raised questions about unintended effects on alcohol use patterns, with evidence supporting both the substitution hypothesis and the complementarity hypothesis. The substitution hypothesis proposes that policy changes would lead people to replace the use of one intoxicating substance for another, which would result in individuals opting to use cannabis instead of alcohol due to reductions in the price and legal/societal consequences of cannabis use. The complementarity hypothesis proposes that more flexible cannabis policies would result in individuals increasing the use of multiple substances, including simultaneous cannabis/alcohol use 38-42.

There is a gap in the literature regarding shifts in simultaneous cannabis/alcohol use after implementation of recreational cannabis laws (RCLs). Existing studies of the effects of RCL on cannabis/alcohol use focus either on each substance separately<sup>36, 37</sup> or only on cannabis/alcohol co-use in specific states<sup>27, 43</sup> or nationally.<sup>29</sup> The only study specifically examining simultaneous cannabis/alcohol use was performed over a short period (2014–2016) which may not be sufficient time to observe changes in substance use patterns related to RCLs.<sup>44</sup> Therefore, little is known about how implementation of RCLs may affect the prevalence of simultaneous cannabis/alcohol use in the US.

Our study examined trends and changes in simultaneous cannabis/alcohol use prevalence before and after RCL implementation by age groups, which both builds on previous research demonstrating age differences and incorporates age restrictions inherent in RCLs. We focused on implementation of legal supply mechanisms (e.g., presence of recreational dispensaries in a state) due to RCLs, which more directly reflects access to legal cannabis for those aged 21+. We hypothesized that following RCL implementation, simultaneous cannabis/alcohol use would (1) increase among adults aged 21+ years, because legal recreational use is limited to adults 21+ and previous work suggests that RCLs are associated with increased cannabis use in adults<sup>26, 28</sup>; (2) result in more pronounced increases among adults aged 51+ years, considering documented increases in cannabis and alcohol use separately 45, 46 and findings from statelevel research<sup>44</sup>; and (3) not be associated with changes in simultaneous cannabis/alcohol use among adolescents and young adults below the legal age (12–20 years old) based on prior work which indicates no difference in cannabis use alone and cannabis/alcohol co-use related to cannabis laws in this age group. 29, 30, 35, 47

# **METHODS**

We used restricted-access data from individuals aged 12+ who participated in the 2008-2019 National Survey on Drug Use and Health (NSDUH) (n=817,359). Data included respondents' state of residence which enabled us to determine state RCL exposure status. The 2019 survey was the most recently available at the time of analysis (June 2021 to April 2022). The NSDUH uses a multistage probability design for annual cross-sectional household surveys of the U.S. non-institutionalized population aged 12 and older. The NSDUH includes survey weights to adjust for the probability of selection at each sampling stage, nonresponse and coverage. Interview response rates over the study period varied from 64 to 76%.

Our outcome was self-report of simultaneous cannabis/ alcohol use. In the NSDUH, survey participants were asked "what other drug or drugs did you use while you were drinking or within a couple of hours of drinking?" Participants who reported using marijuana or hashish were classified as "using marijuana or hashish at the same time or within a couple of hours of the respondent's last alcohol use", 49 as a dichotomous variable (e.g., yes, no).

Our primary exposure was living in a state that implemented RCL and had an operational legal channel for obtaining cannabis for recreational purposes (i.e., legal cannabis supply). This definition includes the adoption of laws allowing home cannabis cultivation or the presence of a legal recreational dispensary in the state, whichever came first. Individual interview dates were compared with RCL and MCL operationalization dates, which were obtained from multiple sources, to determine exposure status.<sup>50–53</sup> Where discrepancies in RCL/MCL dates between sources were noted, we referred to the specific text of the statute for clarification. These dates have been used in previous work. 54, 55 Individuals interviewed in a state that did not implement any form of cannabis legalization by 2019 were classified as "Never MCL/RCL" exposure; those in states that eventually implemented MCL only were classified as "Before MCL." Those interviewed after MCL implementation in a state that did not implement RCL by 2019 were categorized as "After MCL/Never RCL" while those interviewed prior to RCL implementation were categorized as "After MCL/Before RCL." Individuals interviewed after RCL implementation were classified as "After MCL/ After RCL." State classifications over time are presented in Appendix Table 1.

Because a state's MCL/RCL exposure status could change over the study period, for descriptive analyses, we also created a time-invariant three-level exposure variable reflecting state's MCL/RCL status by the end of the analysis period in 2019. This included states that never implemented any form of cannabis legalization (Never MCL/RCL), states that legalized medical cannabis but not recreational cannabis (MCL only/No RCL), and states that legalized recreational cannabis (Ever RCL) by the end of the analysis period. In regression models, we used the time-varying indicator of state cannabis law status

based on the date of the respondent interview as described above. Because our primary interest was in examining changes in simultaneous cannabis/marijuana in response to RCL only, we focused on contrasts during the period after MCL operationalization (After MCL/Before RCL vs. After MCL/After RCL.)

Age at interview was categorized as follows: 12–20, 21–30, 31–40, 41–50, and 51+ years old. The rationale for this categorization was to classify individuals at each life decade and to separate participants under the age of 21, the legal age for purchasing alcohol and cannabis. Other individual-level covariates included gender, racial/ethnic group, education, family income, and urbanicity. Statelevel covariates were based on 2010 U.S. Census data on the proportion of each state's population that was white, male, aged 10–24 years, aged 25+ with at least a high school education, state unemployment rates, and median household income.

# **Statistical Analysis**

We first described the cumulative prevalence of simultaneous cannabis/alcohol use and examined differences by sociodemographic characteristics, grouping respondents by state RCL exposure status at the end of the observation period, 2019 (Never MCL/RCL, MCL only/No RCL, Ever RCL). Next, to test associations between RCLs and simultaneous cannabis/ alcohol use, we utilized a two-stage process. First, we generated adjusted predicted prevalences of simultaneous cannabis/ alcohol use by RCL exposure status group by age. Next, to examine changes in prevalence of simultaneous use after versus before RCL enactment (i.e., after MCL/after RCL vs. after MCL/before RCL), we contrasted the model-based marginal predictions, computing adjusted odds ratios (aOR) and 95% confidence intervals (95%CI). In the first step, we used the lme4 R package to fit a multi-level logistic regression, including an interaction between the RCL exposure group variable and age group. Models included state random intercepts to account for the clustering of individuals within states. Categorical year fixed effects were also included to account for secular trends in simultaneous use across all states over the observation period. We further controlled for individual-level and state-level covariates, as listed above. Following prior research, 54-56 we did not apply survey weights, and rather included the individual-level indicators listed above that are related to the NSDUH sampling design.<sup>57</sup> In the second step of the process, we used the emmeans R package to generate adjusted odds ratios for the contrast of interest, after versus before RCL, from the model-based prevalences.

Our models controlled for several individual- and state-level factors that might confound the relationships between RCL and simultaneous cannabis/alcohol use, but other sources of potential unobserved confounding remain possible. Therefore, we conducted a sensitivity analysis using *e*-values to evaluate the potential impact of time-varying unmeasured

confounding<sup>56, 58, 59</sup> on our results. Small *e*-values closer to 1.0 suggest that little unmeasured confounding may account for observed associations; larger *e*-values indicate that results are increasingly robust to unmeasured confounding. *E*-values were obtained for the estimated aOR and lower level of the 95%CI (LL95%CI) using the EValue package in R software. <sup>56, 58, 59</sup>

This manuscript was prepared according to STROBE guidelines for cross-sectional studies<sup>60</sup> and approved by the Columbia University Institutional Review Board (approval number AAAS4624).

## **RESULTS**

Demographic characteristics were similar when comparing people in states by cannabis legalization status as of 2019 (Table 1).

# Overall Trends in Simultaneous Cannabis/ Alcohol Use by Age

From 2008 to 2019, the overall prevalence of simultaneous cannabis/alcohol use increased in adults. The largest increases were observed among those aged 51+ years old (from 0.63% [95%CI, 0.35–0.92] to 1.91% [1.59–2.23]), followed by participants aged 41–50 years (from 1.54% [1.18–1.90] to 3.61% [3.12–4.11]), those aged 31–40 years (from 2.82% [2.28–3.35] to 6.10% [5.49–6.70]), and those aged 21–30 years old (from 6.07% [5.46–6.68] to 10.00% [9.34–10.66]) (results not shown in figures). However, for respondents aged 12–20 years old, prevalence declined about 12% (from 4.31% [3.99–4.64] in 2008 to 3.84% [3.44–4.18] in 2019).

Figure 1 displays the prevalence of simultaneous cannabis/alcohol use in states by age group, according to state RCL status at the end of the observation period in 2019 (i.e., Never MCL/RCL, MCL only/No RCL, and RCL). Overall, simultaneous use prevalence was lower in never MCL/RCL relative to MCL or RCL.

# Changes in Simultaneous Cannabis/Alcohol Use by Age After RCL Enactment (Table 2)

Simultaneous cannabis/alcohol use increased in the After MCL/After RCL period among respondents aged 21–30 years, 31–40, and 41–50 but not among respondents aged 12–20 or 51+ (Table 2). For example, comparing the period after RCL to before RCL, the prevalence of simultaneous use among respondents aged 21–30 increased from 9.20 to 10.40% (aOR=1.15 [95%CI=1.04–1.27]). Similarly, among participants aged 31–40 years and 41–50 years, prevalence increased from 5.12 to 6.12% (aOR=1.21 [1.04–1.41]) and from 2.93 to 4.68% (aOR=1.63 [1.34–1.98]) respectively. Small but nonsignificant increases were observed among respondents aged 51 or older (aOR=1.25 [0.99, 1.58]). In contrast, there was a decrease in prevalence following RCL

Table 1 Demographic Characteristics, Self-reported Simultaneous Cannabis/Alcohol Use, and State-Level Covariates by States Cannabis Law Status in 2019. National Survey on Drug Use and Health (NSDUH), 2008–2019

	Never MCL/RCL		MCL only/No RCL		Ever RCL	
	Weighted n's	% Weighted	Weighted n's	% Weighted	Weighted n's	% Weighted
Characteristics						
Gender						
Male	42154400	48.40	54353500	48.29	31136700	48.98
Female	44947500	51.60	58197600	51.71	32428800	51.02
Age						
12–20	13075500	15.01	15694800	13.95	9265600	14.58
21–30	14284500	16.40	17594900	15.63	10594200	16.67
31–40	13666400	15.69	16753300	14.89	10167700	15.99
41–50	13782100	15.82	17618400	15.65	10124000	15.93
51+	32293500	37.08	44889800	39.88	23414100	36.83
Race/ethnicity						
Non-Hispanic white	58044500	66.64	75550200	67.12	36538800	57.48
Non-Hispanic Black	13098600	15.04	14119800	12.55	4207800	6.62
Hispanic	11806700	13.55	14989900	13.32	14781500	23.25
Non-Hispanic other	4152100	4.77	7891200	7.01	8037400	12.64
Education						
Less than HS	12100900	15.42	13077200	12.78	7750200	13.45
HS graduate	22654300	28.87	29339200	28.68	14002200	24.31
Some college	22405200	28.56	28288500	27.65	16673400	28.94
College graduate	21298000	27.15	31609400	30.89	19182000	33.30
Family income						
<\$20.000	16244500	18.65	19159700	17.02	10233900	16.10
\$20,000-\$49,999	28511900	32.73	34186800	30.37	18745100	29.49
\$50.000-\$74.999	14935800	17.15	18576000	16.51	10114100	15.91
\$75,000+	27409700	31.47	40628600	36.10	24472400	38.50
Urbanicity	_, ,					
Large metro	36841000	42.30	67020800	59.55	41904300	65.92
Small metro	31497100	36.16	31250300	27.76	16836400	26.49
Nonmetro	18763900	21.54	14279900	12.69	4824800	7.59
Simultaneous cannabis/alcohol use	2192300	2.52	3607300	3.22	2842900	4.49

State-level cannabis laws were categorized as a time-invariant three-level variable (Never MCL/RCL, MCL only/No RCL, and Ever RCL) as of RCL status in 2019

All results are weighted and rounded to conform to SAMSHA disclosure requirements to ensure confidentiality

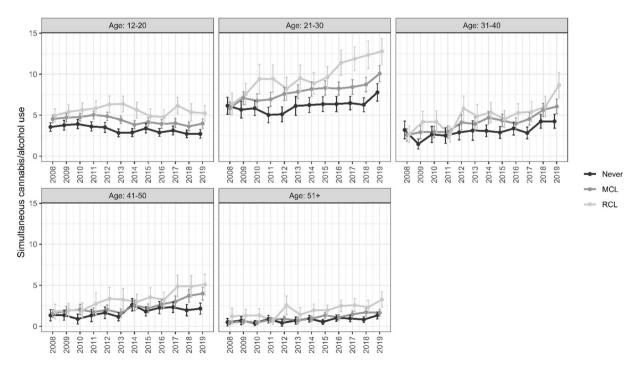


Figure 1 Trends of prevalences of simultaneous cannabis/alcohol use and implementation of recreational cannabis laws (RCL) during 2008–2019. Note: State-level cannabis law status was classified by 2019 and categorized as a time-invariant the following three-level variable: (1) Never — refers to states that have never implemented medical cannabis laws or recreational cannabis laws, (2) MCL — refers to states that only implemented medical cannabis laws, and (3) RCL — refers to states implemented recreational cannabis laws.

Table 2 Simultaneous Cannabis/Alcohol Use After Versus Before Legalization of Recreational Cannabis by Age Groups Among U.S. Individuals. NSDUH 2008–2019

Age groups	% who report simultaneous calcohol use	AOR (95%CI)	
	After MCL/ Before RCL	After MCL/ After RCL	
12–20 21–30 31–40 41–50 51+	9.31 9.20 5.12 2.93 1.72	8.44 10.40 6.12 4.68 2.13	0.90 (0.78, 1.04) 1.15 (1.04, 1.27) 1.21 (1.04, 1.41) 1.63 (1.34, 1.98) 1.25 (0.99, 1.58)

NSDUH National Survey on Drug Use and Health, RCL recreational cannabis laws, AOR adjusted odds ratio

All states that legalized recreational cannabis previously legalized medical cannabis. The before versus after RCL contrast therefore compared simultaneous cannabis/alcohol prevalence in states after MCL but before RCL relative to simultaneous cannabis/alcohol prevalence in states after MCL and after RCL

Individual- and state-level predictors: state random effects, year fixed effects, gender, race/ethnicity, family income, and urbanicity, % white, % male, % ages 10–24, % of adults (<25) with at least a high school education, unemployment, and state's median household income

For point estimates with corresponding lower limit 95% confidence interval (LL95%CI) greater than 1, we estimated e-values to quantify the minimum strength of the relationship between an unmeasured/uncontrolled confounder and both our exposure (RCL) and outcome (simultaneous cannabis/alcohol use) needed to reduce the aOR and the lower limit of the 95% confidence interval (LL95%CI) to the null. For age group 21–30 years, these were as follows: ae-value for aOR = 1.55 and LL95%CI = 1.23; for age group 31–40 years, these were as follows: ae-value for aOR = 1.71 and LL95%CI = 1.22; and for age group 41–50 years, these were as follows: ae-value for aOR = 2.63 and LL95%CI = 2.01

among respondents aged 12–21 (from 9.31 to 8.44%); however, the adjusted odds ratio overlapped the null (aOR=0.90 [0.78, 1.04]).

In sensitivity analyses, *e*-value results suggested that a moderate degree of unmeasured confounding would be required to explain the observed results if no relationship existed between RCLs and simultaneous use. For example, the observed adjusted odds ratio for the 21–30-year-old group could be explained by an unmeasured confounder that was associated with both the exposure (RCL) and the outcome (simultaneous use) by a risk ratio of 1.23 above the measured confounders, but weaker confounding could not do so. *E*-value results among those aged 41–50 were the most robust to potential unmeasured confounding (*e*-value 95%CI lower limit=2.01).

# **DISCUSSION**

This study aimed to investigate changes in simultaneous cannabis/alcohol use before and after RCL implementation by different age groups, and found increases in simultaneous use after RCLs in adults aged 21–50 years. Our results showed no changes in simultaneous cannabis/alcohol use among individuals aged 12–20 and older adults (51+ years) associated with RCLs. These findings confirm our hypotheses of increases in adults aged 21+ and no changes in youth aged 12–20, which are in line with prior research focused on RCL

in youth reporting no shifts in cannabis and alcohol use in adolescents aged 14–18 years old,<sup>37</sup> no shifts in cannabis/alcohol co-use in those aged 18–25, and declines in adolescents aged 12–17 years.<sup>29</sup>

The availability and opportunity to access cannabis through legal supply chains such as dispensaries, present in most RCL states, may explain why we observed increases in simultaneous cannabis/alcohol use in those aged 21–50 but not 12–20 years after RCLs in this sample. These findings build upon prior MCL research showing that states allowing dispensaries had a greater likelihood of alcohol-related outcomes in adults aged 21+. Also, prior RCL studies reported increases in the prevalence of cannabis/alcohol co-use and simultaneous use, <sup>29, 43, 44</sup> consistent with the complementarity hypothesis.<sup>38–42</sup> Some of the possible explanations for the complementary hypothesis and simultaneous cannabis/alcohol use include an individual's search for enhancement of intoxicating effects<sup>17-20</sup> and declines in inhibitory control and decisionmaking caused by the use of one substance making an individual more prone to use the other available substance. 61–64 Our work confirms these findings and extends them by reporting increased simultaneous use after RCL with cannabis supply implementation using a nationally representative sample across age groups over a long period (2008–2019).<sup>29, 65</sup>

RCLs were not associated with simultaneous cannabis/ alcohol use in individuals aged < 21 which aligns with previous findings from research examining effects of MCL and cannabis use alone and cannabis/alcohol co-use, 29, 30, 35, 47 and data showing shifts in cannabis risk perception did not cooccur with an increase in cannabis use in this age group.<sup>35</sup> This finding could be explained by the effective restrictions in access to legal supply chains, enforcement of minimum age requirements for cannabis purchase, marketing restrictions on commercial ads targeting this age group (e.g., no advertisements in places where more than 30% of viewers are < 21 years), and prevention strategies (e.g., community- and school-based campaigns) in some RCL states. 32, 33, 65 However, RCL states have different legislation regarding supply chains, regulatory mechanisms for types of products allowed, and prevention strategies. Therefore, further research should examine the impact of various sources of cannabis legal supply and types of prevention strategies in place in different RCL states.

Finally, there was a large increase in the prevalence of simultaneous cannabis/alcohol in older adults (51+ years) across all U.S. states. The overall increase in simultaneous use is in line with prior literature reporting that adults 50+ years experienced the largest increases in cannabis use of any age group. 12, 66, 67 Thus, discussions about cannabis/alcohol co-use may be warranted in this population, including medical providers who ask about alcohol/cannabis use patterns in older adults 68

Our study has some limitations. First, this study was conducted using self-reported data on simultaneous alcohol/cannabis use and individuals' perceptions of their own alcohol

and cannabis use patterns which may be related to state RCL status. However, the NSDUH collects this sensitive information using computer-assisted self-interviewing which should reduce differential measurement error. Second, our analyses examined all RCL states as a single category and did not examine cannabis policy provisions (e.g., products permitted, cultivation restrictions, pricing control, the tax imposed, and consumption restrictions) or the density of recreational cannabis and alcohol retail outlets, which may lead to varied outcomes within RCL states. However, our exposure definition followed prior recommendations on conducting cannabis legislation research, such as using supply dates instead of effective dates of recreational cannabis legislation. Using supply dates is important because states may pass a law and take longer to authorize cannabis dispensaries and/or home cultivation. 32,33 Third, we did not report overall findings, just age-stratified results as our focus was to investigate changes in simultaneous use by age groups. Fourth, we did not assess differences in alcohol policies across states (e.g., prices, alcohol sale hours). Some of the potential confounding effects of alcohol policies would be controlled through the use of state random effects. However, alcohol policies changing over this time period may contribute to uncontrolled confounding. Nevertheless, this study has significant strengths, including the use of nationally representative samples across multiple years (2008–2019), and a survey design that provided for accurate national- and state-level estimates. We used RCL variables based on supply dates instead of effective date, which allowed specific investigation of the effects of increased legal access to cannabis either by purchasing at a dispensary or through home cultivation; however, we were not able to make comparisons between implementation (i.e., supply dates) and enactment (i.e., effective dates) of the RCLs which could have provided valuable information on different policies components, future studies should address this

Implementation of RCLs was associated with increases in simultaneous cannabis/alcohol use in individuals aged 21-50 years; however, no changes in simultaneous cannabis/alcohol use were observed in individuals younger than 21 years or those older than 51+ years old. This study contributes to our understanding of age group changes in simultaneous cannabis/ alcohol use after the legalization of adult cannabis use in the U.S. beyond medical laws. It also extends research on changes in the prevalence of simultaneous use after changes in the legal cannabis supply. Our findings coupled with previous research suggest that there may be a need to develop strategies to reduce harms related to simultaneous cannabis/alcohol use in adults aged 21-50, especially in states with RCLs. Future studies should investigate changes in cultural norms, perceived harm and motives related to simultaneous cannabis/ alcohol use, and the effects of specific cannabis policy provisions as more U.S. states legalize cannabis for adult recreational use.

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All analyses were conducted at the New York Federal Statistical Research Data Center, a Census Bureau administered facility providing secure access to restricted-access NSDUH microdata. Statistical output was reviewed by Substance Abuse and Mental Health Services Administration (SAMSHA) staff and conformed to SAMSHA disclosure requirements to ensure confidentiality, including sample size rounding (to the nearest hundred) and suppression of values less than 100 or with large standard errors.

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#### Declarations:

**Conflict of Interest:** All authors have no conflict of interest related to this present work.

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