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Association Between Marijuana Laws and Suicide Among 12- to 25-Year-Olds in the United States From 2000 to 2019

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Objective: Cannabis use is associated with suicide-related outcomes in both adolescents and adults, and may be increasing amid shifting cannabis policies. However, little is known about the impact of medical marijuana legalization (MML) and recreational marijuana legalization (RML) policies on youth suicide. Using 20 years of national data, we examined associations between MML, RML, and suicide-related mortality among US individuals aged 12 to 25 years, and assessed whether they varied based on age and sex.

Method: Suicide deaths (N = 113,512) from the 2000-2019 National Vital Statistics System Multiple Cause of Death files for age groups 12 to 13, 14 to 16, 17 to 19, 20 to 22, and 23 to 25 years were examined in relation to time-varying cannabis law status using a staggered adoption difference-in-difference (DiD) approach with a negative binomial regression to determine associations between MML, RML, and suicide rates, controlling for individual- and state-level covariates and accounting for the varying effective dates of MML and RML by state.

Results: The overall unadjusted annual suicide rate was 10.93/100,000, varying from 9.76 (states without marijuana laws (ML)) to 12.78 (MML states) to 16.68 (RML states). In multivariable analysis, both MML (incidence rate ratio [IRR] = 1.10, 95% CI: 1.05-1.15) and RML (IRR = 1.16, 95% CI: 1.06-1.27) were associated with higher suicide rates among female youth compared to those in states without ML. Youth aged 14 to 16 years had higher rates of suicide in states with RML compared to states with MML (IRR = 1.14, 95% CI: 1.00-1.30) and states without ML (IRR = 1.09, 95% CI: 1.00-1.20). Findings were consistent across sensitivity analyses.

Conclusion: MML and RML were associated with increased suicide-related mortality in female youth and 14- to- 16-year-old individuals of both sexes. Mechanisms through which cannabis policies are related to increased youth suicide warrant further study and should inform legislative reform.

Key words: recreational marijuana legislation; medical marijuana legislation; suicide; adolescents; sex differences

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Cannabis legalization, for medical and/or recreational use, by a majority of states in the US over the past 25 years has dramatically shifted societal perceptions and use patterns among Americans.[1] As of 2021, 36 states and the District of Columbia (DC) had passed medical marijuana laws (MML), and 18 states and DC also had passed recreational marijuana laws (RML).[2] How these policy changes have affected population-wide health indices of US youth remains a topic of significant debate[3]; however, is critical to understand, given the rapid changes in brain development that occur during the 12- to 25-year-old interval and the sensitivity to cannabis exposure, particularly delta-9-tetrahydrocannabinol (delta-9-THC) during this time period.[4-8]

One critical health index is suicide.[9] Cannabis use is associated with suicide-related outcomes in adolescents and adults.[6,10] This is of increasing importance, given the rise in rates of adolescent depression and suicide that preceded the coronavirus epidemic but were exacerbated by it.[11-13] Meta-analytic reports indicate that cannabis use during adolescence is associated with increased risk for suicidal ideation and non-fatal suicide attempts in young adulthood. [6,10] A dose−response effect has been reported,[3] with earlier age of onset, daily, and persistent cannabis use across adolescence conveying higher risk for suicide-related outcomes.[10] Growing evidence demonstrates that adolescent-onset cannabis use is associated with increased risk of depression,[3,6,10] anxiety,[3] and psychosis[3,14] in adulthood.

The impact of US marijuana laws (ML) on suicide rates is poorly understood. Few studies have investigated associations between cannabis policy and suicide-related outcomes,[15-18] and results are mixed. In a study of US mortality data between 1990 and 2007, MML was associated with reduced suicides among men aged 20 to 29 and 30 to 39 years.[15] In contrast, no relationship between MML and suicide-related outcomes was found among US adults in an overlapping time window (2001-2010) after controlling for individual-level demographic factors and a wide array of state-level covariates.[16] RML passage was associated with increased rates of self-harm in US adults younger than 40 years.[18] The association between cannabis use and risk of suicide is larger in youth samples than in adults. If RMLs and MMLs alter suicide-related outcomes in young people, a population shown to be vulnerable to cannabis-associated adverse health outcomes, this would have important implications for public health and policy.[3]

In the present study, we addressed these knowledge gaps by examining relationships between changes in RML, MML, and suicide-related mortality in US adolescents and young adults aged 12 to 25 years between 2000 and 2019. Specific aims were to identify whether cannabis legalization (ie, RML and MML vs no ML) was associated with changes in suicide-related mortality in US youth. If associations were present, we sought to characterize their directionality and specificity in regard to sex and age.

METHOD

Data

Detailed mortality files from January 1, 2000, to December 31, 2019, were obtained from the National Center for Health Statistics National Vital Statistics System.[19] This includes the most recent 20 years of death data for which yearly covariates are also available. Deaths by suicide were selected for 12- to 25-year-old youth based on the *International Statistical Classification of Diseases, Tenth Revision (ICD-10)* cause of death codes (X60-X84, Y87.0, and *U03). Information was extracted on the number of suicide deaths by month and year, age, sex, race, ethnicity, and urbanicity, and was aggregated to state level. To compute monthly suicide rates, we obtained population estimates from the Surveillance, Epidemiology, and End Results (SEER) Program.[20] The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies[21] was used, and the study was determined to be exempt from human subjects review by the Ohio State University Institutional Review Board. The primary exposure variable was state-level MML and RML. Effective dates were determined by review of publicly available state policies. We created a 3-level time-varying variable by month and year for each state (0, no ML; 1, MML only; 2, RML). States were coded initially as 0 or 1, depending on whether they had MML in effect prior to 2000. States transitioned from 0 to 1 or 1 to 2 during the month and year of the effective date of the MML or RML law, respectively. By 2019, a total of 23 states had effective MML but not RML, 10 states and DC had effective RML; the remaining states did not enact ML (sTable S1, available online, for details).

Covariates

Secondary independent state-level time-varying covariates were selected based on association with prior research[15] and came from multiple data sources (Table S2, available online). State-level variables were matched to year of mortality data when available; missing data were imputed from the last observation carried forward. State-level sociodemographic variables were abstracted from the Area Health Resource File[22] and American Community Survey[23] and included the following: per capita income (dollar amount) and proportion of non-Hispanic Black individuals, Hispanic individuals, non-Hispanic White individuals, male individuals, and persons who were unemployed, living in poverty, uninsured under 65 years, and aged 15 to 24 years. Alcohol policy variables were obtained from the Alcohol Policy Information System[24] and included information on beer excise taxes (dollar amount), zero-tolerance drunk driving laws (dichotomous), and blood alcohol limit policies (dichotomous). Smoke-free policies and cigarette excise tax legislation were obtained from the State Tobacco Activities Tracking and Evaluation System.[25] A smoke-free variable was created and coded as the sum of laws governing bars, restaurants, and private workspaces (0 = no law; 1 = partial restrictions; 2 = complete ban; range: 0-6); cigarette excise tax was dollar amount.[16] Gun laws were obtained from the State Firearm Laws Database,[26] an online resource of all firearm-related laws by state and year and the Giffords Law Center.[27] An overall firearm variable created by combining 8 laws (background checks, license requirements, waiting periods, reporting lost and stolen, safe storage, dealer regulations, bulk buying, and open carry) was used based on prior research.[28,29] Scores ranged from 0 to 16 (each law: absence = 0; partial adoption = 1; complete adoption = 2). Variables related to health providers were abstracted from the Area Health Resource File.[22] Number of primary care providers, pediatricians, adult psychiatrists, and child psychiatrists were coded as ratios per 100,000 population. The number of community mental health clinics was included as a count variable. State mental health expenditures were available from 2001 to 2014 (dollar amounts).[30]

Individual-level covariates (age, race, ethnicity, sex, county, and state of residence at time of death) were extracted from mortality data files. Age was grouped into 5 categories: 12 to 13, 14 to 16, 17 to 19, 20 to 22, 23 to 25 years. Race and ethnicity were coded as non-Hispanic White, non-Hispanic Black, Hispanic, and other.

Statistical Analyses

Analyses were conducted using SAS v9.4. Statistical significance was assessed at $\alpha = 0.05$. Missing data on state-level health care providers in the full dataset were minimal (<1%) and were imputed from the last observation carried forward. Specifically, some data on ratios for general practitioners, pediatricians, psychiatrists, and child psychiatrists are missing for years 2009 and 2014 and were imputed using data from years 2008 and 2013, respectively. Unadjusted annual suicide rates were calculated per 100,000 persons. Our approach uses a staggered adoption difference-in-difference (DiD)[31] model and closely resembles that used by other authors to evaluate the impact of ML in similar studies.[32,33] This approach is similar to a standard DiD analysis but applies regression modeling and uses time-varying cannabis law status as the primary exposure variable. This primary exposure variable was calculated as a state−month/year variable based on the year and month of effective dates that MML and RML laws went into effect for each state. States were categorized each month of each year of the study as no marijuana laws (no-ML), MML only, and RML (with MML). By using a time-varying cannabis law status exposure variable based upon varying effective dates of MML and RML, differences within states before and after law enactment and between states over time are accounted for in the analyses. With this approach, each state that has a cannabis law in effect serves as its own control, and the model contrasts aggregated post-law years to pre-law years while controlling for overall trends over time. Multivariable negative binomial regression models using robust standard errors and a log (population) offset estimated incidence rate ratios (IRR) and 95% CI to test possible differences in suicide rates by ML (no ML, MML, RML). Generalized estimating equations (GEE) with an exchangeable working covariance matrix and robust Huber−White standard errors[34] accounted for correlated data at the state level. All models included a 3-way interaction (ML, sex, age). Generalized contrasts using the robust covariance matrix estimated marginal effects of sex-by-ML and age-by-ML 2-way interactions as well as marginal main effects for ML, sex, and age. We used a hierarchical testing strategy to first test significance of interaction terms, followed by testing individual contrasts if interaction terms were significant. Score statistics for type 3 GEE determined overall significance of the interaction terms. All models included year as a categorical variable (to address non-linear changes in suicide rates over time), month, state, and all state level covariates listed in Table S1, available online. Our statistical model is described in detail in Supplement 1, available online.

Sensitivity Analyses

Four sensitivity analyses were performed to ensure robust incidence rate ratio estimates and to test whether differences in suicide outcomes observed in relation to ML status, age, and sex varied as a function of other measured and unmeasured factors: First, we re-ran our main analysis changing the ML exposure variable to reflect a 6-month lag from the effective date of policy onset to ensure that associations between ML and suicide were not attributed to suicides that occurred in the months after passage but prior to large-scale implementation of ML going into effect. The second sensitivity analysis paralleled our main analysis but was conducted on a subset of 23 states and DC that passed any ML, excluding the 27 states that had no ML during the study period. This test enabled us to examine variation in suicide deaths in relation to ML within states that had established cannabis policy or changed their policy during the study period, ignoring states with no ML. The third sensitivity analysis focused on mental health service expenditures across states. For this analysis, we ran parallel statistical models with and without mental health expenditures with the goal of determining whether variation in state-level mental health expenditures influenced the relationships between ML and suicide identified in our main analyses. Regarding our dependent variable of interest for this third sensitivity analysis, state-level mental health expenditure data are available only for the years 2001-2014. Given this, our mental health expenditures sensitivity analysis focused on this time window, similar to previous ML studies.[16] This approach ensures that results on the subset of years with mental health expenditure data are consistent with the larger dataset and allows us to test the impact of mental health expenditures on our outcomes. Finally, E-values were calculated for ML to quantify the effect of unmeasured confounding. E-value is the minimum strength of association that an unmeasured confounder needs with both exposure and outcome to fully explain away a specific exposure−outcome association. Larger E-values indicate that estimates are more robust to unmeasured confounding.[35-37]

RESULTS

Overall Impact of Marijuana Laws on Suicide Rates

The average unadjusted annual suicide rate was 10.93 in 100,000. Rates differed by sex and age; the male youth suicide rate was 3 times greater than that of female youth (16.71 vs 5.14/100,000). The unadjusted rate was lowest for no ML (9.76) compared with MML (12.78) and RML (16.68) per 100,000 (Figure 1). Similar findings were noted on multivariable analysis (Table 1). Male youth rates were 2.68 times higher (95% CI: 2.57-2.80) than those for female youth. Rates increased with age, and were 2.49 times higher (95% CI: 2.34-2.64) among 14- to 16-year-old youth and 4.86 times higher (95% CI: 4.40-5.37) among 23- to 25-year-old youth compared with 12- to 13-year-old youth.

Interaction between Marijuana Laws, Sex, and Age

There was differential association of ML with suicide risk based on sex and age ($p < .001$ for age-by-sex-by-ML 3-way interaction and sex-by-ML 2-way interaction, age-by-ML 2-way interaction not significant ($p = .40$)). Female youth living in states with effective MML and RML had higher covariate-adjusted suicide rates compared to female youth in states without effective ML, irrespective of age (Table 2). Female youth rates were significantly elevated in states with effective MML compared to states without a ML (range, 10%, ages 17-19 years, 95% CI: 1.05-1.16, to 14%, ages 20-22 years, 95% CI: 1.07-1.21). Except for 12- to 13-year-old and 17- to 19-year-old youth, female youth rates were also significantly elevated in states with effective RML compared to states without an ML (range, 14%, ages 14-16 years, 95% CI: 1.04-1.30, to 20%, ages 20-22 years, 95% CI: 1.08-1.34). Collapsing age groups, states with effective MML had a 10% higher rate (95% CI: 1.05-1.15) and states with effective RML had a 16% higher rate (95% CI: 1.06-1.27) compared to states without an ML.

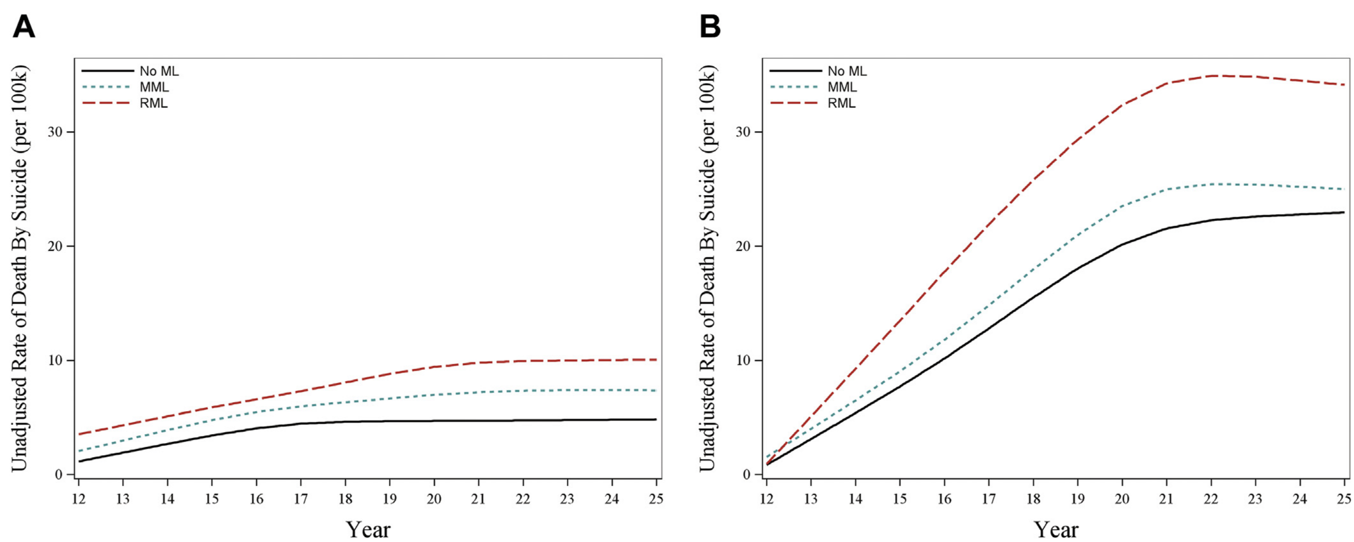
In contrast to female youth, no consistently significant associations occurred between ML and suicide rates in male youth. Across all ages, there was no significant difference in male youth suicide rates in states with effective RML vs states without an ML (IRR = 1.00, 95% CI: 0.93-1.08) and states with effective RML vs states with effective MML (IRR = 0.97, 95% CI: 0.91-1.03). Risk in states with effective MML was slightly lower than in states without an ML (IRR = 0.97, 95% CI: 0.93-0.99). Conversely, male youth aged 14 to 16 years had 15% higher suicide rates in states with effective RML vs states with effective MML (95% CI: 1.03-1.28).

Combining male and female cases, youth aged 14 to 16 years had higher covariate-adjusted rates in states with effective RML compared to states without an ML (IRR = 1.14, 95% CI: 1.00-1.30) and states with effective RML vs states with effective MML (IRR = 1.09, 95% CI: 1.00-1.20).

Sensitivity Analyses

Differential association of ML with suicide risk based on sex and age were robust to sensitivity testing

FIGURE 1 Suicide Deaths Among US Female and Male Youth by Age and Marijuana Law Status



Note: Unadjusted annual rates of death by suicide among US female youth aged 12 to 25 years (A) and US male youth aged 12-25 years (B), calculated at every age (years), and stratified by marijuana law status (RML, MML, No ML). Results are presented using locally estimated scatterplot smoothing (LOESS). MML = medical marijuana law; No ML= no marijuana law; RML = recreational marijuana law. Please note color figures are available online.

TABLE 1 Effects of Marijuana Laws, Sex, and Age on Suicide Deaths in US Youth

Model	Comparison	Reference	IRR estimate	95% CI
Marijuana Law	MML	No ML	1.03	0.99-1.07
	RML		1.08	0.99-1.17
	RML	MML	1.05	0.98-1.11
Sex	**Male**	**Female**	**2.68**	**2.57-2.80**
Age	14-16	12-13	**2.49**	**2.34-2.64**
	17-19		**3.67**	**3.40-3.96**
	20-22		**4.67**	**4.21-5.17**
	23-25		**4.86**	**4.40-5.37**

Note: *Table shows results of final model for direct effects of ML, sex, and age on incident rate ratio (IRR) for suicide deaths in US youth aged 12 to 25 years. IRR for suicide death incidence was derived using negative binominal regression adjusted for individual- and state-level covariates. Boldface numbers indicate statistically significant results at $p < .05$. IRR = incidence rate ratio; MML = medical marijuana law; No ML= no marijuana law; RML = recreational marijuana law.*

(Table 3, Tables S3 and S4, available online). Among female cases, effect of ML was largely consistent between the final model and various sensitivity analyses. When analyzing data up to 2015 only, with and without controlling for state mental health expenditures, each ML comparison produced identical results as estimated in the full model. When evaluating the subset of states in which any ML occurred, the ML effect increased relative to the model, including all 50 states and DC. States with effective MML had 10% higher rates (95% CI: 1.06-1.15) compared to states without an ML; states with effective RML had 19% higher rates (95% CI: 1.11-1.28) compared to states without ML, and states with effective RML had 8% higher rates (95% CI: 1.02-1.14) compared to states with effective MML. When testing the 6-month lag on ML effect, parameter estimates and 95% CIs were identical to estimates reported in the subset analysis of states in which any ML occurred. IRR E-values were consistent across analyses and generally showed a moderate effect size (range, 1.31-1.67), indicating that the effect of MLs reported are relatively robust against

TABLE 2 Effects of Marijuana Laws on Suicide Deaths in US Youth by Sex and Age Group

	MML vs no ML	RML vs no ML	RML vs MML
Group	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Female			
12-13	1.03 (0.90, 1.17)	1.20 (0.99, 1.47)	**1.17 (1.00, 1.38)**
14-16	**1.12 (1.04, 1.19)**	**1.17 (1.04, 1.30)**	1.04 (0.96, 1.14)
17-19	**1.10 (1.05, 1.16)**	1.09 (0.97, 1.24)	0.99 (0.88, 1.11)
20-22	**1.14 (1.07, 1.21)**	**1.20 (1.08, 1.34)**	1.06 (0.98, 1.14)
23-25	**1.11 (1.03, 1.18)**	**1.14 (1.05, 1.24)**	1.03 (0.94, 1.13)
All ages[a]	**1.10 (1.05, 1.15)**	**1.16 (1.06, 1.27)**	1.06 (0.99, 1.13)
Male			
12-13	0.93 (0.84, 1.02)	0.97 (0.78, 1.20)	1.05 (0.90, 1.23)
14-16	0.98 (0.90, 1.06)	1.12 (0.96, 1.31)	**1.15 (1.03, 1.28)**
17-19	0.95 (0.91, 1.00)	0.96 (0.88, 1.04)	1.01 (0.93, 1.09)
20-22	0.98 (0.94, 1.03)	0.97 (0.90, 1.04)	0.99 (0.95, 1.03)
23-25	0.99 (0.95, 1.04)	0.98 (0.92, 1.05)	0.99 (0.95, 1.03)
All ages[a]	**0.97 (0.93, 0.99)**	1.00 (0.93, 1.08)	0.97 (0.91, 1.03)
Male and female			
12-13[b]	0.97 (0.88, 1.09)	1.08 (0.89, 1.31)	1.11 (0.96, 1.28)
14-16[b]	1.04 (0.97, 1.12)	**1.14 (1.00, 1.30)**	**1.09 (1.00, 1.20)**
17-19[b]	1.02 (0.98, 1.07)	1.02 (0.95, 1.11)	1.00 (0.93, 1.07)
20-22[b]	**1.06 (1.01, 1.11)**	1.08 (0.99, 1.17)	1.02 (0.97, 1.08)
23-25[b]	1.05 (0.99, 1.10)	1.06 (0.99, 1.12)	1.01 (0.96, 1.06)

Note: *Table shows results of final model of interaction effect of Sex-by-ML and Age-by-ML effects on incident rate ratio (IRR) of suicide death in US youth aged 12 to 25 years, depicting ML effect on suicide rate separately for female and male youth and both sexes, within each age group and collapsed across age groups. IRR for suicide death incidence was derived using negative binominal regression adjusted for individual- and state-level covariates. Boldface numbers indicate statistically significant results at $p < .05$. IRR= incidence rate ratio; MML = medical marijuana law; No ML= no marijuana law; RML = recreational marijuana law.*

[a]*Marginal effects were measured across all age categories for each sex.*

[b]*Marginal effects were measured for each age category, averaged across sex.*

TABLE 3 Sensitivity Analyses for Marijuana Law Effects on Suicide Deaths in US Female Youth

					E-value	
Model	**Comparison**	**Reference**	**IRR estimate**	**95% CI**	**IRR**	**LCL**
Final	MML	No ML	**1.10**	**1.05-1.15**	1.43	1.28
	RML		**1.16**	**1.06-1.27**	1.59	1.31
	RML	MML	1.06	0.99-1.13	1.31	—
Sensitivity analyses						
6-mo Lag of ML	MML	No ML	**1.10**	**1.06-1.15**	1.43	1.31
	RML		**1.19**	**1.11-1.28**	1.67	1.46
	RML	MML	**1.08**	**1.02-1.14**	1.37	1.16
Subset of states w/ML changes	MML	No ML	**1.10**	**1.06-1.15**	1.43	1.31
	RML		**1.19**	**1.11-1.28**	1.67	1.46
	RML	MML	**1.08**	**1.02-1.14**	1.37	1.16
Years before 2015	MML	No ML	**1.10**	**1.05-1.15**	1.43	1.28
	RML		**1.16**	**1.06-1.27**	1.59	1.31
	RML	MML	1.06	0.99-1.13	1.31	—
Years before 2015/incl MH exp	MML	No ML	**1.10**	**1.05-1.15**	1.43	1.28
	RML		**1.16**	**1.06-1.27**	1.59	1.31
	RML	MML	1.06	0.99-1.13	1.31	—

Note: *Tables shows results of final model and sensitivity analyses in US female youth aged 12 to 25 years for ML effects on suicide death incidence. IRRs for suicide death incidence was derived using negative binominal regression adjusted for individual- and state-level covariates. Boldface numbers indicate statistically significant result at $p < .05$. IRR = incidence rate ratio; incl = including; LCL = lower confidence level; MH Exp = mental health expenditures; MML = medical marijuana law; No ML= no marijuana law; RML = recreational marijuana law; w = with.*

residual confounding related to unmeasured factors with moderate effect, although not to unmeasured confounders having a significant association between suicide events and MLs (eg, comparable to the marginal association between MLs and sex/age). A latent covariate would require an incidence risk ratio of $\geq$1.31 and be associated with MLs to explain the observed association between MLs and suicide rates among female youth. In contrast, sensitivity analyses for male cases showed variable and inconsistent results, with suicide rates and ML being largely unrelated. Finally, our age-by-ML results showing increased suicide rates in 14- to 16-year-old youth in states with effective RML were consistent across sensitivity analyses.

DISCUSSION

Our findings from this national study that investigated the effects of changing cannabis policies on suicide-related outcomes in the US over a 20-year period suggests that ML is associated with an increased risk for suicide deaths in female youth and that ML−suicide associations vary as a function of age. Variation in ML effects on suicide-related outcomes were observed in relation to sex and age, with our primary analyses showing that female youth who lived in states with RML and MML were at greater risk for suicide death compared to those who lived in states without ML, and that ML was associated with increased suicide deaths in 14- to 16-year-old youth regardless of sex. These effects remained significant after controlling for a wide array of confounding variables and were robust to sensitivity tests using 4 alternative approaches to examine policy associations. Furthermore, sex and age associations both exhibited some dose−response characteristics with stronger effects observed in relation to RML compared to MML. Findings are also notable in context of our results showing no evidence for a main effect of ML on youth suicide deaths in the sample collapsed across ages and sexes. Implications of these findings are discussed below in relation to current and future cannabis policy making.

Sex differences identified in the current study were driven by an increase in suicide risk among US female youth living in MML and RML states. Female youth have higher rates of suicide attempts but lower rates of suicide deaths than US male youth,[9] although suicide rates have increased more rapidly for female compared to male youth over the past 2 decades.[38] Our results showed that male youth were 3 times more likely than female youth to die by suicide (16.71 vs 5.14/100,000. However, ML was associated with increased risk for suicide deaths in female youth. Specifically, we found that female youth who lived in MML and RML states had a 10% and 16% greater risk of suicide, respectively, compared to those who lived in no-ML states. This association was remarkably consistent, remaining significant after adjusting for a wide array of individual and state-level covariates and following sensitivity testing. In contrast, the effects of MML and RML on suicide risk in male youth were less precise and showed more variability in outcomes when different sensitivity tests were used.

Age differences in ML−suicide associations were also noted when the sample was collapsed across sexes, driven by an increase in suicide risk among middle adolescents living in RML states. Specifically, we found a 9% to 14% greater risk for suicide in 14- to 16-year old youth living in RML states compared to same-age youth living in states with MML or no ML. This age window is a sensitive neurodevelopmental period in which an inflection in emotional reactivity and risk-taking behaviors occurs.[39] Multiple studies demonstrate that adolescents who start using cannabis before age 16 years are at elevated risk for developing cannabis use and other psychiatric disorders.[3,10,14] Similar to sex associations, our age-by-ML associations were also robust to covariate adjustment and sensitivity testing using alternative analytic approaches.

It is unclear how ML is associated with increased risk of suicide death in female youth aged 13 to 24 years and youth of both sexes aged 14 to 16 years. Our study is limited in its capacity to explain mechanisms behind these associations. ML may increase suicide risk in female youth and middle adolescents directly by altering cannabis use patterns[40,41] and increasing the use of high−THC potency products that are more deleterious for these subgroups.[3,8,42] This is particularly important, given ongoing trends of increasing THC potency in the past decade,[43] which has resulted in >70% of contemporary medical and recreational products sold at licensed outlets and dispensaries containing high concentrations of THC (>15%).[44,45] Little is known about how policy, regulatory systems, and market conditions interact to influence the availability of high−THC potency products, and how the availability of these products affects downstream health outcomes for US youth and adults.[46,47] Regarding sex-specific effects, growing evidence from preclinical and clinical studies indicate sex differences in development, clinical and behavioral presentation, and central nervous system correlates of cannabis use.[48] Women who use cannabis report greater subjective psychoactive effects, withdrawal severity, cannabis-related problems, and higher rates of comorbid mood and anxiety disorders compared to men.[48] In addition, women typically start using cannabis later than men and progress more quickly from first use to dependence (known as the "telescoping" phenomenon).[48] Of note, male−female differences in age of onset and prevalence rates of cannabis use have decreased over the past 2 decades, suggesting that adolescent girls may be starting earlier and using more similarly to adolescent boys relative to their counterparts from prior decades.[3,48] In addition, sex differences in environmental exposures (eg, interpersonal violence) and premorbid psychiatric conditions (eg, depression) may interact with the state ML climate and contribute risk for adolescent cannabis use and suicidal thoughts and behaviors.[49] Any of these factors, alone or in combination, could contribute to elevated risk for suicide in female youth who use cannabis compared to male youth. Regarding age-specific effects, accumulating evidence from preclinical and human studies also indicates that early- to middle-adolescent−onset cannabis exposure, particularly from high-potency product use, is associated with poorer developmental outcomes,[4-8] and that cumulative THC exposure may explain some of the variance in these associations.[50] ML could also influence youth suicide risk through indirect pathways that do not involve adolescent cannabis use by influencing cannabis use patterns of parents/caregivers or peers and affecting parenting practices, peer behaviors, and mental health and substance use treatment utilization.[51,52] Possible mechanisms and pathways behind these ML−suicide associations warrant further exploration.

Prior studies have not examined associations between RML and suicide deaths. Our MML results are inconsistent with findings from previous studies[15-17] examining effects of MML on US suicide rates, although prior studies used data from 1990 to 2010 and none focused on youth populations. These differences may be related to differences in time period studied, sample age range, analytic approach used, and variables controlled for in analyses. Results may reflect changing analytic methods,[15,16] emphasizing the need to cautiously interpret earlier studies that do not control for individual- and state-level covariates related to outcomes of interest, and suggest that future studies should take these variables into account.

Given dramatic shifts in cannabis policy over the past 20 years, it is important for clinicians and policy makers to understand potential downstream public health outcomes related to changing cannabis policy.[1,3] Our findings indicate that adolescents and young adults, in particular female youth, represent vulnerable subgroups at elevated risk for suicide related to MML and RML. Although results indicate a modest effect size (∼10%-16%), at the population level, this translates to nearly 5,000 excess deaths by suicide in female adolescents and young adults related to MML (1,905) and RML (3,047) between 2000 and 2019. Modifying current cannabis policy and instituting risk-mitigating provisions may reduce the effect of ML on youth suicide, but more research is needed to inform policy change. Specific cannabis policies (eg, restrictiveness vs leniency of MML) and provisions (eg, quantity of legal possession) vary widely and contribute variance to adolescent cannabis use behaviors across the US.[53] Future policy research is needed to replicate our results in other datasets and to investigate how ML-suicide associations vary in relation to other individual-level characteristics such as race, ethnicity, gender identity, and sexual orientation, especially as suicide risk may be elevated among minoritized populations[54] and as social justice is commonly cited as a reason for cannabis legalization. Additional research is also needed to clarify whether suicide deaths are related to specific policies and provisions. Future research should also consider how characteristics of the legal marijuana market (eg, store density and types of products sold[55,56]) and illegal market in ML states may affect suicide deaths, particularly as prior research indicates a relationship between ML and high-potency cannabis use.[57] This work can guide evidence-informed policy decisions, which should take the form of risk-mitigating policies in states with current ML or states that are planning to implement MML and RML in the coming years.

This study has several important limitations. One limitation is related to study design. We used an ecological design, and thus our study results provide evidence for state-level associations between changes in ML and changes in suicide rates in subgroups of US youth. Although ecological studies give use a window into population-level associations, they are unable to tell us about individual-level cannabis–suicide relationships.[58] Given our findings, well-designed follow-up studies are warranted to investigate mechanisms underlying individual-level relationships between suicide-related outcomes and medical and recreational cannabis use in US youth living in ML states. There are also some limitations related to variable and covariate selection and specificity. Death records may misclassify suicides as unintentional or undetermined deaths, leading to underreporting of suicide and underestimated associations from this sample. Rising concerns about underreporting of intentional fatal drug overdoses in youth during the opioid epidemic have prompted researchers to advocate for better standardization of medical examiner death assessments and incorporation of psychological autopsies into these procedures, based upon the rationale that accurate identification is needed to inform targeted prevention efforts for both intentional and unintentional overdoses.[59] In addition, the date that ML became effective may not accurately reflect implementation of these policies, which could vary by state. This may have led to overestimates of ML-attributed suicides, particularly during the first year of ML. Our sensitivity analysis examining ML effects with a 6-month time lag on suicide outcomes reduces this potential impact. Another limitation is related to confounders. Although we controlled for multiple individual and state-level potential confounders, it is impossible to exclude confounding due to unmeasured factors. We were unable to control for factors (eg, childhood adversity, psychiatric disorders, family dysfunction) known to increase suicide risk. Some confounding variables are better expressed at the county or city level (eg, urbanicity) and do not translate well to state-to-state comparisons. Given this, next-stage studies should focus on how county-level variation in ML implementation and county-level covariates (eg, rural vs urban) affect suicide-related outcomes in US youth. This is especially important, as the majority of Americans now live in states that have enacted ML, and as emerging data show county-to-county variation in implementation within these states as a result of some cities and counties passing local ordinances that either further regulate or ban cannabis markets.[60] Finally, we did not examine changes in specific methods of suicide because of small cell sizes, which would result in unstable estimates. Future work examining suicide method–specific variation associated with MML and RML may be informative.

However, the study also had several strengths. First, we examined a population-wide sample of American youth from across all 50 states and DC with documented suicide outcomes from national death records. Second, we conducted *a priori* analyses across narrow age-bands to identify distinct age effects. Third, we controlled for multiple potentially confounding individual- and state-level variables. Finally, we conducted 4 sensitivity tests to ensure that our estimates were stable.

In conclusion, the current study found a significant association between MML and RML and increased suicides among US female youth. Male and female youth aged 14 to 16 years, a sensitive neurodevelopmental period, were particularly vulnerable. Mechanisms through which MML and RML are related to suicide risk in female youth and younger-aged adolescents warrant further study and should be used to reform cannabis legislation with the goal of mitigating risk for vulnerable subgroups. Over the past 2 decades, US cannabis policy has been primarily profit driven. A shift to a public health–centric approach is needed. Future US cannabis policy should seek a balance between potential risks and benefits for individuals of all ages across the lifespan, and should not discount risk for negative down-stream consequences of policy change on youth.

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Dr. Brock served as the statistical expert for this research.

Author Contributions
All authors conceptualized and designed this study. MH, DLS, GB, and CAF acquired, analyzed, and interpreted the data. CJH, MH, MAF, DLS, and CAF drafted the manuscript. All authors critically reviewed the manuscript for important intellectual content. MH and GB performed statistical analysis. CAF provided project administration and resources. CJH and CAF supervised the study. MH and DLS accessed and verified the data.

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