

United States marijuana legalization and opioid mortality epidemic during 2010–2020 and pandemic implications

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Abstract: Background: The hypothesis that marijuana availability reduces opioid mortality merits more complete testing, especially in a country with the world's highest opioid death rate and 2nd highest cannabis-use-disorder prevalence.

Methods: The United States opioid mortality rate was compared in states and District of Columbia that had implemented marijuana legalization with states that had not, by applying joinpoint methodology to Centers for Disease Control and Prevention data. Variables included race/ethnicity and fentanyl-type opioids (fentanyls).

Results: After the same rates during 2010–2012, the opioid mortality rate increased more rapidly in marijuana-legalizing than non-legalizing jurisdictions (2010–2020 annual pairwise comparison $p=0.003$ for all opioids and $p=0.0004$ for fentanyls). During the past decade, all four major race/ethnicities in the U.S. had evidence for a statistically-significant greater increase in opioid mortality rates in legalizing than non-legalizing jurisdictions. Among legalizing jurisdictions, the greatest mortality rate increase for all opioids was in non-Hispanic blacks (27%/year, $p=0.0001$) and for fentanyls in Hispanics (45%/year, $p=0.000008$). The greatest annual opioid mortality increase occurred in 2020, the first year of the COVID-19 pandemic, with non-Hispanic blacks having the greatest increase in legalizing vs. non-legalizing opioid-death-rate difference, from 32% higher in legalizing jurisdictions in 2019 to more than double in 2020.

Conclusions: Instead of supporting the marijuana protection hypothesis, ecologic associations at the national level suggest that marijuana legalization has contributed to the U.S.'s opioid epidemic in all major races/ethnicities, and especially in blacks. If so, the increased use of marijuana during the 2020–2022 pandemic may thereby worsen the country's opioid crisis.

Keywords: Marijuana protection hypothesis ■ U.S. opioid mortality epidemic ■ Marijuana legalization ■ Race/ethnicity ■ COVID-19 pandemic

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INTRODUCTION

The United States (U.S.) has, by far, the world's highest opioid death rate and, as of 2019, was 2nd among all countries and territories in cannabis-use-

disorder prevalence (Fig. A.1).¹ The country just set a record for overdose deaths during a 12-month period, more than 100,000 and nearly twice the prior year² and of which 70–80% are opioid deaths. Are these dire statistics related, and if so, how?

Three early reports based on a limited number of states in the U.S. presented data supporting the marijuana-protection hypothesis: *availability of marijuana reduces deaths from opioids*.^{3–5} A report in 2018 concluded that medical cannabis legalization was associated with a 30% reduction in Schedule III opioid Medicaid prescriptions, no change in Schedule II opioid prescriptions, and an estimate that, if all the states had legalized medical cannabis by 2014, Medicaid annual spending on opioid prescriptions would be reduced by 17.8 million dollars.⁶ Another report in 2018 attributed reductions in opioid prescribing in the Medicare Part D population to medicinal cannabis laws, and especially in states that permit dispensaries.⁷ A subsequent review concluded that these data were compelling and warranted further exploration of cannabis as an adjunct or alternative treatment for opioid use disorder.⁸ The marijuana industry's campaign to advertise legalization then included reduction in opioid mortality as an advantage (Supplemental Fig. A.2). Most recently, the number of marijuana storefront dispensaries per county in states and the District of Columbia (D.C.) that legalized marijuana was found to be inversely correlated with the county's opioid-related mortality rate.⁹ The more prevalent the marijuana dispensaries, the lower the opioid death rate.

Other studies have not supported the hypothesis. An initial reduction in opioid mortality after medicinal legalization was found to have reversed to an increase that exceeded the pre-legalization opioid death rate and was greater in legalizing than non-legalizing states.¹⁰ Another analysis found little evidence of an association between medical marijuana law enactment and nonmedical prescription opioid use or prescription opioid misuse.¹¹ A study of Colorado data did not find evidence that recreational legalization attenuated the state's increasing opioid death rate.¹² In a national epidemiologic survey of

the U.S., nonmedical prescription opioid use increased 5.8-fold (95%CI=4.2–7.9) and opioid use disorder increased 7.9-fold (95%CI=5.0–12.3) within 3 years of using cannabis.¹³ In a 4-year prospective-cohort study of 1514 patients with chronic non-cancer pain, those who used cannabis daily or near-daily used more opioids than those who did not.¹⁴ In an individual-level analysis of a nationally representative sample, medical cannabis use was positively associated with greater use and misuse of prescription opioids.¹⁵ Among college students, marijuana users were 12 times more likely to use opioids than non-users ($p < 0.02$) and the level of marijuana use was associated with greater likelihood of using opioids ($p < 0.02$).¹⁶ Among pregnant women, the rate of opioid-related treatment admissions was 2.5-fold in states that legalized medicinal marijuana.¹⁷ Both of two large U.S. studies of driving-while-intoxicated arrests showed that drivers testing positive for marijuana also tested positive for opioids more than those testing negative for marijuana.¹⁸ Self-reported marijuana use during injury recovery was associated with an increased amount and duration of opioid use.¹⁹ And for alcohol, when recreational marijuana was legalized in Canada and alcohol-related vehicle accidents were expected to decrease, there was no evidence for this effect in British Columbia.²⁰ In Norway and Israel, patients on opioids who were provided cannabis prescriptions had some subsequent decrease in opioid use, but overall the reductions were marginal.^{21,22} Reviews of randomized trials have concluded that for acute pain cannabinoids were no better than placebo²³ and for chronic pain only marginally better than conventional pain management with pharmacotherapy, physical therapy, or a combination of these.²⁴ In the most recent report, a state-by-state analysis comparing 2006–2011 with 2000–2005 found no overall association between state medical cannabis laws and the rate of opioid overdose.²⁵

To more adequately test the *marijuana-protection hypothesis* with more recent data, we evaluated all 50 states and D.C. during the last decade (2010–2020) by comparing opioid mortality rates in jurisdictions states that had or had not by the start of 2020 legalized marijuana for all opioids and the fentanyl group of synthetic opioids, and recreational marijuana legalization. We also analyzed race/ethnicity, which had not, to our knowledge, previously been analyzed with respect to marijuana legalization *per se*. The COVID-19 pandemic that began in March 2020 significantly altered prior opioid overdose and mortality trends and is therefore separately and provisionally analyzed.

METHODS

Age-adjusted opioid death data in the U.S. were obtained from CDC WONDER.²⁶ Trend analysis was performed with Joinpoint Regression Program version 4.9.0.0,²⁷ applying weighted least squares, logarithmic transformation, and standard errors provided by the Program. The Joinpoint Regression Program identifies when a trend changes to another trend, the average annual percent change (AAPC) and p-values for each trend detected, and relative comparison of concomitant trends via pairwise comparison with either parallel or non-parallel methodology for which we selected the latter. Our primary comparisons and most subtype comparisons were of trends that were not significantly different in the initial years (2010–2012) and hence difference-in-difference method was not necessary and for which we also quantitated the difference between joinpoint-derived regression curves from the area between the curves (ABC).

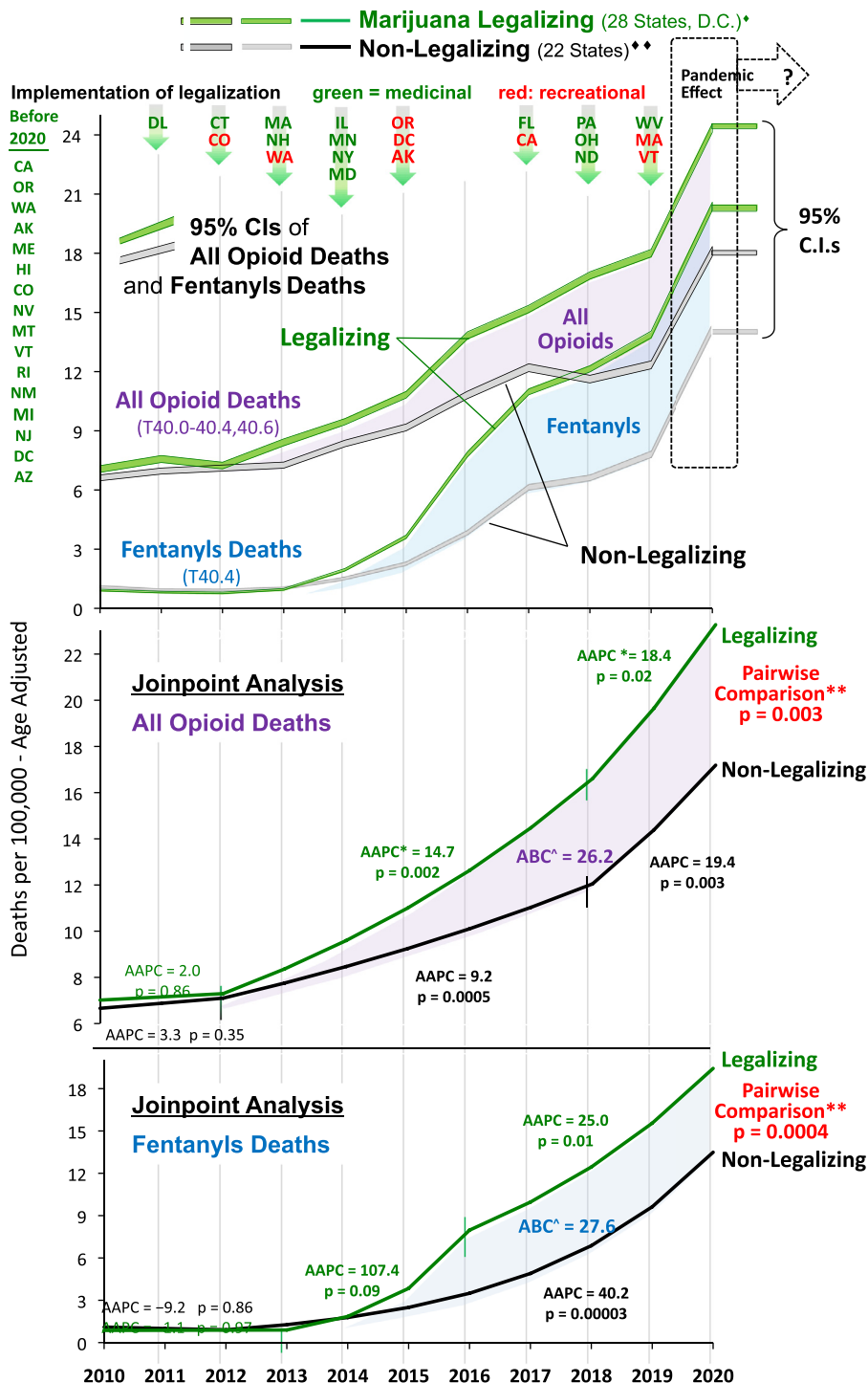
International Classification of Disease (ICD) codes for accidental poisoning (X40–X44), intentional self-poisoning (X60–X64), and other poisoning (Y10–Y14) were used in conjunction with following opioid T-Codes: T40.0 opium, T40.1 heroin, T40.2 other opioids, T40.3 methadone, T40.4 fentanyl and its semisynthetic derivatives (hereafter referred to as *fentanyls*), T40.6 other synthetic narcotics.²⁸ These categories include morphine, hydromorphone, oxycodone, fentanyl, semisynthetic fentanyl moieties, heroin, opium, codeine, meperidine, methadone, propoxyphene, tramadol, and other/unspecified narcotics. Because of the dramatic increase in fentanyls deaths since 2014, this category (T40.6) was also separately analyzed.

Supplemental Table A.1 lists each state and D.C. by whether and when marijuana legalization for medicinal or recreational use was implemented. The legalization implementation dates before 2015 are those published by Powell et al.⁴ Those after 2015 are either from Powell et al.,⁴ Martins et al.,²⁹ or additional information indicated in Supplemental Table A.1.^{30–34}

As of the start of 2020, 29 jurisdictions (28 states and D.C.) had implemented marijuana legalization (the Legalizing Group), as shown at the top of Fig. 1 and listed in Supplemental Table A.1, and 22 states that had not (Non-Legalizing Group), as delineated in Supplemental Table A.1.^{30–34} Georgia, North Carolina, South Carolina, Texas and Wisconsin were included in the non-legalizing group since they legalized only CBD oil for medicinal use and primarily for epilepsy. Arkansas was not included in the Legalizing Group with the assumption that medicinal licenses were not statewide until 2020 (Supplemental Table A.1). Including Arkansas in the Legalizing Group

Fig. 1. 95% CIs (top panel) and Joinpoint/AAPC* Analysis (middle and bottom panels) of Annual Opioid Death Rates, 2010–2020, of Cumulative Aggregate of Marijuana Legalizing Jurisdictions (green data)^ and of Non-Legalizing Jurisdictions (black data)^, U.S., by All Opioids and Fentanyl.

* AAPC - average annual percent change ** non-parallel, joinpoint analysis
 ♦ 28 states and D.C., in temporal order of legislation implementation: CA-California, OR-Oregon, WA-Washington, AK-Alaska, ME-Maine, HI-Hawaii, CO-Colorado, NV-Nevada, MT-Montana, VT-Vermont, RI-Rhode Island, NM-New Mexico, MI-Michigan, NJ-New Jersey, DC-D.C., AZ-Arizona, DE-Delaware, CT-Connecticut, MA-Massachusetts, NH-New Hampshire, IL-Illinois, MN-Minnesota, NY-New York, MD-Maryland, FL-Florida, PA-Pennsylvania, OH-Ohio, ND-North Dakota, WV-West Virginia
 ♦♦ 22 remaining states
 ^ AUC - area between the curves, in deaths per 100,000
 Data Source: CDC WONDER.²⁶



did not alter the results (Supplemental Figure A.3). Using year of legalization instead of year of implementation of legalization accentuated the difference in the all-opioids results and did not significantly alter the fentanyl results (Supplemental Figure A.4). Difference-in-difference methodology was unnecessary to compare subsequent trends since the rates in the two groups were nearly identical for the initial three years of comparison. Also, joinpoint methodology has both parallel and non-parallel pairwise comparison capability.

THEORY/CALCULATION

To more adequately test the marijuana-protection hypothesis, we evaluated all 50 states and D.C. during the last decade (2010–2020) by comparing opioid mortality rates in 22 states that by start of 2020 had not legalized marijuana with a cumulative aggregate of 28 states and D.C. that had. Variables included race/ethnicity and the fentanyl category of synthetic opioids, the latter since they account for most of the recent increase in opioid mortality. Recreational marijuana legalization was assessed in five evaluable states and D.C. The COVID-19 pandemic that began in March 2020 significantly altered prior opioid overdose and mortality trends and is therefore separately and provisionally analyzed.

RESULTS AND DISCUSSION

All opioids and fentanyl comparisons

During 2010–2012, the annual opioid death rates were similar in the Legalizing and Non-Legalizing Groups, with overlapping 95% confidence intervals (CIs) in 2010 and 2012 (Fig. 1 top panel) and similar non-statistically significant trends (AAPC=2.0, $p = 0.86$ and AAPC=3.3, $p = 0.35$, respectively) (Fig. 1 middle panel). Thereafter, the annual opioid death rate increased in both groups, continuously more rapidly during 2012–2020 in the Legalizing Group whereas the increase in the Non-Legalizing Group slowed and stabilized during 2017–2018 before increasing again during 2019–2020 (Fig. 1 top panel). Joinpoint analysis identified a faster rate of increase in the opioid death in the Legalizing Group, with AAPCs of 14.7 ($p = 0.002$) vs. 9.2 ($p = 0.0005$) during 2012–2018 and an overall 2010–2020 non-parallel pairwise comparisons of $p = 0.003$ (Fig. 1 middle panel). Over the entire 2010–2020 decade, the mean rate in the Legalizing and Non-Legalizing Groups increased 16.8 (227%) and 11.1 (160%) deaths per 100,000 per year, respectively, and the Legalizing vs. Non-Legalizing ABC was 26.2 and 27.6

deaths per 100,000 for all opioids and fentanyl, respectively (Fig. 1 middle and bottom panels).

The initial greater increase in the Legalizing Group occurred before the fentanyl epidemic. By 2016, however, the opioid death rate increase was primarily due to fentanyl, especially in the Legalizing Group (Fig. 1 top panel). During 2020, the first year of the pandemic, the opioid death rate accelerated in both Legalizing and Non-Legalizing Groups, due nearly entirely to fentanyl deaths (Fig. 1 top panel). Over the entire 2010–2020 decade, the fentanyl death rate increase was significantly greater in the Legalizing Group (joinpoint non-parallel pairwise comparison $p = 0.0004$) (Fig. 1 bottom panel).

Race/ethnicity trends

Each of the four most common categories of race/ethnicity in the U.S. had evidence for a statistically-significant greater increase in opioid mortality rates during 2010–2020 in the marijuana Legalizing than Non-Legalizing Groups, as measured by annual pairwise comparisons (Fig. 2). In the Legalizing Group, the fastest mortality rate increase for all opioids occurred in non-Hispanic blacks (AAPC=27.0, $p = 0.0001$), whereas for fentanyl it was in Hispanics (AAPC=45.0, $p = 0.0000008$). Non-Hispanic blacks had the greatest absolute differences (ABC=52.2 deaths/100,000) (Fig. 2). Non-Hispanic whites had the greatest statistically-significant differential rate increase between legalizing and non-legalizing jurisdictions, for both all-opioid and fentanyl mortality (annual pairwise comparisons of $p = 0.0002$ and $p = 0.0001$, respectively) (Fig. 2). For all opioids, Asians had no difference in rate increases between legalizing and non-legalizing jurisdictions but for fentanyl they had a distinctly greater increase in legalizing than non-legalizing jurisdictions (pairwise comparison $p = 0.0009$) (Fig. 2).

In terms of year-to-year changes in the annual death rate opioid death rate, it increased steadily overall and in each racial/ethnic population until 2016 after which it declined for 2 years until 2019, the year before the pandemic, mainly due to fentanyl (Fig. 3). Non-Hispanic blacks had the greatest single-year mortality increase prior to the pandemic, both for all opioids and fentanyl (Fig. 3) and by 2019 had the highest death rates for both all opioids and fentanyl (Fig. 4 middle panel). In 1999, Hispanics had the greatest difference between legalizing and non-legalizing jurisdictions, 165% higher in the Legalizing Group for all opioids and 249% higher for fentanyl (Fig. 4 bottom panel).

Fig. 2. Joinpoint/AAPC* Analysis of Pre-Pandemic Annual All Opioid (solid curves) and Fentanyl (dashed curves) Death Rates, 2010–2019, of Legalizing Aggregate (green data) and Non-Legalizing Jurisdictions (black data), U.S., by Race/Ethnicity.

Left Panels: All-Opioid Death Rates; Right Panels: Fentanyls Death Rates

* AAPC - average annual percent change ** non-parallel, joinpoint analysis

^ AUC - area between the curves, in deaths per 100,000

Data Source: CDC WONDER.²⁶

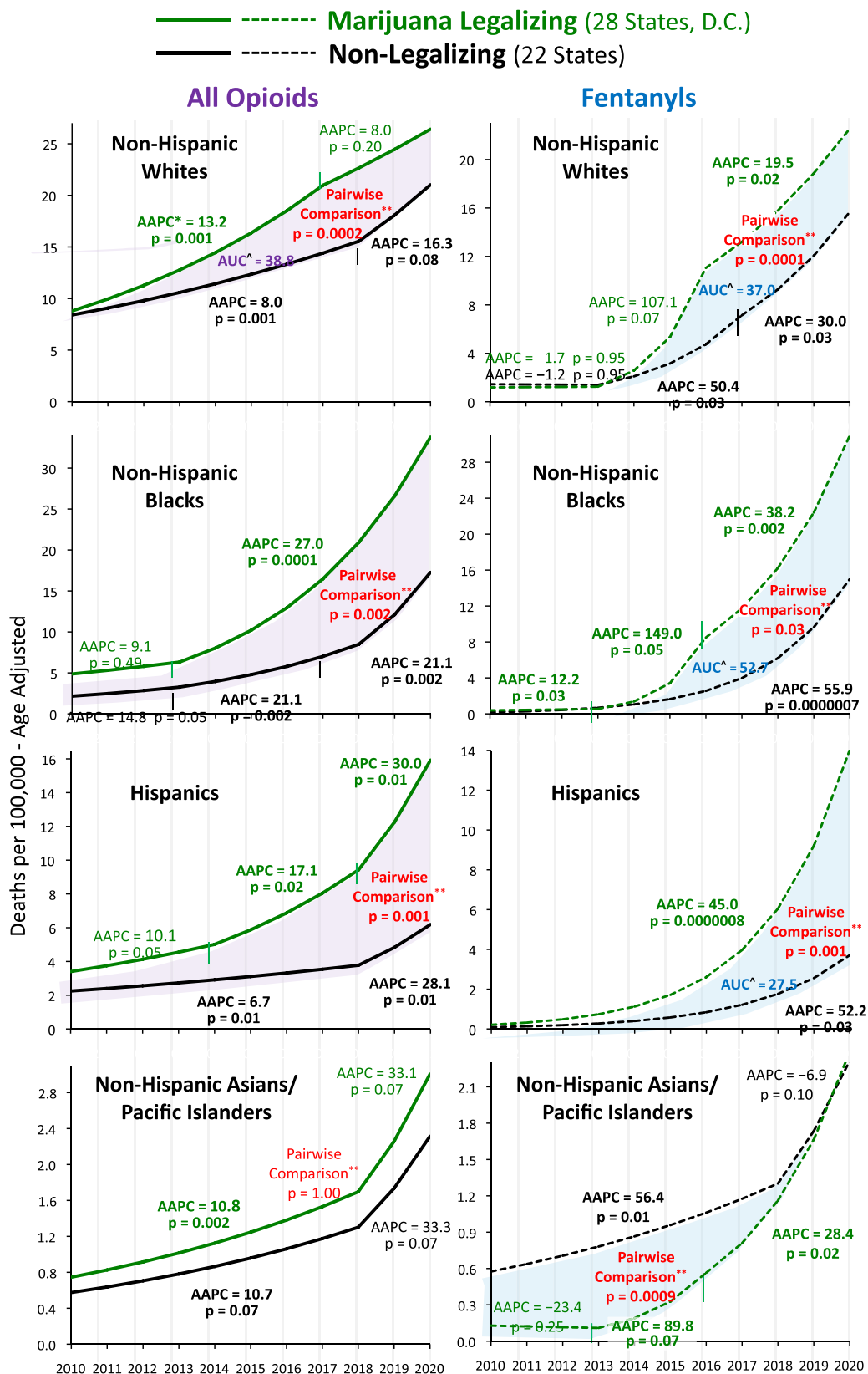


Fig. 3. Annual Change (from year before) in Opioid Death Rate, 2010–2020, U.S., Overall and by Race/Ethnicity and by Portion due to Fentanyl (blue zones).

* Labeled percentages are increases in all opioid deaths from year before

Data Source: CDC WONDER.²⁶

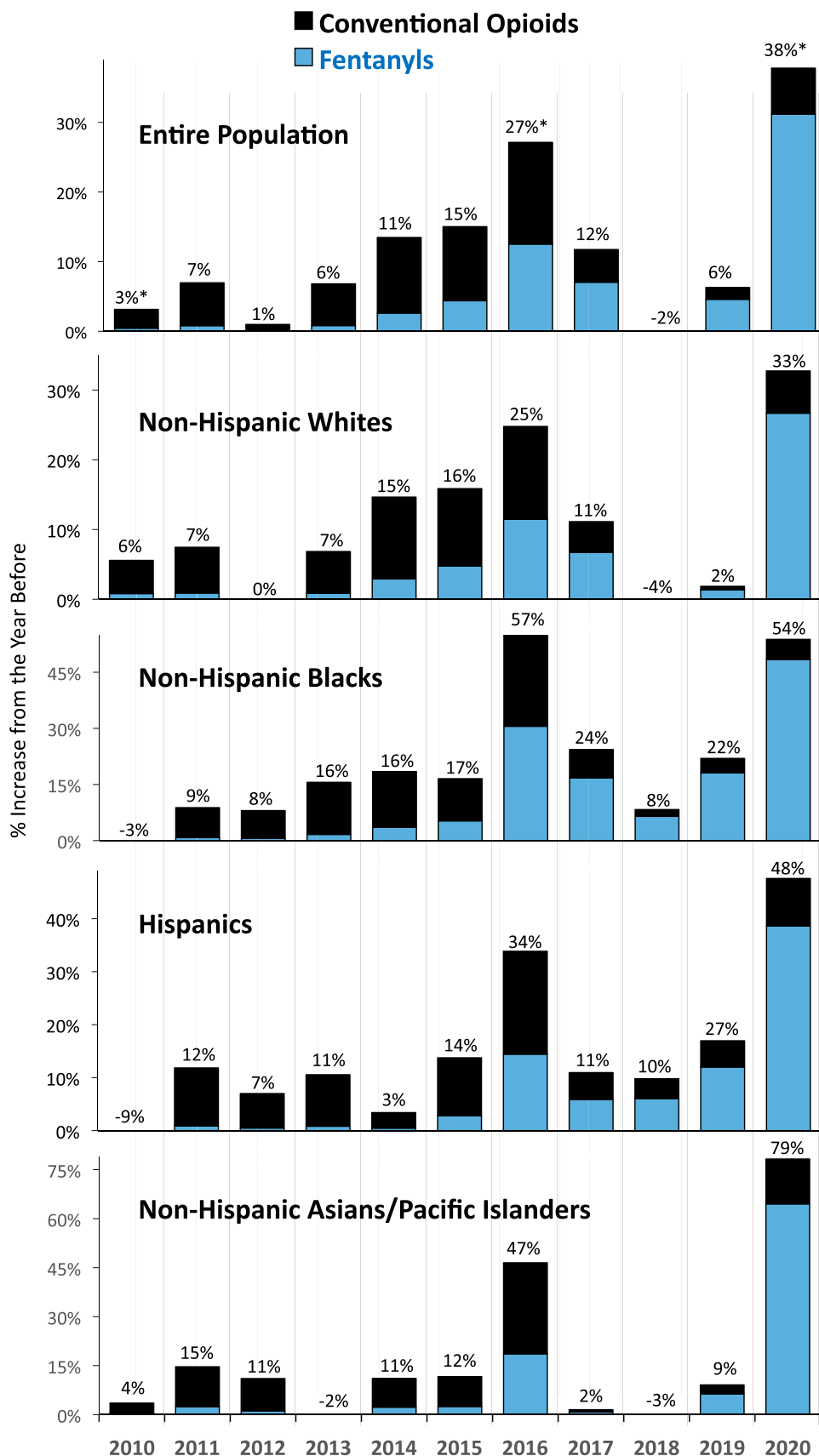
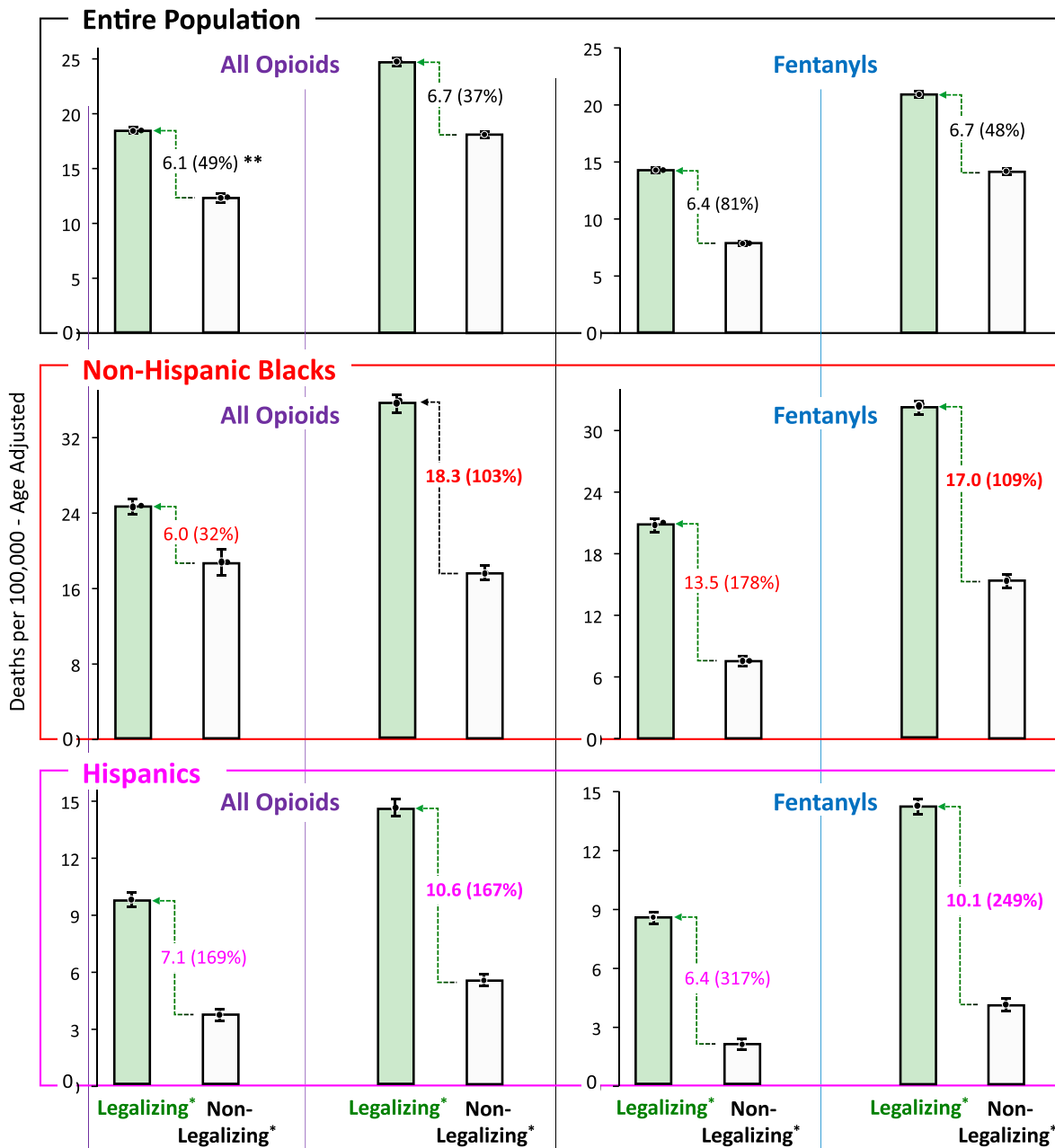


Fig. 4. All Opioid and Fentanyl Death Rate Means & 95% C.I.s among Entire Population, Non-Hispanic Blacks and Hispanics, 2019 and 2020, by Jurisdiction Marijuana Legalization Implementation Status.
 * 29 legalizing and 22 non-legalizing jurisdictions as of January 1, 2020
 ** Absolute difference and % greater the legalizing mean was compared to the non-legalizing mean.
 Data Source: CDC WONDER.²⁶



Recreational legalization

Fig. 5 shows the 6 jurisdictions that legalized recreational use prior to 2017 and are evaluable for comparison of their pre-recreational-legalization opioid death rate trend after recreational legalization implementation and before the pandemic. D.C. had a reversal of what was a slightly decreasing rate prior to legalization to an exponentially

increasing rate that began within 1 year after medicinal legalization implementation was even more rapid after recreational legalization. California also had an exponential increase in its opioid trend within 1 year after recreational legalization. Nevada, Oregon, and Washington had a reversal of a previous decreasing death rate within 1, 3 and 5 years after recreational legalization. Colorado had an increase 6 years after statewide recreational use began.

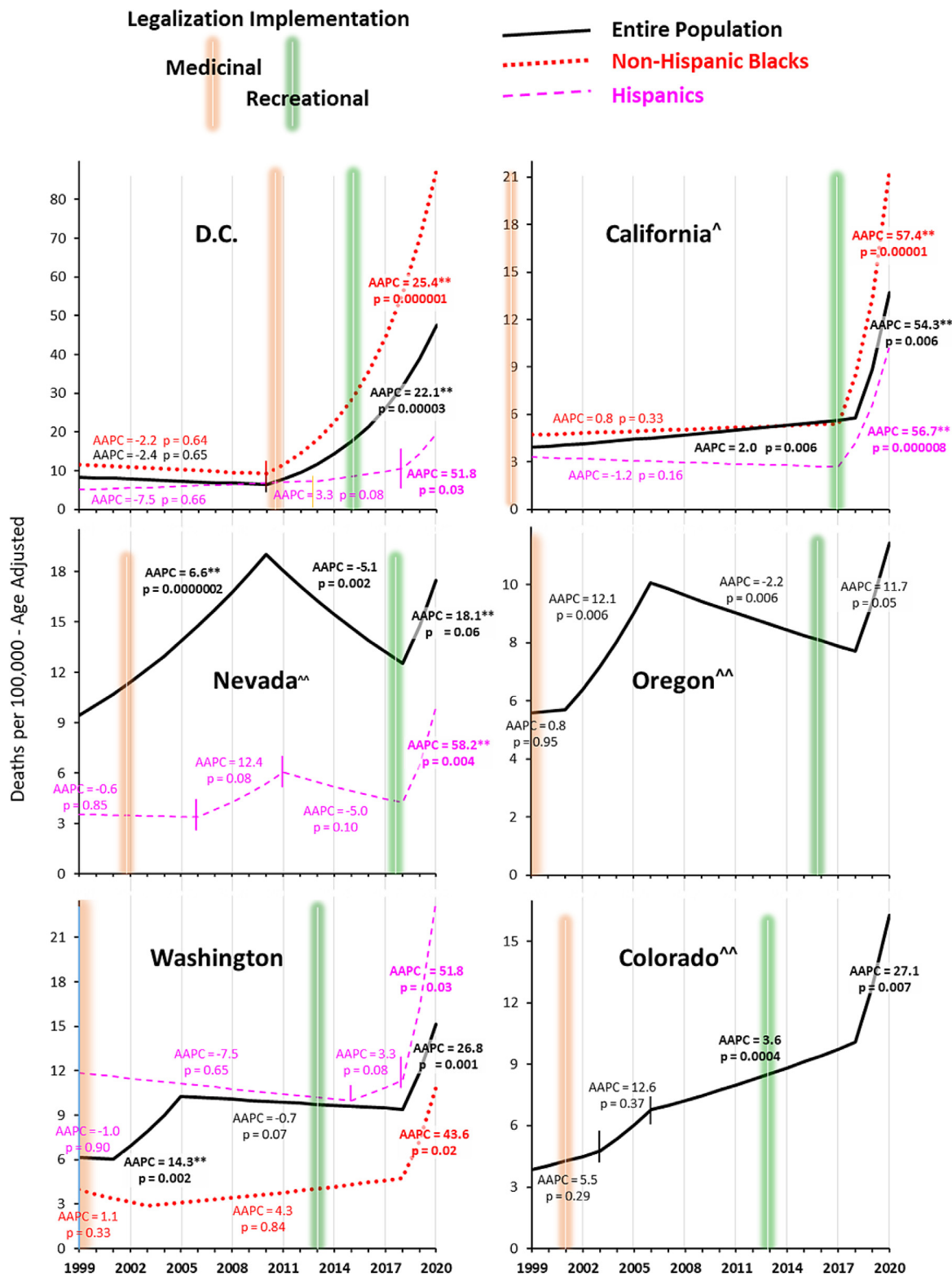
Fig. 5. Joinpoint/AAPC* Analysis of Annual All-Opioid Death Rate, 1999–2020, in Jurisdictions that Implemented Recreational Legalization of Marijuana before 2019.

* AAPC – Average annual percent change **Exponential increase

^ California legalized medicinal use in 1996

^^ Race/ethnicity evaluation limited by population size

Data Source: CDC WONDER.²⁶



Non-Hispanic blacks in California had an exponential opioid death rate increase that began within 1 year of recreational legalization (AAPC=57.4, $p=0.00001$) (Fig. 5). The non-Hispanic black rate in the Nation's capital became the highest in the country in 2019 and 2nd highest in 2020. Hispanics had a reversal of a previous decreasing death rate within 1 year after recreational legalization in California and Nevada and within 3 years in Washington (Fig. 5). None of the jurisdictions had evidence for a decrease in, or even a slowing of, their pre-recreational implementation trend after recreational implementation, either overall or in the evaluable Hispanic and non-Hispanic black trends.

Initial impact of COVID-19 pandemic

During the first year of the COVID-19 pandemic, 2020, the overall opioid death rate in the U.S. increased 38% from the previous year, the greatest annual increase since at least 1999 when the metric was first tracked and 39% greater than the greatest prior annual increase since 1999, in 2016 (Fig. 3 top panel). Since 1999, the U.S. went from its least year of annual opioid mortality increase, 2018, to its worst increase, in 2020, in just 2 years (Fig. 3). Asians/Pacific Islanders had the greatest increase from 2019 to 2020, 79%, and non-Hispanics had the second greatest increase, 54%, followed by Hispanics, 45% (Fig. 3). Fentanyl accounted for more of the pandemic increases in non-Hispanic blacks than in any of the other race/ethnicities (Fig. 3).

In terms of the marijuana legalization status, the increase in both all opioid and fentanyl death rate from 2019 to 2020 was greater in the Legalizing Group for the entire population and for each of the race/ethnicities (Fig. 4). The greatest differential from 2019 to 2020 was in non-Hispanic blacks, from 6 deaths/100,000 (32%) higher in the Legalizing Group in 1999 for all opioids to more than double (18.3 deaths per 100,000 (103%) in 2020 (Fig. 4 middle panel). Asians had the greatest relative increase from 2019 to 2020 (Fig. 3 bottom panel) but the least difference between Legalizing and Non-Legalizing Groups.

Summary

As analyzed, the U.S. data we investigated do not support the *marijuana protection hypothesis*. Undoubtedly, marijuana can help some avoid opioid addiction and overdosing, but at the population level this benefit is not apparent in the U.S. We found no evidence for a reduction in either all opioids or fentanyl death rate in any of the four most common race/ethnicities during the last decade among marijuana legalizing jurisdictions, whether after medicinal or recreational legalization. On the contrary, our results indicate that marijuana legalization is associated with wors-

ening of opioid mortality, whether it was primarily due to conventional opioids, during 2013–2015, or to fentanyl, during 2015–2020.

Gateway potential and biologic mechanisms

The critical issue then is whether the association of opioid mortality with marijuana legalization is causal or unrelated, and if causal, how much of the opioid mortality increase is due to marijuana legalization. Several causal mechanisms can be considered. Biologically, a gateway explanation for the marijuana-opioid connection is plausible since cannabinoids act in part via opioid receptors³⁵ and increase dopamine concentrations similarly to that caused by opioids.^{36,37} Behaviorally and socially, marijuana may be a conduit to the use and eventual abuse of opioids and other addicting substances.^{38–44} A national study of 43,093 cannabis user in the U.S. found that 10%, 20%, and 30% of them had progressed to illicit drug use within 3, 5 and 7 years, respectively, of first exposure to cannabis.⁴² A study of 580 youth followed from ages 6 to 26 found that adolescent-onset marijuana use was associated with opioid misuse in young adulthood, including adjustment for socioecological factors associated with opioid misuse.⁴³ Cannabis use disorder in 21,040 youth aged 10–24 years was linked to a 2.4 (95% CI = 1.39–4.16) higher risk of unintentional overdose death within one year after cannabis disorder diagnosis.⁴⁴

Marijuana's euphoric effect may promote opioid use, including other types such as fentanyl. In a study of U.S. adults with non-medical opioid abuse, opioid use was found to be approximately doubled on days when marijuana was used.⁴⁵ Because in the study this relationship did not appear to depend on pain severity, the authors suggested that marijuana was not used as a substitute for illegal opioids.⁴⁵ Nonetheless, marijuana use was associated with greater illicit opioid use. Also, to the extent that marijuana may ameliorate opioid withdrawal symptoms, users may abuse more opioids since they are not reminded of their addiction situation.

Marijuana's addiction potential is becoming more problematic,⁴⁶ as indicated by the increase in cannabis use disorder prevalence, and especially in the U.S. (Supplemental Fig. A.1). Deaths from marijuana are being increasingly reported, as reported in death certificates reviewed by the CDC. In the U.S., the rate has increased to >1000 deaths per year, and the greatest increase in the rate has been among non-Hispanic blacks (Supplemental Fig. A.5).

Legalizing jurisdictions may also have a culturally greater affinity for substance abuse and be more vulnerable to gateway mechanisms. As noted in Canada, mari-

juana may lead to premature withdrawal from opioid addiction treatment programs.⁴⁷ Although legalization is expected to decrease illicit activity, the black market may paradoxically benefit from access to more abundant hemp and marijuana crops, providing lower prices, and delivering marijuana to users instead of them having to travel to licensed dispensaries.⁴⁸ And, increasingly, because of decreasing wholesale prices of recreational marijuana as legal marketers have proliferated are now partnering with black market operatives to “subsidize our white market with our black market”.⁴⁹

Other studies have documented increases in overdose deaths before and during the pandemic in Hispanic and black Americans.^{50–52} These reports do not specifically mention a possible association with marijuana legalization, but each recommends more research to understand contributing causes.

To the extent that the opioid epidemic may have become worse because of marijuana legalization, it is likely that the opioid mortality acceleration is due more to other factors such as the increasing availability of and lower cost of fentanyl and other non-prescription opioids, the increasing despair of Americans that began before the pandemic and has become worse during it, and the drug culture of the U.S. in general. Also decreased availability of prescription narcotics, as has been accomplished by the medical and pharmacy profession, has increased the demand for and use of black market narcotics. Nonetheless, general legalization of a psychoactive substance increases the drug culture of the society in which it is made available, analogous to the U.S. alcohol post-prohibition history.

Conventional opioids and fentanyl comparisons

The association of marijuana legalization and opioid mortality appears applicable to conventional opioid epidemic before widespread fentanyl availability and to the subsequent fentanyl epidemic. To the extent that the preceding conventional-opioid phase of the opioid epidemic increased opioid addiction, the subsequent increased availability and lower cost of fentanyl may have been facilitated by marijuana legalization. Since most jurisdictions that legalized marijuana had previously decriminalized it, the increased freedom to use previously illicit substances may have also promoted the fentanyl black market. In any event, the opioid mortality increase was greater in legalizing than non-legalizing jurisdictions during both the pre-fentanyl and fentanyl eras. As to race/ethnicity differences, fentanyl has affected Hispanics and black Americans more than other races/ethnicities, as cited in the Introduction, and the combination of opioids with either

cocaine or methamphetamine and other stimulant drugs has been reported to have increased more in non-Hispanic blacks and cocaine/opioid overdose mortality more in Hispanic and Asian Americans.⁵³

Initial pandemic impact

According to preliminary data from the CDC based on data available for analysis on January 2, 2022,⁵⁴ the U.S. had the greatest recorded annual increase in opioid mortality rate during the first year of the pandemic and it further increased 20+% from June 2020 to June 2021.⁵⁵ Our results quantitate the increase in 2020 at 38%, and comparable overall in both legalizing and non-legalizing jurisdictions. Among Hispanics and non-Hispanic blacks, however, the absolute and relative differences between the higher rate in the legalizing than non-legalizing jurisdictions worsened, both for all opioids and for fentanyl. The 2020 rates are stated by the CDC to be under-reported due to incomplete data^{55,56} and hence the actual 2020 increases are probably even greater. Meanwhile, marijuana legalization in the U.S. continues to expand and marijuana sales have skyrocketed during the COVID-19 pandemic.⁵⁷

Limitations

Our investigation has several limitations. Most importantly, the ecological design does not establish attribution or causation. Factors other than marijuana legalization may have resulted in the marijuana legalizing jurisdictions having a higher opioid death rate. Legalizing jurisdictions that are more willing to enable cannabis use may be culturally and psychosocially different from those that are not, in ways that enable opioid abuse such as differences in socioeconomic status, race/ethnicity, or medical and psychiatric diagnoses that may have caused more opioid deaths in legalizing jurisdictions. The economic issue is particularly concerning, given how opioid use disorder is considered as a “disease of despair” brought about by economic hardship. On the other hand, the 2020 gross domestic product per capita in the legalizing states we analyzed was greater than in the non-legalizing states, with means (95% CI) of \$65,584 (\$63,139–\$68,029) and \$56,023 (\$54,252–\$57,794), retrospectively ($p = 0.02$) (Supplemental Table A.2).⁵⁸ With only six evaluable recreational-legalizing jurisdictions, potential differences in the impact of medicinal and recreational legalization could not be quantitated, albeit in the U.S. the degree of overlap between medicinal and recreational cannabis users has been estimated to be nearly 90%.⁵⁹

On the other hand, ecologic associations have been used to support most of the studies that we have cited, including one that theoretically contradicts our results with the

county-level analysis cited in the Introduction. In it, the authors found that the number of marijuana storefront dispensaries during 2014–2017 was inversely correlated with opioid mortality rate during 2014–2018 jurisdictions that by 2017 had legalized marijuana.⁹ The authors did not, however, adjust dispensary store number for population size and thereby likely represented disproportionate usage by more populous counties and by relatively small factions of the community of marijuana users. Also, the impact of legalization *per se* was not directly assessed since jurisdictions that legalized toward the end of the surveillance interval were included. Also, counties in legalizing jurisdictions were not compared with counties in non-legalizing jurisdictions. In a secondary analysis that included the rest of the U.S. that had not legalized marijuana, nearly all of the inverse correlations of dispensaries with opioid death rates were weaker or statistically insignificant. The authors also acknowledged that the source of dispensary information they selected (Weedmaps) had multiple limitations.

Strengths

The current investigation also has several advantages over prior reports. It adds 9, 6, 4, 2 and 1 additional follow-up years to the prior studies.^{3,4,5,12,11}, respectively Compared to the most recently reported state-level analysis²⁵ that presented 2000–2011 data, we included more recent data, up to 2019 and preliminary data for 2020. In comparison to a report that showed a reversal of initial benefit to worsening opioid mortality,¹⁰ our analysis adds two more years of data and D.C., and further strengthens the reversal observation. It also differs in that our control group was states that had not legalized marijuana whereas their control group began with all states and excluded those that legalized when they did. Our analysis of their data shows a divergence in the opioid death rates during 2012–2017 that is similar to what we observed during those years (Fig. 1). Also, we included separate analyses of the T40.4 category of fentanyl and semi-synthetic analogues and we included heroin and opium that were either not assessed^{3,4,11,12} or specified^{5,12} in prior studies.

Comparison with other conclusions

The National Academy of Sciences,⁶⁰ International Association for the Study of Pain,⁶¹ and other experts^{62–64} have concluded that jurisdiction regulations that allow medical cannabis as an opioid substitute for chronic pain or addiction have at best equivocal evidence regarding safety, efficacy, and comparative effectiveness, and substantial evidence that substituting opioid addiction treatments with cannabis is potentially harmful.

IMPLICATIONS

Opioid mortality trends in the United States, a world leader in both opioid mortality and cannabis use disorder, do not support the hypothesis that marijuana availability reduces opioid mortality. During the past decade, the country's opioid mortality trends in marijuana legalizing and non-legalizing jurisdictions suggest the opposite. Non-Hispanic blacks and Hispanics in particular need assistance in reversing trends that may have been facilitated by marijuana legalization. Worsening of its opioid mortality epidemic during the first year of the COVID-19 pandemic, especially deaths from fentanyl and including prescription semi-synthetic opioids,² and its potential causal relationship with the country's increased marijuana legalization, availability and utilization merits in-depth research. Until then, recommendations to legalize marijuana should not be based on attenuating the opioid crisis, and jurisdictions and other countries considering legalization should be prepared to provide more drug overdose prevention.

DECLARATION OF COMPETING INTEREST

All authors have no interests to disclose.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.jnma.2022.03.004](https://doi.org/10.1016/j.jnma.2022.03.004).

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