In cases of opioid overdose, do medical marijuana laws matter?
A case-control study among National Health Interview Survey participants, 1986-2011

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Abstract

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While the proportion of U.S. ambulatory, office-based visits with a primary symptom or diagnosis of pain has remained consistent from 2000 to 2010, the frequency of opioid prescribing among these visits nearly doubled from 11.3% to 19.6% [1]. Concurrently, the U.S. experienced an epidemic of opioid-related morbidity and mortality [2]. Medical marijuana, allowed in states with medical marijuana laws (MMLs), may serve as an alternative to opioids in the treatment of severe or chronic pain [3]. If marijuana is a substitute for opioids, MMLs that increase marijuana use may also be inadvertently decreasing opioid use. It has been hypothesized that this mechanism, marijuana for opioid substitution, may also be driving reductions in opioid-related morbidity and mortality [4, 5]. This dissertation has three aims. The first aim is to assess whether the hypothesis, that state MMLs can reduce opioid-related mortality, is plausible and whether it is consistent with the available literature. The second aim is to replicate prior state-level finding using individual-level data among participants surveyed in the National Health Interview Survey (NHIS), between 1986 and 2009. These individuals are followed up for mortality up to December 31st, 2011. The final aim is to assess whether MMLs have a heterogeneous impact across subpopulations defined by age, sex, and/or race/ethnicity.

In Chapter 1, we find evidence, from a limited number of quantitative studies, that show associations between more liberal marijuana policies and reductions in opioid prescribing, opioid positivity (i.e., use), opioid-related treatment admissions, and opioid-related overdose. From surveys, we found that a majority of medical marijuana patients use marijuana for indications where opioids are commonly prescribed and report reductions in prescription drug use, including opioids specifically. We found the overall quality of the quantitative studies to be

moderate to strong. While results were farily consistent across studies, the reviewed studies all shared similar designs and assumptions. Further, regional heterogentiy in MMLs as well as opioid overdoses is never addressed.

In Chapter 2, among all NHIS adult participants eligible for mortality follow-up and surveyed between 1986 and 2009, we observed 791 cases who died of an opioid overdose. Compared to controls, cases were more likely to be male, middle-aged, non-Hispanic White, separated/divorced; less educated, and have a family income below the poverty threshold. After adjusting for matched calendar year, participant sex, age, race/ethnicity, marital status, educational attainment, and poverty level, we find no overall association between state MMLs and the rate of opioid overdose. Adjusting for region depreciated the association towards a protective effect. Upon stratifying by region, we find that state MMLs were associated with a reduced rate of opioid overdoses in the West between 2006-2011, but not in the Northeast.

In Chapter 3, we find no evidence that the association between state MMLs and opioid overdose is heterogeneous by race/ethnicity or sex. However, we do find evidence that age-dependent heterogentiy is present, and that this heterogeneity is magnified in the West. We find that Western MMLs are associated with a reduced overdose rate for individuals under the age of 60, but not for older adults. In the final chapter, we provide an overview of our findings in the context of the available literature, a discussion of the major strengths and weakness of our study findings, and a recommendation for the direction of future studies.

In conclusion, we find that hypothesis that MMLs can reduce opioid-related mortality is plausible, and that the likely mechanism is substitution. However, in our study, our results were not consistent with this hypothesis overall, and signficant reductions were only present after stratifying by region and by sampling frame. The discrepancy between our findings and prior studies should be explored, particularly in light of how regional variations may impact measures of association.

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This work is dedicated to my parents, who have supported me throughout.

Chapter 1

Medical marijuana and opioid substitution: A review of the literature

Abstract

Background: In this chapter, we assess whether the hypothesis, that medical marijuana laws reduce opioid overdose mortality, is consistent with the available literature. We provide some historical context of marijuana and opioids, including their historical legal status, as well a comprehensive literature search aimed at assessing the plausibility of marijuana-opioid substitution. This includes a review of quantitative studies assessing impacts of marijuana policies as well as surveys assessing opioid use medical marijuana patients.

Search Description: The systematic review was conducted by searching PubMed, Scopus, the Cochrane Library, the National Bureau of Economic Research, and the ProQuest Dissertation Database for existing peer-reviewed studies in English using the search terms ("medical marijuana laws" or "medical marijuana policy" or "medical cannabis law/policy") or ("marijuana" or "cannabis" or "cannabinoid" or "sativex" or "dronabinol" or "marinol") and ("opioid" or "opiate" or "heroin" or "opium" or "pain killers" or "analgesics") and ("dependence" or "treatment" or "addiction" or "overdose").

Results: Nine quantitative and twelve qualitative studies were identified. A variety of methods, including difference-in-difference and synthetic controls, were utilized, and most studies found reductions in opioid-related outcomes after passage of medical marijuana laws. Qualitative studies of current medical marijuana patients often report reductions in prescription medication use as well as specifically, substituting marijuana for prescription opioids. Future studies should note the regional variations in opioid mortality as as well as heterogeneity in MMLs.

Conclusions: In summary, the literature appears to be consistent with the hypothesis that medical cannabis laws can reduce opioid use and consequent opioid-related morbidity and mortality.

Overview

The purpose of this review is to assess whether the hypothesis, that medical marijuana laws reduce opioid overdose mortality, is consistent with the available literature. While the focus of this review will be on the epidemiological literature, brief summaries of evidence from neuroscience and efficacy trials will also be introduced. For our systematic review, we will provide evidence from two relevant domains: 1) studies assessing the impact of cannabis policy on opioid use or opioid-related outcomes, and 2) demographic surveys of medical cannabis patients.

Introduction

While both marijuana and opioids have been used medicinally for thousands of years, their respective histories in Western medicine vary strikingly. Since W.B. O'Shaughnessy introduced marijuana to the west in the early nineteenth-century [1], the use of marijuana or marijuana extracts for medicinal purposes spread rapidly. Marijuana was often compared favorably over opioids, as described in the excerpt below from Walton's comprehensive 1938 report:

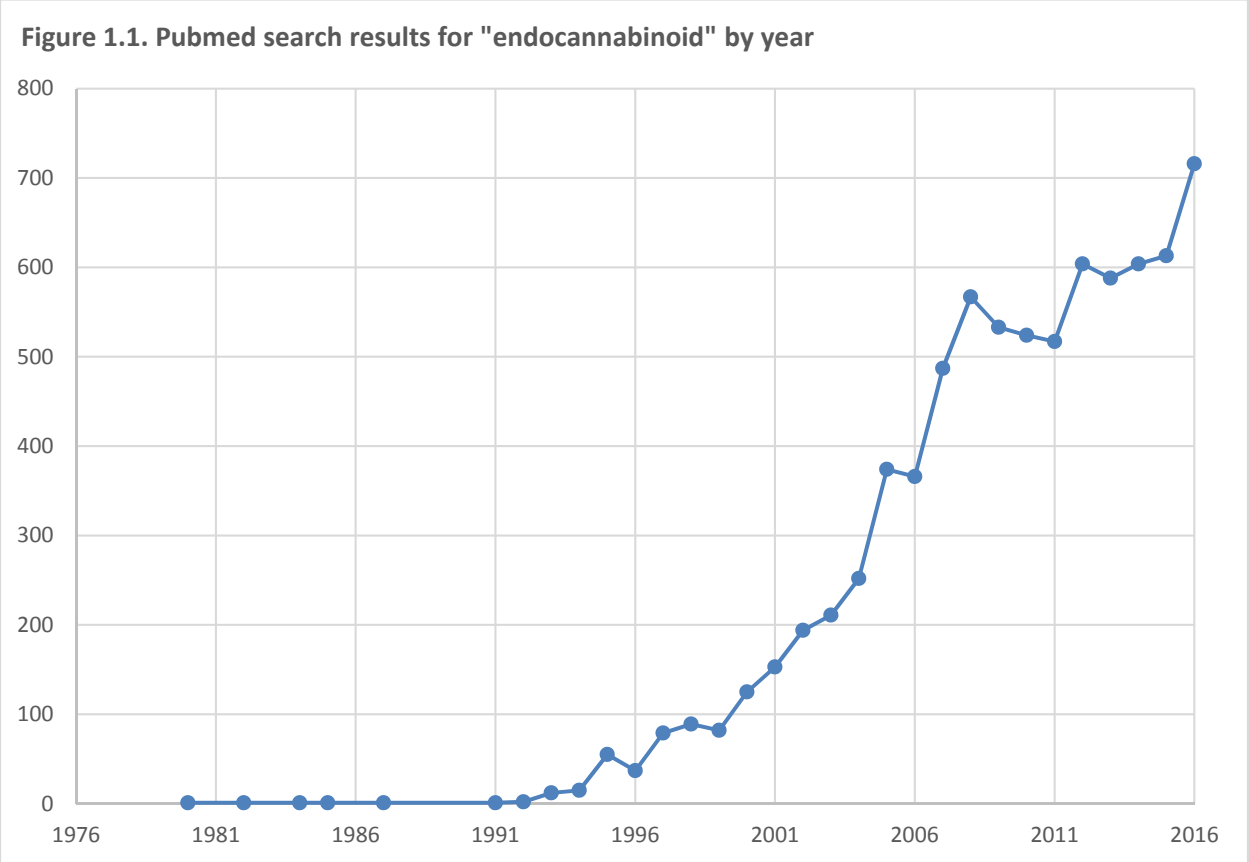
> "*In fact, the most attractive feature of the hemp narcotic was probably the fact that they did not exhibit certain of the notorious disadvantages of the opiates. The hemp narcotics do not constipate at all, they more often increase than decrease appetite, they do not particularly depress the respiratory center even in large doses, they rarely or never cause pruritus or cutaneous eruptions and, most importantly, the liability of developing addiction is very much less than with opiates* [2]".

However, with the introduction of the hypodermic syringe in 1856, water-insoluble marijuana products lost favor to faster-acting opioids, which were administered widely during the Civil War [1]. Still, marijuana-based medications were commercially manufactured and marketed in the United States up to the 1937 Marihuana Tax Act [1], which curbed medicinal use outright. Against the advice of the American Medical Association [3], marijuana was removed from the U.S. Pharmacopeia in 1941, and any use, including medicinal, was criminalized by 1942 [4].

In contrast, the medicinal use of opioids in the United States was used sparingly during most of the twentieth century, as most physicians felt any benefit from long-term use would be negated by “risk of addiction, increased disability, and lack of efficacy over time [5]“. However, beginning in 1996, opioid prescriptions began to increase significantly. A large factor was a focused promotional campaign targeting the treatment of non-malignant chronic pain, which resulted in OxyContin prescriptions increasing tenfold from 670,000 in 1997 to 6.2 million in 2002 [6]. The extension of opioid therapy from an acute pain analgesic to a chronic pain treatment occurred despite any evidence of long-term efficacy [7], and remains unclear today [8].

Yet, the increased utilization of opioids in the treatment of non-malignant pain conditions has continued largely unimpeded. By 2005, 10 million US adults were prescribed long-term opioid therapy, with the average volume of opioid analgesics increasing from 100 morphine equivalent milligrams (MME) per person in 1997 to almost 700 MME in 2007 [9], and sales of prescription opioids correlate strongly with rates of opioid overdose mortality [10]. The rate of opioid overdoses, responsible for 28,647 deaths in 2014 alone, has tripled since 2000 [11]. Explicably, new approaches to the treatment of chronic pain conditions are needed [12]. However, to date, research on the therapeutic efficacy of marijuana is limited. Most efficacy studies are small in sample size, do not assess long-term effects, and often lack methodological rigor [13], and systematic reviews of these studies have yet come to a consensus on whether marijuana is efficacious for the treatment of chronic pain [13-15]. One thing for certain, however, is the reignition of research interest in the medicinal properties of marijuana over the past few decades. This rekindling was largely driven by the discovery of cannabinoid receptors and the identification of the endocannabinoid system [16-18], and is evident in the number of published articles featuring the term “endocannabinoid” in PubMed (Figure 1.1). The endocannabinoid system consists of the aforementioned receptors, CB1 and CB2, endogenous cannabinoids like anandamide, and metabolizing enzymes like fatty acid amide hydrolase (FAAH). Cannabinoid

receptors have been found to mediate acute anxiolysis and analgesia after exercise (e.g., a runner's high) [19], anandamide is known to modulate emotional states like anxiety [20], and individuals with an inactive FAAH gene mutation experience higher levels of anandamide and lower levels of marijuana craving after abstinence [21]. The endocannabinoid system overlaps with the opioid system, interacting together to regulate pain experiences, mood regulation, and reward processing [22, 23]. Moreover, marijuana as an adjunct therapy in combination with opioids may have opioid sparing properties, allowing for lower doses of opioids than without [24], and acute activation or chronic inhibition of the cannabinoid system is now a promising pharmacological target for opioid withdrawal [25, 26].



In summary, marijuana may represent a potential substitute for opioids, either as a primary or adjunct treatment for chronic pain. Substitution between these two substances has been observed previously, albeit in a legal regime and in the context of mostly non-medical use.

Chandra and Chandra found evidence that opium and hashish were substitutes in the Punjab province of British India (1907-1918), based on historical price and consumption data [27]. This review will focus on similar examples of substitution in the United States.

Description of the search

The systematic review was conducted by searching PubMed, Scopus, the Cochrane Library, the National Bureau of Economic Research, and the ProQuest Dissertation Database for existing peer-reviewed studies in English using the search terms ("medical marijuana laws" or "medical marijuana policy" or "medical cannabis law/policy") or ("marijuana" or "cannabis" or "cannabinoid" or "sativex" or "dronabinol" or "marinol") and ("opioid" or "opiate" or "heroin" or "opium" or "pain killers" or "analgesics") and ("dependence" or "treatment" or "addiction" or "overdose"). An initial review by title and abstract was conducted first to identify relevant papers, which were stored in an EndNote library. After removing duplicates, 2,029 articles were obtained. Next, the title and abstract of each selected paper was assessed according to our inclusion criteria. To be included, a paper must report on either: 1) the potential for marijuana/opioid substitution; or 2) opioid use among medical cannabis patients. Non-human studies were excluded.

Search Results

Of the 2,030 records identified for screening, 1,994 were removed after abstract review, with the majority of exclusions identified as non-human studies. Of the remaining 36 studies, 15 were excluded after a full-text review (see Figure 1.2). The remaining 21 studies are discussed below.

Quantitative studies assessing changes in cannabis policy on hard drug use

Of the 21 studies, nine were identified as quantitative studies assessing the impact of changes in cannabis policy on opioid use or related outcomes [28-35]. The earliest study, written by Model [28], assessed the impact of cannabis decriminalization policies on standard metropolitan

statistical area-level emergency room episodes from the Drug Abuse Warning Network (DAWN) between 1975-1978. Using a difference-in-difference study design, Model found that decriminalization was associated with increases in the number of emergency room episodes involving cannabis and a decrease in episodes involving other drugs.

Whilst Model focused on the repeal of cannabis criminalization, the remaining studies focus on the introduction of medical cannabis laws in the U.S. The first of these studies, Bachhuber et. al. [29], found a 25% reduction in the mean overdose rate associated with MML implementation, and a significant trend over time from 1999-2010. In line with Model's earlier work, Chu [30] found a 15-20% decrease in heroin-related admissions associated with MML implementation, using data from the U.S. Treatment Episode Data Set (TEDS) from 1999-2011. These findings were further supported by Powell et. al. [32], who assessed the impact of MML on opioid analgesic treatment admissions (TEDS), age-adjusted opioid overdose rates, state-level morphine equivalent milligrams dispensed, and self-reported nonmedical use. The authors found significant reductions in all outcomes, with the strongest associations observed when state MMLs provided legal access to dispensaries. As a follow-up, Smart [35] used available state-level medical cannabis program enrollment data as a surrogate for MML implementation. Using an age-stratified outcome, Smart found that a one percent increase in MML registration rates was associated with an 11-15% reduction in opioid-related overdose mortality for adults aged 46-65.

The results above detail observed associations between MMLs and opioid morbidity and mortality. The remaining studies discuss potential mechanisms behind these findings, specifically whether MMLs reduce opioid use or prescribing. Wen et. al. [31], using a pooled cross-sectional design and the National Survey on Drug Use and Health (NSDUH) between 2004-2012, found no association between MML implementation and self-reported nonmedical use of prescription opioids. Powell [32], using the same NSDUH data aggregated at the state-

level, found that while MML implementation itself was not associated with reduction in the prevalence of nonmedical use, legal marijuana dispensary access was. Kim et. al. [34], using an objective measure of opioid use (i.e., opioid positivity in blood/urine analysis), found a significant reduction in opioid use associated with crashing in a state with MML for drivers 21-40 but not for other ages. In regards to opioid prescribing, Bradford and Bradford [33, 36] found that operational MMLs were associated with reductions in the average daily dose of opioid analgesics dispensed using Medicare Part D Prescription Drug Event Data (2010-2013) and Fee-for-Service Medicaid prescribing data.

Strengths and limitations of quantitative studies

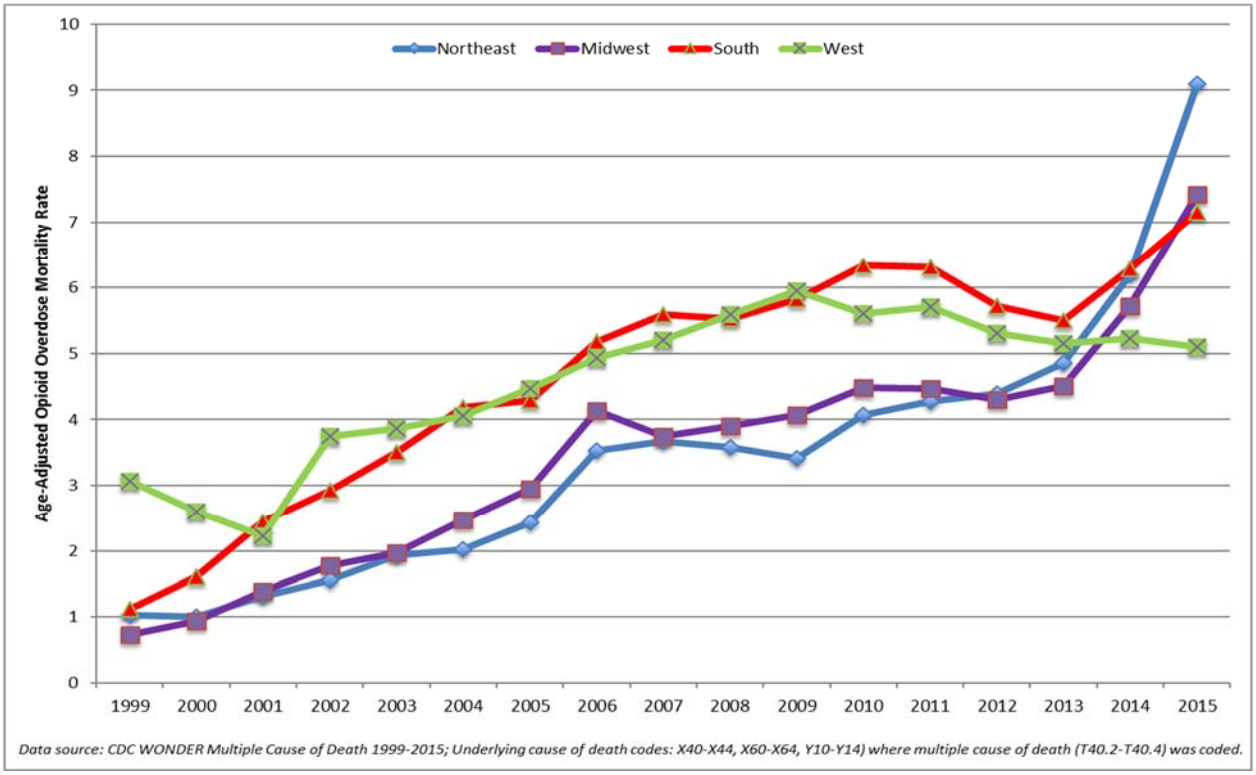
To assess the quality of these studies, we adopted a modified version of the Quality Assessment Tool for Quantitative Studies [37]. Here, we focus on five domains: sample selection, study design, exposure assessment, outcome assessment, and statistical analysis (see Table 1.2). Domains pertaining to randomized trials were obmitted (e.g., blinding). *Sample selection*: Four studies including Model [28], Chu [30], Bradford [33, 38] and Kim [34] utilize more select samples that may hamper the transportability of their findings to different populations. This may occur if the population utilizing emergency room or treatment services is not representative of the target population. The remaining studies used outcomes that were derived either from a nationally representative sample or recorded through the National Vital Statistics System. *Study design*: all studies utilized either ecologic time-series or pooled cross-sectional designs. *Exposure assessment:* While Model assessed marijuana decriminalization and not MMLs, the authors did examine whether specific provisions of these policies were consistent across all four exposed states. In contrast, Bachhuber utilized a binary indicator of MML implementation, ignoring potential heterogeneity in MMLs [39]. Other studies either separately assessed or included policy provisions like access to legal dispensaries [30], legal home cultivation, allowances for chronic/severe pain, or patient registry [31, 32]. The remaining

studies used a more stringent measure of MML, operational status, which is defined as access to medical marijuana through either home cultivation or active dispensary [33, 34, 38]. *Outcome assessment*: a broad range in outcomes is exhibited, including hospital or treatment admissions involving heroin or other drugs, opioid prescribing in Medicare and Medicaid, self-reported and objective measures of opioid use, and opioid-related treatment admissions and overdose. *Statistical Analysis*: Though the studies differ on unit of analysis, sample, and time, the methods are largely the same. All studies except Kim et. al. and Smart et. al. [34, 35] employ a difference-in-difference design by including a state fixed effect, though both Kim and Smart include sensitivity analyses featuring state fixed effects. In brief, this method contrasts the before vs. after change/trend in exposure status changers to the change/trend observed in a control group. While this method requires a sufficient sample of exposed units with before and after data, it does preclude the need to control for MML propensity (i.e., having ever passed an MML) that arises when using a binary MML indicator and no state fixed effect (e.g., in multilevel models) [40]. Regarding control for potential confounding factors, all of the studies assessing MMLs include some measure of prescription drug monitoring programs (PDMPs), a contemporaneous policy to MMLs that specifically aims to reduce morbidity/mortality related to prescription drugs. Analogous to the heterogeneity observed in MMLs, PDMPs provisions vary, though the proactive status of a program (i.e., if states are required/permitted to report suspicious or statistically outlying prescribing) is a more robust measure of PDMP effectiveness than PDMP enactment alone [41].

In summary, most of the studies are of moderate quality with some that are high, defined as having no weak domain ratings [32, 33, 35, 38]. For some, the outcome may not be relevant. The hospital and treatment admissions in Model [28] and Chu [30] are of drugs other than marijuana and heroin, respectively. Furthermore, the population that utilizes emergency rooms or accesses treatment may differ from the population at large. Similarly, the deceased driver

sample in Kim [34] is drawn from select states that perform majority drug testing of its deceased drivers. Bachhuber [29] did not consider heterogeneity in MMLs, and given the aggregated nature of the data, is unable to examine differential impacts across age groups. The outcome in Wen [31] is reported nonmedical use of prescription opioids, which excludes any measure of legitimate/medical opioid use. The remaining studies [32, 33, 35, 38], while largely similar in design and methods, circumvent many of these limitations related to selection, exposure heterogeneity, and outcome specificity.

Figure 1.3. Age-adjusted opioid overdose mortality rates by region: 1999-2015 CDC WONDERS



However, none of these studies address the geographic concentration of MMLs in the West and the Northeast [42], which may be pertinent given known regional variations in opioid overdose mortality (see Figure 1.3). For example, if the Western region is positively associated with opioid overdose (e.g., if there are more overdoses in the West) and positively associated with MMLs

(e.g., if there are more MMLs in the West), any estimated measures of association may be positively biased and conservative (e.g., towards the null when assessing a protective effect). Alternatively, if the Western region is negatively associated with opioid overdose, as it appears to be from 2009 onwards, then any findings may be negatively biased and susceptible to false positive results (i.e. Type I error). Furthermore, it is worth noting that in the Northeast, the only other region with operational MMLs in our data, the trend in the annual rate of opioid overdose is nearly opposite of that observed in the West. While MMLs are present in both regions, they may be qualitatively different in terms of regulation and access. This heterogentiy in exposure may necessitate either regional stratification or a more sensitive MML classification (e.g., active vs. inactive).

Qualitative studies assessing opioid use among medical cannabis patients

The remaining twelve studies are surveys [43-54], with the majority profiling current or prospective medical cannabis patients, and either assess beliefs regarding cannabis/opioid substitution or changes in opioid use related to medical cannabis. For example, in a survey of Canadian palliative care patients (n=68) in 2003, Gallagher et. al. [43] found that the majority of patients agreed “cannabis was safer than morphine” and were more comfortable with cannabis for pain or nausea. In a retrospective chart review of 139 patients legally qualified for medical cannabis in Washington state, Aggarwal et. al. [44] found 20% of patients had histories indicating cannabis as more effective than previously prescribed pain medications, or reported reductions in concomitantly used opioids. Among surveys of current medical cannabis patients from California (2009-2011), British Columbia (2012), and Rhode Island (2015), 60-80% of patients reported using cannabis as a substitute for prescription drugs [45-47, 50], with the majority of patients in one survey reporting using cannabis to relieve pain [46]. Using more in-depth qualitative interviews of cannabis patients (n=19) and caregivers (n=9) in Michigan, Peters et. al. [48] found that all patients who had previously been treated with opioids claimed

they had reduced or eliminated use of prescription painkillers, and had reported eased withdrawal from opioids due to cannabis use.

In an examination of medical cannabis patients in the Netherlands, virtually all patients reported some prescription medication use in the six months prior to medical cannabis initiation, with 44% reporting past six-month opioid analgesic use [49]. In one qualitative study of Baby Boomers in the San Francisco Bay Area (n=97), those who reported using cannabis as an alternative to prescription drugs were primarily driven by perceptions of cannabis being safer, having less adverse side effects, lower risk of addiction, and greater effectiveness in relieving symptoms [51]. In two profiles of prescription opioid use among medical cannabis patients in Michigan, 63% reported using prescription pain medication within the previous month for pain relief, though the majority indicated a strong desire to reduce pain medication use [52], and medical cannabis initiation was associated with a 64% reduction in opioid use, decreased number and side effects of pain medications, and improved quality of life [53]. Finally, in an online and in-person survey of Canadian medical cannabis patients, 80% reported using cannabis as a substitute for pain medication, with the majority of these patients identifying chronic pain as their primary indication for cannabis use [54].

Summary

Overall, we consider the body of evidence regarding the potential for MMLs to reduce opioid-related mortality to be moderate. The reviewed quantitative studies share similar findings across a breadth of data sources and outcomes. While there are a number of limitations to the studies, most are minor (e.g., transportability of results) and present in some (e.g., crude exposure measurement) and either addressed or circumvented in others. Partly by design, the one limitation shared across all studies is the potential for confounding. This may be residual due to an unstable and/or unreliable measure (e.g., PDMP enactment) or unmeasured. Geographic region meets criteria as a potential confounder, is measured, and to date, has not been

accounted for. Further, given that MMLs in the West may be qualitatively different from MMLs in the Northeast [42], assessing regional heterogeneity in the association between MMLs and overdose may also warranted

In summary, the literature appears to support the hypothesis that medical cannabis laws may reduce opioid use and consequent opioid-related morbidity and mortality. However, the current body of evidence, due to shared design and/or data source, share similar limitations. Replicating these observed associations using novel methods, holding varying assumptions, and in unqiue data sources has not yet been preformed. Further, prior studies have yet to account for regional heterogentiy in the outcome or exposure. Future research should assess whether these regional variations are driving the observed associations as well as the potential for regional heterogeneity in the impact of MMLs

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Figure 1.2. PRISMA Flow Diagram

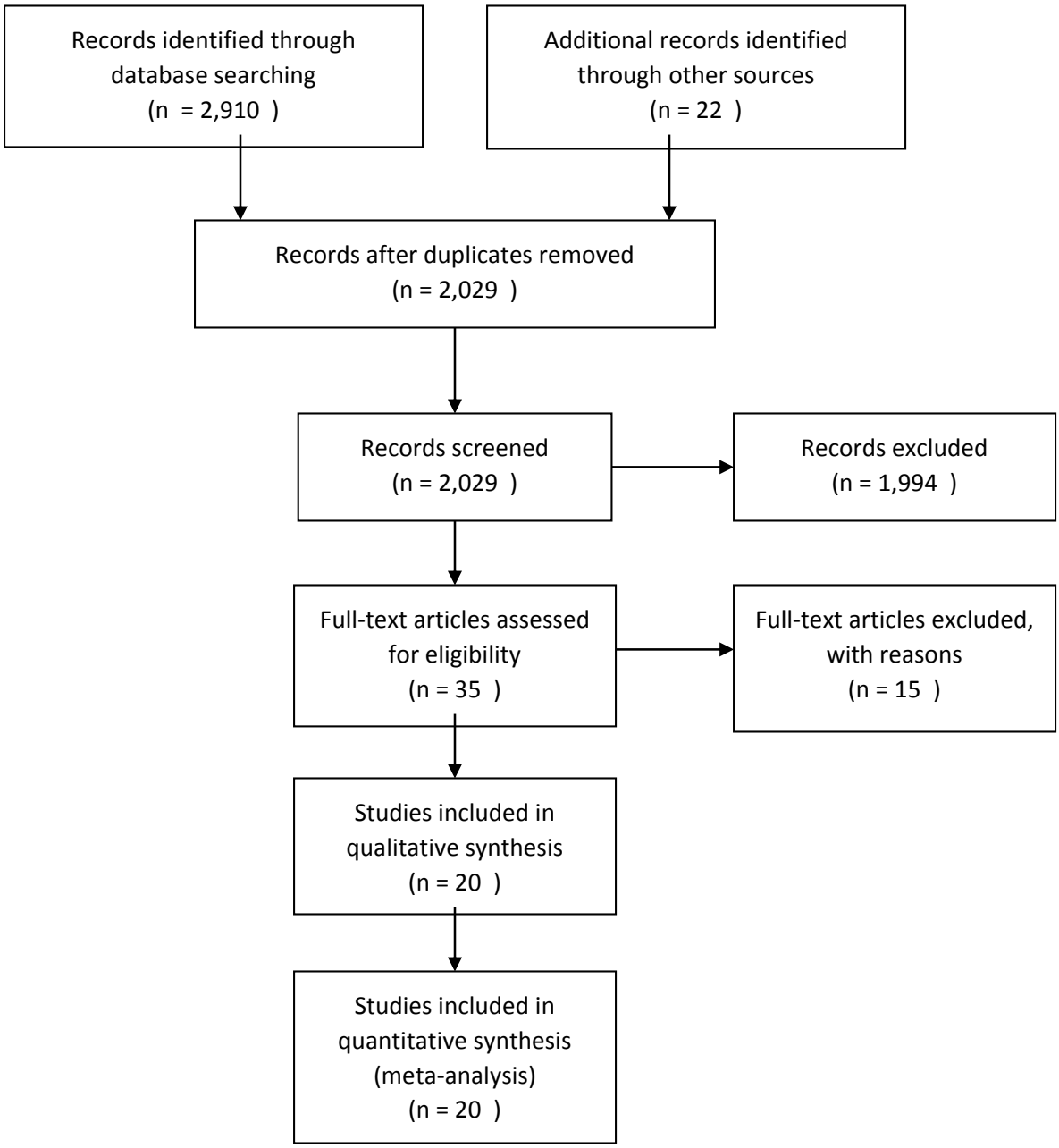

Table 1.1. Quantitative studies assessing changes in cannabis policy on hard drug use

Author (Year)	Title	Study Design / Data Source	Comparison Group	Outcomes	Control Variables	Results
Model (1993) **[27]**	The effect of marijuana decriminalization on hospital emergency drug episodes, 1975-1978	Time-series analysis using standard metropolitan statistical area (SMSA) level data on hospital emergency room drug episodes from the Drug Abuse Warning Network	Within-SMSA before vs. after marijuana decriminalization (difference-in-difference (DiD))	Hospital emergency room episodes involving marijuana and episodes involving other drugs	SMSA and period fixed effects, aggregated demographic characteristics at SMSA level, random error	Changes in marijuana's legal status were accompanied by increases in the number ER marijuana episodes and decreases in the number of mentions of other drugs, indicating substitution towards marijuana and away from other drugs
Bachhuber (2014) **[28]**	Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010.	Ecological time-series, 50 U.S. states; CDC Mortality Data from 1999-2010	Within-state before vs. after MML implementation (DiD)	Age-adjusted opioid analgesic overdose death rate (CDC)	State and year fixed effects, 3 prescription drug monitoring program (PDMP) indicators, unemployment rates	States with MML had 25% lower mean overdose rate, trend over time significant
Chu (2015) **[29]**	Do medical marijuana laws increase hard drug use?	Ecological time-series, 50 U.S. States from 1992-2011; Treatment Episode Data Set	Within-state before vs. after MML implementation (DiD)	Adult heroin-related treatment admissions (TEDS)	State and year fixed effects, state-specific time trends, marijuana decriminalization	States with MML had 15-20% decrease in heroin-related treatment admissions
Wen (2015) **[30]**	The effect of medical marijuana laws on adolescent and adult use of marijuana, alcohol, and other substances	Pooled cross-sectional time-series, 50 U.S. states; National Survey on Drug Use and Health (NSDUH) restricted data, 2004-2012	Within-state before vs. after MML implementation (DiD)	Self-reported nonmedical use of prescription pain medications	State and year fixed effects, state-specific linear time trends, individual and state level demographic and economic characteristics	Non-significant immediate or delayed effect of MML implementation on non-medical use of prescription pain medication (trend towards significance)

Author (Year)	Title	Study Design / Data Source	Comparison Group	Outcomes	Control Variables	Results
Powell (2015) **[31]**	Do Medical Marijuana Laws Reduce Addictions and Deaths Related to Pain Killers?	Ecological time-series; TEDS 1992-2013; CDC Mortality 1999-2013; Automation of Reports and Consolidated Orders System (ARCOS) 2000-2011; state-level NSDUH	Within-state before vs. after MML implementation (DiD); synthetic controls;	Pain-reliever specific treatment admissions (TEDS); age-adjusted opioid-related overdose rate (CDC); morphine equivalent milligrams dispensed	State and year fixed effects; percent of state that is male, white, and age distribution, state unemployment rate; 3 PDMP indicators	States with legal access to dispensaries have reductions (10-20%) in opioid-related treatment admissions, opioid-related overdose mortality, legal opioid dispensing, and self-reported nonmedical use of prescription opioids
Bradford (2016) **[32]**	Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D.	Physician-state level time-series analysis; Medicare Part D Prescription Drug Event Analytical File 2010-2013	Within-physician before vs. after MML implementation (DiD)	Average daily dose of analgesics, per physician per year (Medicare Part D)	Physician and state characteristics, county-level demographic variables; clustering at physician level	States with MML had a reduction of 1,826 daily doses for pain, filled per physician per year.
Kim (2016) **[33]**	State Medical Marijuana Laws and the Prevalence of Opioids Detected Among Fatally Injured Drivers	Pooled cross-sectional time-series, 18 U.S. states from 1999-2013; Fatality Analysis Reporting System (FARS)	Within-state (DiD) and between-state before vs. after MML	Opioid positivity in fatally injured driver (FARS)	State fixed (and random) effects, year fixed effects, 4 PDMP indicators, driver age, gender, and blood alcohol content	21-40 year old drivers crashing in states with MML had half the odds of testing positive for opioids

Author (Year)	Title	Study Design / Data Source	Comparison Group	Outcomes	Control Variables	Results
Smart (2016) **[34]**	The kids aren't alright but older adults are just fine: Effects of medical marijuana market growth on substance use and abuse.	Ecological time-series; 50 US states; CDC Mortality Data from 1990-2013	MML states with lower vs. higher registration rates per capita, (DiD)	Opioid analgesic overdose death rate (CDC) stratified by age	State and time fixed effects, state demographics and economic characteristics, substance-related policies influencing marijuana use	One percent increase in registration rates associated with 11-15% reduction in opioid-related overdose mortality for adults aged 45-64
Bradford (2017) **[37]**	Medical Marijuana Laws May Be Associated With A Decline In The Number Of Prescriptions For Medicaid Enrollees	State/quarter level time-series analysis; Fee for service Medicaid Prescriptions 2007-2014	Within-state/quarter before vs. after MML implementation (DiD)	Average daily dose of analgesics, per state/quarter	Physician and state characteristics, county-level demographic variables; clustering at physician level	The use of prescription drugs for pain in fee-for-service Medicaid was lower in states with medical marijuana laws than in states without such laws.

Table 1.2. Modified Quality Assessment Tool For Quantitative Studies

Components	Item	Model (1993) [27]	Bachhuber (2014) [28]	Chu (2015) [29]	Wen (2015) [30]	Powell (2015) [31]	Bradford (2016) [32]	Bradford (2017) [37]	Kim (2016) [33]	Smart (2016) [34]
Sample Selection	Q1. Are the individuals selected to participate in the study likely to be representative of the target population? (1=Very likely; 2=Somewhat likely; 3=Not likely; 4=Can't tell)	2	1	2	1	1	2	2	2	1
	Q2. What percentage of the selected individuals agreed to participate? (1=80-100% agreement; 2=60-79% agreement; 3=less than 60%; 4=Not applicable; 5=Can't tell)	1	1	1	2	1	1	1	1	1
	Overall Rating (1=strong, 2=moderate, 3=Weak)	2	1	2	1	1	1	1	2	1
Study Design	Q1. Indicate the Study Design	ECT	ECT	ECT	PCT	ECT	ECT	ECT	PCT	ECT
	Was the study described as randomized?	No	No	No	No	No	No	No	No	No
	If YES, was the method of randomization described?									
	If YES, was the method appropriate?									

	Overall Rating (1=strong, 2=moderate, 3=Weak)	1	1	1	1	1	1	1	1	1
**abbreviations: ECT (ecologic time-series); PCT (pooled cross-sectional)*										
Exposure Assessment	Were the data collection tools shown to be valid? (1=Yes, 2=No; 3=Can't tell)	1	1	1	1	1	1	1	1	2
	Were data collection tools shown to be reliable? (1=Yes, 2=No; 3=Can't tell)	1	1	1	1	1	1	1	1	1
	Overall Rating (1=strong, 2=moderate, 3=Weak)	2	2	1	1	1	1	1	1	1
Outcome Assessment	Were the data collection tools shown to be valid? (1=Yes, 2=No; 3=Can't tell)	1	1	1	1	1	1	1	1	1
	Were data collection tools shown to be reliable? (1=Yes, 2=No; 3=Can't tell)	1	1	1	1	1	1	1	1	1
	Overall Rating (1=strong, 2=moderate, 3=Weak)	1	1	1	2	1	1	1	2	1

Statistical analysis	Indicate the unit of allocation (e.g., community, organization/institution, practice/office, individual)	2	2	2	1	2	2	2	1	2
	Indicate the unit of analysis	SMSA/ Quarter	State/ Year	State/ Year	Individual	State/ Year	Physician/ Year	State/ Quarter	Individual	State/ Year
	Are the statistical methods appropriate for the study design? (1=Yes; 2=No; 3=Can't tell)	1	1	1	1	1	1	1	1	1
	Fixed effect?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
	Additional design controls?	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
	Overall Rating (1=strong, 2=moderate, 3=Weak)	1	1	1	1	1	1	1	1	1
Global Rating	1=STRONG (no WEAK ratings); 2=MODERATE (one Weak rating); 3=WEAK (two or more WEAK ratings)	2	2	2	2	1	1	1	2	1

Table 1.3. Qualitative studies assessing opioid use among medical cannabis patients

Author (Year)	Title	Study Design	Sample Characteristics	Health Status	Relevant Results
Gallagher (2003) **[41]**	Attitudes and beliefs about the use of Cannabis for symptom control in a palliative population	Survey of palliative care patients (n=68) on attitudes and beliefs about the medical use of cannabis	Mean age of 56.6 (range 29-92), 55.4% female, 86% white; 64% post-high school education;	Self-reported pain (VAS), mean pain score 4.9, mean nausea score 2.9, and mean anxiety score of 3.5	46% agreed that "cannabis was safer than morphine"; 81% felt comfortable with cannabis use for pain and/or nausea
Aggarwal (2009) **[42]**	Characteristics of patients with chronic pain accessing treatment with medical cannabis in Washington State	Retrospective chart reviews of 139 patients legally qualified for medical cannabis use in Washington state	87 males, median age 47 years; 52 females, median age 48 years; Sample combined had 236.4 patient-years of authorized use	88% reported >1 chronic pain syndrome; 82% myofascial pain; 64% neuropathic pain; 52% disco-genic back pain; 26% osteoarthritic pain; 14% fibromyalgia, most common	19% of patients' charts had recorded medical histories indicating cannabis as better than all other pain medications used previously, or report reductions in dosages of concomitantly used opioids
Reiman (2009) **[43]**	Cannabis as a substitute for alcohol and other drugs.	Anonymous survey collected at dispensary in Berkeley, California (n=350)	Sample was 68% male, 54% single, 66% white, mean age 39 years, 74% with insurance, 41% work full-time, 81% completed some college	71% reported having a chronic medical condition, 52% reported use for pain related condition	40% reported cannabis a substitute for alcohol, 26% as substitute for illicit drugs, and 66% as substitute for prescription drugs
Reinarman (2011) **[44]**	Who are medical marijuana patients? Population characteristics from nine California assessment clinics.	Survey of marijuana patients (n=1,746) from nine clinics in California	73% male and 61% white, 18% 18-24 years old, 28% 25-34 years, 20% 45-54 years, and 13% over 55. 50% over HS education	Pain from back/spine/neck most common indication (31%), followed by sleep disorders (16%), anxiety/depression (13%) and muscle spasms (10%)	79% reported using prescription medications as alternative treatment modalities, majority report using cannabis to relieve pain (83%). Lower prevalence of alcohol and illicit drugs than general population
Lucas (2012) **[45]**	Cannabis as a substitute for alcohol and other drugs: A dispensary-based survey of substitution	Survey of marijuana patients (n=404) from four sites in British Columbia, Canada	67% male, 71% white, mean age of 44.1 years old (17-71 range), 55% single, 18% work full-time, 31% have some college education	46% report being disabled and unable to work, and 86% state they suffer from a chronic condition	68% report cannabis a substitute for prescription drugs. Reasons include fewer side effects (40%), less withdrawal (68%) and better symptom management (54%)

Author (Year)	Title	Study Design	Sample Characteristics	Health Status	Relevant Results
Peters (2013) **[46]**	Patients and caregivers report using medical marijuana to decrease prescription narcotics use	In depth qualitative interviews of convenience and snowball sample of marijuana patients (n=19) and caregivers (n=9) in Michigan, U.S.	36% female, 53% some HS education, 37% college education	21% reported severe pain/post-surgical trauma, 21% arthritis, 22% knee or hip pain, 7% cancer, 7% back, neck, or muscle pain	All patients who were taking opiate pain killers claimed they reduced or eliminated use of prescription pain killers, preferred marijuana over opiates, and had eased withdrawal from opiates due to marijuana use
Hazekamp (2013) **[47]**	The prevalence and incidence of medicinal cannabis on prescription in the Netherlands	Retrospective study of all patients with at least one marijuana prescription in the Netherlands between 2003-2010 (n=5,540)	5,540 patients receiving approximately 35,000 combined cannabis dispensations. 57% female, mean age 55.6 years (14-93 range)	Overall, medical cannabis was prescribed for an average of 251 days, with an average daily dose of 0.68 grams per day (0.71 vs. 0.65 grams for males vs. females, respectively)	Virtually all patients used some prescription medication in 6 months preceding start of cannabis use, 45% psycholeptics, 44% opioid analgesics, 36% anti-ulcer agents, and 31% NSAIDS.
Zaller (2015) **[48]**	Profiles of Medicinal Cannabis Patients Attending Compassion Centers in Rhode Island	Survey of marijuana patients (n=200) from two Compassion Centers in Rhode Island	Mean age of 41, 73% male, 80% white, 31% full-time workers, 89% insured, 67% some college education or higher	Patients reported modest pain severity and pain interference (Brief Pain Inventory), average score of 5 and 5.4 (out of 10)	42% reported ever having used cannabis as a substitute for alcohol or illicit drugs, these individuals had 2.4 times the odds of having high pain interference
Lau (2015) **[49]**	A safer alternative: Cannabis substitution as harm reduction.	Qualitative study of Baby Boomer (born 1946-1964) marijuana users in San Francisco Bay Area (n=97)	62 men and 35 women, median age 58 (range 48-68), 71% white, 34% had medical cannabis recommendation, all were long-term cannabis users	12% of participants reported cannabis as a safer alternative and more effective than prescription drugs at relieving their symptoms, like chronic pain	Substitution based on perceptions that cannabis is safer, has less adverse side effects, and has low risk of addiction, along with greater effectiveness in relieving symptoms

Author (Year)	Title	Study Design	Sample Characteristics	Health Status	Relevant Results
Perron (2015) **[50]**	Use of prescription pain medications among medical cannabis patients: comparisons of pain levels, functioning, and patterns of alcohol and other drug use.	Survey of marijuana patients in Michigan who reported using cannabis specifically for pain reduction (n=273)	Mean age 40.3 years, 69% male, 50% married or cohabitating, 99% white, and 59% reported some college education	63% reported using prescription pain medication (PPM) within past-month for pain relief. PPM users were significantly older and had higher levels of current pain and lower levels of functioning than non-PPM users	Among PPM users, cannabis was perceived to be more efficacious than PPMs, and indicated a strong desire to reduce PPM use for pain. Use of PPM among marijuana patients was not correlated with more serious forms of alcohol or other drug involvement
Boehnke (2016) **[51]**	Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain	Survey of medical marijuana patients with chronic pain from a Michigan dispensary (n=244)	64% male, age 18-25 (17%), age 26-35 (22%), age 36-45 (17%), age 46-55 (14%), age 56-65 (25%), 79% report daily cannabis use	64% reported having used opioids before cannabis. 18% reported opioid use after cannabis initiation	Among study participants, medical marijuana use associated with 64% reduction in opioid use, decreased number and side effects of medications, and improved quality of life
Lucas (2016) **[52]**	Substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: The impact of contextual factors.	Survey of Canadian marijuana patients, online and in person (n=473)	68% male, 90% European/Canadian, median age of 40 (range 17-78 years), 38% HS education, and 58% post-secondary	Most prominent conditions were pain (32%), anxiety/depression (18%), arthritis (15%), HIV (10%), gastrointestinal disorder (7%)	80% reported using cannabis as a substitute for prescription drugs, and this was largely driven by patients who identified chronic pain as their primary indication for cannabis use

Chapter 2

Medical Marijuana Laws and Opioid Overdose: A case-control study

Abstract

Background: Medical marijuana, allowed in states with medical marijuana laws (MMLs), may offer a safer alternative for opioids for some types of pain treatment. These laws have previously been associated with reductions in opioid-related overdose. We attempt to replicate this finding within a nationally representative population-based cohort.

Study design: Nested case-control study with incidence-density sampling.

Methods: Participants surveyed in the National Health Interview Survey (NHIS) between 1986-2009 were followed up for incident opioid overdose up to December 31st, 2011. Overdose decedents are classified as cases. Between 2000-2011, all cases arising in a given year were matched to adult controls who were surveyed that given year and eligible for mortality follow-up. The exposure distribution is contrasted between cases and controls, allowing an approximation of the rate ratio of overdose associated with MMLs.

Results: From our underlying cohort, 791 opioid overdose decedents arose between 2000 and 2011. These cases were matched on calendar year to 723,920 controls. Overall, compared to controls, cases were more likely to be male, middle-aged, non-Hispanic White, separated/divorced; less educated, and have a family income below the poverty threshold. We found no overall association between state MMLs and the rate of opioid overdose. In the West, an overdose was more likely to occurr in states with MML than without between 2000 and 2005. However, between 2006 and 2011, an overdose was less likely to occur in states with an MML in the West (OR=0.51, $p<0.001$). In the Northeast in either period, MML was not significantly associated with overdose.

Conclusions: MMLs in the West appear to have a protective effect on the rate of overdose, but only after 2006. This may reflect heterogeneity in state MMLs, as MMLs in the West are less restrictive. Further investigation of the mechanisms driving observed reductions is warranted.

Introduction

In the United States, the prescription may be the problem. While the proportion of ambulatory, office-based visits with a primary symptom or diagnosis of pain has remained consistent from 2000 to 2010, the frequency of opioid prescribing among these visits nearly doubled from 11.3% to 19.6% [1]. By 2010, the quantity of opioid analgesics sold was enough to dose every American adult with 5 mg hydrocodone, every four hours for one month [2]. Concurrent with this rise in prescribing has been a tide of opioid overdose mortality and treatment admissions [3]. Increased utilization of clinical alternatives to prescription opioids may aid in curbing this epidemic [1]. Marijuana may provide a safe and efficacious alternative in palliative care [4-6].

Currently, medical marijuana is only available in states that have enacted medical marijuana laws (MMLs). In these states, marijuana may be substituting for opioids [7, 8]. Severe or chronic pain is among the most common indications cited by medical marijuana patients [9], and the majority of surveyed patients report using marijuana as a substitute for prescription drugs, including opioids [10-12]. There is also some indication that states with MMLs have a reduced burden of opioid overdose mortality, compared to states without MMLs. For example, studies have found that state MMLs are associated with lower opioid overdose mortality [13], and that states with licensed dispensaries have lower opioid-related treatment admissions as well as overdose mortality, when compared to states without MMLs [14]. The purported mechanism driving this hypothesis, marijuana substitution for opioids, is further supported by studies linking state MMLs with reductions in opioid prescribing to Medicare and Medicaid beneficiaries [15, 16] and opioid positivity among fatally injured drivers [17].

However, considerable heterogeneity exists among current state MMLs [18], and this heterogeneity may be region-specific. For example, state MMLs in the West are more likely to be looser, “nonmedical” programs [19], and loose regulation of these programs is associated with higher rates of adult marijuana use [20]. Further, regional differences in reported

nonmedical use of prescription opioids among those aged 12 [21] and age-adjusted opioid overdose mortality (see Figure 1.2) have been observed. Any assessment of the impact of state MMLs should consider these sources of potential sources of heterogeneity.

In summary, prior studies have indicated state MMLs may be protective against opioid overdose mortality [13, 14], which if true, has significant policy and public implications. Here, we attempt to replicate these findings among a nationally representative, population-based sample. If the earlier findings are valid, we should expect to see a similar association within our sample. Furthermore, with access to individual-level data, our study can uniquely control for potential confounding factors. For example, with state-level data, it may be difficult to adequately control for factors like age, race/ethnicity, or socioeconomic status. In lieu of unavailable individual-level measures, state-level studies often rely on aggregate measures like percent unemployment or age-standardization. Furthermore, when attempting to assess whether an association differs across subgroups (e.g., if state MMLs have a greater/weaker association among younger/older cohorts), individual-level data on such subgroups is necessary.

Thus, the primary aim of this study is to assess whether the rate of opioid overdose varies between individuals residing in states with vs. without a MML between 2000 and 2011. To do so, we will conduct a case-control study with incidence-density sampling, nested within a dynamic, population-based cohort.

Methods

Source Population

Data for this study stems from study participants surveyed in the National Health Interview Survey (NHIS) between the years 1986-2011. The NHIS is an annually conducted household survey. For participants surveyed between the years 1986-2009, detailed mortality follow-up data through December 31, 2011 is available via linkage with death certificate records from the

National Death Index (NDI) for approximately 94% of eligible respondents [22]. Death data include International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-9 and ICD-10) underlying and multiple cause of death codes. Table 2.1 provides unweighted sample size for each year, including the proportion eligible for mortality linkage as well as the proportion of each yearly sample deceased by the end of 2011.

Once surveyed, NHIS participants enter into our dynamic, underlying cohort. Our cohort is dynamic in that each year, individuals enter our cohort (with each subsequent annual NHIS survey wave) and exit when they pass away. By the end of 2009, our underlying cohort will have 1,609,887 members with known mortality data who were adults when interviewed. Mortality follow-up on an additional 665,773 members who were under age 18 at time of interview is also available if the participant is 18 years or older at time of death. Among adults eligible for mortality-linkage, over 17% were deceased by the end of 2011 (n=266,429 deaths).

Study Design

For this study, we utilize a nested case-control design with incidence-density sampling [23]. The case-control study is nested within our dynamic, underlying cohort, and controls are sampled as cases arise (i.e., incidence-density sampling) [23]. Prior to our study analytical years (2000-2011), our source population will consist of all previous participants surveyed in the 1986-1999 NHIS (see Appendix Figure 1). In 2000, all eligible fatal opioid overdoses (decedent ≥18 years old) occurring within our source population, including those under 18 at time of interview, will be considered **cases** *for that year*. Cases arising within a particular year (e.g., 2000) are matched to controls who are interviewed that same year (e.g., 2000 NHIS adult sample). This results in an analytical sample consisting of 12 calendar-matched case-control groups. We further split the sample in half, based upon a sampling redesign that occurred between the 2005 and 2006

NHIS (see Figure 2.1). This redesign resulted in an approximately 13% sample reduction relative to the previous design [24].

As shown in Figure 2.1, cases and controls are matched on calendar year, i.e., a case-control study with incidence-density sampling. Control selection is independent of exposure status (via the random probability sample of households), and the source population is clearly defined. Additionally, controls enter into our source population and are eligible to emerge as cases in later years, with one exception: Controls interviewed in the 2010 and 2011 NHIS are not mortality-linked, and are only eligible to serve as controls. Within each matched calendar group, the exposure distribution (i.e., proportion arising/residing in a state with a MML) is contrasted to estimate the relative rate of opioid overdose.

Main measures

Outcomes

The primary outcome is prescription opioid overdose mortality, defined as fatal drug overdoses (*International Statistical Classification of Diseases, 10th revision [ICD-10],* codes X40-X44, X60-X64, and Y10-Y14) where an opioid analgesic was also coded (T40.2-T40.4). Note, this outcome does not include fatal drug overdoses in which the presence of an illicit opioid (i.e., opium or heroin) but not a pharmaceutical opioid was found.

Exposure

The primary exposure variable will be current residence in a state with an operational MML, defined as an effective law with allowances for home cultivation or the presence of active dispensaries. Importantly, current residence is measured at time of death for cases and time of survey for controls. The table of laws, including quarter and year when MML is operational, is provided in Table 2.2.

State MMLs vary considerably across states and year implemented. This includes variations in policy dimensions (e.g., allowances for home cultivation, dispensaries) as well as degree of medicalization or restrictiveness [19]. Due to this heterogeneity, we classified MMLs as operational only if the law contained allowances for home cultivation or provided an operational dispensary. This specification should reduce bias related to exposure misclassification [18].

Individual-level measures

For both cases and controls, data on age, sex, race/ethnicity (white, black, other), marital status (married/cohabitate, widowed, separated/divorced, never married/single, unknown), educational attainment (less than HS, HS degree/GED, some college, BA/technical degree, post-college), poverty status (above or below poverty threshold) is coded. For cases, data on age, marital status and educational attainment is measured at time of death and is culled from the mortality data. If unknown at time of death, we use data on marital status and education at time of survey for cases. See Appendix Table 1 for a complete data dictionary.

State and regional measures

Due to potential regional differences, region (Northeast, South, Midwest, West) is included as a covariate. If regional heterogentiy is present, results will be stratified by region. Further, other state policies may confound any estimated association between state MMLs and opioid overdose. In particular, just as MMLs are increasing across states, prescription drug monitoring programs (PDMPs) are similarly becoming ubiquitous and may confound the association between MMLs and opioid overdoses. Here we use whether a state is “permitted or required to identify suspicious or statistically outlying prescribing”, a more robust measure of PDMP effectiveness than PDMP enactment alone [25]. Data on proactive PDMP enactment via LawAtlas is provided in Appendix Table 3.

Analytical Plan

First, we identified all prescription opioid overdoses occurring between 2000 and 2011 and saved them in a separate file. Second, we returned to the full data file (including cases), and restricted our sample to NHIS adult participants surveyed between 2000 and 2011 and were eligible for mortality follow-up. Third, we merged cases with controls, matching them on calendar year. Fourth, by calendar year, we compare the proportion of cases that were exposed vs. unexposed. This is repeated for biennial and frame-specific estimates. Finally, to assess whether the association between MML and overdose varies by census region, we will stratify by region to provide region-specific estimates of rates and measures of association.

Next, we use a multivariable logistic regression with a fixed effect for calendar year, the time-varying MML status, and the state and individual-level factors described above. To account for the sampling redesign that occurred between 2005 and 2006, we provide results stratified by sampling frame as well as full model including an interaction term between MML status and sampling frame. If the association between MML and opioid overdose varies between sampling frames, it could be a result of the redesign if the rate of controls sampled in states with and without MML is not consistent across frames.However, while the overall sample size is reduced for the second sampling frame, the proportion sampled within each state is consistent throughout the analytical period. Alternatively, a significant interaction could result from the inclusion of more exposed states in the second sampling frame. To assess this, we will perform a sensitivity analysis in which we exclude the four states that switched exposure status in the second sampling frame: Rhode Island (2006), New Mexico (2007), Michigan (2008), and Arizona (2011).

Results

From our underlying cohort, 791 opioid decedent cases arose between the years 2000 and 2011 (Table 2.3). These cases were matched on calendar year to 723,920 controls who were eligible for mortality follow-up, were 18 years or older at time of interview, and were surveyed in

the same year as their matched cases arose (Table 2.3). Across all years, compared to controls, cases were more likely to be male, middle-aged, non-Hispanic White, separated/divorced; less educated, and have a family income below the poverty threshold.

To assess trends across time, we group annual calendar matches into biennial groups Table 2.4 shows that across all regions, within each biennial group, the proportion of cases exposed is greater than the proportion of controls who are exposed. This also held when cases and controls were grouped by sampling frame. For example, between 2000 and 2005, 254 cases arose, of which 26% were exposed. In comparison, 367,519 controls were sampled between this period, of which 18% were exposed. Between 2006-2010, 556 cases arose (27% exposed) and were compared to 356,401 controls (25% exposed).

Between 2000 and 2005, the rate of opioid overdose was 22% higher in states with MML, after accounting for individual and state-level factors. However, between 2006 and 2011, the rate was 13% lower in states with MML (Table 2.5). This represented an approximately 30% reduction in the association between MML and overdose between sampling frames. Controlling for individual-level factors did not depreciate this association, but accounting for region and PDMPs did significantly attenuate this measure In order to determine whether this association is a consequence of adding more exposed states over time, we excluded the four states that implemented MMLs in the second sampling frame. This exclusion only strengthened the observed association.

Finally, we assessed whether the association between MML and opioid overdose was heterogeneous across census regions. We found that the observed overall protective association we observed can primarily be attributed to reductions in the West. In both regions, more overdoses occurred in states with MML between 2000 and 2005. However, between 2006 and 2011, an overdose was much less likely to occur in states with an MML in the West

(OR=0.51, p<0.001). In the Northeast between 2006-2011, MML was not significantly associated with overdose.

Conclusions

Using a nationally representative, population-based sample, we found a 30% reduction in the overall association between MML and overdose between the first (2000-2005) and second (2006-2011) sampling frames. Further, we found that these reductions were primarily attributed to a reduced odds of overdose associated with residential MML status for participants living in the West, where we observed a strong protective effect. MML was not significantly associated with overdose in the Northeast in either sampling period.

Our results align with other recent studies that found associations between state MMLs and reductions in opioid-related treatment admissions and mortality [13, 14] and prescription drug utilization among Medicare and Medicaid beneficiaries [15, 16]. However, unlike these previous studies, we found the protective impact of MML was limited to the West. While the absence of an MML influence in the Northeast was unexpected, these results should be interpreted with caution as our study may not be adequately powered to examine an effect in this region (n=86).

Study limitations warrant mention. First, our design cannot account for unobserved or unmeasured sources of confounding. While our design addresses regional variations and includes individual-level controls, other unaccounted sources of confounding could have introduced bias into our estimates if they were occurring simultaneously with state MMLs as well as influencing the rate of opioid overdose. Here, we include a measure of "whether a state PDMP is permitted or required to identify suspicious reporting" as a controlling factor. While this measure does not account for the large variability in PDMPs, it does represent a robust measure of PDMP effectiveness [26]. Future studies may also be interested in examining the joint impacts of these PDMPs and MMLs. Second, our design assumes that sampling is

consistent across our analytical years and, importantly, independent of exposure status. This is by design: our case-control study substitutes newly sampled survey cohorts as the denominator, which allows for accurate measurements of a time-varying exposure. As our analytical years span across two different sampling frames, we chose to “difference out” any influence of a sampling redesign by contrasting the MML/overdose association between the two frames.

In summary, we found that MML was associated with a reduced rate of opioid overdoses in the West but not in the Northeast. This may be due to differences in how MMLs were operationalized between these two regions. For example, a recent study indexing the degree of medicalization of state MMLs found that earlier MML states, found primarily in the West, were more likely to be less restrictive and “nonmedical” [19]. The extent to which a state MML is restrictive may influence the availability of medical marijuana, which in turn may affect the magnitude of potential substitution for other drugs, if any. For example, a follow-up study found that looser regulation of state MMLs to be associated with higher rates of adult marijuana use [20], which align with our finding of lower rates of opioid overdose among states with MML in the West. The restrictiveness of current and future MMLs is an ongoing debate, with newer states adopting more “medicalized” programs in which patient enrollment and marijuana availability may be lacking [19]. This may be consequence of the laws determining which conditions are elibilbe for marijuana recommendations, with some states adopting a more restrictive approach. For example, MMLs in Connecticut, Maine, Massachusettes, Minnesota, New York, and the District of Columbia do not, or did not initially, include severe or chronic pain as an approved condition. Future studies should assess the consequences of variations in indications approved by state MMLs in regards to patient enrollment as well as secondary outcomes like opioid use and morbidity.

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Table 2.1. NHIS Survey participants by linked mortality eligibility and status

NHIS Year	Persons (n)	*Among all persons surveyed (n)*						*Among > age 18 and eligible*			
		Eligible	*%*	< age 18	*%*	Ineligible	*%*	Alive	*%*	Deceased	*%*
1986	62,052	43,843	*0.71*	17,419	*0.28*	790	*0.01*	30,444	*0.69*	13,399	*0.31*
1987	122,859	86,646	*0.71*	34,672	*0.28*	1,541	*0.01*	61,313	*0.71*	25,333	*0.29*
1988	122,310	86,844	*0.71*	33,994	*0.28*	1,472	*0.01*	62,484	*0.72*	24,360	*0.28*
1989	116,929	83,105	*0.71*	32,398	*0.28*	1,426	*0.01*	61,184	*0.74*	21,921	*0.26*
1990	119,361	85,099	*0.71*	33,287	*0.28*	1,245	*0.01*	64,032	*0.75*	21,067	*0.25*
1991	120,032	84,826	*0.71*	33,694	*0.28*	1,512	*0.01*	64,916	*0.77*	19,910	*0.23*
1992	128,412	89,914	*0.70*	36,679	*0.29*	1,819	*0.01*	70,140	*0.78*	19,774	*0.22*
1993	109,671	77,415	*0.71*	30,550	*0.28*	1,706	*0.02*	61,228	*0.79*	16,187	*0.21*
1994	116,179	81,481	*0.70*	32,504	*0.28*	2,194	*0.02*	64,848	*0.80*	16,633	*0.20*
1995	102,467	70,971	*0.69*	29,737	*0.29*	1,759	*0.02*	58,045	*0.82*	12,926	*0.18*
1996	63,402	43,899	*0.69*	18,140	*0.29*	1,363	*0.02*	36,775	*0.84*	7,124	*0.16*
1997	103,477	67,986	*0.66*	29,800	*0.29*	5,691	*0.05*	57,323	*0.84*	10,663	*0.16*
1998	98,785	63,308	*0.64*	28,130	*0.28*	7,347	*0.07*	54,124	*0.85*	9,184	*0.15*
1999	97,059	62,327	*0.64*	27,276	*0.28*	7,456	*0.08*	54,184	*0.87*	8,143	*0.13*
2000	100,618	64,502	*0.64*	28,508	*0.28*	7,608	*0.08*	57,002	*0.88*	7,500	*0.12*
2001	100,760	64,000	*0.64*	28,586	*0.28*	8,174	*0.08*	57,449	*0.90*	6,551	*0.10*
2002	93,386	59,269	*0.63*	26,196	*0.28*	7,921	*0.08*	53,623	*0.90*	5,646	*0.10*
2003	92,148	57,245	*0.62*	25,545	*0.28*	9,358	*0.10*	52,459	*0.92*	4,786	*0.08*
2004	94,460	60,072	*0.64*	26,175	*0.28*	8,213	*0.09*	55,783	*0.93*	4,289	*0.07*
2005	98,649	61,929	*0.63*	26,827	*0.27*	9,893	*0.10*	58,035	*0.94*	3,894	*0.06*
2006	75,716	50,970	*0.67*	20,963	*0.28*	3,783	*0.05*	48,577	*0.95*	2,393	*0.05*
2007	75,764	50,901	*0.67*	20,812	*0.27*	4,051	*0.05*	48,928	*0.96*	1,973	*0.04*
2008	74,236	50,934	*0.69*	20,003	*0.27*	3,299	*0.04*	49,410	*0.97*	1,524	*0.03*
2009	88,446	62,401	*0.71*	23,878	*0.27*	2,167	*0.02*	61,152	*0.98*	1,249	*0.02*
Total	2,377,178	1,609,887	*0.68*	665,773	*0.28*	101,788	*0.04*	1,343,458	*0.83*	266,429	*0.17*

Figure 2.1. Comparison groups matched on calendar year

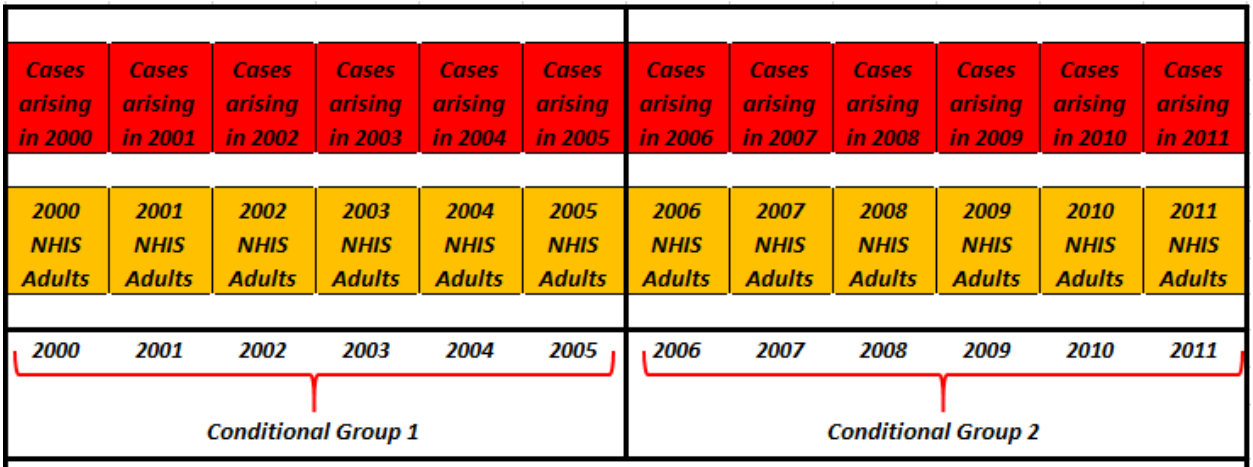

Figure 1. *Analtical sample for study. Cases in red arise from the underlying source population. Controls in orange are NHIS sample adults who are interviewed **within the same year** their matched cases arise. Sample is split into two conditional groups, based upon two separate NHIS sampling frames: 1997-2005 and 2006-onwards.*

Table 2.2. The 25 medical marijuana laws (MMLs) by operational status (i.e., allowances for home cultivation or presence of dispensaries) for the study period (1986-2011)

State name	Operational date	First year coded	First year coded
California	Nov-96	1997	1997
Washington	Nov-98	1999	1999
Oregon	Dec-98	1999	1999
Alaska	Mar-99	1999	1999
Maine	Dec-99	2000	2000
Hawaii	Dec-00	2001	2001
Colorado	Jun-01	2002	2002
Nevada	Oct-01	2002	2002
Vermont	Jul-04	2005	2005
Montana	Nov-04	2005	2005
Rhode Island	Jan-06	2006	2006
New Mexico	Jul-07	2008	2008
Michigan	Dec-08	2009	2009
Arizona	Nov-10	2011	2011
District of Columbia	Not operational	-	-
New Jersey	Not operational	-	-
Delaware	Not operational	-	-
Connecticut	Not operational	-	-
Massachusetts	Not operational	-	-
New Hampshire	Not operational	-	-
Illinois	Not operational	-	-
Minnesota	Not operational	-	-
Maryland	Not operational	-	-
New York	Not operational	-	-
Pennsylvania	Not operational	-	-
Ohio	Not operational	-	-

Table 2.3. *Characteristics of study sample; NHIS participants who died (cases) or were interviewed (controls) between the years 2000-2011.*

	Rx Overdose Decedents (n=791)	Controls (n=723,920)	Chi-square p-value
Sex			
Male	478 (0.60)	342,005 (0.47)	<.001
Female	313 (0.40)	381,915 (0.53)	
Age			
18-29 years	143 (0.18)	158,011 (0.22)	<.001
30-45 years	296 (0.37)	228,838 (0.32)	
46-60 years	289 (0.37)	188,012 (0.26)	
61+ years	63 (0.08)	149,059 (0.21)	
Race			
White	720 (0.91)	565,568 (0.78)	<.001
Black	47 (0.06)	103,423 (0.14)	
Other	24 (0.03)	54,929 (0.08)	
Marital Status			
Married/Cohabitant	274 (0.35)	455,833 (0.63)	<.001
Widowed	36 (0.05)	44,071 (0.06)	
Separated/Divorced	192 (0.24)	76,733 (0.11)	
Never Married / Single	274 (0.35)	144,837 (0.20)	
Unknown	15 (0.02)	2,446 (0.003)	
Education			
Never Attended	16 (0.02)	4,412 (0.01)	<.001
Less than HS	234 (0.30)	133,614 (0.18)	
HS Degree / GED	290 (0.37)	208,056 (0.29)	
Some College	158 (0.20)	135,009 (0.19)	
BA/ Technical Degree	63 (0.09)	174,022 (0.24)	
Post College	23 (0.03)	56,067 (0.08)	
Unknown	7 (0.01)	12,740 (0.02)	
Federal Poverty Threshold			
Above Threshold	571 (0.72)	497,214 (0.69)	<.001
Below Threshold	133 (0.17)	77,041 (0.11)	
Unknown	87 (0.11)	149,665 (0.21)	

Region			
Northeast	86 (0.11)	125,084 (0.17)	<.001
Midwest	151 (0.19)	153,697 (0.21)	
South	316 (0.40)	265,393 (0.37)	
West	237 (0.30)	179,746 (0.25)	

***** *Poverty status is based on family income and family size using the U.S. Census Bureau poverty thresholds*

Table 2.4. *Odds of medical marijuana law (MML) exposure for cases and controls, NHIS by matched calendar year.*

2000-2001		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
	MML	18	0.24	21629	0.17	1.59
	No MML	56	0.76	107061	0.83	(0.94-2.71)
	Total	74		128690		
2002-2003		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
	MML	23	0.29	21678	0.19	1.77
	No MML	57	0.71	95011	0.81	(1.09-2.87)
	Total	80		116689		
2004-2005		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
	MML	24	0.24	23089	0.19	1.35
	No MML	76	0.76	99051	0.81	(0.86-2.14)
	Total	100		122140		
2006-2007		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
	MML	36	0.23	21482	0.21	1.11
	No MML	121	0.77	80496	0.79	(0.77-1.62)
	Total	157		101978		
2008-2009		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
	MML	51	0.26	28532	0.25	1.03
	No MML	148	0.74	84899	0.75	(0.75-1.41)
	Total	199		113431		
2010-2011		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
	MML	62	0.31	40378	0.29	1.12
	No MML	138	0.69	100614	0.71	(0.83-1.51)
	Total	200		140992		
By sampling frame						
2000-2005		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
	MML	65	0.26	66396	0.18	1.56
	No MML	189	0.74	301123	0.82	(1.18-2.07)
	Total	254		367519		
2006-2010		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
	MML	149	0.27	90392	0.25	1.08
	No MML	407	0.73	266009	0.75	(0.89-1.30)
	Total	556		356401		

Table 2.5. *Estimated odds ratios (OR) for Rx overdose associated with medical marijuana law (MML) status stratified by sampling frame, and test of differences in association by sampling frame, NHIS participants 2000-2011.*

	OR (p-value) 2000-2005	OR (p-value) 2006-2011
MML vs. No MML		
crude model (year only)	1.43 (0.019)	1.09 (0.366)
state-level adjusted model	1.21 (0.344)	0.83 (0.324)
individual-level adjusted model	1.41 (0.025)	1.03 (0.740)
adjusted at both levels	1.22 (0.313)	0.87 (0.449)
	Ratio of OR's	
	2006-2011 vs. 2000-2005	
Ratio of MML vs. No MML by frame		
crude model (year only)	0.76 (0.133)	
state-level adjusted model	0.70 (0.053)	
individual-level adjusted model	0.76 (0.128)	
adjusted at both levels	0.71 (0.060)	
MML vs. No MML	**OR (p-value) 2000-2005**	**OR (p-value) 2006-2011**
Northeast		
state-level adjusted model	1.61 (0.556)	1.73 (0.218)
West		
state-level adjusted model	3.65 (<.001)	0.51 (<.001)
Ratio of MML vs. No MML by frame	**Ratio of OR's 2006-2011 vs. 2000-2005**	
Northeast		
state-level adjusted model	1.99 (0.428)	
West		
state-level adjusted model	0.10 (<.001)	

**crude model adjusts for analytical year only (the calendar match of cases and controls)*
**state-level model adjusts for census region and presence of "proactive" prescription monitoring programs.*
**individual-level model adjusted for age, race/ethnicity, sex, marital status, education, and poverty status.*
**adjusted at both levels includes all individual and state-level adjustments*

Chapter 3

Cui Bono? An assessment of heterogeneity in determining who benefits

Abstract

Background: Prior studies have indicated that state medical marijuana laws (MMLs) may have a protective effect on opioid overdose. This protective impact may vary across subgroups defined by age, sex, and/or race/ethnicity. Assessing for the presence of this heterogeneity may be helpful in evaluating how, and for whom, these laws are most effective, which may inform future policy. Here, we assess whether the reduction observed in the previous chapter is heterogeneous across population subgroups defined by age, gender, and race/ethnicity.

Study design: Nested case-control study with incidence-density sampling.

Methods: Participants surveyed in the National Health Interview Survey (NHIS) between 1986-2009 are follow-up for incident opioid overdose up to December 31st, 2011. Overdose decedents are classified as cases. Between 2000-2011, all cases arising within a given year are compared to the incoming NHIS adult cohort for that year. The exposure distributed is contrasted for groups matched on calendar year, allowing an approximation of the rate ratio of overdose associated with MMLs.

Results: From our underlying cohort, 791 opioid overdose decedents arose between 2000 and 2011. Across all years, compared to controls, cases were more likely to be male, middle-aged, non-Hispanic White, separated/divorced; less educated, and have a family income below the poverty threshold. No heterogeneity by gender or race/ethnicity was observed. In the West, MMLs were associated with significant reductions in opioid overdose for participants under 60 years old, but not among older groups.

Conclusions: State MMLs are associated with reductions in opioid overdose, but not among older age groups. Future studies should assess whether this age heterogeneity persists with changes in the age distribution of medical marijuana patients.

Introduction

There is growing evidence that state MMLs may be reducing the burden of prescription opioid mortality. Previous studies have found associations between state MMLs and reductions in opioid prescribing [1, 2], opioid-related treatment admissions[3], as well as opioid-related overdose mortality [3, 4]. In the previous chapter, we assessed whether state MMLs were associated with a reduced rate of opioid overdose among participants surveyed in the National Health Interview Survey (NHIS) between the years 1986-2011. No signficiant associations were observed overall or in the Northeast. In the West, MMLs went from being positively associated with overdose between 2000-2005 to negatively associated with overdose between 2006-2011. However, it is unclear whether these associations vary across subpopulations. Investigating potential heterogentiy in the association between MMLs and overdose may inform stakeholders or inform future policy. For instance, even among individuals residing within the same state, MMLs may have a heterogeneous impact across different subpopulations (e.g., state MMLs may confer a benefit to non-Hispanic Whites only). Measures of association pooled across subpopulations may not reflect this heterogeneity, may conceal valid associations within subgroups, and provide little insight into how these laws operate.

For example, to date, state MMLs have been associated with increased marijuana use in adults [5-7] but not in adolescents [8-10]. As the purported mechanism underlying the association between state MMLs and opioid overdose involves marijuana for opioids substitution, any observed reductions in overdose mortality related to MMLs may also be age-specific. For example, among drivers who died with one hour of crashing in the United States, crashing in a state with a MML was associated with a reduced odds of testing positive for opioids, compared to crashing in a state before a future MML is passed [11], but only among drivers aged 21-45. Similarly, another study found that a one percent increase in MML registration rates was associated with an 11-15% reduction in opioid-related overdose mortality for adults aged 45-64

[12]. Similarly, we expect MML to confer benefits on age groups most likely to become medical marijuana users: young and middle-aged adults.

Alternatively, the impact of state MMLs may be heterogeneous by race/ethnicity. Racial differences exist in opioid prescribing practices [13] as well as in opioid overdose mortality [14]. Further, among pain-related emergency department visits in the US, non-Hispanic White patients are more likely to receive an opioid prescription than non-Hispanic Black patients [13], and, compared to Michigan pharmacies located in predominately white areas, predominately minority pharmacies are less likely to have a sufficient supply of prescription opioids [15]. Somewhat ironically, while non-Hispanic Whites may have easier access to these prescriptions, they are also more likely to overdose [16] and are the only racial/ethnic group in the US to observe an *increase* in mortality rate from 1999-2013 [14]. However, it remains unclear whether state MMLs operate differently by race, which may occur if different racial groups were more or less likely to become medical marijuana users.

Similarly, state MMLs may act heterogeneously by gender. While the prevalence of marijuana use increased for both men and women between 2002 and 2014 in the United States, this increase was greater for men [17, 18]. Further, surveys of medical marijuana patients tend to find that the vast majority are male [19], though sex differences in medical marijuana program participation may be decreasing over time [20]. In regards to MMLs, one previous study found state MMLs to be associated with reductions in suicides among young males but not for females [21]. We expect any influence of MMLs on opioid overdose to be similarly concentrated among those most likely to seek out recommendations for medical marijuana: young adults, non-Hispanic Whites, and males.

Finally, as observed in the previous chapter, we expect regional heterogeneity in state MMLs. State MMLs in the West are more likely to be looser, “nonmedical” programs [22], and loose

regulation of these programs is associated with higher rates of adult marijuana use [6]. Further, regional differences in reported nonmedical use of prescription opioids among those aged 12 and older [23] and age-adjusted opioid overdose mortatliy (see Figure 1.2) have been previously observed. However, largely due to power limitations, we assess the presence of age/race/gender heterogeneity across all regions. Region-specific heterogeneity is assessed when the count of cases permits.

Methods

Source Population and Study Design

The source population and study design are identical to those described in Chapter 2. Briefly, we source our underlying population from participants surveyed in the National Health Interview Survey (NHIS) between the years 1986-2011. Individuals enter into our underlying source population upon survey, and are follow-up for mortality up to December 31, 2011.
Starting in year 2000, we will begin identifying incidences of opioid overdose mortality that arise from our source population. These decedents will serve as cases in our nested case-control design. For control selection, we use incidence-density sampling. Cases arising within a particular year (e.g., 2000) are matched to controls who are interviewed that same year (e.g., 2000 NHIS adult sample). This results in 12 calendar-matched groups (2000-2011). Within each group, the exposure distribution (i.e., proportion arising/residing in a state with a MML) is contrasted to estimate the relative rate of opioid overdose (Figure 2.1).

Main measures

Outcomes

The primary outcome is prescription opioid overdose mortality, defined as fatal drug overdoses (*International Statistical Classification of Diseases, 10th revision [ICD-10],* codes X40-X44, X60-X64, and Y10-Y14) where an opioid analgesic was also coded (T40.2-T40.4).

Exposure

The primary exposure variable will be current residence in a state with an operational MML, defined as an effective law with allowances for home cultivation or the presence of active dispensaries (Table 2.2). Importantly, current residence is measured at time of death for cases and time of survey for controls.

Individual-level measures

For both cases and controls, data on age, sex, and race/ethnicity (white, black, other) is coded. For cases, data on age is measured at time of death and is culled from the mortality data. See Appendix Table 2 for a complete data dictionary.

State and regional measures

Due to potential regional differences, region (Northeast, South, Midwest, and West) is included as a covariate. Further, other state policies may confound any estimated association between state MMLs and opioid overdose. In particular, just as MMLs are increasing across states, prescription drug monitoring programs (PDMPs) are similarly becoming ubiquitous and may confound the association between MMLs and opioid overdoses. Here we use whether a state is "permitted or required to identify suspicious or statistically outlying prescribing", a more robust measure of PDMP effectiveness than PDMP enactment alone [24]. Data on proactive PDMP enactment via LawAtlas is provided in Appendix Table 3.

Analytical Plan

After cases are identified and matched to controls on calendar year, we contrast the exposure distribution for cases vs. controls, separately for each sampling frame. This allows us to estimate relative overdose rates by exposure group. Relative rates are estimated within strata of age, sex, and race/ethnicity. Next, we use a multivariable logistic regression with a fixed effect for calendar year, the time-varying MML status, and the state and individual-level factors

described above. To assess whether the MML-overdose association varies by age/sex/race, an interaction term between MML and demographic group is included.

Although the MML association appears to vary by sampling region, we pool participants across regions due to sample size concerns when stratifying by demographics. Consequently, any MML association observed is likely conservative/underestimated. Region-specific measures of association are estimated for models with a significant interaction and adequate power.

Results

From our underlying cohort, 791 opioid decedent cases arose between the years 2000 and 2011. These cases were matched on calendar year to 723,920 controls who were eligible for mortality follow-up, were 18 years or older at time of interview, and were surveyed in the same year as their matched cases arose (Table 2.3).

After pooling across sampling frame and stratifying by age (Table 3.1), we contrast the exposure distribution for cases vs. controls. For 18-29 year olds, the proportion exposed among cases (15% in 2000-2005 and 18% in 2006-2010) is less than the proportion exposed among controls (19% and 27%, respectively). For 30-45 year olds, the proportion exposed was nearly equal for cases and controls, for both sampling frames. For 40-60 year olds, the proportion exposed was greater among cases in the first period, but nearly equal in the second. For those 61+ years old, cases had a higher proportion exposed compared to controls for both sampling periods. After stratifying by race (Table 3.2), we see a higher proportion exposed among White cases in the first sampling period compared to White controls, and near identical proportions in the second. Estimated proportions for the other racial groups are suppressed for the first sampling period, and proportions for the second frame are provided with caution due to small cell counts. Finally, after stratifying by sex, the proportion exposed was higher among cases for

all groups and sampling periods sans males in 2006-2010, where the proportion exposed was 25% for cases and 26% for controls.

In either sampling frame, the association between MML and overdose rates did not appear to vary by race/ethnicity or sex (Table 3.4). However, this association did vary by age in both sampling frames. In the first frame, MML was associated with an increase in overdose for adults aged 46-60 years old, but was not associated with reductions for any other age group. In the second sampling frame, MML was associated with a reduced odds of overdose among the youngest age group and increased odds in the oldest.

To assess whether these estimates vary by region, region-specific model estimates were calculated. We found that the age heterogeneity observed is limited to the West (Table 3.5). In the first sampling frame, MMLs appear to increase the odds of overdose, and these odds worsened with increasing age. However, in the second sampling frame, for all age groups except the oldest (61+ years), MML was associated with reduced odds of overdose, with the strongest associations observed for those 18-30 years old and 46-60 years old. In the Northeast, MML was not associated with the rate of opioid overdose, and no age heterogeneity was observed in either sampling frame.

Conclusions

The aim of this study was to assess potential heterogeneity in the MML-overdose association. Here, we found that MMLs appear to be acting heterogeneously across age groups, but not by race/ethnicity and or sex. We found that overall, participants aged 18-30 years old who lived in states with MML were much less likely to overdose than their similarly aged counterparts in states without MML. Further, this age heterogeneity was only present in the West, where among participants aged 46-60 years old, MML was also associated with a reduced rate of overdose.

Our finding regarding the heterogeneous impact of MML by age groups is worth noting. Primarily in the West, the reduced odds of overdose associated with MML appears to be driven by large reductions in those aged 46-60 years old. In the second sampling period, we also observed a significant reduction in overdose associated with MML for adults aged 18-30 and a non-significant reduction for adults aged 30-45. This coheres with a previous finding that showed state MMLs to be associated with reductions in opioid positivity in fatally injured drivers aged 21-45, as well as another finding that found a one percent increase in MML registration rates was associated with an 11-15% reduction in opioid-related overdose mortality for adults aged 45-64 [12]. Taken together, these findings suggest the observed reduction in opioid overdose associated with MMLs may be explained by reductions in opioid use. The absence of a protective effect of MML among those 61+ years and older is also noteworthy, but may reflect low levels of medical marijuana use among this age group. Future studies should assess whether this age heterogeneity persists if older patients increasingly turn to medical marijuana.

The association between MML and opioid overdose exhibited little heterogeneity by gender and/or race/ethnicity. In regards to gender, the absence of heterogeneity may reflect decreasing gender differences in medical marijuana program enrollment over time [20]. For race/ethnicity, the absence of heterogeneity may also reflect a lack of disparity in medical marijuana program participation or marijuana use. However, due to the limited number of overdose events observed among the two minority race groups, our study is likely not powered to assess such heterogeneity. Similarly, while we did not observe an association between state MMLs and a reduced rate of opioid overdose for participants residing in the Northeast, our study may be underpowered to detect such an effect.

The limitations of this study warrant discussion. Our study design assumes that incoming NHIS adult survey samples (between 2000-2011) is a suitable substitute for a denominator. This assumptions requires that the survey sampling is independent of exposure status and

consistent across survey years. We address changes in the sampling frame between 2005 and 2006 by estimating measures of association separately for the two periods. Second, our study is vulnerable to sources of unmeasured confounding. We attempt to address this issue by stratifying by region and by whether the state has a proactive PDMP, but future studies should consider other potential sources.

In summary, we find that the observed reduction in overdoses associated with MML is age-dependent, largely driven by reductions in those under 60, and present in our data only in the West. Future studies should continue to assess whether these age-dependent disparate outcomes persist. For example, medical marijuana program enrollment were to increase disproportionately among senior groups, we should expect to see disproportionate reductions in opioid-related outcomes among this age group.

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Table 3.1. *Odds of medical marijuana law (MML) exposure for cases and controls, NHIS by matched calendar year, and stratified by age group.*

			Case (n)	(%)	Control (n)	(%)	Odds Ratio
18-29 years old	2000-2005	MML	6	0.15	15476	0.19	0.71
		No MML	35	0.85	64087	0.81	(0.30-1.69)
		Total	41		79563		
	2006-2010		Case (n)	(%)	Control (n)	(%)	Odds Ratio
		MML	18	0.18	21092	0.27	0.58
		No MML	84	0.82	57356	0.73	(0.35-0.97)
		Total	102		78448		
30-45 years old	2000-2005		Case (n)	(%)	Control (n)	(%)	Odds Ratio
		MML	20	0.19	23204	0.19	1.02
		No MML	83	0.81	98155	0.81	(0.63-1.66)
		Total	103		121359		
	2006-2010		Case (n)	(%)	Control (n)	(%)	Odds Ratio
		MML	51	0.26	28239	0.26	1.01
		No MML	142	0.74	79240	0.74	(0.73-1.39)
		Total	193		107479		
46-60 years old	2000-2005		Case (n)	(%)	Control (n)	(%)	Odds Ratio
		MML	25	0.33	16094	0.17	2.38
		No MML	50	0.67	76553	0.83	(1.47-3.85)
		Total	75		92647		
	2006-2010		Case (n)	(%)	Control (n)	(%)	Odds Ratio
		MML	57	0.27	23592	0.25	1.10
		No MML	157	0.73	71773	0.75	(0.82-1.50)
		Total	214		95365		
60+ years	2000-2005		Case (n)	(%)	Control (n)	(%)	Odds Ratio
		MML	6	0.38	15476	0.20	2.42
		No MML	10	0.63	62328	0.80	(0.88-6.65)
		Total	16		77804		
	2006-2010		Case (n)	(%)	Control (n)	(%)	Odds Ratio
		MML	23	0.49	17469	0.23	3.16
		No MML	24	0.51	57640	0.77	(1.78-5.60)
		Total	47		75109		

Table 3.2. *Odds of medical marijuana law (MML) exposure for cases and controls, NHIS by matched calendar year, and stratified by race.*

			Case (n)	(%)	Control (n)	(%)	Odds Ratio
White	**2000-2005**	**MML**	51	0.24	52920	0.18	1.40
		No MML	166	0.76	241118	0.82	(1.03-1.92)
		Total	217		294038		
	2006-2010		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
		MML	134	0.27	68535	0.25	1.08
		No MML	369	0.73	202995	0.75	(0.88-1.31)
		Total	503		271530		
Black	**2000-2005**		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
		MML	SUPPRESSED	N/A	3850	0.08	N/A
		No MML	SUPPRESSED	N/A	44667	0.92	
		Total	SUPPRESSED		48517		
	2006-2010		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
		MML	8	0.22	6581	0.12	2.10
		No MML	28	0.78	48315	0.88	(0.96-4.60)
		Total	36		54896		
Other	**2000-2005**		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
		MML	SUPPRESSED	N/A	9626	0.39	N/A
		No MML	SUPPRESSED	N/A	15328	0.61	
		Total	SUPPRESSED		24954		
	2006-2010		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
		MML	7	0.41	15276	0.51	0.67
		No MML	10	0.59	14699	0.49	(0.26-1.77)
		Total	17		29975		

Table 3.3. *Odds of medical marijuana law (MML) exposure for cases and controls, NHIS by matched calendar year, and stratified by sex.*

Male	**2000-2005**		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
		MML	33	0.23	31942	0.18	1.29
		No MML	113	0.77	141367	0.82	(0.88-1.91)
		Total	146		173309		
	2006-2010		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
		MML	83	0.25	43684	0.26	0.95
		No MML	249	0.75	125012	0.74	(0.74-1.22)
		Total	332		168696		
Female	**2000-2005**		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
		MML	24	0.27	34454	0.18	1.71
		No MML	65	0.73	159756	0.82	(1.07-2.73)
		Total	89		194210		
	2006-2010		**Case (n)**	**(%)**	**Control (n)**	**(%)**	**Odds Ratio**
		MML	66	0.29	46708	0.25	1.26
		No MML	158	0.71	140997	0.75	(0.95-1.69)
		Total	224		187705		

Table 3.4. *Estimated odds ratios (OR) for Rx overdose associated with medical marijuana law (MML) status stratified by sampling frame, and test of differences in association by age, sex, race/ethnicity, NHIS participants 2000-2011.*

	OR 2000-2005	**OR 2006-2011**
MML vs. No MML		
stratified by sampling period	1.22 (0.313)	0.87 (0.449)
Age-stratified estimates		
Test of overall interaction	**X^2= 4.38 (0.036)**	**X^2= 11.26 (<.001)**
18-30 years	**0.59 (0.253)**	**0.44 (0.008)**
30-45 years	**0.84 (0.539)**	**0.78 (0.267)**
46-60 years	**1.97 (0.014)**	**0.84 (0.433)**
61+ years	**2.69 (0.063)**	**2.42 (0.008)**
Race-stratified estimates		
Test of overall interaction	X^2= 0.29 (0.587)	X^2= 0.09 (0.765)
White	1.17 (0.432)	0.88 (0.482)
Black	0.97 (0.981)	1.82 (0.164)
Other	2.98 (0.197)	0.52 (0.205)
Sex stratified estimates		
Test of overall interaction	X^2= 0.81 (0.368)	X^2= 2.16 (0.141)
Male	1.08 (0.749)	0.74 (0.140)
Female	1.43 (0.191)	0.99 (0.945)

**all models adjust for calendar year, region, "proactive" drug monitoring programs, and age/sex/race.*
**White/Black groups include participants identifying as Hispanic, and other includes all other race groups including Indian, Native Alaskan, Asian, and other/multiple race groups.*

Table 3.5. *Estimated odds ratios (OR) for Rx overdose associated with medical marijuana law (MML) status stratified by sampling frame, and test of differences in association by age across regions. NHIS participants 2000-2011.*

	WEST		**NORTHEAST**	
	OR 2000-2005	**OR 2006-2011**	**OR 2000-2005**	**OR 2006-2011**
Age-stratified estimates *Test of overall interaction*	**X^2= 2.76 (0.096)**	**X^2= 8.49 (0.004)**	X^2= 0.97 (0.325)	X^2= 0.53 (0.468)
18-30 years	**1.37 (0.650)**	**0.17 (<.001)**	7.18 (0.123)	3.07 (0.179)
30-45 years	**3.33 (0.018)**	**0.63 (0.200)**	1.47 (0.727)	1.82 (0.377)
46-60 years	**4.63 (0.001)**	**0.52 (0.033)**	7.18 (0.123)	1.42 (0.555)
61+ years	**8.66 (0.050)**	**1.13 (0.843)**	7.18 (0.123)	3.07 (0.179)

**all models adjust for calendar year, "proactive" drug monitoring programs, and age/sex/race.*

Conclusion

The purpose of this dissertation was to assess whether state medcial marijuana laws were associated with a reduction in opioid overdose mortality. In the first chapter, we reviewed the exisiting evidence. We found consistent results across nine qualitative studies suggesting a protective association conferred on these laws on opioid morbidity and mortality [1-3] as well as opioid use and prescribing [4, 5]. From surveys assessing opioid use among medical marijuana patients, we found that marijuana patients frequently reported reducing or curbing opioid use in favor of marijuana. Overall, the main limitations we observed with the quantitative studies was the unaddressed regional heterogeneity in exposure and outcome, as well as the homogentiy in methods shared across all studies.

Our second chapter improves upon the literature by providing evidence from a novel design among a nationally representative sample. All of the prior studies mentioned above have employed ecologic time series or pooled cross-sectional designs, and almost universally, employed a difference-in-difference method to contrast a before vs. after trends in exposed states to the trend observed in a group of control states. In the second chapter, we use a case-control study with incidence density sampling to assess whether the rate of opioid overdose is associated with residing in a state with a medical marijuana law. This novel approach allows esimtation of the relative rate of opioid overdose in states with and without MML. Further, our study controls for region, a previously unaccounted potential source of confounding. We found that while adjusting for region did considerably attenuate the overall association between MMLs and opioid overdose, there was still evidence of regional heterogeneity in this association. We found that state MMLs were associated with a reduced rate of opioid overdose only in the West and only between 2006-2011. In fact, the reverese association was observed in the West between 2000-2005. .

In our third chapter, we find that this association varied by age, such that the beneficial impact of these laws were limited to those under the age of 60. This coheres with a previous finding that showed state MMLs to be associated with reductions in opioid positivity in fatally injured drivers aged 21-45 [4], as well as another finding that found a one percent increase in MML registration rates was associated with an 11-15% reduction in opioid-related overdose mortality for adults aged 45-64 [3].In this context, these findings suggest a potential mechansims in which MMLs may reduce opioid overdose: reductions in opioid use among certain age groups . These age-specific findings might be reflect disproportionate marijuana-opioid substitution in certain age groups, or may even be indicative of later cohorts, once exposed to intensely negative public messaging regarding marijuana, not being as receptive to potential substitution.

Future research should focus on the factors driving observed regional variations in opioid overdose mortality. For example, since 2009, the West is the only region to exhibit decreases in their age-adjusted opioid overdose mortality (Figure 1.2). Currently, state MMLs are largely concentrated in the West or the Northeast. However, state MMLs in the West are qualtitatively different than state MMLs in the Northeast, particularly in terms of medical marijuana program "medicalization" (i.e., regulation), patient enrollment, and marijuana access [3, 6]. Western MMLs are more loosely regulated, more likely to have nonmandatory (and consequently, higher) rates of patient enrollment, and greater access to marijuana through home cultivation or dispensary. This may explain the absence of a protective effect of MMLs in the Northeast, where MMLs tend to be more tightly regulated and less likely to list severe or chornic pain as an approved indication.

However, as in New York, even restricitive MMLs may expand over time, and future research could assess changes in opioid morbidity/mortality associated with these changes. Future research should also continue to assess subsets of the population in which these laws confer the most benefit. For example, we did not observe a protective effect of these laws on adults

over the age of 60, even in the West. This may reflect an underutilization of medical marijuana among this age group, relative to younger ages, which may change over time. For example, a recent study using 2010-2013 Medicare prescription data found a reduction in pain-related presriptions associated with state MML implementation, suggesting a recent increase in medical marijuana utilization among Medicare eligible seniors.

Finally, our study included drug overdoses in which a synthetic opioid, including fentaynl, was indiciated as an underlying casue of death. While this classification rules out drug overdoses in which heroin or opium, but not other synthetic opioids, was listed as the only an underlying cause, it does not rule out the potential presence of heroin or opium in our overdose cases. While fentanyl-only overdoses cannot be distinguished with our data, our study years (2000-2011) occur prior to recent increases in fentanyl-related deaths, which began escalating in 2014, so fentanly does not figure as a complicating factor in explanation of the study results. Further, only a small percentage of cases had an overdose also involving heroin or opium (5.2%). The most common polydrug substance among our overdose cases (Appendix Table 3) was the presence of benzodiazepines (25.0%) and alcohol (10.5%). Future studies should assess whether the presence of these polydrug substances amongst overdose decedents is influenced by MML status.

In summary, in cases of opioid overdose, it appears as if medical marijuana laws (MMLs) may matter in the West but have minimal impact elsewhere. The impact of these laws also appear to be age-dependent, though this may change as the age distribution of medical marijuana patients continues to shift. Future research should focus on regional heterogeneity in MML policy provisions, which may be influencing divergent regional trends in opioid overdoses.

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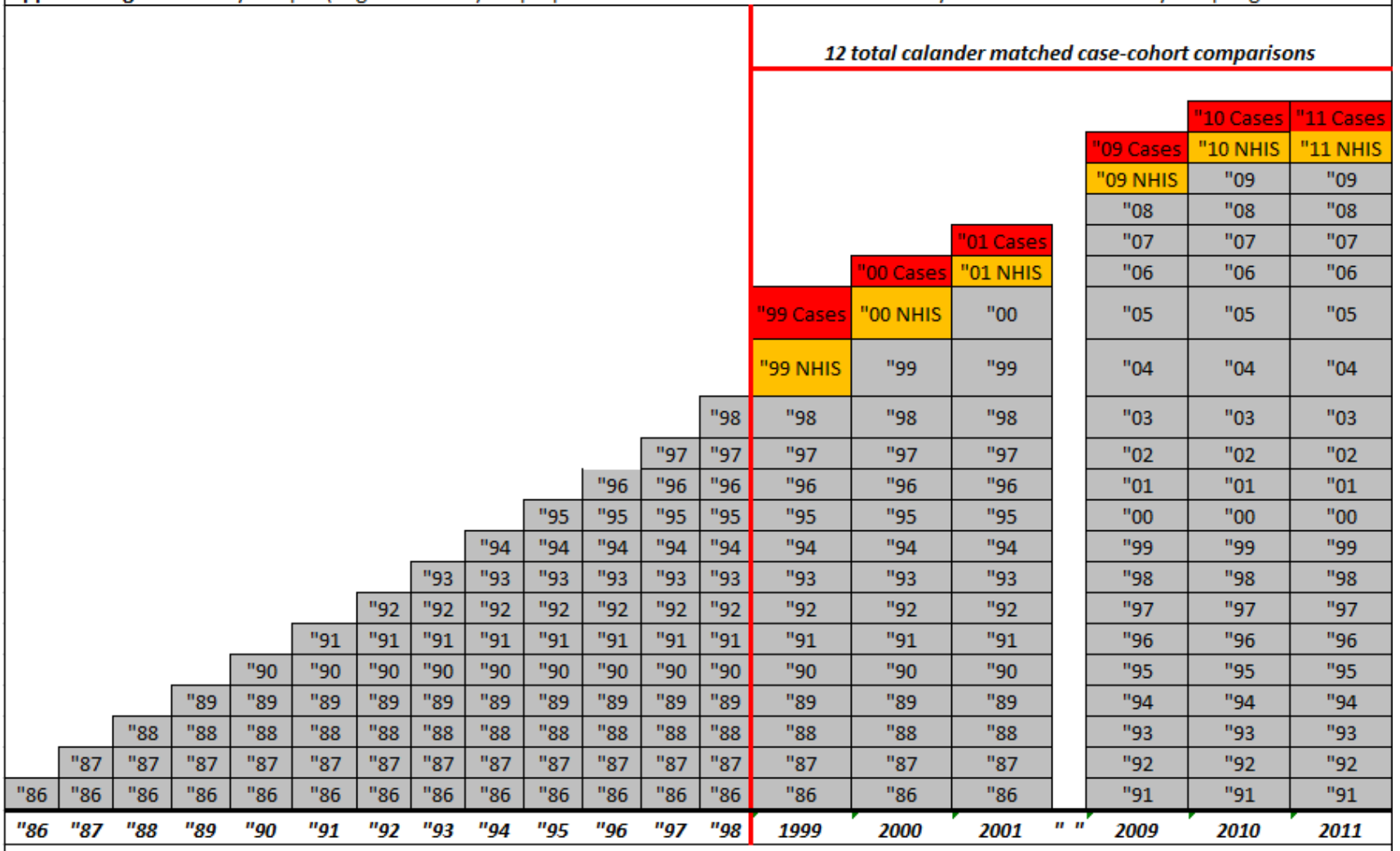
Appendices

Appendix Figure 1. Study sample (in gold and red) for proposed series of nested case-control study with incidence density sampling.



Cases (in red) arise from dynamic cohort (in grey). The exposure distribution (residing in state with MML) among cases is contrasted to the exposure distribution among a random household sample of adults (weighted to be nationally representative) surveyed* ***in the same year in which the cases arise.*

***Sample Adults from the 2010 and 2011 NHIS, for whom mortality information is unvailable, do not enter into our dynamic cohort.*

Appendix Table 1. *Data dictionary for analysis*			
Outcomes	**Criteria**		**Coding**
Prescription Opioid Overdose	ICD-10 Underlying Cause of Death Codes: **X40-X44, X60-64; X85, Y10-Y14**; ICD-10 Contributing Cause **T40.2-T40.4**.		1=decedent; 0=non-decedent
All Opioid-related Overdose	Additional ICD-10 Underlying Contributing Cause codes **T40.0-T40.1**.		1=decedent; 0=non-decedent
CVD-related Mortality	ICD-10 Underlying Cause of Death Codes: TBD		1=decedent; 0=non-decedent
Individual-level measures	**Cases (RXOD=1)**	**Controls (RXOD=0)**	**Coding**
Sex	at survey	at survey	1=Male, 2=Female
Race/Ethnicity	at survey	at survey	1=White; 2=Black; 3=Other
Poverty Status	at survey	at survey	1=Above Threshold, 2=Below Threshold; 3=Unknown
Age	***at death***	at survey	1=18-30 years; 2=31-55 years; 3=56+ years
Marital status	***at death***	at survey	1=Married/Cohabitant; 2=Widowed; 3=Separated/Divorced; 4=Never Married/Single; 5=Unknown
Education	***at death***	at survey	1=Never Attended, 2=Less than HS; 3=HS Degree/GED; 4= Some College; 5=BA/Technical Degree; 6=Post College; 7=Unknown
State-level measures	**Cases (RXOD=1)**	**Controls (RXOD=0)**	**Coding**
Region	***at death***	at survey	1=Northeast; 2=Midwest; 3=South; 4=West
Prescription Drug Monitoring Programs	***at death***	at survey	1=Proactive PDMP; 0=No PDMP
Medical Marijuana Law	***at death***	at survey	1=Operational MML; 0=No MML

Appendix Table 2. *Initial year in which states were coded positive for implementation of a "proactive" prescription drug-monitoring program (PDMP).*

State	Initial year coded
Hawaii	2000
Idaho	2000
Massachusetts	2000
Nevada	2000
Oklahoma	2000
Rhode Island	2000
California	2003
Maine	2004
Wyoming	2004
Alabama	2005
Kentucky	2005
New Mexico	2005
Mississippi	2006
North Carolina	2006
South Carolina	2006
Louisiana	2007
North Dakota	2007
Vermont	2007
Virginia	2007
Arizona	2008
Indiana	2008
Alaska	2009
Florida	2011
Ohio	2011
South Dakota	2011

*proactive PDMP is defined as whether the program is "permitted or required to identify suspicious or statistically outlying prescribing," Data obtained through LawAtlas.

Appendix Table 3. *Polydrug use among cases (n=791)*	
Polydrug substance	**n (%)**
Heroin / Opium	41 (5.2%)
Alcohol	83 (10.5%)
Benzodiazepine	198 (25.0%)
*Heroin/opium use identified with ICD-10 contributing casue of death codes: T40.0-T40.1 *Alcohol use identified with ICD-10 codes: T51.0, T51.9 *Benzodiazepine use identified with ICD-10 codes: T42.4	