Cannabis substitution for prescription drugs: understanding longitudinal trends in the era of legal cannabis

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Abstract

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The effects of changes in cannabis laws continue to be of great interest to researchers, medical professionals, and policymakers as individual US states implement legal cannabis markets and cannabinoids are better studied. Cannabis may serve as a substitute for a number of substances including several classes of prescription drugs. In order to evaluate cannabis-for-prescription drug substitution in the period following legal dispensary opening in Washington State (July 2014-December 2017), we evaluated the effect of increased cannabis demand on opioid dispensing outcomes in individual counties. We instrumented county-quarter level cannabis sales using state-regulated dispensary density, estimating within-county changes in the number of individuals dispensed opioids per quarter. Effects of increasing retail cannabis sales on short- and long-term dispensing were small in magnitude and not statistically significant. Small effects for long-term high dose dispensing (approximately 3% of dispensing) may reflect substitution

among the individuals at the highest risk for opioid use disorder; however, we did not find consistent evidence for substitution in the early period during recreational cannabis rollout in Washington. We also evaluated post-cannabis policy change substitution effects for antianxiety and antidepressant medication use in their respective indications among individuals with employer-sponsored insurance within US states (2010-2017). Medical cannabis policy did not lead to measurable changes in the level of use of antianxiety medications or antidepressants within their respective conditions; however, there may be noteworthy state and time-related heterogeneity as evidenced in event studies. In synthetic control models for Colorado and Washington, which legalized recreational cannabis in 2012, the use of antianxiety medications in anxiety and antidepressants in depression was not impacted by recreational cannabis policy change. Together, these findings may reflect little substitution for these classes in the first few years after cannabis policy enactment.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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DEDICATION

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Chapter 1. INTRODUCTION

1.1 SUBSTITUTION

Medical product substitution is often discussed in the context of policy decisions in healthcare and public health. Substitution reflects a conscious choice to consume one good in place of another, and two goods are considered to be economic substitutes if the demand for one product is observed to increase as the price of the other increases. In the United States, there are many examples of new policies and products informed by substitution. For example, cost-containment policies have encouraged greater use of generic and high-value prescription drugs, and harm-reduction programs have introduced new products into circulation such as the nicotine patch for smoking and methadone as an alternative to heroin.

Substitution is an important consideration for policy decisions in the opioid epidemic. In the early 2000s, the introduction of an abuse-deterrent formulation of Oxycontin® was intended to stem problematic use of the substance. However, this change shifted many substance-users from prescription opioids to heroin and other illicit substances, contributing to what is described as 'the second wave of the US opioid epidemic'.[1] Subsequent opioid policy has focused in part on preventing opioid deaths through supply-side changes such as opioid prescribing limits and more specific treatment guidelines. Such reduced access to opioids has prompted calls for alternative therapies to manage pain.[2]

1.2 MEDICAL CANNABIS

Cannabis has been used throughout history as a medicine and has recently reemerged after periods of prohibition and criminalization in the US. Analgesia is among cannabis' most well-documented properties, though a wide variety of clinical effects are reported by users. There is considerable interest the therapeutic potential of cannabis. Documented efficacy for seizures and spasms led to the recent approval of cannabinoid products in severe epilepsy[3] and multiple sclerosis (MS).[4] Other novel cannabinoid-therapies[5] are in early product development and two Food and Drug Administration-approved products have been on the market for more than fifteen years: nabilone for nausea and vomiting in cancer (approved 2006)[6] and dronabinol in HIV (approved 1985).[7]

Medical cannabis has been available in some states since the late 1990s, though it has been restricted to a relatively short list of qualifying conditions including cancer, Crohn's disease, and HIV. Findings from patient surveys confirm that cannabis is most commonly used medically for chronic pain,[8,9] which is consistent with the published clinical evidence to date.[10] There is less known about cannabis in other conditions, despite a number of new conditions becoming eligible for medical cannabis in individual states.[8] The use of cannabis continues to be debated in mental health,[11] though three states allowed medical cannabis for anxiety as of 2019.[12] A large portion of medical patients may use cannabis for mental health conditions,[13] despite mixed evidence to support clinical safety and efficacy.[14]

1.3 Recreational cannabis

As of 2019, cannabis was a fast-moving recreationally legal industry in 11 US states and the District of Columbia (DC). With its way paved by the legalization of medical cannabis, recreational cannabis has had broadening acceptance in recreational states.[15] In Washington State, which legalized cannabis in 2012 as ballot initiative 502[16], there has been a marked increase in cannabis use over time[17] which has correlated with wider access to cannabis. In 2019, licensed cannabis dispensaries were operating in seven states and offered many products in differing forms and potencies for relatively low prices.[18]

1.4 Cannabis and prescription drugs

US states continue to liberalize cannabis policy and launch legal markets. The cannabis industry is already well-established in Canada and has grown rapidly in the US in anticipation of federal legalization. Like tobacco and alcohol markets before it, cannabis will interact with other established markets for recreational and medical products, including pharmaceuticals.

A number of analyses have been conducted to evaluate effects of cannabis policy change. Based on a targeted literature review, at least fifteen studies (Table 1.1) have focused specifically on opioids and opioid outcomes and/or other prescription drugs. A majority of these studies have utilized generalized difference-in-difference designs, with most reporting statistically significant effects of cannabis policy; however, more recently published studies have challenged some of the earlier findings.[19]

Cannabis policy was first associated with the opioid epidemic when researchers reported that medical policy changes were associated with improved health outcomes[20–22] (e.g. reduced opioid overdose deaths, reduced opioid use disorder [OUD]) and prescription drug cost savings.[23–26] The proposed mechanism for these effects was individuals' substitution behavior. This hypothesis was further strengthened by reports of substitution in survey-based studies.[13,27–29]

Optimism about cannabis and opioids and subsequent privately-funded studies and advertising have contributed to the push to legalize cannabis to improve opioid-related outcomes[30] despite there being only modest evidence for how cannabis could lead to "opioid sparing."[31] There is even less evidence for how cannabis policy will impact the use of other prescription drugs.

1.5 Cannabis Policy

Since 1996, more than half of all US states have legalized cannabis or cannabinoid products for medical use in some capacity, but cannabis has remained a Federally scheduled substance. The year 2020 saw record numbers of cannabis policy reform bills presented in state legislatures. The legal cannabis market saw continued growth of cannabis advertising and an increasing number of unsubstantiated medical claims of health benefits.[32] These trends demonstrate the momentum behind cannabis in the US, making it a critical time to evaluate cannabis effects to inform subsequent policy.

Table 1.1. Previous policy analyses of cannabis laws

Author year	Data level	Medical or recreational	Data source (timeframe)	Approach	Primary outcome	Covariates considered
Bachuber 2014[33]	State-year	Medical	State-level death certificates (1999-2010)	DID	Opioid mortality rate	Presence of a prescription drug monitoring program, identification for dispensing laws, laws for state oversight of pain management clinics, unemployment rates
Bradford 2016[25]	Physician-year	Medical	Medicare (2010-2013)	DID	Number of daily doses	Physician and state characteristics
Bradford 2017[24]	State-quarter-drug class	Medical	Medicaid (2007-2014)	DID	Average number of daily doses (of medications for several indications)	Presence of a prescription drug monitoring program, number of physicians, household income, recreational MJ, Medicaid expansion
Ozluk 2017[34]	Person-year	Medical	MEPS (1996-2014)	DID (two-part model)	Opioid spending, total number of pills	Individual level demographic and economics, state unemployment, median household income, state average personal income, state uninsurance rate, prescription drug monitoring programs, marijuana decriminalization
Livingston 2017[21]	Colorado-year	Recreational	Multiple Cause of Death files (2000-2015)	ITS	Opioid-related deaths	Prescription drug monitoring programs
Wen 2018[23]	State-quarter	Medical and recreational	Medicaid (2011-2016)	DID	Number of opioid prescriptions	Physician supply, buprenorphine-waivered physician supply, economics, concurrent policies, pain clinic, Medicaid expansion
Powell 2018[35]	State-year	Medical	TEDS (1999-2012), National Vital Statistics System (1999-2013), DEA ARCOS (2000-2013)	DID and SC	Opioid-related treatment admissions, mortality, and distribution of opioid to states from producers of meds	State demographic measures, unemployment, alcohol tax, PDMP
Liang 2018[36]	State-quarter	Medical (also evaluated dispensaries)	Medicaid (1993-2014)	DID	Number opioid prescriptions, total doses in MME, and related Medicaid spending	Time-varying cannabis policies, policy, and socioeconomic covariates
Chan 2019[37]	State-year	Medical and recreational	Unclear	DID	Opioid mortality	Unclear
Flexon 2019[38]	Patient-year	Medical	National Survey on Drug Use and Health (2015-2017)	Multilevel model	Opioid use, opioid misuse	Age, sex, race/ethnicity, self-reported health, smoking, health insurance, family income, county metro status, marital status, education, employment
Raji 2019[39]	State	Medical and recreational	Optum (2016)	Cross-sectional study (multilevel)	Probability of 30- or 90-day opioid prescription	Patient characteristics

Shah 2019[40]	Patient-year	Medical	IMS lifelink+ (2006-2014)	DID (multilevel)	Probability of any opioid use, long-term, high-risk	State, Year, patient-year-level characteristics (demographics and payer, pain diagnosis, trauma, surgery, childbirth, dental, any inpatient stay), state-level (PMP, pain clinic laws, unemployment, number of physicians)
Shi 2019[41]	State-quarter	Recreational	Medicaid (2010-2017)	DID	Number opioid prescriptions, total doses in MME, and related Medicaid spending	Medical, PDMP, Medicaid expansion, income, poverty unemployment
Shover 2019[19] *	State-year	Medical	State-level death certificates (1999-2017)	DID	Opioid mortality	Unemployment, prescription drug monitoring program, pain clinic oversight laws, pharmacy patient identification laws
McMichael 2020[42]	State-provider-year	Medical and recreational	Symphony Health (private and public payers, 2011-2018)	DID (multilevel)	Number of opioid MMEs, total days supply, number of unique patients prescribed	Medicaid expansion, prescription drug monitoring program, pain clinic laws

Abbreviations: DEA ARCOS = Drug Enforcement Agency Automated Reports and Consolidated Ordering System, DID = difference-in-differences; ITS = interrupted time series; MEPS = Medical Expenditure Panel Survey, MME = milligram of morphine equivalent, PDMP = prescription drug monitoring program; SC = synthetic control, TEDS = Treatment Episode Dataset

*Reanalysis of Bachhuber 2014, with more recent data.

Chapter 2. CANNABIS SALES AND OPIOID DISPENSING IN WASHINGTON STATE

2.1 OVERVIEW

The extent to which increased access to recreational cannabis will impact prescription opioid use is unclear. This study aimed to estimate the relationship between cannabis demand and prescription opioid dispensing in counties in Washington State following recreational cannabis dispensaries opening in July 2014. We linked administrative data on cannabis sales and retail cannabis dispensary licensing records with opioid dispensing data from State surveillance activities. This secondary data analysis relied on data from 39 counties in Washington State evaluated over 14 quarters (Q3 2014 to Q4 2017) and longitudinal panel methods to estimate the effect of increased cannabis sales on counts of individuals receiving prescription opioids, adjusting for fixed effects of time and county as well as key time-varying demographic and economic characteristics. We accounted for sales endogeneity using state-regulated dispensary density per population as an instrumental variable. Opioid dispensing outcomes included the primary outcomes any opioid, long-term, and short-term dispensing as well as secondary outcomes long-term high dose (50 milligrams of morphine equivalent [MME] or more, 90 MME or more, 120 MME or more), and new opioid dispensing.

Increases in cannabis sales did not produce reductions in any, long-term, or short-term opioid dispensing. Effects estimated in linear specifications of the instrumental variable models were positive (increases of 2-4% of the average number of individuals dispensed opioids across the study period) and not statistically significant for long-term and short-term outcomes. High-dose outcomes showed larger relative effects (increases of 4-17%) that were not statistically significant. Non-linear instrumental variable models confirmed these results. We did not find strong evidence of cannabis-for-opioids substitution in the period following recreational dispensary opening in Washington State. Policy makers should consider the magnitude of potential substitution along with other health-related outcomes of policy change.

2.2 INTRODUCTION

Recently, cannabis been at the center of drug policy debates in the US. Analgesia is among the most commonly listed therapeutic effects of cannabis. Pain appears as the primary eligible conditions for obtaining a medical cannabis license in US states and is the most frequently reported medical use of cannabis in patient surveys.[8,9] From a policy perspective, wider use of cannabis as a substitute for opioids in pain management could result in fewer negative opioid outcomes such as opioid use disorder (OUD), accidental overdose, and death. Evidence for this is mounting; several quasi-experimental studies of US states found that cannabis policy changes are associated with reduced opioid overdose deaths.[20,21] Other studies suggest that cannabis as a substitute could bring cost savings to Medicare/Medicaid through reduced prescribing.[23–26] Such effects may be mediated through individual-level substitution behavior as reported in survey-based studies[13,27–29,43,44] and putative "opioid-sparing" effects.[45]

In November 2012, Washington State's Initiative 502[16] effectively legalized recreational cannabis possession and consumption, also removing prohibitions for producing, processing, and selling cannabis. The legal market saw the first opening of recreational dispensaries in July 2014 and as of April 2020, there were 446 licensed cannabis dispensaries in the state.[46] Recent evidence from surveys suggested that legalization and commercialization of recreational cannabis in Washington State increased demand for the substance over time.[17,47] The Washington State Liquor and Cannabis Board (LCB) administers and regulates the production and sale of retail and medical cannabis, tracking licensing, production, sales, and compliance figures via a traceability system. Under the LCB's oversight, overall cannabis sales have increased steadily since July 2014.

As policies shift over time, the extent to which patients will rely upon newly available recreational cannabis products for pain management is unclear.[28] The main objective of this work was to estimate the causal effect of cannabis demand on opioid dispensing in counties in Washington State in the period following recreational cannabis legalization and opening of dispensaries. Given the substitution and opioid-sparing mechanisms in chronic pain as noted in recent literature,[48,49] we hypothesized that increases in cannabis sales would lead to reductions in long-term and high dose prescription opioid dispensing.

2.3 Methods

2.3.1 *Data*

We combined several sources of publicly available administrative and surveillance data, aggregating and linking at the county-quarter level.

2.3.1.1 Opioid dispensing

We utilized quarterly county-level data on Washington State's Bree Collaborative prescribing metrics.[50] These opioid dispensing outcomes were available via the State Department of Health Opioid Prescribing Dashboard, which aggregates data from the state's Prescription Monitoring Program (PMP). Selected outcomes and their definitions are shown in Table 2.2. In the literature, opioid dispensing outcomes may vary in their definitions. However, repeated prescriptions in a given period and/or a large number of days supplied are commonly evaluated under the heading of long-term episodes of dispensing.[51] We note that here we use "long-term" for what was originally referred to as "chronic" dispensing in Bree documentation. We also generated a new outcome, included in the below table, "short-term" opioid dispensing, which was defined as the difference between any opioid dispensing and long-term opioid dispensing. This derived dispensing outcome does not represent acute dispensing, rather, it is a composite for any short-term dispensing. We selected any, short-term, and long-term opioid dispensing as primary outcomes for this analysis, though we also report long-term high-dose (HD) outcomes and new long-term dispensing as secondary outcomes. These rates represent a subset of all long-term opioid dispensing. HD outcomes are defined according to the milligrams of morphine equivalent (MME) dispensed in a quarter. Opioid outcome datasets were extracted in March of 2019 and consisted of 28 quarters over the period of Q1 2012 to Q4 2018.

Table 2.2. Opioid dispensing outcomes

#	Outcome	Definition	Analysis
1	Any opioid	Number of patients, per 1000 population, with at least one opioid prescription submitted to the PMP in a calendar quarter	Primary
2	Long-term opioid	Number of patients, per 1000 population, with at least 60 days' supply of prescription opioids submitted to the PMP in a calendar quarter	Primary

3	HD Long-term 50 MME	Number of patients, per 1000 population, who have filled prescriptions for at least 60 days' supply of opioids during the quarter and whose prescriptions provided a dose of 50 MME/day* or more, averaged over the quarter	Secondary
4	HD Long-term 90 MME	Number of patients, per 1000 population, who have filled prescriptions for at least 60 days' supply of opioids during the quarter and whose prescriptions provided a dose of 90 MME/day* or more, averaged over the quarter	Secondary
5	HD Long-term 120 MME	Number of patients, per 1000 population, who have filled prescriptions for at least 60 days' supply of opioids during the quarter and whose prescriptions provided a dose of 120 MME/day* or more, averaged over the quarter	Secondary
6	New long-term opioid	Number of patients with long-term opioid prescriptions, per 1000 population, who were new opioid patients in the past quarter, and are long-term opioid patients (i.e. prescribed 60 or more days' supply) in the present quarter. Patients with no opioid prescriptions in the quarter prior to the previous quarter are excluded. Patients with tramadol prescriptions in the third and fourth quarters of 2014 were excluded as new opioid patients because of the possibility that they might have had long-term prescriptions.	Secondary
7	Short-term opioid	Generated by subtracting the any opioid outcome from the long-term opioid outcome	Primary

Note: Per the Washington State Department of Health's Opioid Dashboard reporting, MME/day was calculated by dividing the total MME dispensed during a quarter by the number of days in the quarter. Total MME is calculated as the (strength per unit)*(quantity)*(MME Factor). Data are for all ages in the form of sex- and age-adjusted rates. Population is also reported. Long-term opioid dispensing was originally referred to as chronic dispensing.
Abbreviations: HD = high dose, MME = milligram of morphine, equivalent, PMP = prescription monitoring program

2.3.1.2 Cannabis sales and dispensary density

We obtained monthly cannabis sales and retail dispensary licensing data from the Washington State LCB frequently requested lists page on the LCB website. These data are tracked for administrative purposes as part of i502. Data consisted of licensing, production, sales, and compliance figures that are routinely entered within a traceability system.

Each dispensary in Washington State must be granted a license for retail cannabis which is updated in annual license renewal. We linked data on dispensary characteristics (i.e., address, location) to cannabis sales activity by dispensaries' license number and aggregated counts of active dispensaries and total sales over date and county to create a dataset at the county-month level. To be defined as an "active dispensary" in a given month, a dispensary must have had non-zero sales. We also included information on the number of licenses allotted to a particular county by the LCB.

Due to the structure of the LCB data, the linked county-month data only had county-months with positive sales and dispensaries, so we generated additional entries as county-months with appropriate zeros. We then created a quarterly form of these data, summing over sales and averaging over the allotted number of licenses, dispensary counts, and proportion of allotted licenses granted.

2.3.1.3 Other covariates

We utilized covariate data from the Area Health Resource File (AHRF), which aggregates annual demographic, economic, and health resource data.[52] We selected key county-level time-varying covariates that plausibly impact cannabis sales and/or opioid dispensing. A complete list is provided in 5.1.5. Due to lags in collecting population sociodemographic and health data, a majority of these covariates were only available through 2017. As such, we restricted the analytic dataset to this time frame. We prioritized cannabis sales and opioid dispensing outcomes at the quarterly level in order to make most efficient use of these data. However, we note that the majority of the covariate data are only collected the annual level, which is a general limitation of longitudinal designs with more frequent panels, like this one.

2.3.1.4 Cannabis access

While we ultimately did not pursue access to dispensaries in modeling, we derived a number of spatial cannabis dispensary measures. We used spatial methods and the Google application program interface (API) to geocode dispensaries, and we derived average driving distances using the latitude and longitudes of population-weighted county centroids from the 2010 Census.

2.3.2 *Statistical analysis*

We used panel data methods to estimate causal relationships between cannabis demand and opioid use in counties in Washington State in the period following recreational cannabis legalization.

2.3.2.1 Modeling approach

Outcomes were analyzed as counts of individuals dispensed opioids per quarter with the log transformed population included in models. Counts were derived from the age- and gender-adjusted rates and the reported county population sizes. The exposure, total cannabis sales, was divided by the county quarterly population in thousands and scaled to be in $10K units. The proposed instrumental variable, cannabis dispensary density, was divided by the quarterly population in thousands.

A reduced list of eight time-varying covariates was specified for the final model in order to prioritize relevance and parsimony. Selected time-varying covariates were those thought to impact utilization of cannabis and opioids. Since the opioid dispensing count variables were already age and gender-adjusted, the final model included the proportion white, proportion living in poverty, proportion unemployed, median household income, median per capita income, proportion under age 65 that are uninsured, proportion of those eligible who are Medicare Part D enrolled, and the number of active medical doctors per 1000 population.

Beginning with a naïve regression, we increased models in complexity by including the log of the population, clustering around county, a fixed effect of time, time-varying covariates, and finally, a fixed effect of county. A fixed effect of time was incorporated to account for several changes in the cannabis market over the study period which included a tax rate change in Q3 of 2015[53] and the incorporation of recreational and medical markets beginning in Q3 of 2016.[54] Prior to Q3 2016, cannabis total sales reflected recreational sales, as well as state and local taxes. After this time, the cannabis retail and medical markets were integrated. For ease of interpretation, we utilized a linear specification. However, we also tested consistency of the model results using a generalized linear model with log link and family negative binomial for over-dispersed count data.

2.3.2.2 Instrumental variable selection

There was some concern about the potential for time-varying endogeneity of cannabis sales, which motivated an instrumental variable (IV) approach. Endogeneity produces a biased effect estimate and results from omitted variables that are correlated with regressors (i.e., unobserved confounders), simultaneity, and/or measurement error. Primarily, we were concerned with omitted variable bias even after accounting for the aforementioned time-varying factors. Often, the included covariates can be used to test assumptions about the directionality of bias provided that the relationships are known. For example, we might expect to observe a reduction in the effect estimates (i.e., evidence of a positive bias) with the inclusion of insurance status, an important covariate due to state-level Medicaid expansion over the study period.[55] Particularly in states that began expansion in 2014, expansion may have led to increased demand for prescription drugs through moral hazard or pent up demand. However, several analyses have reported that demand for opioids did not increase following Medicaid expansion[56,57] and this is less concerning since Washington was a state with early expansion as of 2011.

Previous studies of the cannabis-opioid relationship may be subject to a negative bias (i.e., overly low effect estimates) rather than actual substitution, whereby an omitted variable was positively associated with cannabis changes and negatively associated with changing opioid use or outcomes. Our study period has been characterized by several noteworthy changes in drug policy and preferences. Opioid prescribing limits and rescheduling of hydrocodone (national) were shown to have reduced dispensing in Washington and other states.[58–61] Over the same period, medical providers' prescribing practices may have shifted as a result of fear of patient outcomes and legal sanctions.[62] The general stigma around cannabis use may have shifted as evidenced by increased usage among older adults.[63,64] Some of these changes may be common causes of cannabis and opioid use, which prompted concerns about endogeneity in this study. In utilizing panel data, simultaneity is also of concern. In particular, changes in cannabis and opioid use may be determined at the same time.

We explored several potential instruments including dispensary density and cannabis access-related measures, providing evidence to support the use of dispensary density as a valid instrument. Instruments were also supported by background knowledge. Specifically, dispensary density is related to sales, where higher densities predict higher total sales. This may arise from greater between-dispensary competition producing greater product quality and lower prices, which fell quickly within the months after retail dispensaries opening. It also follows that dispensary density should not impact opioid dispensing other than through sales since product needs to be sold and used in order to exert an effect. Lastly, the LCB controls the allotment of dispensary licenses provides with caps on available licenses. This may indicate that dispensary density is in large part exogenously determined in the early phases of dispensary rollout. Other than population density, we did not find evidence to suggest that LCB used demographics or economic considerations to approve licenses. We also show that use of dispensary density as an instrument can balance potential key observed confounders, which provides support for exchangeability as discussed further below.[65]

2.3.2.3 Evaluating instruments

First, we confirmed the endogeneity of sales using a Wu-Hausman test, with a null hypothesis that sales can be treated as exogenous.[66] We then evaluated the proposed instruments on the assumptions for reliable application of an instrumental variable approach. To satisfy the relevance criterion, we tested whether dispensary density is associated with sales conditional on covariates using a Robust F-test and the Partial R-squared, which reflects correlation between the instrument and endogenous predictor after partialling out the effects of the other included covariates. This "first-stage" model was a linear specification with county clustering, county and time fixed effects, and the aforementioned eight time-varying covariates. At this time, the spatial instruments were eliminated due to poor correlation and the potential for finite sample bias (6.2.2).

A second criterion requires that instrument be uncorrelated with the outcome except through cannabis sales (i.e., the exclusion restriction) was previously discussed. This condition cannot be tested empirically but is supported by background knowledge. Lastly, exchangeability assumes that the instrument does not share common causes with the outcome (i.e., independence). Checks of covariate balance presuppose that if the instrumental variable is uncorrelated with the observed time-varying covariates it is less likely to be correlated with unobserved time-varying confounders.[65] First, we examined the baseline (Q3 2014) covariates across quartiles of change in the primary regressor, cannabis sales, and the potential instrument, dispensary density. The change was calculated from Q3 2014 to Q4 2017. Second, we calculated the mean values of each covariate across groups defined by the median cannabis sales and dispensary density. By definition, we expected that the covariates would be better balanced across levels of the instrument.[67] Lastly, we estimated standardized mean differences from reduced form regressions of the binary forms of instrument and exposure (defined as above or below the median value) to demonstrate that dispensary density balanced time-varying covariates.

2.3.2.4 Instrumental variable modeling approach

Dispensary density was selected as the primary instrument. We specified two IV regressions, a two-stage least squares (2SLS) model and a negative binomial two-stage residual inclusion (2SRI) model. The 2SRI approach has been shown to produce consistent estimation of the average-treatment effect for non-linear applications[68] with negative binomial family being the most appropriate distribution for these count dispensing data. Both models share a linear first stage as described above. The final 2SRI models were run as generalized linear models and included clustering on county, fixed effects of time and county, and time-varying covariates as previously noted. The negative binomial dispersion parameter was estimated using maximum likelihood while the final model was maximized using iteratively reweighted least squares and a maximum of 250 iterations. Ninety-five percent confidence intervals for two-stage models were derived using standard errors from bootstrapped two-stage models with 5000 samples.

2.3.2.5 Additional study details

Table 1.1 includes additional background on previous studies related to opioids and cannabis policy change. Chapter 5 includes additional information on sales and dispensary data sources, the spatial analysis, and the integration of recreational and medical cannabis markets in Washington State.

An Institution Review Board approval for this study was not required as human participants were not involved and the data do not contain any identifying information. Data aggregation, linkage, and generation of most figures were completed using R version 3.6.0. All analyses were conducted using Stata Version 15.1. Chapter 6 includes additional tables and figures as well as a causal model (6.1).

2.4 RESULTS

2.4.1 *Baseline characteristics*

Thirty-nine counties in Washington State provided 14 quarters of data (n=546) from Q3 2014 through Q4 2017. Baseline demographic and economic characteristics of the counties are shown in Table 2.3, both overall and stratified by quintiles of the average change in retail cannabis sales over the study period. The average change in quarterly retail cannabis sales over the study period ranges from an increase of $5K per 1000 population (i.e., $5 per person) in the lowest quintile to an increase of $52K per 1000 population (i.e., $52 per person) in the highest quintile.

On average, counties in the lowest quintile of change in cannabis sales (i.e., Columbia, Douglas, Franklin, Garfield, Lincoln, Pend Oreille, Stevens, and Wahkiakum) had slightly greater proportions of older and white individuals, smaller populations, and fewer active medical doctors per 1000 population. Counties in the central quintiles (including King County) tended to have higher population and median incomes, lower rates of unemployment and uninsurance, and more active physicians.

The same characteristics are shown overall and across quintiles of the change in retail cannabis dispensary density in Table 2.4. The average change in quarterly density of cannabis dispensaries over the study period ranged from an increase of 0.01 per 1000 population in the lowest quintile to an increase of 0.17 per 1000 population in the highest quintile.

Demographic and economic characteristics were slightly more balanced across quintiles of cannabis dispensary density. However, the population flipped such that the highest quintile of dispensary density had the smallest average population. This was expected since there are several counties in Washington with extremely small populations.

2.4.2 *Cannabis sales and dispensary density*

Cannabis sales per population increased over the study period from zero to an average of $29K per 1000 population (standard deviation [SD]: 18) across counties in Q4 2017 (Figure 2.1). In Q1 2019, this figure had increased to $32K per 1000 population (SD: 18).

Dispensary density also increased steadily over this time (Figure 2.1). In Q4 2017, the average across counties was 0.09 per 1000 population (SD: 0.06). This increased to 0.11 (SD: 0.09) in Q1 2019. The most recent quarterly data may depict how sales and dispensary density may be leveling off; however, there were noteworthy increases in sales in the summer quarters.

Over the same period, access to retail cannabis dispensaries also increased. Additional information is provided in 6.2.

2.4.3 *Opioid dispensing*

The rate of any opioid dispensing adjusted for age and gender across counties declined over the study period from 103 per 1000 population (SD: 19) to 85 (SD: 15) (Figure 2.2). The rate of short-term and long-term dispensing per 1000 population decreased from 74 (SD: 10) to 61 (SD: 8) and from 28 (SD: 10) to 24 (SD: 8), respectively.

2.4.4 *Dispensary density as an instrumental variable*

From the first stage model of cannabis sales regressed on dispensary density, it was estimated that every increase of 0.1 dispensary per 1000 population, the cannabis sales are increased by $15K per 1000 population (i.e., $15 per person) (Table 2.5). This confirmed that cannabis dispensary density was strongly associated with cannabis sales (Robust F-statistic [1,38] = 16.38, p=0.0002). As an instrument, dispensary density balanced key covariates. Across the median value of sales, the mean values of key covariates were statistically significantly different (Table 2.6). Mean values were less likely to be statistically significantly different across median levels of dispensary density (Table 2.7). Thus, the instrument provided additional covariate balance (Figure 2.3).

Accounting for fixed effects of time and county, means were no longer statistically significantly different across medians of sales and dispensary density (Table 2.7). In this case, the instrument did not provide additional balance, except for the proportion with Medicare Part D enrollment and poverty (Figure 2.4), which were considered to be key covariates for the evaluated relationship.

2.4.5 *Effect of cannabis sales on opioid dispensing primary outcomes*

2.4.5.1 Covariate-adjusted models

Estimates of the effect of cannabis sales on opioid dispensing are shown in Table 2.8. A naïve model suggested that increased cannabis sales reduced opioid dispensing for all three outcomes, any, short-term, and long-term dispensing. Applying additional levels of control including clustering on county, fixed effects of time, and health insurance reduced the positive bias, producing more negative effect estimates; however, none of the estimates was statistically significant. Including the full set of covariates attenuated the effects but they remained null. The addition of a county fixed effect increased all effect estimates in a positive direction, though none achieved statistical significance.

2.4.5.2 Instrumental variable approach

With dispensary density as the instrument (Table 2.8), increases in cannabis sales did not produce statistically significant changes in opioid dispensing. While effect estimates were increased relative to non-instrumental variable models, these estimates still only accounted for a relatively small proportion of the mean of dispensing over the study period (between 2-4% across the primary outcomes).

Non-linear specifications of covariate-adjusted and instrumental variable models were all null and consistent with the main models (6.2.1). However, in better accounting for overdispersion, the non-linear instrumental variable model effect estimates were much smaller than those from the linear model.

2.4.6 *Effect of cannabis sales on opioid dispensing secondary outcomes*

Secondary outcomes long-term high-dose opioid dispensing as well as new long-term opioid dispensing displayed similar patterns to the primary outcomes (6.2). While not statistically significant, the effect estimates from secondary outcomes accounted for a slightly larger proportion of mean dispensing over the study (4-17%).

In non-linear specifications with the fully adjusted model (6.2.1), increases in cannabis sales led to significant reductions in long-term HD dispensing for 90MME and for 120MME: an increase of $10K in sales per 1000 population decreased the number of people dispensed long-term HD opioid of 90MME by 17 individuals (95%CI: -32, -2) and 120MME by 15 (95%CI: -27, -3). The non-linear IV models demonstrated a similar pattern that was not statistically significant.

2.5 DISCUSSION

Adjusting for time trends, county-level variation, and time-varying sociodemographic and economic characteristics, increases in sales of retail cannabis did not cause detectable declines in opioid dispensing during the period directly after the opening of the first retail cannabis dispensaries in Washington State. Accounting for remaining endogeneity, instrumental variable models confirmed these results. Broadly, findings from this study may be consistent with minimal cannabis-for-opioid substitution among patients with a need for pain management. If this is true, liberalizing cannabis policy may have less of a direct beneficial effect on opioid utilization than has been suggested previously.

A majority of the study of potential cannabis substitution to date consists of policy analyses using state-level data and the timing of policy change. These investigations have proposed substitution as a mechanism for how cannabis laws may reduce opioid use and related negative outcomes.[23–26,35,69] But, the magnitude of the observed effects of cannabis policy[20,33,37,70,71] has been large in relation to targeted opioid policies, and newer studies provide conflicting evidence.[19,72] To date, several investigations have utilized data from Washington State's cannabis seed-to-sale tracking system.[17,73–75] Most of these studies have aimed to characterize the newly formed market or to quantify the extent to which the sales data are consistent with alternative methods of measuring exposure such as surveys. To our knowledge, ours is the first study of its kind to utilize cannabis sales as a proxy for demand to evaluate opioid substitution effects.

Despite specifying instrumental variable models in order to account for endogeneity, we did not find robust or consistent evidence for a cannabis-opioid substitution relationship operating during the time period of interest. There are several methodological reasons why this may be the case even if cannabis was serviced as an opioid substitute. Cannabis sales and prices were fluctuating over the study period.[18] Prior studies evaluating retail and medical cannabis price changes have cautioned against short-run evaluation of recreational cannabis policy effects[73] suggesting that the time period immediately following recreational dispensary opening may not offer a wide enough policy evaluation window. In addition, medical cannabis policy changes in Washington beginning earlier on (2007) may have already encouraged substitution, that is, any large demand shifts may have already occurred. However, this is less plausible since at the time of recreational dispensary opening, Washington State did not have a well-developed legal medical cannabis system. This later led to the integration of medical and recreational markets in 2016 under the Cannabis Patient Protection Act.

Linear instrumental variable models of opioid dispensing produced numerically positive effect estimates, despite being statistically null. Here the instruments may be better accounting for negative bias that may have characterized previous studies of cannabis and opioids. We do not consider this finding to be suggestive of potential complementary use; however, cannabis has previously been associated with misuse of opioids in chronic opioid therapy.[76,77] The "gateway hypothesis" has been invoked to describe how cannabis use may lead to the use of stronger, often illicit substances. A recent analysis of surveys from the National Epidemiologic Survey on Alcohol & Related Conditions (NESARC) reported that cannabis use substantially increased the risk of non-medical use of prescription opioids in subsequent survey waves.[78] But, the gateway hypothesis has mostly abandoned due to low-quality evidence.[79] Moreover, studies that link cannabis use with opioid harm have often evaluated very different samples than the general population requiring pain management.

Wide confidence intervals are common in instrumental variable approaches since these models sacrifice efficiency in attempting to improve bias. Despite not achieving statistical significance, our instrumental variable estimates differed in magnitude from two-way fixed effects estimate. Many authors use such differences as an indication that instrumental variables are appropriate, but instrumental variable effect estimates may still be subject to residual bias. We provide justification for dispensary density as an instrument in several checks of instrument assumptions. In addition, we control for a number of time-varying demographic and economic features of counties that may provide a common cause of the instrument and outcome. However, exclusion and exchangeability are unverifiable. Cannabis dispensary density may be correlated with opioid dispensing in other ways than those reflected in the specified models. This would result in residual time-varying confounding and bias in effect estimates.

In defining instrumental variables, we may fail to account for common causes of dispensary density and opioid dispensing. In particular, regional preferences and attitudes may shape all substance use policy. We lack information on how municipal bans and moratoria on cannabis retail zoning have evolved over time in several Washington counties and how this could lead to between-county differences in dispensaries and sales. Such bans and moratoria have been imposed within cities and towns, though the Liquor and Cannabis Board has the final decision over granting licenses. Plots of cannabis sales and dispensary density in states with some ban or moratorium over the study are provided in 6.2.3. As of April 2020, 82 jurisdictions and 6 entire counties prohibited cannabis retail;[80] however, prohibitions vary. Certain prohibitions only apply to new retail cannabis. This means that counties may have bans but active retail dispensaries over the study time frame. One recent example is Yakima, where State Court of Appeals recently upheld Yakima's efforts to close cannabis retailers in unincorporated areas.[81] Regional bans and zoning within jurisdictions may provide avenues for future study.

Non-linear models were more appropriate for these count data, and in models of HD opioid dispensing produced some statistically significant negative effect estimates. However, it is possible that these effects may reflect downward pressure on long-term opioid dispensing (i.e., negative bias) from opioid policy and guidelines. Key policy events in Washington were House Bill 1426 (May 2017), which specified that medical bodies should begin to formulate prescribing rules, and Apple Health (Medicaid) opioid prescribing limits (November 2017), which placed restrictions on the amount of opioids that can be dispensed over a given period.[82] These state-wide changes were accounted for in part by the inclusion of time fixed effects in models, though we cannot rule out county- and time-varying policy shocks to opioid dispensing. On the other hand, we also hypothesized that substitution effects would be more visible in higher risk opioid outcomes. It is plausible that a large number of cannabis users could shift the distribution of patients dispensed opioids from long-term HD to other categories of dispensing. High dose opioids should be evaluated alongside cannabis in further study, especially given that dosing and long-term dispensing are the focuses of recent policy efforts.

Overall null results may suggest that there is no strong substitution relationship. While cannabinoid compounds have demonstrated analgesic efficacy in some studies,[83] there continues to be scientific debate over whether cannabis should be recommended as a substitute for opioids in chronic pain.[84] To be a close substitute, cannabis should reduce the quantity of opioids used without leading to a loss in the level of analgesia (i.e., an opioid-sparing effect).[85] Clinical support for this is limited to date.[45] A recent cohort study of 1500 Australian patients with chronic non-cancer pain did not find increased rates of discontinuation or reduced opioid prescribing associated with cannabis use.[86] Meanwhile, several ongoing clinical trials are evaluating opioid sparing.[87] These studies may find that while cannabis has some utility when used alongside opioids, it does not lead to a reduction in dose or duration of use. This would be consistent with our findings.

This study has several limitations. First, cannabis sales data are collected for administration and regulatory decisions rather than for research purposes. These data may be subject to inaccuracy in reporting. Other authors have highlighted how poor quality data are the result of the tracking system design, user errors, and changes in platforms.[88] Because the present study covered only the period prior to changes in the sales tracking platform in November 2017 and because the data represents county-aggregated rather than dispensary-level measures, we believe the bias from measurement error will be lessened. Secondly, the vast majority of cannabis sales in these data represented recreational sales rather than qualified medical sales or recreational sales intended for medical use. It was not possible to differentiate sales in these data, which was further complicated by the recreational and medical market integration in Q3 2016. In not accounting for cannabis product strength and composition, we may have failed to detect the relationship of interest. Product composition may be a key focus of future analyses, since cannabinoids have different mechanisms of action in pain.[89]

Several factors may impact the interpretability of these findings. One caveat is that aggregate data do not allow for conclusions about individual-level substitution. Even at the individual-level, sales and quantity dispensed do not reflect actual consumption of cannabis or opioids for medical reasons. Findings from region-level analyses must be used alongside survey data and clinical studies of opioid sparing effects in order to answer this question more completely. Individual-level data may also help alleviate concern about simultaneity, where it may be possible to identify pain patients switching to cannabis because for example, it is easier to obtain (i.e., previous opioid users), as well as those never initiating opioids due to their cannabis use (i.e., non-initiators).

This work has distinct implications for policy and future research. Several states have been considering opioid outcomes to inform medical and recreational cannabis policy decisions.[30,90] But, cannabis may not be a "magic bullet" for the opioid epidemic. We found little evidence of cannabis-for-opioids substitution during the period following recreational cannabis dispensary opening in Washington State. Cannabis may provide a safer alternative to opioids with potential to influence downstream outcomes like opioid use disorder and mortality, though there is mixed evidence for these effects to date. Finding from this study are one consideration when evaluating the benefits and risks of further cannabis policy changes. Future analyses may focus on the interaction between cannabis and opioid policy, as well as the adequacy of cannabis as a substitute for opioids and other medications.

2.6 TABLES & FIGURES

Table 2.3. Baseline (Q3 2014) demographic and economic characteristics, across quintiles of the change in cannabis sales for 39 counties in Washington State

Quantile of change in cannabis sales	**1**	**2**	**3**	**4**	**5**	**Overall**
Average difference in cannabis sales (2017 Q4 –2014 Q3), in $10K per 1000 population	0.51	2.03	2.81	3.43	5.20	2.95
Population	25555	86764	119290	521656	134579	178671
Proportion white	92.9	88.3	90.3	84.0	88.7	88.9
Proportion male, <15 years	9.2	11.0	8.6	8.9	7.9	9.2
Proportion male, 15-19 years	3.4	3.7	3.2	3.2	3.3	3.3
Proportion male, 20-24 years	2.6	3.3	3.6	4.2	4.6	3.6
Proportion male, 24-44 years	10.2	11.6	11.6	12.9	11.4	11.6
Proportion male, 45-64 years	14.3	12.9	13.9	13.2	13.2	13.5
Proportion male, 65+ years	10.5	8.0	9.1	7.6	9.4	8.9
Proportion female, <15 years	8.9	10.4	8.3	8.7	7.7	8.8
Proportion female, 15-19 years	3.2	3.3	3.0	3.0	3.2	3.1
Proportion female, 20-24 years	2.3	3.0	3.2	3.7	4.1	3.2
Proportion female, 24-44 years	10.0	11.2	10.9	12.1	10.8	11.0
Proportion female, 45-64 years	14.3	13.1	14.5	13.6	13.9	13.9
Proportion female, 65+ years	11.2	8.5	10.1	8.9	10.5	9.8
Proportion living in poverty	16.3	18.4	13.3	14.6	17.8	16.0
Proportion unemployed	8.2	8.6	7.1	6.8	7.7	7.7
Median household income (annualized)	48176	46534	54192	57608	47427	50873
Median per capita income (annualized)	37706	37597	45129	46645	39454	41354
Proportion uninsured under 65 years	12.7	15.9	12.2	11.0	11.3	12.6
Proportion of over 65 population, Medicare part D	15.3	19.8	14.3	13.0	13.2	15.2
Active medical doctors per 1000 population	0.61	1.13	1.84	2.16	1.70	1.48

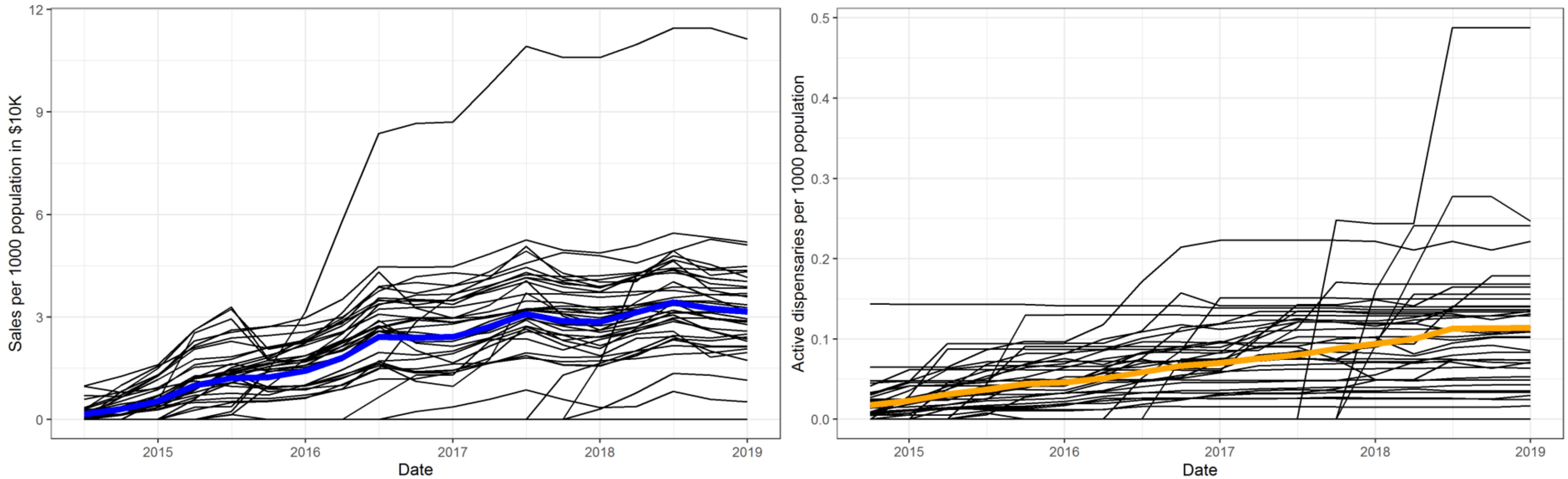
Notes: County membership in Group 1: Columbia, Douglas, Franklin, Garfield, Lincoln, Pend Oreille, Stevens, Wahkiakum; Group 2: Adams, Benton, Ferry, Grant, Klickitat, Lewis, Okanogan, Yakima; Group 3: Chelan, Clark, Island, Mason, San Juan, Skamania, Walla Walla, Whatcom; Group 4: Clallam, Cowlitz, King, Kitsap, Kittitas, Pierce, Skagit, Snohomish; Group 5: Asotin, Grays Harbor, Jefferson, Pacific, Spokane, Thurston, Whitman.

Table 2.4. Baseline (Q3 2014) demographic and economic characteristics, across quintiles of the change in cannabis dispensaries for 39 counties in Washington State

Quantile of change in cannabis sales	**1**	**2**	**3**	**4**	**5**	**Overall**
Average difference in retail cannabis dispensary density (2017 Q4 –2014 Q3), dispensaries per 1000 population	0.01	0.05	0.08	0.11	0.17	0.08
Population	106115	565075	105357	79950	16599	178671
Proportion white	92.5	84.7	88.2	89.2	89.9	88.9
Proportion male, <15 years	10.1	9.9	9.6	7.7	8.6	9.2
Proportion male, 15-19 years	3.5	3.4	3.3	3.5	3.1	3.3
Proportion male, 20-24 years	2.9	3.6	3.4	5.4	2.8	3.6
Proportion male, 24-44 years	11.7	13.1	11.6	11.4	9.9	11.6
Proportion male, 45-64 years	13.4	13.1	13.6	13.0	14.5	13.5
Proportion male, 65+ years	8.6	6.9	8.9	9.2	11.3	8.9
Proportion female, <15 years	9.7	9.5	9.0	7.5	8.2	8.8
Proportion female, 15-19 years	3.2	3.3	2.9	3.4	2.8	3.1
Proportion female, 20-24 years	2.6	3.3	2.9	4.8	2.4	3.2
Proportion female, 24-44 years	11.3	12.4	11.1	10.3	9.8	11.0
Proportion female, 45-64 years	13.4	13.4	14.1	13.6	15.1	13.9
Proportion female, 65+ years	9.6	8.1	9.6	10.2	11.8	9.8
Proportion living in poverty	14.6	15.8	15.4	17.8	16.6	16.0
Proportion unemployed	7.6	7.2	7.5	7.4	8.9	7.7
Median household income (annualized)	51590	55041	51523	49065	46617	50873
Median per capita income (annualized)	39761	44435	41515	42211	38489	41354
Proportion uninsured under 65 years	12.4	11.9	12.9	12.9	13.3	12.6
Proportion of over 65 population, Medicare part D	48.4	37.4	42.0	45.6	51.0	44.7
Active medical doctors per 1000 population	1.0	2.3	1.7	1.5	0.9	1.5

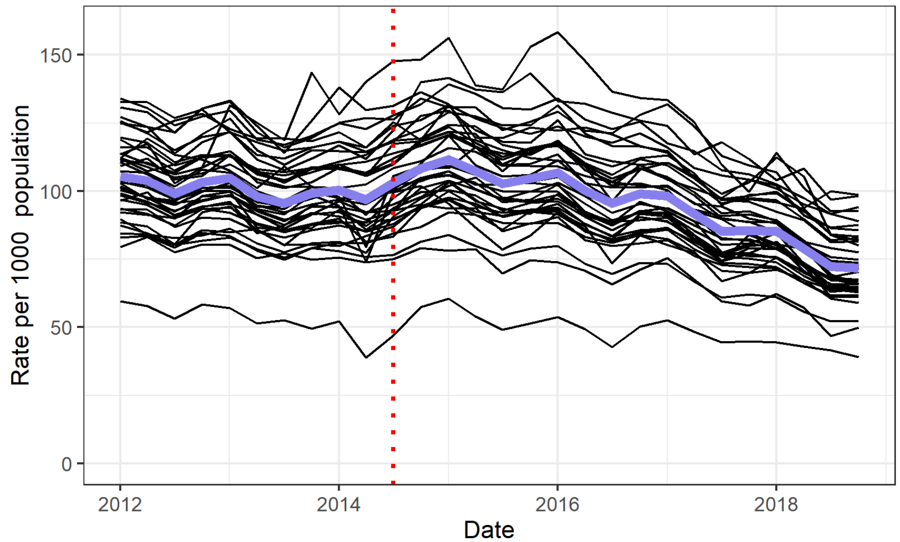
Notes: County membership in Group 1: Benton, Clark, Columbia, Douglas, Franklin, Garfield, Lewis, Lincoln; Group 2: Cowlitz, King, Pierce, Snohomish, Spokane, Stevens, Walla Walla, Yakima; Group 3: Chelan, Grant, Island, Kitsap, Klickitat, Okanogan, Pend Oreille, Thurston; Group 4: Clallam, Grays Harbor, Kittitas, Mason, San Juan, Skagit, Whatcom, Whitman; Group 5: Adams, Asotin, Ferry, Jefferson, Pacific, Skamania, Wahkiakum.

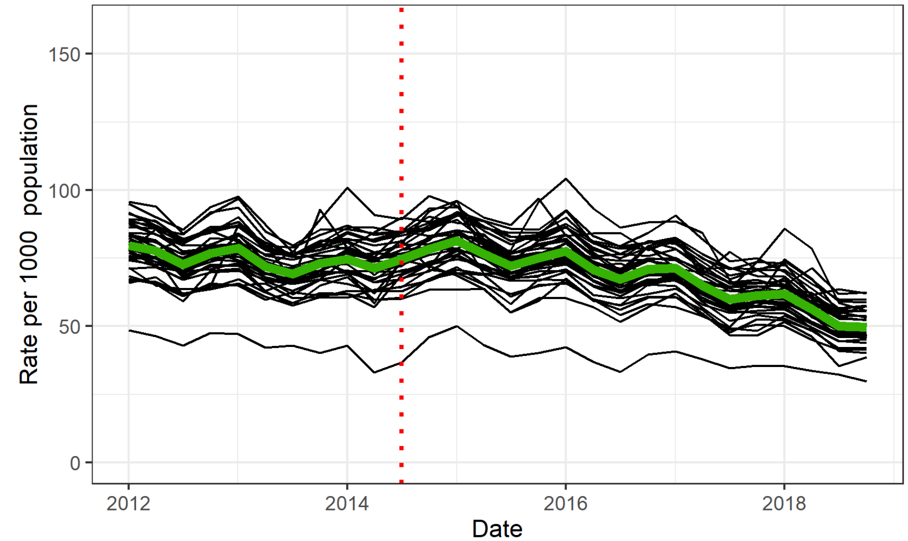
Figure 2.1. Changes in cannabis sales per population and recreational cannabis dispensary density in Washington State (2014-2019)

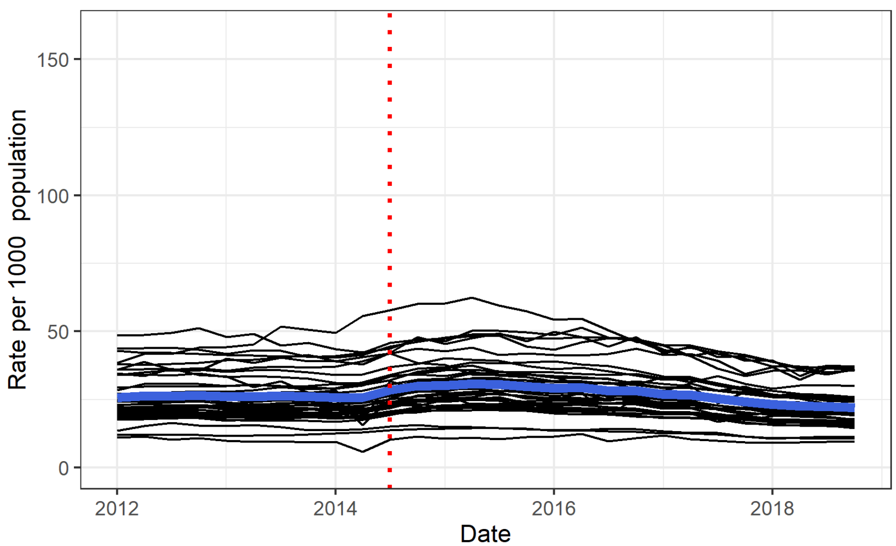


Notes: Figures depict the change in retail cannabis outcomes across counties in Washington State: sales per thousand population in $10K (upper left, blue) and active dispensaries per thousand population (upper right, orange). To be defined as an "active dispensary" in a given month, a dispensary must have had non-zero sales. Scales are not consistent across figures. The thicker, solid-colored lines reflect the average, unadjusted values.

Figure 2.2. Changes in the rate of opioid dispensing in Washington State (2012-2018)







Notes: Figures depict the rate of opioid dispensing across counties in Washington State for outcomes: any (upper left, purple), short-term (upper right, green), and long-term (lower left, blue). Dispensing outcomes were defined: any = number of patients, per 1000 population, with at least one opioid prescription submitted to the PMP in a calendar quarter, long-term = number of patients, per 1000 population, with at least 60 days' supply of prescription opioids submitted to the PMP in a calendar quarter, short-term = difference between any dispensing and long-term dispensing. Rates are age and gender adjusted. The thicker, solid-colored lines reflect the average, not-population adjusted rate. The dotted line reflects the timing of the first recreational cannabis dispensary opening in Washington State (Q3 2014).

Table 2.5. Regression of cannabis sales on cannabis dispensary density in Washington State (2014-2017)

Model	**Estimate**	**95%CI**	**p-value**
Dispensary density, dispensaries per 1000 population	15.0	[7.7, 22.3]	<0.001
Adjusted R-squared	0.80	--	--
Partial R-squared	0.19	--	--
Robust F-test (1,38)	16.38	--	0.0002
Test of endogeneity, F (1,38)	3.54	--	0.07

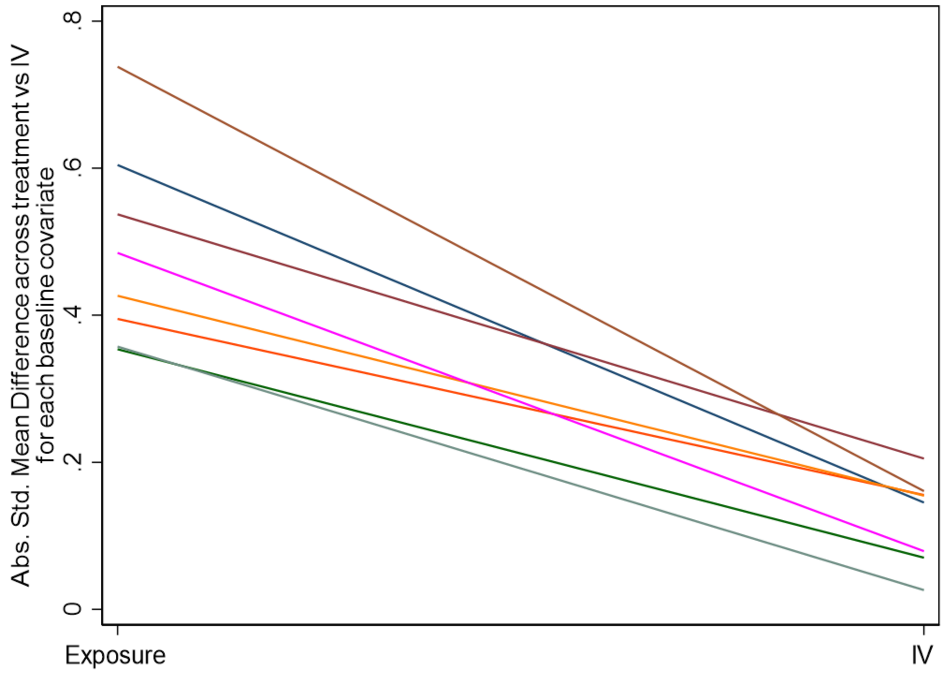
Notes: This first-stage linear model for use in two-stage models with instrumental variables included a fixed effect of time and county, clustering on county, as well as control for the following covariates: proportion white, proportion living in poverty, proportion unemployed, median household income, median per capita income, proportion under age 65 that are uninsured, proportion of those eligible who are Medicare part D enrolled, and the number of active medical doctors per 1000 population. Reported statistics account for county-level clustering.

Table 2.6. Mean values of key covariates across median value of cannabis sales and instrumental variable, dispensary density

	Cannabis sales			**Dispensary density**		
	Lower sales	**Upper sales**		**Lower density**	**Upper density**	
	Mean (SD)	Mean (SD)	p-value	Mean (SD)	Mean (SD)	p-value
Proportion white	0.9 (0.05)	0.88 (0.06)	<0.001	0.88 (0.07)	0.89 (0.05)	0.41
Proportion living in poverty	15.27 (3.32)	13.88 (3.58)	<0.001	14.3 (3.42)	14.85 (3.6)	0.07
Proportion unemployed	7.12 (1.5)	6.21 (1.39)	<0.001	6.77 (1.52)	6.55 (1.5)	0.09
Median household income (annualized)	51563 (8001)	56789 (10574)	<0.001	55173 (10596)	53178 (8675)	0.02
Median per capita income (annualized)	42284 (8076)	45324 (8669)	<0.001	43692 (9061)	43916 (7930)	0.76
Proportion uninsured under 65 years	10.16 (3.2)	8.08 (1.9)	<0.001	9.35 (3.21)	8.89 (2.37)	0.06
Proportion of over 65 population enrolled in Medicare part D	48.47 (9.75)	43.8 (11.62)	<0.001	45.29 (11.92)	46.98 (9.88)	0.07
Active medical doctors per 1000 population	1.22 (0.94)	1.71 (1.02)	<0.001	1.5 (1.13)	1.42 (0.87)	0.36

Abbreviation: SD = Standard deviation

Figure 2.3. Standardized mean differences across median value of cannabis sales and instrumental variable, dispensary density, for key covariates



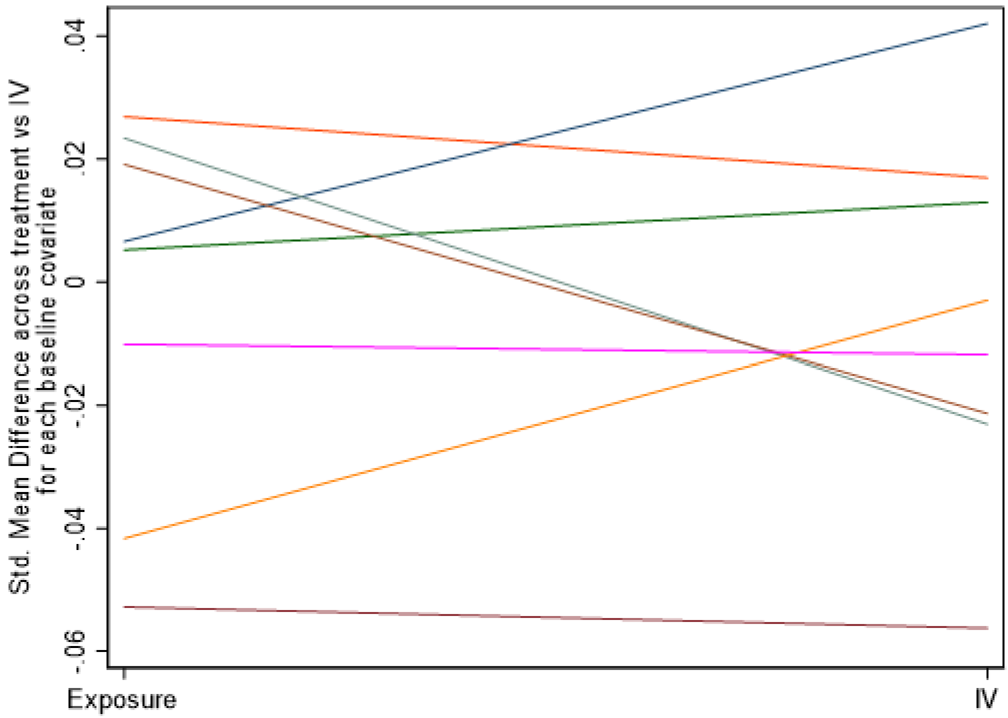
Abbreviations: Abs = absolute, IV = instrumental variable, Std = standardized
Note: Within the figure, exposure refers to cannabis sales and the instrument refers to the density of dispensaries in counts per thousand population. We derived binary variables for the instrument and exposure using the median values. We regressed each standardized time-varying covariate on either the treatment or the instrument. Presented are the absolute values of the beta coefficients (or standardized mean differences) from these regressions. Evaluated covariates include proportion unemployment, proportion Medicare Part D enrollment, proportion white, proportion living in poverty, median household income, median per capita income, proportion uninsured under 65 years, and active medical doctors per 1000 population.

Table 2.7. Mean values of key covariates across median value of cannabis sales and instrumental variable, dispensary density, adjusting for fixed effects of time and county

	Cannabis sales			**Dispensary density**		
	Lower sales	**Upper sales**		**Lower density**	**Upper density**	
	Mean (SD)	Mean (SD)	p-value	Mean (SD)	Mean (SD)	p-value
Proportion white	0.89 (0)	0.89 (0)	0.61	0.89 (0)	0.89 (0)	0.23
Proportion living in poverty	14.56 (1.02)	14.59 (1.03)	0.75	14.56 (0.92)	14.58 (1.12)	0.85
Proportion unemployed	6.66 (0.29)	6.67 (0.25)	0.9	6.66 (0.25)	6.67 (0.29)	0.44
Median household income (annualized)	54253 (1679)	54098 (1404)	0.24	54252 (1567)	54099(1528)	0.25
Median per capita income (annualized)	43774 (891)	43834 (562)	0.35	43832 (897)	43777 (553)	0.39
Proportion uninsured under 65 years	9.11 (0.5)	9.13 (0.41)	0.68	9.13 (0.47)	9.11 (0.44)	0.66
Proportion of over 65 population enrolled in Medicare part D	46.2 (1.77)	46.07 (1.27)	0.3	46.14 (1.77)	46.13 (1.29)	0.95
Active medical doctors per 1000 population	1.47 (0.07)	1.46 (0.05)	0.55	1.47 (0.07)	1.46 (0.05)	0.51

Abbreviation: SD = Standard deviation

Figure 2.4. Standardized mean differences across median value of cannabis sales and instrumental variable, dispensary density, for key covariates, adjusting for fixed effects of time and county



Abbreviations: IV = instrumental variable, Std = standardized
Notes: Within the figure, exposure refers to cannabis sales and the instrument refers to the density of dispensaries in counts per thousand population. We derived binary variables for the instrument and exposure using the median values. We regressed each standardized time-varying covariate on either the treatment or the instrument with the log of the county population as well as time and county fixed effects. Presented are the values of the beta coefficients (or standardized mean differences) from these regressions. The blue line with a large increase is the proportion unemployment. The light orange line with an increase towards zero is the proportion of Medicare Part D enrollment. The dark orange line with a slight decrease towards zero is proportion living in poverty. Other covariates with mostly proportionate or negligible changes across exposure and instrument were proportion white, median household income, median per capita income, proportion uninsured under 65 years, and active medical doctors per 1000 population.

Table 2.8. Estimated effect of cannabis sales on the number of individuals dispensed opioids in Washington State (2014-2017)

	I. Any opioid dispensing		**II. Short-term dispensing**		**III. Long-term opioid dispensing**	
	Mean	SD	Mean	SD	Mean	SD
Outcome	16684	29411	12678	23428	4007	6126
Population	183440	364999	183440	364999	183440	364999
Model	**Estimate**	**95%CI**	**Estimate**	**95%CI**	**Estimate**	**95%CI**
A. Naïve model controlling for population	**-1986**	**[-3029, -942]**	**-1607**	**[-2461, -752]**	**-379**	**[-578, -179]**
B. Add clustering on county	-1986	[-4367, 396]	-1607	[-3560, 347]	-379	[-823, 65]
C. Add fixed effect of time	-2886	[-6240, 1268]	-1993	[-5044, 1057]	-492	[-1218, 233]
D. Add health insurance covariate	-3430	[-7139, 461]	-2740	[-5934, 452]	-689	[-1411, 33.2]
E. Add all covariates	-2247	[-5114, 621]	-1748	[-4040, 543]	-63	[-150, 22]
F. Add county fixed effect	81	[-220, 382]	79	[-176, 332]	3	[-52, 57]
G. Add instrumental variable (2SLS) *	530	[-85,1147]	467	[-63,998]	64	[-56,183]

Abbreviations: CI = confidence interval, HD= high dose, IV = instrumental variable, MME = milligrams of morphine equivalent, SD = standard deviation, 2SLS = two-stage least squares
Notes: Estimates are from separate linear models that are nested. All models from the second model onward include clustering on county. The interpretation of the estimate is for each $10K per 1000 population increase in cannabis sales, the change in the number of individuals dispensed opioids. Estimates that are bolded are statistically significant at $p \leq 0.05$. Covariate adjusted models controlled for the following: proportion white, proportion living in poverty, proportion unemployed, median household income, median per capita income, proportion under age 65 that are uninsured, proportion of those eligible who are Medicare part D enrolled, and the number of active medical doctors per 1000 population.
*Normal-based confidence intervals for the two-staged models were generated from bootstrapped standard errors to account for uncertainty in the model stages.

Chapter 3. CANNABIS POLICY AND USE OF MEDICATIONS FOR MENTAL HEALTH IN THE UNITED STATES

3.1 OVERVIEW

Changes in cannabis policy and access to the substance may impact the use of medications including antidepressant and antianxiety drugs. We evaluated the effect of cannabis policy change on utilization of (1) antianxiety medications among people with anxiety and (2) antidepressant medications among people with depression. This secondary data analysis relied on publicly available data and Marketscan, which provided a claims-based source of data on medication use in a sample of Americans with employer-sponsored insurance. We linked enrollee-level claims with state and policy data for quarters from 2010 through 2017. For each quarter, we included all enrollees with continuous insurance coverage in the previous four quarters and a recent diagnosis code for depression or anxiety. Antianxiety and antidepressant prescriptions were identified using medication class groupings in the claims data. Utilization was defined as an indicator for at least one prescription in a given quarter.

To evaluate the effect of medical cannabis policy change, we used a traditional difference-in-differences approach for enrollees within states with a policy change and those within states with no previous policy that did not alter their policy over the study period. The use of a therapeutic class of interest in a given quarter was regressed on enrollee-level characteristics (age, gender, previous medication use, comorbidity), a fixed effect of state and quarter, state-level time-varying characteristics (income, density of physicians, unemployment), and the presence of an enacted medical cannabis policy. To evaluate recreational policy change on the prevalence of antianxiety and antidepressant use in their respective indications, we utilized a synthetic control design at the state level with Washington and Colorado, the two states with the most time elapsed since recreational cannabis policy change in 2012. The donor pool consisted of all states with no medical or recreational policy change (i.e., no treatment) over the evaluated time period. A synthetic control state for each treated state was constructed using the levels of pre-policy outcomes and aforementioned covariates. We compared treated states and their synthetic controls on the difference in prevalence of medication use after the policy change. We used a placebo test in untreated states for inference on the observed effects in treated states.

Over the entire study period, the average prevalence of medication use was 51% for antidepressants in enrollees with depression and 24% for antianxiety medications in enrollees with anxiety. Medical cannabis policy change did not reduce utilization of medication classes of interest in either condition, with effect sizes from fully adjusted models of less than one percentage point. In synthetic control analyses of Washington and Colorado, recreational policy changes did not significantly alter use of either class in its respective indication. We did not find evidence of cannabis substitution for antianxiety medications in anxiety or antidepressants in depression in the period following medical and recreational cannabis policy change. These findings contribute to the evolving body of evidence on the effects of cannabis policy.

3.2 INTRODUCTION

Recently anxiety disorders have been discussed as potential qualifying conditions for medical cannabis in several US states. As of 2019, three states allowed medical cannabis for use in some forms of anxiety.[91,92] However, cannabis use in mental health conditions is complicated with the literature providing conflicting reports of both therapeutic benefit and harm.[14] This mixed evidence for cannabis may be related to the many observed therapeutic effects of cannabis. A number of different cannabinoids, including cannabidiol (CBD) and tetrahydrocannabinol (THC), may have differential and opposing mechanisms in the brain. These component chemicals also vary in proportion and potency across cannabis products.[93] Depending on composition and an individual's brain chemistry, cannabis may produce a spectrum of clinical effects from relaxation to psychosis.[14]

The available evidence on cannabis in mental health is limited by study design. In cross sectional analyses, cannabis use occurs alongside many conditions, prompting questions about reverse causality. In small samples[94,95], cannabis has been associated with worsening depressive symptoms, but in larger population-based studies, it has been found to have no association with risk of mood and anxiety disorders.[96] One meta-analysis found only a small increase in the risk of elevated anxiety in the general population, but authors concluded there were few robust studies of this association.[97] Cannabis use has also been linked to substance use disorders.[96] Such uncertainty has led many healthcare providers to not recommend cannabis, though they acknowledge that it may provide some symptom relief.[98] On the other hand, some researchers affirm the therapeutic potential of cannabis in mental health conditions,[99] and several clinical studies have been initiated.[100,101] Despite the lagging evidence, anxiety and depression are among the most common medical reasons for use as reported by patients using medical cannabis.[102,103]

The 2010s were characterized by many changes in overall healthcare access and cannabis policy. A number of US states legalized recreational cannabis, the price of the substance declined,[104] access to cannabis broadened,[104] and the regular use of the drug increased.[105] Over this same period, there was little medical guidance around cannabis and expanding, often problematic cannabis marketing. Social media, news, and other advertisements from the cannabis industry were observed promoting unsubstantiated claims for the effectiveness in some conditions.[106,107] Such trends are of growing concern in the mental health space. A recent survey found 47% of Americans believed relief from stress, anxiety, and depression to be among the benefits of cannabis, whereas only 15% believed that these problems were risks of cannabis use.[108]

Increased use of cannabis for medical purposes may lead to changes in medication utilization. With mounting clinical evidence for safety and efficacy in chronic pain[109], there is an interest in cannabis use and “opioid sparing.”[45] In mental health, it unclear how cannabis will impact medication use. We evaluated whether medical cannabis and recreational cannabis policy changes have impacted medication use among enrollees with anxiety and depression. Since these conditions do not qualify for medical cannabis in most US states, we hypothesized that medical policy would not impact use of medications. We also expected that recreational policy change would lead to reductions in medication since this would be consistent with substitution and with the general trends in cannabis use.

3.3 METHODS

3.3.1 *Data*

We combined commercial claims data with policy and economic data from several publicly available sources.

3.3.1.1 Study sample

The IBM MarketScan® Research Databases represent between 30-50 million enrollees with employer-sponsored insurance annually in the US, providing a claims-based data source to evaluate policy effects of cannabis. Enrollees were identified within Marketscan between 2010 and 2018. To be included in the eligible sample within a given quarter, an enrollee must have been at least 18 years of age, with four quarters of previous enrollment, and an outpatient diagnosis code for a condition of interest. Enrollees must also have had no missing data on individual-level covariates of interest.

3.3.1.2 Selected conditions

In the main analysis, we prioritized samples of enrollees with diagnosis codes to improve the specificity of this analysis to detect potential substitution effects. Moreover, outcomes evaluated in the broader sample of enrollees may mask substitution effects. Within the anxiety sample, we did not include dysthymia, panic disorder, post-traumatic stress disorder (PTSD), or disorders with panic and with anxiety features (e.g., adjustment disorder with anxiety). While substitution may occur in these conditions, several are contraindicated for cannabis (e.g., panic disorder) or already eligible for cannabis (e.g., PTSD, in states with medical cannabis). The use of cholesterol lowering medications in enrollees with pure hypercholesterolemia (PH) was selected as a negative control outcome to facilitate a falsification test.

Within annual datasets of outpatient claims, we identified enrollees with International Classification of Diseases (ICD) diagnosis codes (ICD-9 and 10) of interest present in any of the four available diagnosis code fields in the preceding four quarters.

Table 3.9. Selected diagnoses and drug classes

Diagnosis grouping	**ICD-9/10 codes**	**Therapeutic class**	**Marketscan class code**
Depression	29620-29626, 29630-29636, F320-F325, F329, F330-F333, F339, F3341, F3342	Antidepressants	69
Anxiety	30000,30002, F419, F411	Anxiolytics (ASH barbiturates, ASH benzodiazepines, ASH NEC)	73, 74, 75
Pure hypercholesterolemia	2720, E7800, E7801	Antihyperlipidemic Drugs, NEC	53

Abbreviations: ASH = anxiolytic sedative hypnotic; NEC = not elsewhere classified

3.3.1.3 Outcome

Prescription claims data were identified using the prespecified therapeutic class codes. We included claims where the days supplied was more than one but less than 100. This encompasses the most common days supplied (i.e., 30 days and 90 days). Exposure was defined by a unique combination of enrollee identification number, National Drug Code (NDC), and date. The main outcome of interest was the presence of at least one drug claim with one of the prespecified therapeutic class codes within the current quarter. We subsequently refer to this as "medication use."

3.3.1.4 Policy changes

We identified the quarter of cannabis policy effective date by updating data from Powell *et al.* 2015[15] and Shah *et al.* 2019[40], which covered the timing of cannabis policies through November 2014. We used the National Conference of State Legislatures (NCSL) State Cannabis Laws Tables, Weedmaps.com, and the Pro Con.org Table on Cannabis Legal Status to identify the timing of recent policy changes and their effective dates. To be included among states with a current medical cannabis policy, a state must have a comprehensive medical cannabis program. For example, some states have recently adopted policies around the limited use of some cannabinoid products such as CBD oil in specific severe conditions (e.g., "compassionate use"). These would not be covered under this model since they would likely represent a very small population of users. We also considered the timing of medical and recreational dispensary opening as the policy change of interest, as previous studies have suggested active dispensaries to be an important change.[15] For recent openings of dispensaries, we obtained dates through searches of media sources using key words (e.g. "first legal medical dispensaries" with state name). Additional information is included in 7.1.

The timing of policy change was defined with a covariate for the presence of effective medical cannabis policy, recreational policy, or active dispensaries. Of the 13 states with medical policies prior to 2010, nine implemented recreational policies in the time period of interest (group A in the table below). Of the 20 states (and the District of Columbia [DC]) that implemented medical policy in the time period of interest, two of these also implemented recreational policy (group C in Table 3.10). Additional information on dispensaries is provided in 7.1.

Table 3.10. Timing of medical and recreational cannabis policy effective date

	Medical cannabis policy pre-2010	**Medical cannabis policy 2010-2018**	**No medical policy change**
Recreational cannabis policy 2010-2018	(a) 9 states	(c) 2 states + DC	(e) 0 states
No recreational policy change	(b) 4 states	(d) 18 states	(f) 17 states

a. Alaska, California, Colorado, Maine, Michigan, Nevada, Oregon, Vermont, Washington
b. Hawaii, Montana, New Mexico, Rhode Island
c. Illinois, Massachusetts
d. Arizona, Arkansas, Connecticut, Delaware, Florida, Louisiana, Maryland, Minnesota, Missouri, New Hampshire, New Jersey, New York, North Dakota, Ohio, Oklahoma, Pennsylvania, Utah, West Virginia
f. Alabama, Georgia, Idaho, Indiana, Iowa, Kansas, Kentucky, Mississippi, Nebraska, North Carolina, South Carolina, South Dakota, Tennessee, Texas, Virginia, Wisconsin, Wyoming

3.3.1.5 Covariates

We included enrollee-level covariates for gender, age, and employment status, and derived several covariates to account for enrollee-level features that may influence medical utilization. These included the Charlson Comorbidity Index (CCI)[110] based on inpatient and outpatient diagnosis codes in the current and previous four quarters, a count of the number of any previous prescriptions in the current and previous four quarters, and the time since most recent diagnosis code of interest. Enrollee’s geographic locations were defined by their listed state of residence. We also included state-level covariates for unemployment, income, and density of physicians, state-level features that may influence patterns of medical utilization. Additional information is included in 7.3.

3.3.1.6 Missingness

The initial samples represented enrollee-quarters for 36 calendar quarters (Q1 2010 – Q4 2018). We evaluated the degree of missingness in enrollee and state-level variables. We imputed the missing state (e.g., cases coded “Nation-unknown region”) for a number of enrollees using their reported metropolitan statistical area (MSA) codes. In cases where MSA covered several states, we selected the most populous state. In addition, data on state population was not available for all states for the year 2010 but was filled in using available annual estimates of the resident population from the 2010 Census.[111] Population was then used for the purpose of calculating density of physicians; however, physician density was not available for 2018 for any state, meaning that the full adjusted models represent the quarters from 2010 through 2017.

3.3.2 *Statistical analysis*

We used several panel data methods to evaluate the relationship between cannabis policy changes and medication use over the period between 2010 and 2017.

3.3.2.1 Modeling approach, difference-in-differences for medical cannabis

For the analysis of the effect of medical cannabis policy change, we used a difference-in-differences (DID) approach specifying a generalized DID model where the policy changes are time-varying at the state level and the policy timing varies across states.

$$Y_{ist} = \beta \, New \, MCL_{st} + X_{ist}\gamma + Z_{st}\varphi + \omega_s + v_t + e_{ist} \tag{3.1}$$

In the Equation (3.1), the probability of use of the class of interest for enrollee $\underline{i}$ residing in state, s at quarter t was a linear combination of MCL_t, an indicator for whether a state had a medical cannabis policy in quarter t, X_{ist} a vector of covariates at the enrollee level, Z_{st} a vector containing both time-varying state-level economic trends. We also included fixed effects of time, v_t, and state, w_s. A linear model was selected for ease of interpretation and because prevalence of medication use in the selected cohorts were not rare. However, we included a logistic specification for robustness check. The main analysis consisted of a two-way fixed effects model with further adjustment for covariates and with errors clustered at the state level to account for the nesting of enrollees within state. The coefficient on medical cannabis was therefore an estimate of the average treatment effect, or an average marginal effect.

3.3.2.2 Additional analyses

We devised several methodological robustness checks and secondary analyses.

3.3.2.2.1 Age

Cannabis policy may act differentially across age groups through mechanisms such as different preferences, targeted advertising, and access. We evaluated the effect of age by stratified on age group.

3.3.2.2.2 Dispensaries

Previous policy analyses concerning opioids have utilized the timing of medical and recreational cannabis enactment as the relevant policy break, though some authors have considered the opening of dispensaries to be the more impactful change, possibly mediated by increased access.[26,112,113] While some states allow medical cannabis but do not have active dispensaries, other states have had relatively long gaps between date of policy effective date and the opening of dispensaries. A secondary analysis evaluated the timing of medical dispensary opening as the policy change.

3.3.2.2.3 State-level model

We selected an enrollee-level analysis because a state-level model would discard the enrollee level variance, averaging over enrollee-level characteristics that may be particularly meaningful (e.g., age). According to some literature, it is recommended to aggregate data so that the outcomes are at the level of the level of the treatment of interest[114]; however given the greater availability of micro and longitudinal data, many models are done at the enrollee level. We estimated state-level models to evaluate sensitivity to level of analysis though results should not differ markedly.

3.3.2.2.4 Falsification test

A third sample of enrollees and a corresponding medication class was defined to serve as a falsification test (i.e., a test of selection on shock) for any observed substitution effects associated with policy change in the anxiety and depression samples. This sample and outcome combination represents a setting where we would expect no impact of cannabis policy change on the outcome. A significant policy effect in this sample provides evidence for residual confounding. We selected pure hypercholesterolemia (PH) an inherited metabolic condition requiring daily antihyperlipidemic therapy. PH represented an appropriate negative control group since we are unaware of any reports of cannabis being utilized in this indication or in place of statin drugs.

3.3.2.2.5 Counts and days supplied

The aforementioned analyses evaluated the effect of cannabis policy on medication use within samples defined by a diagnosis code. However, cannabis policy change may operate more subtly on the magnitude or duration of medication use. This may be relevant whether a medication is taken daily, in the case of antidepressants, or as needed, in the case of many antianxiety medications. To this end, we aggregated claims data to derive state-quarterly counts of the total number of prescriptions for particular class and the total number of days supplied. We also derived number of Marketscan enrollees for each state-quarter not restricting on diagnosis codes as in previous analyses. In linear models, we regressed the log of the average prescription count per enrollee and the days supplied per enrollee on the log of the enrollee count, the fixed effects of time and state, age groups, proportion male, unemployment, income, and density of physicians. Errors were clustered at the state level. These analyses evaluated several classes including antihyperlipidemic, antidepressants, barbiturates, benzodiazepines, other anxiolytic sedative hypnotics, as well as opiate agonists and partial opiate agonists. Opioid classes were included to gain intuition about how cannabis may differentially impact classes, and since previous analyses have suggested an effect of medical policy on opioid utilization.

3.3.2.2.6 Group-time DID

Recent work has discussed how traditional methods for DID models suffer from bias when used for data with multiple time periods and variation in the timing of treatment (i.e., staggered adoption of policies) or heterogeneous treatment effects. Callaway & Sant'Anna (2020) [CS] recently proposed an alternative approach which estimates group-time average treatment effects in a modified DID setup.[115] Importantly, CS does not impose any requirement of treatment effect homogeneity across groups or time. We used CS to evaluate the robustness of the medical cannabis policy results for medication use. Additional information is provided in 7.4.

We specified several models for medical cannabis policy using CS. These include models of using unconditional and conditional parallel trends assumptions (i.e., unadjusted vs. covariate adjusted), models with differing control states (i.e., never-treated vs. combination of never and not-yet-treated states). We also derived "event study" parameters and plotted policy effects by time since medical cannabis policy change (i.e., dynamic effects). Timepoints prior to policy change, time zero, in these plots tested the parallel "pre-policy" trends and should not be significantly different from zero. If pre-trends holds it is more likely that post-trends will hold in the policy-absent scenario. These tests lend support for utilization of a DID approach but cannot confirm that identifying assumptions hold at the time of policy change or in periods after the change. Statistical inference was complicated by a small number of groups. Here we prioritized aggregated treatment effect parameters which can be interpreted similarly to average treatment effects in the treated.

These aggregates were based on a larger sample of ever-treated states and provide more stable estimates of policy effects.

3.3.2.3 Modeling approach, synthetic control for recreational cannabis

A synthetic control (SC) approach was selected to evaluate the effect of recreational cannabis policy change in a subset of states. Described thoroughly by Abadie *et al.* 2010[116,117] synthetic controls are often favored in policy analysis since the approach allows for a small number of treated and/or control states. This is relevant for the recreational cannabis analysis, where few states contribute enough data over the study period to consider the impact of the policy change. Synthetic control methods also allowed for evaluation of temporal trends from policy change where DID are limited by the assumption of requirements around parallel trends. Washington and Colorado were selected because they enacted policies at roughly the same time in Q4 of 2012 with each contributing five years of data after the policy changes.

Synthetic control methods maximize the observed similarities between the treatment case and its synthetic control, which is a derived from a "donor pool." This enforced similarity in the pre-policy period supports the use of the weighted post-policy trends as a counterfactual since it is likely that unobserved similarities between the treated and synthetic control are also maximized. In the SC procedure, untreated states were assigned weights to derive the outcomes in the "synthetic state", which provides the counterfactual outcomes. Weights were derived from a modeling procedure that minimizes the difference in outcome and selected predictors between untreated and a single treated state during the pre-policy period. The difference is summarized by the mean squared prediction error (MSPE).

The donor pool included states with no changes in medical or recreational policy during the study period. This list consisted of states with previous medical policy change: California, Hawaii, Michigan, Montana, New Mexico, Rhode Island, and Vermont, and states with no policy change: Alabama, Georgia, Idaho, Indiana, Iowa, Kansas, Kentucky, Mississippi, Nebraska, North Carolina, South Carolina, South Dakota, Tennessee, Texas, Virginia, Wisconsin, and Wyoming. Thus, the final donor pool contained 24 states. Covariates used to derive the synthetic control were the same as those used in the main medical cannabis analyses. Typical in SC methods, we also included the prevalence of the outcome medication use in the pre-treatment period (quarter 1 in

2010, 2011, and 2012) and the log of the enrollee count since these analyses were undertaken at the state-quarter level.

The treatment effect was visualized as the difference between the treated state and the synthetic control in the post-policy period. This difference estimates the average treatment effect in the treated. For interpreting the strength and significance of effects, we utilized the placebo approach from Abadie et al. 2010.[118] Briefly, the synthetic control procedure was run separately after treating each of the states within the donor pool as the intervention state while using the remaining donors as control. This "placebo" intervention state was then compared to its own synthetic control.

In all models, fit was evaluated using plots and the root mean squared prediction error (RMSPE) from the placebo analysis, where small RMSPE indicates a good synthetic control. Placebo states with MSPE at or greater than five times the MSPE in the treated state were removed from plots and consideration in subsequent testing. We also calculated and plotted the ratio of the post to the pre-policy period MSPE for the treated state and all placebos. A higher ratio is indicative of small pre-policy MSPE and may also indicate a higher post-policy error. A p-value was derived from placebo tests as the proportion of all states evaluated that had a MSPE at or above the treated state. This value was then used to evaluate the average treatment effect in the treated state using $p \leq 0.05$ to determine whether the observed effects in the treated state were due to chance.

3.3.2.4 Sensitivity analysis

A number of states included in the donor pool had small samples and thus very unstable prevalence estimates. Despite analytic control for enrollee sample size, some of these states still contributed to synthetic control weights. Thus, in a sensitivity analysis, we removed states with at least 5 quarters containing samples of less than 2000 enrollees. These states were Hawaii, Idaho, Montana, South Dakota, Vermont, and Wyoming. We also evaluated the effect of recreational dispensary opening using the synthetic control approach, which occurred more than a year after the recreational policy change in both states.

3.3.2.5 Additional study details

Chapter 7 includes additional methods details. An Institution Review Board approval for this study was not required for this study as human participants were not involved, and the data do not contain any identifying information. The IBM Watson MarketScan Research ® Databases was accessed under a user agreement with the University of Washington. Data aggregation, linkage, and generation of most figures were completed using SAS version 9.4 and R version 3.6.0. Traditional DID models for medical cannabis analyses were conducted using Stata Version 15.1. The group-time DID approaches used the package *did* in R, while the synthetic control analyses were undertaken using the *Synth* and *SCtools* packages. Chapter 8 includes additional tables and figures.

3.4 RESULTS

3.4.1 *Sample characteristics*

The study samples each consisted of more than 25M enrollee-quarters representing all fifty states and the District of Columbia (DC) and the 32 quarters from Q1 2010 through Q4 of 2017. Sample attrition is described in Table 3.11. There were approximately 8% of enrollee-quarters with missing state, of which approximately 1% could be imputed using metropolitan statistical area (MSA). No enrollee level data was missing for age and gender; however, state-level data on income, employment and density of physicians was not available for Puerto Rico, which made up a very small subset of the sample and was not further considered.

Over the study period, 17 states did not have any changes in cannabis policy, while 20 states and DC changed their medical cannabis status (Figure 3.1). Thirteen states had an existing medical cannabis policy in place as of Q1 2010 and were not included in the analytic sample for medical cannabis. Ten states and DC changed their recreational cannabis status during the study period.

Average enrollee- and state-level characteristics through 2017 are shown in Table 3.12 and Table 3.13 aggregated over groups of enrollees within the analysis states and within states with a previous medical cannabis policy change. Enrollees with anxiety and depression tended to be in their 40s and female, with lower CCI scores and moderate numbers of prescriptions. Enrollees with PH were more frequently older (50s) with slightly higher numbers of comorbidities. At the state-level, the mean number of medical doctors per 1000 population was 2.8, with unemployment 6.3%, and mean income $45K per capita. In general, states included in the analytic sample did not differ markedly from states with previous medical cannabis policy.

3.4.2 *Medication use*

Over the study period, the average quarterly share or prevalence of antianxiety use among enrollees with anxiety in analysis states was 24% (SD: 4). The average quarterly prevalence of antidepressant among enrollees with depression was approximately 51% (SD: 8), while the prevalence of antihyperlipidemic use in PH was 37% (SD: 7).

Enrollees living in states with no medical cannabis policy change had slightly higher prevalence of antianxiety use than those living in states with pre-existing medical policies and states which enacted new policy (Figure 3.2). This was also true for antidepressants in depression (Figure 3.3) and antihyperlipidemic medications in PH (Figure 3.4). Over time, the average prevalence of all medication use appears to have increased, with more substantial changes for antidepressant use and antihyperlipidemic use than antianxiety. At least some of the quarterly and annual variation in prevalence of medication use resulted from fluctuation in counts of enrolled individuals over time (i.e., insurance "churn"); however, some of this may be attributed to design and idiosyncrasies of the Marketscan data. Additional information is provided in 7.2.

The prevalence of antianxiety use among enrollees with anxiety was more stable overall and even slightly declines after 2016 (Figure 3.2). While there were some noteworthy intersections of curves for enrollees within states with prior policies and policy change states, prevalence trends appear to be largely similar across states with no medical cannabis policy change and states that changed their policy over the study period. Enrollees within these states were the focus of subsequent analysis of medical cannabis policy.

3.4.3 *Effect of cannabis policy on medication use*

3.4.3.1 Main models (medical cannabis)

Estimates of the effect of medical cannabis policy change on the prevalence of medication use are shown in Table 3.14. Effect estimates suggest that enacting a medical cannabis policy did not change or even slightly increased antianxiety medication utilization. While the effect estimate for antianxiety use in anxiety was statistically significant, it was less than a percentage point in magnitude (0.30, 95% confidence interval [CI]: 0.05, 0.56). There was no detectable effect of a medical policy on antidepressant use in depression.

3.4.3.2 Age analyses (medical cannabis)

Prevalence of medication use increased with age. There was some evidence for age-specific effects of a medical policy on antianxiety use anxiety (Table 3.15). In particular, medical cannabis effect estimates reflected statistically significant increases in antianxiety usage among middle-aged and older enrollees; however, these increases were still less than one percentage point.

3.4.3.3 Secondary analyses and robustness checks (medical cannabis)

In general, antianxiety effect estimates from traditional DID models tended to be in the opposite direction (positive) from antidepressant and antihyperlipidemic effect estimates (negative).
We found little consistency in the evidence for an increase in antianxiety use in anxiety. Results were robust to logistic specification but not the removing of states contributing a small number of enrollees (Chapter 8) suggesting key differences across control states. The antianxiety effect was not robust to altering the policy to the timing of medical dispensary opening (Table 3.16).

Evaluating the effect of medical policy on antihyperlipidemic use in PH served as a falsification test, providing intuition about the potential for bias within the main models (Table 3.14, Table 3.15). The estimate for antihyperlipidemic use in PH was statistically significant and negative in the covariate-adjusted model. Antianxiety and antihyperlipidemic effect estimates were in the opposite directions and not overlapping in confidence intervals, though still both relatively small in magnitude. This indicates a potential for bias in these traditional DID models given that a null result is anticipated in the PH sample.

Event study plots from using the group-time approach (CS) models provided support for pre-trends as indicated by stable, near-zero, not statistically significant effect estimates prior to policy change (Figure 3.5).

Overall estimates of the average treatment effect in the treated from group-time models confirmed medical cannabis policy did not lead to increases the use of either medication class in its indication (Table 3.18, Table 3.19). The magnitude on effect estimates were mostly larger than in traditional DID models (Table 3.19). Antianxiety effect sizes were in the oppositive direction (i.e., negative), suggesting the traditional DID models may be subject to bias. Results based on the unconditional and conditional parallel trends assumptions were similar to each other, though the estimates from a conditional model were larger in magnitude with larger standard errors (Table 3.18, Table 3.19, Table 3.20).

Event studies were also used to evaluate how the effect of medical cannabis policy on medication use could differ based on the amount of time that it had existed. Effect estimates were generally stable in the early period directly following policy change but tended to be reduced (i.e., more negative) approximately four years after the policy change. Because this reduction was consistent across all outcomes, it may be an artefact in the data rather than actual policy effects. Confidence intervals mostly all contained the null (Figure 3.5). Event studies with differing numbers of treated groups (Figure 3.6) suggest that the aggregated effect estimates (Table 3.18, Table 3.19, Table 3.20) may be driven by states that changed their policies later than Q1 of 2014. This group contained several states contributing the largest number of enrollees and consisted of Minnesota, New York, Louisiana, Pennsylvania, Ohio, Arkansas, North Dakota, and Florida.

Analysis of the effect of medical policy change on state-level prescription counts and on days supplied derived from the larger sample of all enrollees (1.27B enrollee-quarters) demonstrated no statistically significant changes (Chapter 8). While the effect estimates were at or below zero for all classes including opiate agonists, they were positive for benzodiazepines, which mirrors the primary result on use in enrollees with anxiety.

3.4.3.4 Synthetic control (recreational cannabis)

The average quarterly prevalence of use of antianxiety medications in anxiety was 26% for Colorado (SD: 1) and 23% for Washington (SD: 1) in the post-policy period. For antidepressant use in depression, the average use was 50% for Colorado (SD: 1) and 48% for Washington. We derived synthetic controls to evaluate effects of recreational cannabis policy change on the state-level prevalence of medication use among those with anxiety or depression in Colorado and Washington. The weights of the 24 states included in the donor pool for each treatment state and sample are given in Table 3.21. Donor state weights varied across outcomes within state and across states within outcomes. No states made up more than 50% of the weight with the exception of California for the antianxiety medication outcome in Washington. Michigan provided more that 15% of the weight for both Colorado outcomes, and Nebraska provided more than 10% of the weight for both Washington outcomes. There was some indication that synthetic Washington may be subject to overfitting due to small contributions of many donor states in the antidepressant outcome.

Figure 3.7 depicts the difference in prevalence of medication use (shown in black) between each treatment state and its synthetic control. Curves that are close to zero in the pre-period indicated a good fit.

In the five-year, post-recreational policy period, Colorado displayed an average 1.6 percentage point reduction (SD: 0.80) in the prevalence of antianxiety use among enrollees with anxiety that was mostly stable over time. The effect was less consistent over time in Washington (-0.3 percentage point, SD: 1.7).

For antidepressant use in depression, treated Colorado did not differ markedly from synthetic Colorado in the entire post-recreational policy period (0.4 percentage point, SD: 1.5). While Washington demonstrated a large (~5 percentage points) initial increase in prevalence of antidepressant use after recreational cannabis policy change, this did not persist over time (0.1 percentage point, SD: 2.8).

3.4.3.5 Secondary analyses and robustness checks (recreational cannabis)

Placebo tests (shown as gray lines in Figure 3.7) were used for inference on observed average treatment effects. After removing placebo states with pre-policy MSPE more than five times that of the treated state, many remaining placebo states demonstrated post-recreational cannabis policy trends that were greater in magnitude than treated states. Placebo test findings suggested that the observed differences between treatment states and their synthetic controls were due to chance rather than recreational cannabis policy change. This finding was consistent with observed ratios of post-to-pre-policy MSPE in treated and placebo states. Plots of these ratios are given in Chapter 8. Large ratios are indicative of either low pre-policy MSPE or high post-policy MSPE. In MSPE ratio plots, treated states tended to have lower ratios than many placebo states. Using the MSPE ratio, Colorado was not significantly different than placebo states on antianxiety use ($p=0.67$) or antidepressant use ($p=0.83$). This was also true of Washington for antianxiety medications ($p=0.70$) and antidepressants ($p=0.42$).

In two sensitivity analyses (Chapter 8), we excluded states with very small numbers of enrollees and altered the timing of the policy to the date of first recreational dispensary opening. Results did not differ materially with these changes (all effects not statistically significant). We also further tested the synthetic control model for antianxiety use in Colorado, finding that the selected primary model produced the best fit among several models with different predictors (7.5).

3.5 Discussion

Accounting for time-, state-, and enrollee-level characteristics, adoption of state medical cannabis laws did not significantly impact utilization of antianxiety medications and antidepressants in enrollees with anxiety and depression, respectively. This finding may point to an absence of substitution after policy change. Moreover, it is consistent with the ineligibility of many psychiatric conditions for medical cannabis and limited clinical evidence to date. Recent adoption of recreational cannabis within Colorado and Washington did not lead to significant changes in the prevalence of medication utilization within their respective indications. This set of findings may indicate that substitution for certain psychiatric classes with newly available cannabis is not occurring to an appreciable degree among people with anxiety or depression enrolling in employer-sponsored insurance plans.

Surveys in convenience samples of recent and/or current users of medical cannabis suggest that substitution for antidepressants and antianxiety medications is common in the US and Canada.[27,119–121] Among the previous policy analyses, two studies considered prescription drugs other than opioids.[25,122] Evaluating the number of daily doses filled at the physician-year level, Bradford *et al.* found that medical cannabis policy change reduced the number of daily doses of prescription drugs for anxiety and depression in a Medicare population.[122] A similar analysis focused on the Medicaid population.[25] To our knowledge, ours is the first cannabis policy study to have evaluated individuals with employer-sponsored insurance and to have focused on specific diagnoses and therapeutic classes in mental health.

In the main analysis, medical cannabis policy change produced a small, but statistically significant increase in utilization of antianxiety medications in anxiety. At face value, this challenges the substitution hypothesis. Indeed, there are avenues through which a changing cannabis landscape could lead to increased utilization of certain medications. For example, some authors have described how there may be greater awareness of medical conditions potentially treated with cannabis.[123] Empirical findings may also provide evidence for a complement relationship between cannabis and medications in specific populations, for example, individuals on antiretroviral therapy in HIV[124] or opioid-users undergoing treatment with opioid replacement therapies.[125] Given the likelihood of group-time effect bias as demonstrated in group-time secondary analyses, we do not consider the observed effects on antianxiety medication use to be indicative of a complement relationship. Within subgroups, there may be differential or opposing effects. In age-stratified analyses, younger enrollees had smaller effect estimates for antianxiety use than the older enrollees. Substitution trends by age should be evaluated in survey and population-based studies. Age effects may also be of interest to researchers in geriatric medicine where there has been evidence of increased cannabis use among older adults[63,126,127] and concerns about medication adherence[128] and polypharmacy.[129]

We did not find a consistent effect of cannabis policies on aggregate medication utilization as defined by prescription claims; however, other medication-related outcomes may be more sensitive to cannabis policy. For example, previous analyses of Medicaid and Medicare populations focused on doses.[123,130] In addition, we acknowledge that even small changes in prevalence of use in these conditions may translate into large changes in the overall quantity of medication used, especially for commonly prescribed medications. However, we did not find evidence for this in a secondary analysis at the state-level using the number of prescriptions and days supplied within the broader sample of all enrollees.

Recent drug policy focus has been on benzodiazepines[131], the risk of dependence,[132] and related mortality.[133] This has led to interest in cannabis as a means of reducing reliance on benzodiazepines. A small retrospective study of individuals using benzodiazepines during their initiation of medical cannabis found that 45% discontinued their use after three medical cannabis prescription courses.[134] In our analyses, we expected a greater likelihood of observing substitution effects for antianxiety medications, which are comprised of mostly benzodiazepines. While this was not the case, we did observe some differences between antianxiety and antidepressant utilization outcomes. Antidepressant effects were generally of higher magnitude than antianxiety effects, which is consistent with the higher baseline proportion of use within depression; however, this could also point to antidepressants being more sensitive to available cannabis. This was observed in Bradford *et al.*, where medical cannabis laws were shown to reduce the average number of doses per quarter for depression medications by 13%, but to have no impact on anxiety therapies.[25]

One strength of this work is that it draws upon robust approaches to causal inference. Specifically, the synthetic control and group-time average treatment effects models provided cleaner counterfactual outcomes than traditional DID approaches and allowed for evaluation of the effect of time. Recreational cannabis models using a synthetic control and medical cannabis models using the CS approach demonstrated larger, more negative overall effect estimates than the primary DID approach, despite being not statistically significant. The group-time model for anxiety changed direction, which could indicate that the primary DID approach suffers from negative weights or undue contributions from already treated states.

Despite no observed statistically significant policy effects, these analyses provide some avenues for future evaluation. Medical cannabis event studies provided support for parallel trends in these data and suggested a potential for lagged effects. Medical cannabis CS models with alternative subsets of time since policy highlighted that some states may be driving the effect estimates. Synthetic control models for recreational cannabis in Colorado and Washington also present the possibility for treatment effect heterogeneity which may be consistent with different approaches to rollout of recreational cannabis in these states.[135]

In comparing medical and recreational cannabis policy effect estimates, we did not observe the large differences that we anticipated. However, our models differ in the unit of analysis and the estimation methods. Future policy analyses may consider synthetic control methods for medical cannabis. Using this approach, states can be evaluated both separately and in aggregate with multiple treated units. We still maintain that recreational cannabis policy has the potential to impact medication use to a greater extent than medical cannabis, especially since several states have struggled to develop and maintain robust medical channels, with subsequent barriers and disparities in access. This may channel people towards recreational markets. Dispensaries may be an important modifier in relationship between cannabis policy and outcomes, though in our analysis the timing of dispensary opening did not lead to measurable changes in medication use. Dispensary access may facilitate these relationships,[136] thus recreational cannabis dispensary density should be an important consideration in future studies.

One limitation in most cannabis policy analyses to date is the potential for endogeneity through simultaneity. Our analysis may also suffer from this, though it may be less impacted than analyses of opioids to date. Several states have been examining opioid outcomes to inform medical and recreational cannabis policy decisions[30,90] meaning that the timing of policy may be correlated with pre-policy levels or trends in opioid use. In the mental health space, endogeneity may be introduced by lobbying and voting. Key examples include recreational legalization occurring through voting on ballot initiatives and US Veterans advocating for the addition of PTSD to medical cannabis qualifying lists.[137]

Several limitations of this work concern the data. While there are many advantages of claims data, these claims data did not represent population-based samples. In addition, the Marketscan sample changed over the study period due to data availability; the number of enrollees and claims was reduced in 2015, slowly recovering to earlier levels in later years. This variability could contribute to bias if the reduction in sample was differential by state and time. Conditioning on diagnostic codes and prior enrollment also reduced the sample, making the state-level prevalence estimates unstable and increasing the error variance. In the synthetic control analysis of recreational cannabis, more stable data may have increased the power to detect effects through inclusion of weight from additional states, which could lead to smaller MSPE in donor pool states. Future investigations may utilize nationally representative data, such as the Medication Expenditure Panel Survey (MEPS) or the National Survey on Drug Use and Health (NSDUH).

Due to the structure of inclusion criteria and the normal changes in insurance eligibility/enrollment, samples were unbalanced at the enrollee level. We accounted for the clustering of enrollees within states but did not account for the clustering of repeated enrollee observations within enrollee. Use of mixed models was possible but more computationally intensive, with many million observations. Mixed models also would have required additional assumptions around the structure of the regression model (e.g., correlation among regressors). Ultimately, we were concerned with overall policy effects rather than those at the individual level. This meant that clustering at the level of the policy was the most appropriate approach. Future analyses may consider trends in individual-level use of medications and cannabis policy change but would be more informative if individual level cannabis use data were also available.

This study has several limitations that may impact any claims analysis of utilization patterns. Claims are an imperfect proxy for medication use and do not typically capture prescriptions paid for out of pocket. We did not consider cost which may an important consideration when evaluating substitution, especially since cannabis provide a less expensive alternative to some prescription drugs. We also did not consider broader access to cannabis other than through the timing of dispensaries in a sensitivity analysis. Lastly, these data cover a commercially insured sample, which may represent a less policy-relevant group than individuals with public insurance.

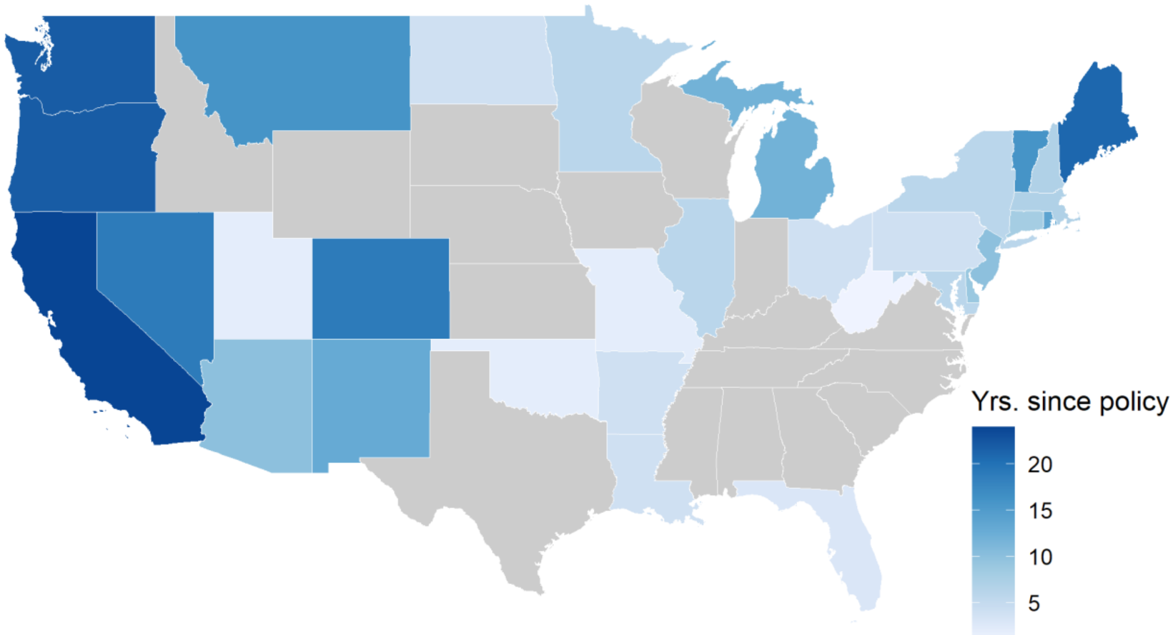
Findings from this analysis add to the rapidly growing literature on cannabis policy effects. While anxiety and depression may be common reasons for cannabis use, we found little evidence for reduced antianxiety medication and antidepressant use following medical cannabis legalization. Additionally, while recreational cannabis markets may be poised to impact medication utilization, Colorado and Washington did not show significant reductions in antianxiety or antidepressant medication use in the five years after recreational cannabis policy change. These findings may be reassuring given the mixed evidence for cannabis effectiveness for mental health conditions to date. Future evaluations should consider representative samples and the relationship between cannabis and benzodiazepine use. We also look forward to studies evaluating causal effects of cannabis use in mental health. Such work is crucial to inform public health, medical guidance, and continued evolution of cannabis policy.

3.6 TABLES & FIGURES

Table 3.11. Study samples in enrollee-quarters

Sample	Anxiety	Depression	Pure hypercholesterolemia
Entire sample (2010-2018)	50,412,915	41,984,530	41,218,353
Missing state*	4,378,329 (8.7%)	3,151,686 (7.5%)	3,042,823 (7.4%)
Remove missing state and filling in with MSA	46,806,509	39,336,818	38,617,268
Restrict 2010-2017	41,362,243	35,878,914	36,216,245
Complete covariates, remove under 18, remove Puerto Rico	37,760,348	33,652,155	35,752,598
Remove enrollees in pre-2010 medical cannabis states	29,852,365	25,723,174	29,161,489

*Includes enrollee-quarters with Marketscan geographic location codes such as ‘Nation, unknown region” (i.e., codes: 1, 2, 3, 10, 14, 15, 21, 29, 30, 40, 45, 50, 51, 60).
Abbreviations: MSA = metropolitan statistical area



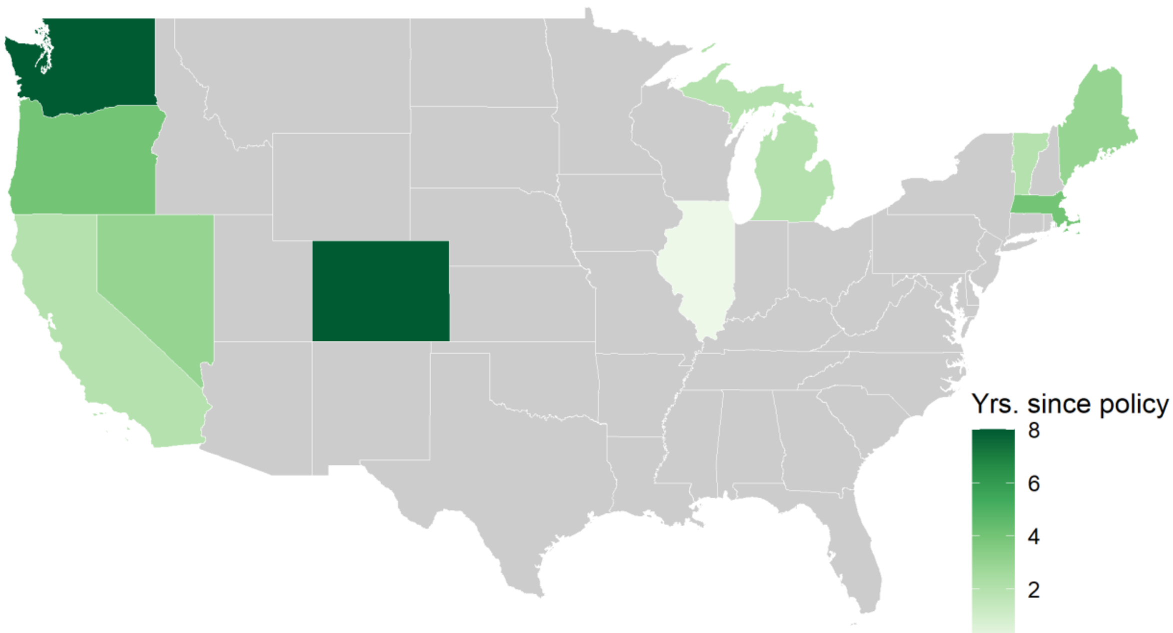


Figure 3.1. Medical and recreational cannabis policy change between 1996 and 2020

Notes: Medical cannabis policy is shown in the top panel, while recreational policy is shown in the bottom panel. States/municipalities not depicted include Alaska (medical cannabis prior to 2010; recreational cannabis in 2015), the District of Columbia (medical cannabis in 2010; recreational cannabis in 2015), and Hawaii (medical cannabis prior to 2010; no recreational cannabis).

Table 3.12. Enrollee-level characteristics

	Anxiety		Depression		Pure hypercholesterolemia	
	Analysis sample states	**Pre-2010 medical cannabis states**	**Analysis sample states**	**Pre-2010 medical cannabis states**	**Analysis sample states**	**Pre-2010 medical cannabis states**
Number of enrollee quarters	29,852,356	7,907,992	25,723,174	7,928,981	29,161,489	6,591,109
Mean age (SD)	42.95 (13.03)	43.00 (13.30)	44.32 (13.17)	44.70 (13.40)	53.15 (9.13)	53.47 (9.11)
Proportion aged 18-29	0.191	0.199	0.171	0.173	0.022	0.022
Proportion aged 30-49	0.447	0.428	0.415	0.392	0.266	0.251
Proportion aged 50+	0.363	0.373	0.414	0.435	0.713	0.727
Proportion male	0.329	0.331	0.300	0.306	0.520	0.527
Charlson Comorbidity Index						
Proportion 0-1	0.973	0.978	0.968	0.974	0.957	0.965
Proportion 2	0.016	0.012	0.018	0.014	0.025	0.021
Proportion 3+	0.011	0.010	0.014	0.013	0.017	0.015
Time since diagnosis code						
0-89 days	0.381	0.370	0.414	0.418	0.319	0.299
90-179 days	0.210	0.204	0.199	0.192	0.237	0.228
180+ days	0.409	0.426	0.387	0.390	0.444	0.472
Count of prescriptions in the previous year						
0-59 prescriptions	0.189	0.180	0.188	0.171	0.228	0.216
60-179 prescriptions	0.696	0.721	0.665	0.700	0.668	0.693
180+ prescriptions	0.116	0.099	0.147	0.129	0.104	0.090

Abbreviation: SD = standard deviation

Table 3.13. State-level characteristics

	Anxiety	**Depression**	**Pure hypercholesterolemia**
Number of state quarters (in analysis states)	1216	1216	1216
Proportion with medication use in current quarter (SD)	0.24 (0.04)	0.53 (0.08)	0.41 (0.07)
Mean number of medical doctors per 1000 population (SD)	2.8 (1.1)	2.8 (1.1)	2.8 (1.1)
Unemployment	0.062	0.062	0.062
Mean annual income (standard deviation)	45,765 (9188)	45,765 (9188)	45,765 (9188)

Abbreviation: SD = standard deviation

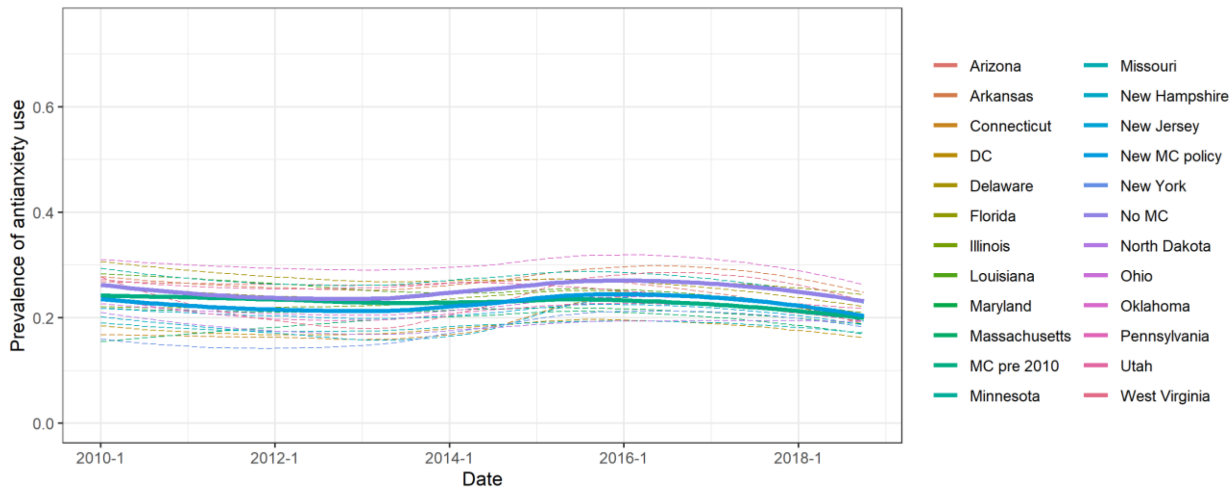


Figure 3.2. Smoothed prevalence of antianxiety use among enrollees with anxiety within US states, by medical cannabis policy status and in individual states with medical policy change between 2010-2018

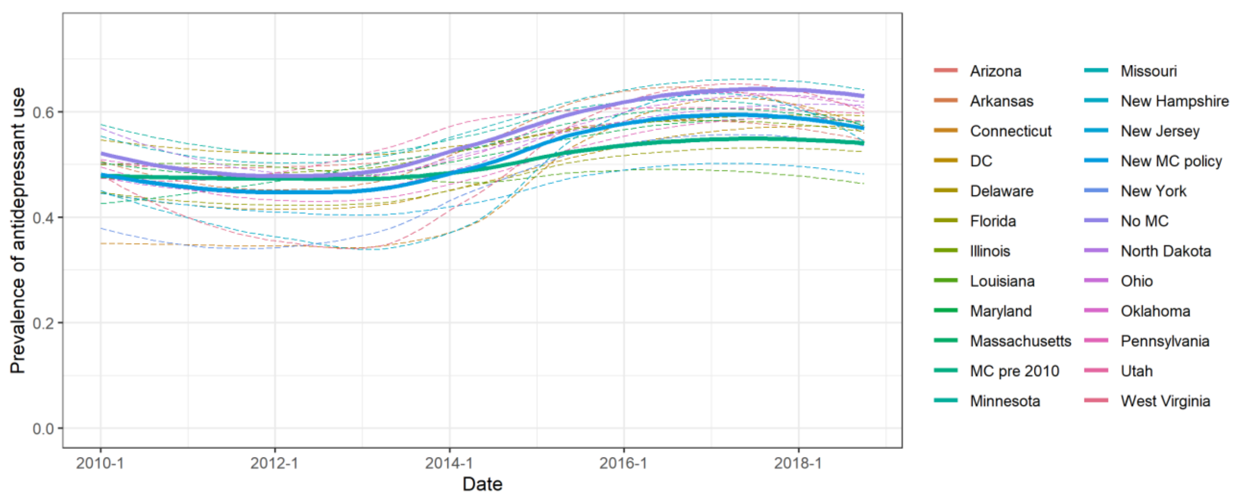


Figure 3.3. Smoothed prevalence of antidepressant use among enrollees with depression within US states, by medical cannabis policy status and in individual states with medical policy change between 2010-2018

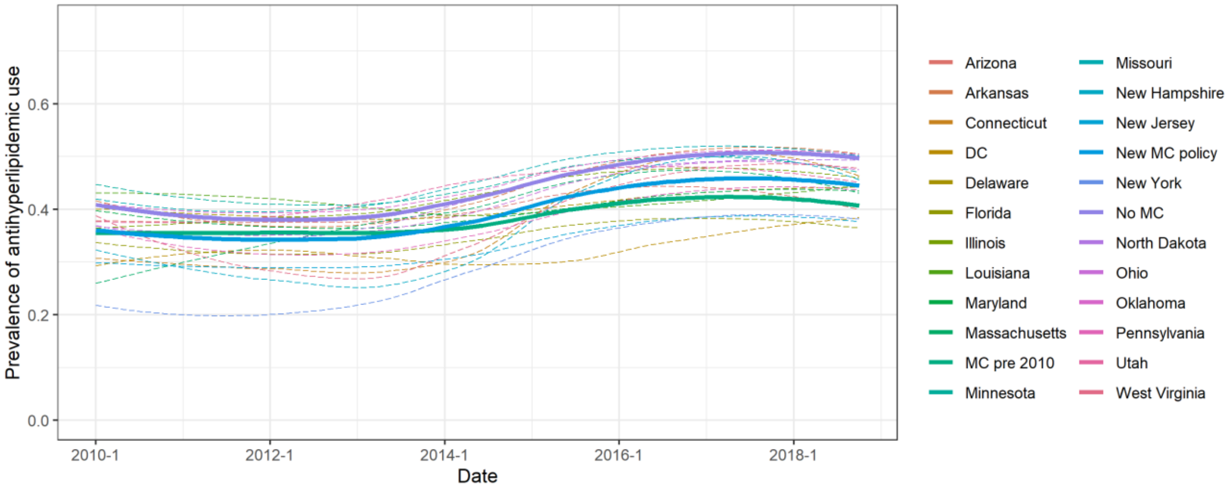


Figure 3.4. Smoothed prevalence of antihyperlipidemic use among enrollees with pure hypercholesterolemia within US states, by medical cannabis policy status and in individual states with medical policy change between 2010-2018

Abbreviation: MC = medical cannabis
Notes: Plotted curves represent locally estimated scatterplot smoothed state-quarterly prevalence over time. Thicker lines indicate averages over groups of states defined by medical cannabis status that are unadjusted for counts of individuals. "No MC" represents the 17 states no medical cannabis (i.e., analytic control states in the primary analysis), "MC pre 2010" the 13 states with medical cannabis policy change prior to 2010 (not included in primary analysis), and "New MC" the 20 states with a medical policy change between 2010 and 2017 (i.e., treatment states in the primary analysis). Dashed lines represent the individual states within the "New MC" group.

Table 3.14. Average marginal effect of medical cannabis policy change on medication usage (2010-2017) from enrollee-level models

	Antianxiety/anxiety (n=29,852,356)		**Antidepressant/depression (n=25,723,174)**		**Antihyperlipidemic/pure hypercholesterolemia (n=29,151,489)**	
Prevalence of medication use (average, all quarters)	23.7%		50.9%		37.3%	
Enrollee-level models	**Estimate (95%CI)**	**SE**	**Estimate (95%CI)**	**SE**	**Estimate (95%CI)**	**SE**
A. State and quarter fixed effects, clustering on state	0.78 (-0.44, 2.00)	0.60	0.17 (-2.44, 2.78)	1.29	1.55 (-1.14, 4.24)	1.33
B. Model A, with demographic/economic covariates	**0.30 (0.05, 0.56)**	**0.13**	-0.11 (-0.71, 0.48)	0.29	**-0.47 (-0.94, -0.57)**	**0.23**

Abbreviations: CI = confidence interval, SE = standard error

Notes: Estimates (percentage points) are from linear models. Individual's use of a medication was regressed as indicated in the model descriptions. Models included fixed effects of state and quarter. The demographic and economic covariate adjusted models controlled for the following enrollee-level characteristics: Age (18-29, 30-49, 50+), sex, Charlson Comorbidity (0-1,2, 3+), number of previous prescriptions (0-59, 60-180, 180+), time since most recent diagnosis (0-89, 90-179, 180+), and state-level characteristics: percent unemployment, median income, and the number of medical doctors per 1000 population. Coefficients are expressed as the average marginal effect of the medicinal policy change in percentage points. Estimates that are bolded are statistically significant at p≤ 0.05. Abbreviations: MC = medical cannabis, RC = recreational cannabis, SE = standard error

Table 3.15. Average marginal effect of medical cannabis policy change on medication usage (2010-2017) from enrollee-level models stratified on age

	Antianxiety/anxiety		**Antidepressant/depression**		**Antihyperlipidemic/pure hypercholesterolemia**	
Model	**Estimate (95%CI)**	**SE**	**Estimate (95%CI)**	**SE**	**Estimate (95%CI)**	**SE**
	n=5,692,475		n=4,406,118		n=632,299	
Prevalence of medication use	14.1%		40.1%		6.5%	
C. Age 18-30	0.00 (-0.36, 0.37)	0.18	-0.15 (-0.68, 0.37)	0.26	-0.29 (-0.81, 0.23)	0.26
	n=13,333,843		n=10,673,254		n=7,748,605	
Prevalence of medication use	23.1%		50.7%		27.0%	
D. Age 30-50	**0.38 (0.12, 0.63)**	**0.13**	0.09 (-0.64, -0.81)	0.36	-0.31 (-0.87, 0.24)	0.27
	n=10,826,047		n=10,643,802		n=20,780,585	
Prevalence of medication use	29.5%		55.6%		42.1%	
E. Age 50+	**0.34 (0.06, 0.74)**	**0.20**	-0.33 (-0.93, 0.27)	0.30	-0.45 (-0.92, 0.31)	0.23

Abbreviations: CI = confidence interval, SE = standard error
Notes: Estimates (percentage points) are from three separate linear models. Individual's use of a medication was regressed as indicated in the model descriptions. Models included fixed effects of state and quarter. The demographic and economic covariate adjusted models controled for the following enrollee-level characteristics: sex, Charlson Comorbidity (0-1,2, 3+), number of previous prescriptions (0-59, 60-180, 180+), time since most recent diagnosis (0-89, 90-179, 180+), and state-level characteristics: percent unemployment, median income, and the number of medical doctors per 1000 population. Coefficients are expressed as the average marginal effect of the medical cannabis policy change in percentage points. Estimates that are bolded are statistically significant at $p \leq 0.05$. Abbreviations: MC = medical cannabis, RC = recreational cannabis, SE = standard error

Table 3.16. Average marginal effect of medical cannabis policy change on medication usage (2010-2017) from enrollee-level models using an alternative policy change

	Antianxiety/anxiety		Antidepressant/depression		Antihyperlipidemic/pure hypercholesterolemia	
	Estimate (95%CI)	**SE**	**Estimate (95%CI)**	**SE**	**Estimate (95%CI)**	**SE**
F. Opening of medical dispensaries as policy change	0.43 (-0.06, 0.92)	0.24	-0.35 (-1.04, 0.34)	0.34	**-0.64 (-1.21, -0.08)**	**0.28**

Abbreviations: CI = confidence interval, SE = standard error

Notes: Estimates (percentage points) are from linear models. Individual's use of a medication was regressed as indicated in the model descriptions. Models included fixed effects of state and quarter. The demographic and economic covariate adjusted models controlled for the following enrollee-level characteristics: Age (18-29, 30-49, 50+), sex, Charlson Comorbidity (0-1,2, 3+), number of previous prescriptions (0-59, 60-180, 180+), time since most recent diagnosis (0-89, 90-179, 180+), and state-level characteristics: percent unemployment, median income, and the number of medical doctors per 1000 population. Coefficients are expressed as the average marginal effect of the medical cannabis policy change in percentage points. Estimates that are bolded are statistically significant at $p \leq 0.05$. Abbreviations: MC = medical cannabis, RC = recreational cannabis, SE = standard error

Table 3.17. Average marginal effect of medical cannabis policy change on medication usage (2010-2017) from state-level models

	Antianxiety/anxiety		Antidepressant/depression		Antihyperlipidemic/pure hypercholesterolemia	
State-level model	n=1216		n=1216		n=1216	
	Estimate (95%CI)	**SE**	**Estimate (95%CI)**	**SE**	**Estimate (95%CI)**	**SE**
G. State and time fixed effects, log of enrollees, clustering on state	0.27 (-0.79, 1.33)	0.52	-1.00 (-3.27, 1.27)	1.11	0.19 (-1.88, 2.26)	1.02
H. Model G with demographic/economic covariates	**0.45 (0.07, 0.84)**	**0.20**	-0.29 (-0.84, 0.25)	0.27	-0.24 (-0.90, 0.41)	0.32

Abbreviations: CI = confidence interval, SE = standard error

Notes: Estimates (percentage points) are from linear models. Individual's use of a medication was regressed as indicated in the model descriptions. Models included fixed effects of state and quarter. The demographic and economic covariate adjusted models control for average levels of the following enrollee-level characteristics: Age (18-29, 30-49, 50+), sex, Charlson Comorbidity (0-1,2, 3+), number of previous prescriptions (0-59, 60-180, 180+), time since most recent diagnosis (0-89, 90-179, 180+), and state-level characteristics: percent unemployment, median income, and the number of medical doctors per 1000 population. Coefficients are expressed as the average marginal effect of the medical cannabis policy change in percentage points. Estimates that are bolded are statistically significant at $p \leq 0.05$. Abbreviations: MC = medical cannabis, RC = recreational cannabis, SE = standard error

Table 3.18. Effect of medical cannabis policy change on antianxiety use in anxiety (2010-2017) from state-level models using a group-time approach

	Unconditional model		**Conditional model**	
Estimate of effect parameter	**Estimate (95%CI)**	**SE**	**Estimate (95%CI)**	**SE**
Simple weighted average	-0.28 (-1.23, 0.68)	0.46	-1.58 (-5.27, 2.11)	2.06
Event study (aggregated)	-0.59 (-1.74, 0.56)	0.69	-3.27 (-9.24, 2.70)	3.00
Event study with balanced groups (4 quarters)	-0.17 (-0.61, 0.26)	0.23	0.12 (-0.89, 1.14)	0.56
Event study with balanced groups (16 quarters)	0.03 (-1.08, 1.13)	0.59	-0.43 (-4.34, 3.47)	2.03

Abbreviations: CI = confidence interval, SE = standard error
Notes: Effect estimates (percentage points) are from models using methods of Callaway & Sant'Anna 2020 (CS). The simple weighted average is the weighted average of group-time treatment effects with the weights proportional to the group size. States without a policy change served as "never treated" controls for states when they change their medical cannabis policies. The "Event study"-type parameters reflect averaging over group time treatment effects for different lengths of an active medical cannabis policy. Event study-type parameters with balanced groups were estimated on the subset of states with a minimum length of exposure to medical policy (either at least 4 quarters or 16 quarters). Two models were specified: an unconditional model using no covariates, and a conditional model using covariates measured at a single pre-policy timepoint. Because the covariates are time-varying in the main difference-in-differences model, an average is used for CS models. Baseline covariates included the log of the count of enrollees, average levels of age (18-29, 30-49, 50+) and sex, and state-level characteristics: percent unemployment, median income, and the number of medical doctors per 1000 population.

Table 3.19. Effect of medical cannabis policy change on antidepressant use in depression (2010-2017) from state-level models using a group-time approach

	Unconditional model		Conditional model	
Estimate of effect parameter	**Estimate (95%CI)**	**SE**	**Estimate (95%CI)**	**SE**
Simple weighted average	-1.43 (-3.40, 0.52)	1.00	-1.78 (-7.00, 3.45)	2.67
Event study (aggregated)	-2.08 (-4.66, 0.49)	1.31	-3.41 (-10.53, 3.70)	3.63
Event study with balanced groups (4 quarters)	-0.93 (-2.00, 0.15)	0.55	-0.18 (-2.60, 2.24)	1.23
Event study with balanced groups (16 quarters)	-0.52 (-3.37, 2.33)	1.46	0.85 (-5.85, 7.55)	3.42

Abbreviations: CI = confidence interval, SE = standard error
Notes: Effect estimates (percentage points) are from models using methods of Callaway & Sant'Anna 2020 (CS). The simple weighted average is the weighted average of group-time treatment effects with the weights proportional to the group size. States without a policy change served as "never treated" controls for states when they change their medical cannabis policies. The "Event study"-type parameters reflect averaging over group time treatment effects for different lengths of an active medical cannabis policy. Event study-type parameters with balanced groups were estimated on the subset of states with a minimum length of exposure to medical policy (either at least 4 quarters or 16 quarters). Two models were specified: an unconditional model using no covariates, and a conditional model using covariates measured at a single pre-policy timepoint. Because the covariates are time-varying in the main difference-in-differences model, an average is used for CS models. Baseline covariates included the log of the count of enrollees, average levels of age (18-29, 30-49, 50+) and sex, and state-level characteristics: percent unemployment, median income, and the number of medical doctors per 1000 population.

Table 3.20. Effect of medical cannabis policy change on antihyperlipidemic agent use in pure hypercholesterolemia (2010-2017) from state-level models using a group-time approach

	Unconditional model		Conditional model	
Estimate of effect parameter	**Estimate (95%CI)**	**SE**	**Estimate (95%CI)**	**SE**
Simple weighted average	-0.81 (-2.62, 1.0)	0.92	1.57 (-5.34, 8.50)	3.54
Event study (aggregated)	-1.51 (-3.58, 0.55	1.05	1.01 (-9.53. 11.56)	5.38
Event study with balanced groups (4 quarters)	-0.45 (-1.36, 0.46)	0.46	0.94 (-2.58, 4.47)	1.80
Event study with balanced groups (16 quarters)	0.34 (-2.19, 2.88)	1.29	0.42 (-4.41, 5.24)	2.46

Abbreviations: CI = confidence interval, SE = standard error
Notes: Effect estimates (percentage points) are from models using methods of Callaway & Sant'Anna 2020 (CS). The simple weighted average is the weighted average of group-time treatment effects with the weights proportional to the group size. States without a policy change served as "never treated" controls for states when they change their medical cannabis policies. The "Event study"-type parameters reflect averaging over group time treatment effects for different lengths of an active medical cannabis policy. Event study-type parameters with balanced groups were estimated on the subset of states with a minimum length of exposure to medical policy (either at least 4 quarters or 16 quarters). Two models were specified: an unconditional model using no covariates, and a conditional model using covariates measured at a single pre-policy timepoint. Because the covariates are time-varying in the main difference-in-differences model, an average is used for CS models. Baseline covariates included the log of the count of enrollees, average levels of age (18-29, 30-49, 50+) and sex, and state-level characteristics: percent unemployment, median income, and the number of medical doctors per 1000 population.

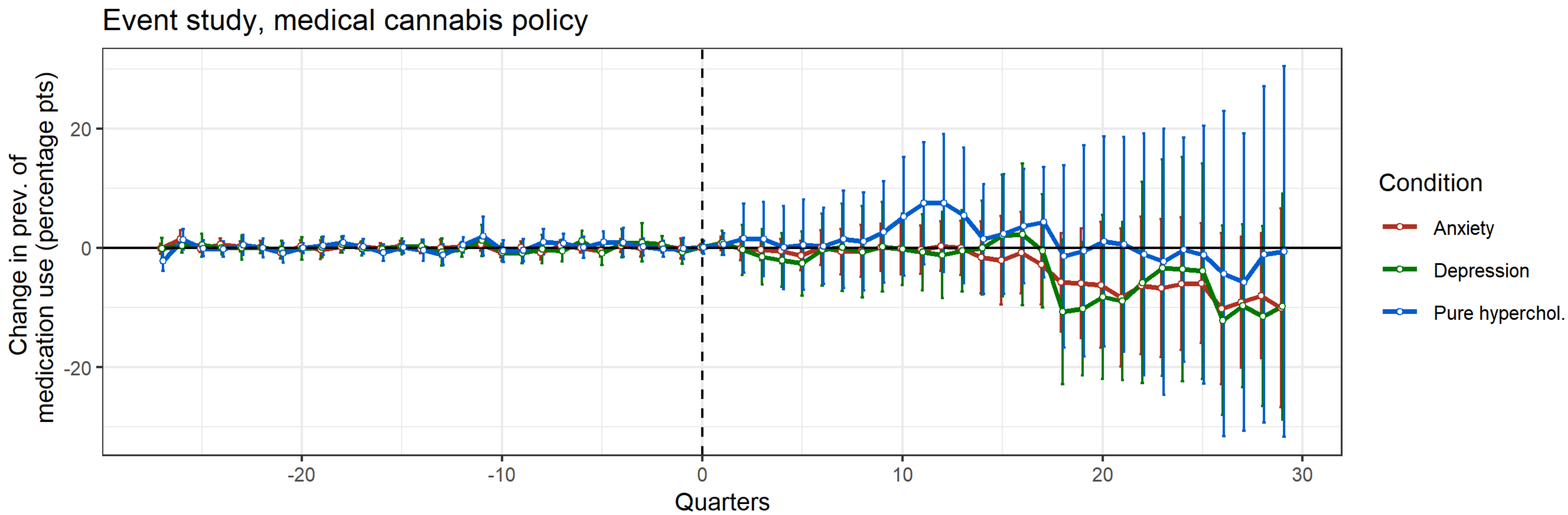


Figure 3.5. Event study of the length of medical cannabis policy exposure for the effect of policy change medication use in anxiety, depression, and pure hypercholesterolemia (2010-2017) from three conditional state-level models

Notes: Effect estimates (percentage points) are from conditional models using the group-time methods of Callaway & Sant'Anna 2020 (CS). The policy change is indicated with a dashed line. Because the covariates are time-varying in the main difference-in-differences model, an average is used for CS models. Baseline covariates include the log of the count of enrollees, average levels of age (18-29, 30-49, 50+) and sex, and state-level characteristics: percent unemployment, median income, and the number of medical doctors per 1000 population. States without a policy change serve as "never treated" controls for states when they change their medical cannabis policies.

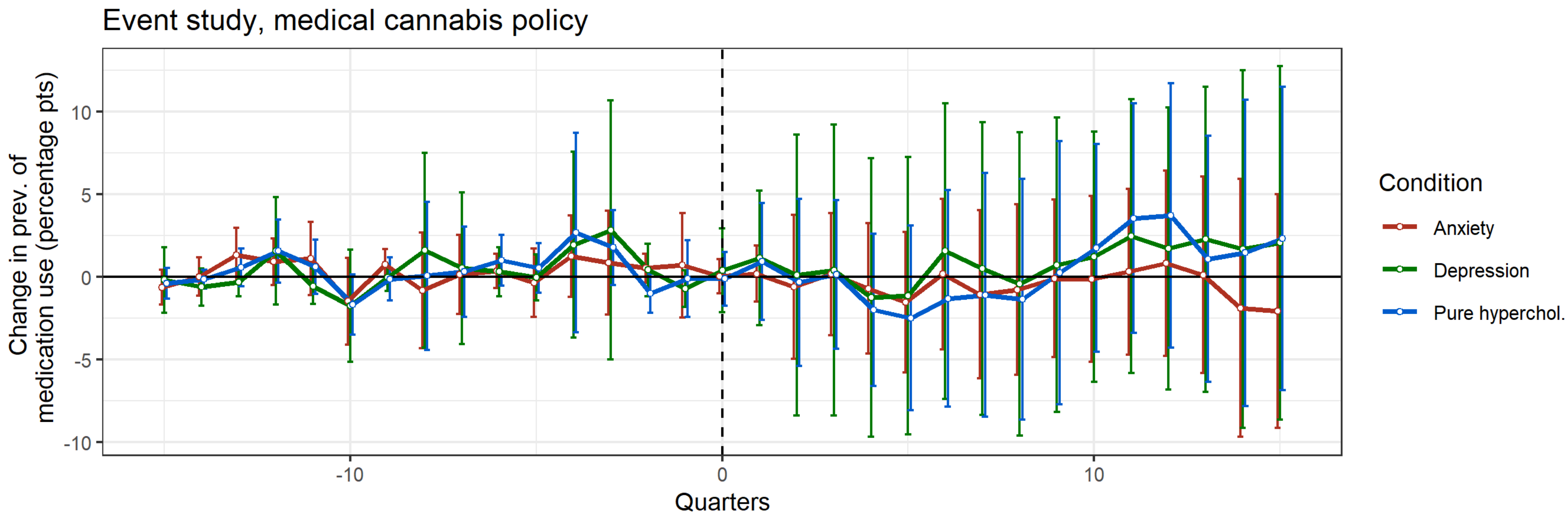


Figure 3.6. Event study of the length of medical cannabis policy exposure for the effect of policy change medication use in anxiety, depression, and pure hypercholesterolemia (2010-2017) from three conditional state-level models restricting to treated states with at least 16 quarters of post-policy time

Notes: Effect estimates (percentage points) are from conditional models using the group-time methods of Callaway & Sant'Anna 2020 (CS). The policy change is indicated with a dashed line. Included states were those that contributed at least 16 quarters of data after the policy change. Because the covariates are time-varying in the main difference-in-differences model, an average is used for CS models. Baseline covariates include the log of the count of enrollees, average levels of age (18-29, 30-49, 50+) and sex, and state-level characteristics: percent unemployment, median income, and the number of medical doctors per 1000 population. States without a policy change serve as "never treated" controls for states when they change their medical cannabis policies.

Table 3.21. Weights of control states in donor pool for evaluating the effect of recreational cannabis policy change on prevalence of medication use, from state-quarter level synthetic control models

	Antianxiety/anxiety		**Antidepressant/depression**	
Control State	**Colorado (Q4 2012)**	**Washington (Q4 2012)**	**Colorado (Q4 2012)**	**Washington (Q4 2012)**
Alabama	0	0.028	0	0.019
California	0	0.508	0.072	0.014
Georgia	0.214	0.002	0	0.001
Hawaii	0	0.056	0	0.054
Idaho	0	0.03	0	0.005
Indiana	0	0	0.003	0.002
Iowa	0.026	0.077	0	0.001
Kansas	0	0	0	0.003
Kentucky	0	0	0.003	0.001
Michigan	0.168	0	0.251	0.192
Mississippi	0	0.001	0	0.001
Montana	0	0	0	0.127
Nebraska	0	0.118	0	0.362
New Mexico	0	0	0.004	0.001
North Carolina	0	0	0.013	0.002
Rhode Island	0	0.065	0.015	0.002
South Carolina	0	0	0.001	0.002
South Dakota	0	0.013	0.208	0.001
Tennessee	0.151	0	0	0.008
Texas	0	0	0.15	0
Vermont	0.006	0.071	0.006	0.142
Virginia	0.197	0.001	0	0.002
Wisconsin	0	0	0.171	0.007
Wyoming	0.237	0.029	0.1	0.05

Notes: Weights were derived using methods described in Abadie 2010. Briefly, weights were estimated from available covariates and a procedure that minimizes the difference in outcome between untreated and a single treated state during the preintervention period. The difference is given by the mean squared prediction error. The donor pool of states consisted of states with preexisting medical cannabis policies prior to 2010 that also did not alter their recreational policies over the period of 2010-2017 as well as states with no active medical cannabis policies. Covariates included logged population (i.e., the sample with condition), the prevalence of medication use in Q1 2010, Q1 2011, Q1 2012 (i.e., the lagged outcomes), average levels of age (18-29, 30-49, 50+) and sex, and state-level characteristics: percent unemployment, median income, and the number of medical doctors per 1000 population.

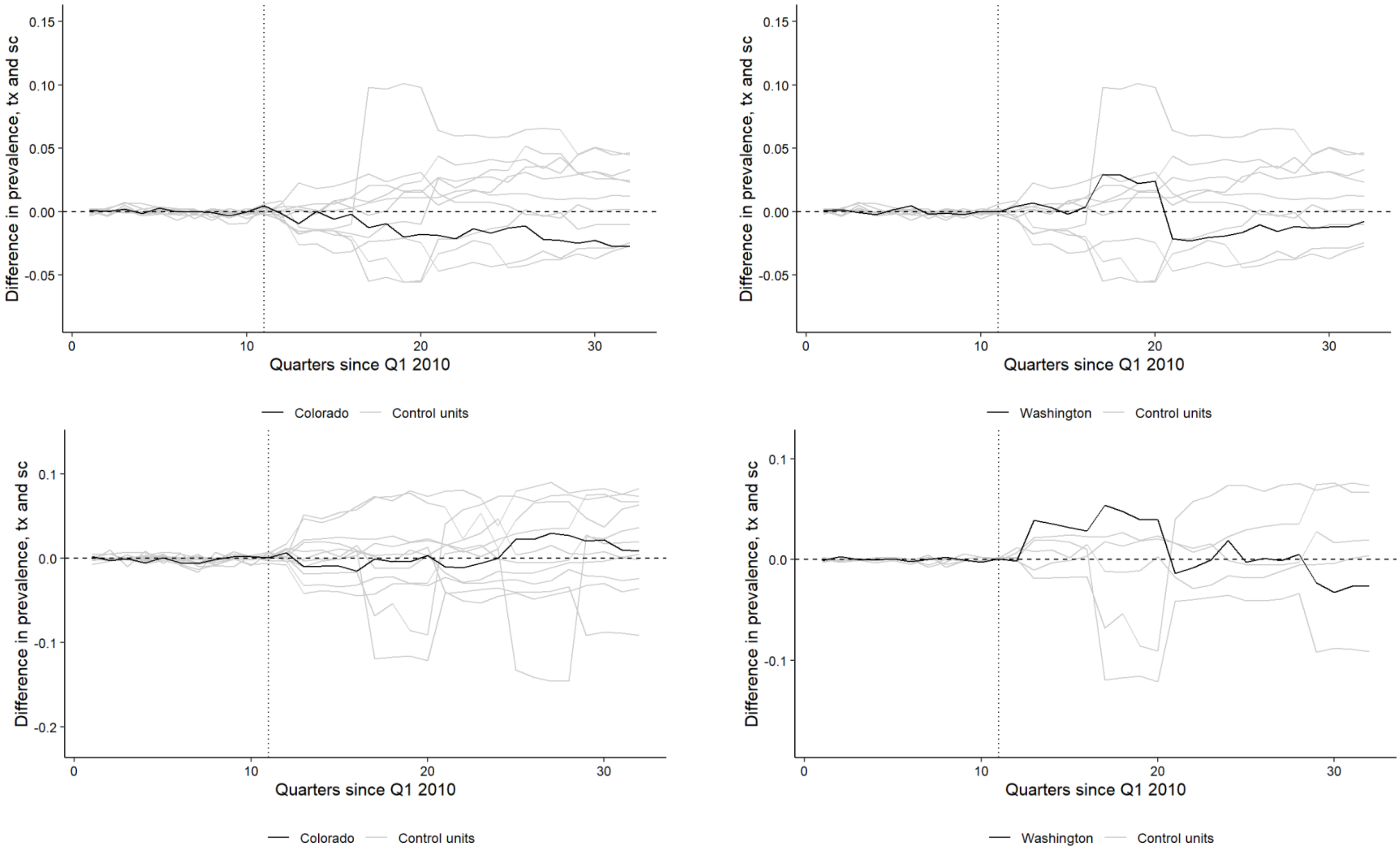


Figure 3.7. Effect of recreational cannabis policy change on the prevalence of medication use outcomes from state-level models using a synthetic control approach

Notes: In the above figure, the top panel represents the treatment effects on antianxiety use in anxiety and the bottom panel antidepressant use in depression. Estimates were derived from synthetic control models. Solid black lines are treated states Colorado (left) and Washington (right). Grey lines reflect placebos for donor pool states.

Chapter 4. SUMMARY OF ENCLOSED WORK

A majority of the previous study on cannabis substitution has focused on opioids due to an interest in ‘opioid sparing’ in the opioid epidemic. Published policy analyses using aggregate state-level data and timing of policy change have cited substitution as a potential mechanism for how medical cannabis policy reduces opioid use and related negative outcomes. But the magnitude of the observed effects of cannabis has been large in relation to targeted opioid policies, and newer studies have provided conflicting evidence. To date, no study has utilized publicly available cannabis sales data, which is collected in several states as part of cannabis traceability programs.

We estimated the effect of cannabis demand and opioid dispensing in Washington State counties in the period following recreational cannabis legalization. We aggregated dispensary-level administrative cannabis sales data collected by the Liquor and Cannabis Board and linked these to county-level opioid dispensing measures for quarters beginning in July 2014 through to December 2017. Accounting for endogeneity of cannabis sales using cannabis dispensary density per population as an instrumental variable, we did not find evidence of cannabis-for-opioids substitution in the post-policy period. This finding may be consistent with little substitution occurring among chronic pain patients.

Few policy analyses have considered cannabis and non-opioid prescription drug use. In many mental health conditions, there is weak evidence for a benefit of cannabis, though anxiety and depression are commonly reported reasons for medical cannabis use. Recreational cannabis policy and dispensaries have broadened access to cannabis, potentially making it easier for individuals to use recreational products for medical purposes. Moreover, there has been wide advertising of recreational cannabis products, with some marketing based on unsubstantiated claims about medical effectiveness.

We evaluated the effect of cannabis policy change on utilization of antianxiety medications in people with anxiety and antidepressants in people with depression. We identified enrollees with diagnosis codes for anxiety and depression and continuous coverage over the previous year in a large database of medical and prescription drug claims of Americans with commercial insurance. We linked individual level data to policy changes using individual enrollee’s states. Medication utilization was identified by prescription claim for at least one medication in the classes of interest in a given calendar quarter. We did not find evidence that medical cannabis policy change reduced the use of anxiety medications in anxiety or antidepressants in depression. In separate analyses of Washington and Colorado, there was no effect of recreational cannabis policy change on medication utilization. No observed effects of these policies may indicate little substitution of cannabis for common mental health medications in their primary indications.

Together, this body of work suggests that cannabis policy change may minimally impact general opioid use and medication use in mental health, at least in the short-term periods following medical and recreational policy change. These are important findings which may temper the optimism around opioid substitution and concern around mental health medication substitution. Ultimately, this work encourages balanced consideration of the available evidence and continued rigorous study of how cannabis policy will impact health outcomes.

BIBLIOGRAPHY

1. Alpert A, Powell D, Pacula RL. *Supply-Side Drug Policy in the Presence of Substitutes: Evidence from the Introduction of Abuse-Deterrent Opioids*. Cambridge, MA; 2017. doi:10.3386/w23031
2. Volkow ND, Collins FS. The Role of Science in Addressing the Opioid Crisis. *N Engl J Med*. 2017;377(4):391-394. doi:10.1056/NEJMsr1706626
3. Food and Drug Administration. *HIGHLIGHTS OF PRESCRIBING INFORMATION These Highlights Do Not Include All the Information Needed to Use EPIDIOLEX ® Safely and Effectively. See Full Prescribing Information for EPIDIOLEX. EPIDIOLEX ® (Cannabidi Ol) Oral Solution, CX [Pending DEA Schedulin*. www.fda.gov/. Accessed May 3, 2019.
4. Rudroff T, Honce JM. Cannabis and Multiple Sclerosis—The Way Forward. *Front Neurol*. 2017;8:299. doi:10.3389/FNEUR.2017.00299
5. Ultra-pure synthetic cannabinoids: the next big innovation in pharma? https://www.pharmaceutical-technology.com/comment/ultra-pure-synthetic-cannabinoids/. Accessed May 1, 2019.
6. *CESAMET^{TM} (Nabilone) Capsules*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018677s011lbl.pdf. Accessed May 1, 2019.
7. *MARINOL ® (Dronabinol)*.; 2004. https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/018651s021lbl.pdf. Accessed May 1, 2019.
8. Boehnke KF, Gangopadhyay S, Clauw DJ, Haffajee RL. Qualifying Conditions Of Medical Cannabis License Holders In The United States. *Health Aff (Millwood)*. 2019;38(2):295-302. doi:10.1377/hlthaff.2018.05266
9. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. *J Pain*. 2016;17(6):739-744. doi:10.1016/j.jpain.2016.03.002
10. Delling FN, Vittinghoff E, Dewland TA, et al. Does cannabis legalisation change healthcare utilisation? A population-based study using the healthcare cost and utilisation project in Colorado, USA. *BMJ Open*. 2019;9(5):e027432. doi:10.1136/bmjopen-2018-027432
11. Walsh Z, Gonzalez R, Crosby K, S. Thiessen M, Carroll C, Bonn-Miller MO. Medical cannabis and mental health: A guided systematic review. *Clin Psychol Rev*. 2017;51:15-29. doi:10.1016/J.CPR.2016.10.002
12. Boehnke KF, Scott JR, Litinas E, et al. Cannabis Use Preferences and Decision-making Among a Cross-sectional Cohort of Medical Cannabis Patients with Chronic Pain. *J Pain*. 2019;20(11):1362-1372. doi:10.1016/j.jpain.2019.05.009
13. Piper BJ, DeKeuster RM, Beals ML, et al. Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep. *J Psychopharmacol*. 2017;31(5):569-575. doi:10.1177/0269881117699616
14. Lowe DJE, Sasiadek JD, Coles AS, George TP. Cannabis and mental illness: a review. *Eur Arch Psychiatry Clin Neurosci*. 2019;269(1):107-120. doi:10.1007/s00406-018-0970-7
15. Pacula RL, Powell D, Heaton P, Sevigny EL. Assessing the effects of medical marijuana

laws on marijuana use: the devil is in the details. *J Policy Anal Manage*. 2015;34(1):7-31. http://www.ncbi.nlm.nih.gov/pubmed/25558490. Accessed September 23, 2019.
16. *Iniative Measure No. 502*.; 2011. https://sos.wa.gov/_assets/elections/initiatives/i502.pdf. Accessed May 2, 2019.
17. Everson EM, Dilley JA, Maher JE, Mack CE. Post-Legalization Opening of Retail Cannabis Stores and Adult Cannabis Use in Washington State, 2009–2016. *Am J Public Health*. 2019;109(9):1294-1301. doi:10.2105/ajph.2019.305191
18. Smart R, Caulkins JP, Kilmer B, Davenport S, Midgette G. Variation in cannabis potency and prices in a newly legal market: evidence from 30 million cannabis sales in Washington state. *Addiction*. 2017;112(12):2167-2177. doi:10.1111/add.13886
19. Shover CL, Davis CS, Gordon SC, Humphreys K. Association between medical cannabis laws and opioid overdose mortality has reversed over time. *Proc Natl Acad Sci U S A*. 2019;116(26):12624-12626. doi:10.1073/pnas.1903434116
20. Powell D, Pacula RL, Jacobson M. Do medical marijuana laws reduce addictions and deaths related to pain killers? *J Health Econ*. 2018;58:29-42. doi:10.1016/J.JHEALECO.2017.12.007
21. Livingston MD, Barnett TE, Delcher C, Wagenaar AC. Recreational cannabis legalization and opioid-related deaths in Colorado, 2000-2015. *Am J Public Health*. 2017;107(11):1827-1829. doi:10.2105/AJPH.2017.304059
22. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med*. 2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005
23. Wen H, Hockenberry JM. Association of Medical and Adult-Use Marijuana Laws With Opioid Prescribing for Medicaid Enrollees. *JAMA Intern Med*. April 2018. doi:10.1001/jamainternmed.2018.1007
24. Bradford AC, Bradford WD, Abraham A, Bagwell Adams G. Association Between US State Medical Cannabis Laws and Opioid Prescribing in the Medicare Part D Population. *JAMA Intern Med*. April 2018. doi:10.1001/jamainternmed.2018.0266
25. Bradford AC, Bradford WD. Medical Marijuana Laws May Be Associated With A Decline In The Number Of Prescriptions For Medicaid Enrollees. *Health Aff*. 2017;36(5):945-951. doi:10.1377/hlthaff.2016.1135
26. Shi Y, Liang D, Bao Y, An R, Wallace MS, Grant I. Recreational marijuana legalization and prescription opioids received by Medicaid enrollees. *Drug Alcohol Depend*. 2019;194:13-19. doi:10.1016/j.drugalcdep.2018.09.016
27. Lucas P, Walsh Z. Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. *Int J Drug Policy*. 2017;42:30-35. doi:10.1016/j.drugpo.2017.01.011
28. Corroon JM, Mischley LK, Sexton M, Sexton M. Cannabis as a substitute for prescription drugs - a cross-sectional study. *J Pain Res*. 2017;10:989-998. doi:10.2147/JPR.S134330
29. Reiman A, Welty M, Solomon P. Cannabis as a Substitute for Opioid-Based Pain Medication: Patient Self-Report. *Cannabis cannabinoid Res*. 2017;2(1):160-166. doi:10.1089/can.2017.0012
30. Voelker R. States Move to Substitute Opioids with Medical Marijuana to Quell Epidemic. *JAMA - J Am Med Assoc*. 2018;320(23):2408-2410. doi:10.1001/jama.2018.17329
31. Le Foll B. Opioid-sparing effects of cannabinoids: Myth or reality? *Prog Neuro-Psychopharmacology Biol Psychiatry*. August 2020:110065.

doi:10.1016/j.pnpbp.2020.110065
32. Shover CL, Vest NA, Chen D, et al. Association of State Policies Allowing Medical Cannabis for Opioid Use Disorder With Dispensary Marketing for This Indication. *JAMA Netw open*. 2020;3(7):e2010001. doi:10.1001/jamanetworkopen.2020.10001
33. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010. *JAMA Intern Med*. 2014;174(10):1668. doi:10.1001/jamainternmed.2014.4005
34. Ozluk P. The Effects of Medical Marijuana Laws on Prescribed Opioids and Other Prescription Drugs. *SSRN Electron J*. 2017:1-44. doi:10.2139/ssrn.3056791
35. Powell D, Pacula RL, Jacobson M. Do medical marijuana laws reduce addictions and deaths related to pain killers? *J Health Econ*. 2018;58:29-42. doi:10.1016/J.JHEALECO.2017.12.007
36. Liang D, Bao Y, Wallace M, Grant I, Shi Y. Medical Cannabis Legalization and Opioid Prescriptions: Evidence on US Medicaid Enrollees during 1993-2014. *Addiction*. July 2018. doi:10.1111/add.14382
37. Chan NW, Burkhardt J, Flyr M. THE EFFECTS OF RECREATIONAL MARIJUANA LEGALIZATION AND DISPENSING ON OPIOID MORTALITY. *Econ Inq*. August 2019:ecin.12819. doi:10.1111/ecin.12819
38. Flexon JL, Stolzenberg L, D'Alessio SJ. The effect of cannabis laws on opioid use. *Int J Drug Policy*. 2019. doi:10.1016/j.drugpo.2019.09.013
39. Raji MA, Abara NO, Salameh H, Westra JR, Kuo Y-F. Association between cannabis laws and opioid prescriptions among privately insured adults in the US. *Prev Med (Baltim)*. 2019;125:62-68. doi:10.1016/J.YPMED.2019.05.012
40. Shah A, Hayes CJ, Lakkad M, Martin BC. Impact of Medical Marijuana Legalization on Opioid Use, Chronic Opioid Use, and High-risk Opioid Use. *J Gen Intern Med*. 2019;34(8):1419-1426. doi:10.1007/s11606-018-4782-2
41. Shi Y. Medical marijuana policies and hospitalizations related to marijuana and opioid pain reliever. *Drug Alcohol Depend*. 2017;173(2017):144-150. doi:10.1016/j.drugalcdep.2017.01.006
42. McMichael BJ, Van Horn RL, Viscusi WK. The impact of cannabis access laws on opioid prescribing. *J Health Econ*. 2020;69:102273. doi:10.1016/j.jhealeco.2019.102273
43. Baron EP, Lucas P, Eades J, Hogue O. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. *J Headache Pain*. 2018;19(1). doi:10.1186/s10194-018-0862-2
44. Bachhuber M, Arnsten JH, Wurm G. Use of Cannabis to Relieve Pain and Promote Sleep by Customers at an Adult Use Dispensary. *J Psychoactive Drugs*. 2019;51(5):400-404. doi:10.1080/02791072.2019.1626953
45. Le Foll B. Opioid-sparing effects of cannabinoids: Myth or reality? *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2020;(August):110065. doi:10.1016/j.pnpbp.2020.110065
46. WSLCB Marijuana Dashboard | Washington State Liquor and Cannabis Board Data Portal (WSLCB). https://data.lcb.wa.gov/stories/s/WSLCB-Marijuana-Dashboard/hbnp-ia6v/. Accessed April 28, 2020.
47. Subbaraman MS, Kerr WC. Subgroup trends in alcohol and cannabis co-use and related harms during the rollout of recreational cannabis legalization in Washington state. *Int J*

Drug Policy. July 2019. doi:10.1016/j.drugpo.2019.07.003
48. Boehnke KF, Scott JR, Litinas E, Sisley S, Williams DA, Clauw DJ. Pills to Pot: Observational Analyses of Cannabis Substitution Among Medical Cannabis Users With Chronic Pain. *J Pain*. 2019;20(7):830-841. doi:10.1016/j.jpain.2019.01.010
49. Nielsen S, Sabioni P, Trigo JM, et al. Opioid-Sparing Effect of Cannabinoids: A Systematic Review and Meta-Analysis. *Neuropsychopharmacology*. 2017;42(9):1752-1765. doi:10.1038/npp.2017.51
50. Dr. Robert Bree Collaborative. *Opioid Prescribing Metrics*.; 2017. http://www.breecollaborative.org/wp-content/uploads/Bree-Opioid-Prescribing-Metrics-Final-2017.pdf. Accessed May 1, 2019.
51. Boudreau D, Von Korff M, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. *Pharmacoepidemiol Drug Saf*. 2009;18(12):1166-1175. doi:10.1002/pds.1833
52. Area Health Resources Files. https://data.hrsa.gov/topics/health-workforce/ahrf. Accessed October 27, 2019.
53. Hansen B, Miller K, Weber C. *The Taxation of Recreational Marijuana: Evidence from Washington State*. Cambridge, MA; 2017. doi:10.3386/w23632
54. Preparations in place for July 1 alignment of medical and recreational marijuana systems | Washington State Liquor and Cannabis Board. https://lcb.wa.gov/pressreleases/alignment-med-and-rec-mj-systems. Accessed April 17, 2020.
55. Goodman-Bacon A, Sandoe E. Did Medicaid Expansion Cause The Opioid Epidemic? There's Little Evidence That It Did. *Heal Aff Blog*. 2017. doi:10.1377/hblog20170823.061640
56. Saloner B, Levin J, Chang H-Y, Jones C, Alexander GC. Changes in Buprenorphine-Naloxone and Opioid Pain Reliever Prescriptions After the Affordable Care Act Medicaid Expansion. *JAMA Netw Open*. 2018;1(4):e181588. doi:10.1001/jamanetworkopen.2018.1588
57. Sharp A, Jones A, Sherwood J, Kutsa O, Honermann B, Millett G. Impact of medicaid expansion on access to opioid analgesic medications and medication-assisted treatment. *Am J Public Health*. 2018;108(5):642-648. doi:10.2105/AJPH.2018.304338
58. Raji MA, Kuo YF, Adhikari D, Baillargeon J, Goodwin JS. Decline in opioid prescribing after federal rescheduling of hydrocodone products. *Pharmacoepidemiol Drug Saf*. 2018;27(5):513-519. doi:10.1002/pds.4376
59. Liu Y, Baker O, Schuur JD, Weiner SG. Effects of Rescheduling Hydrocodone on Opioid Prescribing in Ohio. *Pain Med*. 2019. doi:10.1093/pm/pnz210
60. Sullivan MD, Bauer AM, Fulton-Kehoe D, et al. Trends in Opioid Dosing among Washington State Medicaid Patients before and after Opioid Dosing Guideline Implementation. *J Pain*. 2016;17(5):561-568. doi:10.1016/j.jpain.2015.12.018
61. Tran S, Lavitas P, Stevens K, et al. The effect of a federal controlled substance act schedule change on hydrocodone combination products claims in a medicaid population. *J Manag Care Spec Pharm*. 2017;23(5):532-539. doi:10.18553/jmcp.2017.23.5.532
62. Dineen KK, DuBois JM. BETWEEN A ROCK AND A HARD PLACE: CAN PHYSICIANS PRESCRIBE OPIOIDS TO TREAT PAIN ADEQUATELY WHILE AVOIDING LEGAL SANCTION? *Am J Law Med*. 2016;42(1):7-52. doi:10.1177/0098858816644712
63. Han B, Compton WM, Blanco C, Jones CM. Trends in and correlates of medical

marijuana use among adults in the United States. *Drug Alcohol Depend*. 2018;186:120-129. doi:10.1016/j.drugalcdep.2018.01.022
64. Han BH, Palamar JJ. Marijuana use by middle-aged and older adults in the United States, 2015-2016. *Drug Alcohol Depend*. 2018;191:374-381. doi:10.1016/j.drugalcdep.2018.07.006
65. Labrecque J, Swanson SA. Understanding the Assumptions Underlying Instrumental Variable Analyses: a Brief Review of Falsification Strategies and Related Tools. *Curr Epidemiol Reports*. 2018;5(3):214-220. doi:10.1007/s40471-018-0152-1
66. Hausman JA. Specification tests in econometrics. *Appl Econom*. 2015;38(2):112-134. doi:10.2307/1913827
67. Lousdal ML. An introduction to instrumental variable assumptions, validation and estimation. *Emerg Themes Epidemiol*. 2018;15(1). doi:10.1186/s12982-018-0069-7
68. Terza J V, Basu A, Rathouz PJ. Two-stage residual inclusion estimation : Addressing endogeneity in health econometric modeling. 2008;27:531-543. doi:10.1016/j.jhealeco.2007.09.009
69. Livingston JD, Milne T, Fang ML, Amari E. The effectiveness of interventions for reducing stigma related to substance use disorders: a systematic review. *Addiction*. 2012;107(1):39-50. doi:10.1111/j.1360-0443.2011.03601.x
70. Livingston MD, Barnett TE, Delcher C, Wagenaar AC. Recreational Cannabis Legalization and Opioid-Related Deaths in Colorado, 2000–2015. *Am J Public Heal*. 2017;107:1827-1829. doi:10.2105/AJPH.2017.304059
71. Flexon JL, Stolzenberg L, D'Alessio SJ. The effect of cannabis laws on opioid use. *Int J Drug Policy*. 2019;74:152-159. doi:10.1016/j.drugpo.2019.09.013
72. Raji MA, Abara NO, Salameh H, Westra JR, Kuo Y-F. Association between cannabis laws and opioid prescriptions among privately insured adults in the US. *Prev Med (Baltim)*. 2019;125:62-68. doi:10.1016/j.ypmed.2019.05.012
73. Smart R, Caulkins JP, Kilmer B, Davenport S, Midgette G. Variation in cannabis potency and prices in a newly legal market: evidence from 30 million cannabis sales in Washington state. *Addiction*. 2017;112(12):2167-2177. doi:10.1111/add.13886
74. Caulkins JP, Davenport S, Doanvo A, et al. Triangulating web & general population surveys: Do results match legal cannabis market sales? *Int J Drug Policy*. 2019;73:293-300. doi:10.1016/j.drugpo.2019.06.010
75. Burgard DA, Williams J, Westerman D, et al. Using wastewater-based analysis to monitor the effects of legalized retail sales on cannabis consumption in Washington State, USA. *Addiction*. June 2019. doi:10.1111/add.14641
76. Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: A prospective cohort study. *BMC Health Serv Res*. 2006;6(1):1-10. doi:10.1186/1472-6963-6-46
77. DiBenedetto DJ, Weed VF, Wawrzyniak KM, et al. The association between cannabis use and aberrant behaviors during chronic opioid therapy for chronic pain. *Pain Med (United States)*. 2018;19(10):1997-2008. doi:10.1093/pm/pnx222
78. Olfson M, Wall MM, Liu S-M, Blanco C. Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States. *Am J Psychiatry*. 2018;175(1):47-53. doi:10.1176/appi.ajp.2017.17040413
79. Miller ML, Hurd YL. Testing the Gateway Hypothesis. *Neuropsychopharmacology*. 2017;42(5):985-986. doi:10.1038/npp.2016.279

80. MRSC - Marijuana Regulation in Washington State. http://mrsc.org/Home/Explore-Topics/Legal/Regulation/Marijuana-Regulation-in-Washington-State.aspx. Accessed February 1, 2019.
81. Appeals Court sides with county on marijuana case; Sticky Budz moves to Union Gap | Local | yakimaherald.com. https://www.yakimaherald.com/news/local/appeals-court-sides-with-county-on-marijuana-case-sticky-budz-moves-to-union-gap/article_50638792-0d88-59fe-9058-d93e6895d7f5.html. Accessed April 16, 2020.
82. Public-private safe prescribing initiative results in significant reductions of Medicaid opioid prescriptions | Washington State Health Care Authority. https://www.hca.wa.gov/about-hca/public-private-safe-prescribing-initiative-results-significant-reductions-medicaid-opioid. Accessed April 20, 2020.
83. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA - J Am Med Assoc*. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358
84. Humphreys K, Saitz R. Should Physicians Recommend Replacing Opioids With Cannabis? *JAMA*. February 2019. doi:10.1001/jama.2019.0077
85. Nielsen S, Sabioni P, Trigo JM, et al. Opioid-sparing effect of cannabinoids: A systematic review and meta-analysis. *Neuropsychopharmacology*. 2017;42(9):1752-1765. doi:10.1038/npp.2017.51
86. Campbell G, Hall WD, Peacock A, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. *Lancet Public Heal*. 2018;3(7):e341-e350. doi:10.1016/S2468-2667(18)30110-5
87. Campbell G, Stockings E, Nielsen S. Understanding the evidence for medical cannabis and cannabis-based medicines for the treatment of chronic non-cancer pain. *Eur Arch Psychiatry Clin Neurosci*. 2019;269(1):135-144. doi:10.1007/s00406-018-0960-9
88. Lack of cannabis tracking data in Washington state sparks confusion, missed business opportunities. https://mjbizdaily.com/lack-cannabis-tracking-data-washington-state/. Accessed April 16, 2020.
89. Romero-Sandoval EA, Kolano AL, Alvarado-Vazquez PA. Cannabis and Cannabinoids for Chronic Pain. *Curr Rheumatol Rep*. 2017;19(11):67. doi:10.1007/s11926-017-0693-1
90. Hughes B, Wiessing L, Des Jarlais D, Griffiths P. Could cannabis liberalisation lead to wider changes in drug policies and outcomes? *Int J Drug Policy*. 2018;51:156-159. doi:10.1016/j.drugpo.2017.10.004
91. Boehnke KF, Gangopadhyay S, Clauw DJ, Haffajee RL. Qualifying conditions of medical cannabis license holders in the United States. *Health Aff*. 2019;38(2):295-302. doi:10.1377/hlthaff.2018.05266
92. Medical Marijuana for Anxiety Approved in PA. https://www.partnershipforpublichealth.org/medical-marijuana-for-anxiety-approved-in-pa/. Accessed October 31, 2020.
93. Spindle TR, Bonn-Miller MO, Vandrey R. Changing landscape of cannabis: novel products, formulations, and methods of administration. *Curr Opin Psychol*. 2019;30:98-102. doi:10.1016/j.copsyc.2019.04.002
94. Bahorik AL, Sterling SA, Campbell CI, Weisner C, Ramo D, Satre DD. Medical and non-medical marijuana use in depression: Longitudinal associations with suicidal ideation, everyday functioning, and psychiatry service utilization. *J Affect Disord*. 2018;241:8-14. doi:10.1016/j.jad.2018.05.065

95. Bahorik AL, Leibowitz A, Sterling SA, Travis A, Weisner C, Satre DD. Patterns of marijuana use among psychiatry patients with depression and its impact on recovery. *J Affect Disord*. 2017;213:168-171. doi:10.1016/j.jad.2017.02.016
96. Hill KP, Blanco C, Hasin DS, et al. Cannabis use and risk of psychiatric disorders: Prospective evidence from aUS national longitudinal study. *JAMA - J Am Med Assoc*. 2017;317(10):1070-1071. doi:10.1001/jamapsychiatry.2015.3229
97. Twomey CD. Association of cannabis use with the development of elevated anxiety symptoms in the general population: A meta-analysis. *J Epidemiol Community Health*. 2017;71(8):811-816. doi:10.1136/jech-2016-208145
98. Rosenberg J, Loflin MJE, Hurd YL, Bonn-Miller MO. Prescribing Health Care Providers' Attitudes, Experiences, and Practices Surrounding Cannabis Use in Patients with Anxiety Disorders and Post-Traumatic Stress Disorder. *Cannabis Cannabinoid Res*. 2019;4(2):124-130. doi:10.1089/can.2018.0008
99. Blessing EM, Steenkamp MM, Manzanares J, Marmar CR. Cannabidiol as a Potential Treatment for Anxiety Disorders. *Neurotherapeutics*. 2015;12(4):825-836. doi:10.1007/s13311-015-0387-1
100. Sublingual Cannabidiol for Anxiety - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02548559. Accessed October 31, 2020.
101. Cannabidiol for the Treatment of Anxiety Disorders: An 8-Week Pilot Study - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03549819. Accessed October 31, 2020.
102. Azcarate PM, Zhang AJ, Keyhani S, Steigerwald S, Ishida JH, Cohen BE. Medical Reasons for Marijuana Use, Forms of Use, and Patient Perception of Physician Attitudes Among the US Population. *J Gen Intern Med*. 2020;35(7). doi:10.1007/s11606-020-05800-7
103. Kosiba JD, Maisto SA, Ditre JW. Patient-reported use of medical cannabis for pain, anxiety, and depression symptoms: Systematic review and meta-analysis. *Soc Sci Med*. 2019;233:181-192. doi:10.1016/j.socscimed.2019.06.005
104. Hall W, Lynskey M. Assessing the public health impacts of legalizing recreational cannabis use: the US experience. *World Psychiatry*. 2020;19(2):179-186. doi:10.1002/wps.20735
105. Hasin DS. US Epidemiology of Cannabis Use and Associated Problems. *Neuropsychopharmacology*. 2018;43(1):195-212. doi:10.1038/npp.2017.198
106. Ishida JH, Zhang AJ, Steigerwald S, Cohen BE, Vali M, Keyhani S. Sources of Information and Beliefs About the Health Effects of Marijuana. *J Gen Intern Med*. October 2019. doi:10.1007/s11606-019-05335-6
107. Abraham A, Zhang AJ, Ahn R, Woodbridge A, Korenstein D, Keyhani S. Media Content Analysis of Marijuana's Health Effects in News Coverage. *J Gen Intern Med*. 2018;33(9):1438-1440. doi:10.1007/s11606-018-4492-9
108. Keyhani S, Steigerwald S, Ishida J, et al. Risks and Benefits of Marijuana Use: A National Survey of U.S. Adults. *Ann Intern Med*. 2018;169(5):282-290. doi:10.7326/M18-0810
109. Klimkiewicz A, Jasinska A. The health effects of cannabis and cannabinoids. *Psychiatria*. 2018;15(2):88-92. doi:10.17226/24625
110. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139. doi:10.1097/01.mlr.0000182534.19832.83

111. Census.gov. State Total Population, 2010. 2010. https://www.census.gov/data/tables/time-series/demo/popest/2010s-state-total.html#par_textimage_1574439295.
112. Powell D. Do medical marijuana laws reduce addicitons and deaths related to pain killers? *Natl Bur Econ Res Work Pap*. 2015. http://www.nber.org/papers/w21345.
113. Liang D, Bao Y, Wallace M, Grant I, Shi Y. Medical cannabis legalization and opioid prescriptions: evidence on US Medicaid enrollees during 1993-2014. *Addiction*. 2018;113(11):2060-2070. doi:10.1111/add.14382
114. Wing C, Simon K, Bello-Gomez RA. Designing Difference in Difference Studies: Best Practices for Public Health Policy Research Keywords. *Annu Rev Public Heal*. 2018;39:453-469. doi:10.1146/annurev-publhealth
115. Callaway B, Sant'Anna PHC. Difference-in-Differences with Multiple Time Periods and an Application on the Minimum Wage and Employment. *arXiv*. March 2018. doi:10.2139/ssrn.3148250
116. Abadie A, Diamond A, Hainmueller J. Synthetic Control Methods for Comparative Case Studies: Estimating the Effect of California's Tobacco Control Program. *J Am Stat Assoc*. 2010;105(490):493-505. doi:10.1198/jasa.2009.ap08746
117. Abadie A, Diamond A, Hainmueller J. Comparative Politics and the Synthetic Control Method. *Am J Pol Sci*. 2015;59(2):495-510. doi:10.1111/ajps.12116
118. Abadie A, Diamond A, Hainmueller J. Synthetic Control Methods for Comparative Case Studies: Estimating the Effect of California's Tobacco Control Program. 2010. doi:10.1198/jasa.2009.ap08746
119. Corroon JMJ, Mischley LK, Sexton M. Cannabis as a substitute for prescription drugs - a cross-sectional study. *J Pain Res*. 2017;10:989-998. doi:10.2147/JPR.S134330
120. Piper BJ, DeKeuster RM, Beals ML, et al. Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep. *J Psychopharmacol*. 2017;31(5):569-575. doi:10.1177/0269881117699616
121. Baron EP, Lucas P, Eades J, Hogue O. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. *J Headache Pain*. 2018;19(1):37. doi:10.1186/s10194-018-0862-2
122. Bradford AC, Bradford WD. Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D. *Health Aff*. 2016;35(7):1230-1236. doi:10.1377/hlthaff.2015.1661
123. Bradford AC, Bradford WD. Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D. *Health Aff (Millwood)*. 2016;35(7):1230-1236. doi:10.1377/hlthaff.2015.1661
124. Woolridge E, Barton S, Samuel J, Osorio J, Dougherty A, Holdcroft A. Cannabis use in HIV for pain and other medical symptoms. *J Pain Symptom Manage*. 2005;29(4):358-367. doi:10.1016/j.jpainsymman.2004.07.011
125. Socias ME, Wood E, Lake S, et al. High-intensity cannabis use is associated with retention in opioid agonist treatment: a longitudinal analysis. *Addiction*. 2018;113(12):2250-2258. doi:10.1111/add.14398
126. Lloyd SL, Striley CW. Marijuana Use Among Adults 50 Years or Older in the 21st Century. *Gerontol Geriatr Med*. 2018;4:2333721418781668. doi:10.1177/2333721418781668
127. Han BH, Palamar JJ. Trends in Cannabis Use among Older Adults in the United States,

2015-2018. *JAMA Intern Med*. 2020;180(4):609-611. doi:10.1001/jamainternmed.2019.7517
128. Marcum ZA, Hanlon JT, Murray MD. Improving Medication Adherence and Health Outcomes in Older Adults: An Evidence-Based Review of Randomized Controlled Trials. *Drugs and Aging*. 2017;34(3):191-201. doi:10.1007/s40266-016-0433-7
129. Ailabouni NJ, Marcum ZA, Schmader KE, Gray SL. Medication Use Quality and Safety in Older Adults: 2018 Update. *J Am Geriatr Soc*. 2019;67(12):2458-2462. doi:10.1111/jgs.16243
130. Bradford AC, Bradford WD. Medical Marijuana Laws May Be Associated With A Decline In The Number Of Prescriptions For Medicaid Enrollees. *Health Aff (Millwood)*. 2017;36(5):945-951. doi:10.1377/hlthaff.2016.1135
131. Agarwal SD, Landon BE. Patterns in Outpatient Benzodiazepine Prescribing in the United States. *JAMA Netw Open*. 2019;2(1):e187399. doi:10.1001/jamanetworkopen.2018.7399
132. Soyka M. Treatment of Benzodiazepine Dependence. *N Engl J Med*. 2017;376(12):1147-1157. doi:10.1056/nejmra1611832
133. Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996-2013. *Am J Public Health*. 2016;106(4):686-688. doi:10.2105/AJPH.2016.303061
134. Purcell C, Davis A, Moolman N, Taylor SM. Reduction of Benzodiazepine Use in Patients Prescribed Medical Cannabis. *Cannabis cannabinoid Res*. 2019;4(3):214-218. doi:10.1089/can.2018.0020
135. Carnevale JT, Kagan R, Murphy PJ, Esrick J. A practical framework for regulating for-profit recreational marijuana in US States: Lessons from Colorado and Washington. *Int J Drug Policy*. 2017;42:71-85. doi:10.1016/j.drugpo.2017.03.001
136. Hsu G, Kovács B. Association between county level cannabis dispensary counts and opioid related mortality rates in the United States: Panel data study. *BMJ*. 2021;372. doi:10.1136/bmj.m4957
137. Sarvet AL, Wall MM, Keyes KM, Olfson M, Cerda M, Hasin DS. Self-medication of mood and anxiety disorders with marijuana: Higher in states with medical marijuana laws. *Drug Alcohol Depend*. 2018;186:10-15. doi:10.1016/j.drugalcdep.2018.01.009
138. Frequently Requested Lists | Washington State Liquor and Cannabis Board. https://lcb.wa.gov/records/frequently-requested-lists. Accessed April 22, 2020.
139. Washington State Liquor and Cannabis Board. Washington State Liquor and Cannabis Board Retail License Allocation. 316AD:400. https://lcb.wa.gov/publications/Marijuana/MJ_Retail_Allocation_3-8-16.pdf.
140. Rassen JA, Brookhart MA, Glynn RJ, Mittleman MA, Schneeweiss S. Instrumental variables I: instrumental variables exploit natural variation in nonexperimental data to estimate causal relationships. *J Clin Epidemiol*. 2009;62(12):1226-1232. doi:10.1016/j.jclinepi.2008.12.005
141. Lu H, Zhang X, Holt JB, Kanny D, Croft JB. Quantifying spatial accessibility in public health practice and research: An application to on-premise alcohol outlets, United States, 2013. *Int J Health Geogr*. 2018;17(1). doi:10.1186/s12942-018-0143-y
142. Centers of Population. https://www.census.gov/geographies/reference-files/time-series/geo/centers-population.html. Accessed April 22, 2020.
143. Kleiman MAR, Davenport S, Rowe B, et al. *Estimating the Size of the Medical Cannabis Market in Washington State*.; 2015. https://lcb.wa.gov/publications/Marijuana/BOTEC

reports/BOTEC-MMJ-Report.pdf.
144. Washington State Department of Revenue. *Estimated Sales Tax Collected on Sales of Marijuana and Marijuana Products*.; 2020. https://dor.wa.gov/about/statistics-reports/recreational-and-medical-marijuana-taxes.

Chapter 5. APPENDIX A. ADDITIONAL METHODS DETAIL FOR ANALYSIS OF CANNABIS SALES AND OPIOID DISPENSING IN WASHINGTON STATE

5.1 OVERVIEW OF DATA SOURCES AND TIMEFRAMES

A table of data sources is shown below along with the data utilized for the final analysis. Data sources covered different timeframes. The outcomes dataset contained 28 quarters of data on 39 counties for the 7 outcomes (n=7644). Due to the structure of the LCB data, the linked county-month data only had county-months with positive sales and dispensaries (n=2063), so we generated additional entries county-months with appropriate zeros making a final dataset containing 63 months of data on 39 counties (n=2457). Finally, we created a quarterly form of these data (n=819), summing over sales and averaging over the allotted number of licenses, dispensary counts, and proportion of allotted licenses granted. The sales dataset thus 39 counties for 21 quarters over the period of Q3 2014 to Q3 2019. The complete overlapping dataset covers Q3 2014 – Q4 2017, which represents 14 quarters of data, or 546 unique combinations of county-year-quarter.

Table. Data sources

Source	**Data available**	**Unit**	**Included in final analysis**
Washington Department of Health (DOH) Opioid Dashboard (via Prescription Monitoring Program [PMP])	Aggregate opioid dispensing for any opioid, long-term and high-dose opioids, new long-term	County-quarter	X
WS Liquor Cannabis Board (LCB) Marijuana Dashboard 2.0	Aggregate cannabis sales/tax; business licensing	County-month	X
WS Public Records Request	Cannabis product sales, seed to sale information	Individual sale	
Topshelf Data Platform®	Businesses, aggregate sales, average price/gram	State-month	
WS Municipal Research and Services Center	Municipal cannabis zoning	City-county (Jan 2019)	
Area Health Resources File (AHRF)	Age structure, gender, race, income, poverty, health insurance, physician supply, employment	County-year	X
Opioid policy sources (press releases, guidance documents, health authority information)	Timing of opioid policy, guidelines in Washington State	Month and year	

Table. Dataset timeframes

Quarters	Number of Quarters	Number of BREE Opioid Outcomes	Cannabis sales/shops	Demographics and economic covariates
Q1 2012	1	6 (minus new dispensing)	--	Some
Q2 2012 – Q4 2013	7	7	--	Full
Q1 2014 – Q2 2014	2	7	--	Full
Q3 2014 – Q4 2017	14	7	Sales/shops	Full
Q1 2018 - Q4 2018	4	7	Sales/shops	Some
Q1 2019 – Q3 2019	3	4 (High-dose and new dispensing only)	Sales/shops	Some

5.1.1 *Sales and licensing data files*

Cannabis sales and licensing data are collected by the Liquor and Cannabis Board (LCB) as set forth in i502. These data are publicly available and many can be found on the LCB Webpage for Frequently Requested Lists which are updated often.[138] More detailed transaction level data are available through Public Records Requests. The below table gives an overview of the datasets used.

Table. Cannabis sales and licensing datasets

Data file	**Data**	**Rows**	**Timing**	**Notes**
Licenses (a)	License numbers, addresses, date issued, privilege status	567	Nov 2019	Privilege status appears to be at timing of file creation
Licenses (Old) (b)	License numbers, addresses, date issued, privilege status	765	December 2018	Privilege status appears to be at timing of file creation
Sales I (c)	Sales by license number, monthly	9273 (9324)	Covers July 2014 – October 2017	
Sales II (d)	Sales by license number, monthly	9673	Covers November 2017 - September 2019	These data cover the period after a change in tracking platform.
License Allotment[139]	Counts of allotted licenses by county	39		

5.1.2 *Sales information*

As shown in the above table, three files were utilized: (a and b) the marijuana license applicants file, (c) the marijuana sales activity by license number, and (d) the marijuana sales activity by licenses number - traceability contingency reporting. We combined sales data files (n=18906) and merged with the licensing data file on the license number field. Eleven license numbers had positive sales and no business information such as tradename and address.

Sales data are split into two files as shown in the table above and cover different time periods. We do not have information on how these sales were aggregated. A number of sales are zero or very small numbers (n=92 entries are less than $50 in sales in a given month). Since this is a relatively small number of sales, we did not consider it further.

5.1.3 *Dispensary information*

Within Washington, individuals must obtain retail license to operate a dispensary. These must be renewed on an annual basis. We downloaded a dispensary license number file on two occasions: late 2018 and November 2019. In the “old file” (2018 file) for dispensary license number, there are 218 additional dispensary license numbers that are not reflected in an updated file (2019 file). There are 20 licenses that are reflected in the new but not the old (union of 547 License Numbers). We are less concerned about the 20; these must be new shops as of later in 2019 as is evidenced by the date issued field. It is unclear why the 218 are missing from the updated license file. It does not appear to be related to privilege status (table below).

Table. Privilege status as of November 2019

Category	**Count**
Active (Issued)	12
Closed (permanent)	140
Closed (temporary)	0
Pending (issued)	1
Pending (not issued)	65
Total	218

Using the old file allows 1790 dispensary-date combinations (90 dispensaries) of sales to be identified (of the 18906 total) in the merge. In this final file, 11 license numbers have positive sales (ranging from $33 to 741K) and no identifying dispensary information. However, in most of these cases they are related to a primary license number and are updated with a -1. We reviewed each of these instances, selecting the larger cannabis sales estimate for the primary sales estimate.

5.1.4 *Privilege status*

Cannabis dispensaries must update licenses annually and can come into and out of existence. It appears that dispensaries' license status are noted within the data. Within the dispensary license number file, license numbers have a privilege status and a date issued field. The date issued appears to be the date of the most recent license issuing. Phrasing from the LCB website suggests that the privilege status reflects the timing that the license file was created.

"When active licenses come up for renewal or are undergoing some sort of change their status is changed from "Active" to "Pending (Issued)." Please include "Pending (Issued)" when filtering to see all currently active licenses."

The merged file produces categories of privilege status as shown in the below table. Plots of this timing and sales of dispensaries by privilege status are shown below.

Table. Privilege Status as of November 2019 by Sales and Unique Licenses

Category	**Number Sales-months**	**Number unique licenses**
Active (Issued)	16267	432
Closed (permanent)	1641	74
Closed (temporary)	19	1
Pending (issued)	696	19
Pending (not issued)	272	9
Total	18906	535

Several figures below plot sales trends for individual dispensaries by privilege status.

Figure. Sample of dispensaries with "Closed permanent" privilege status (n=74 in total), blue lines mark the latest license "Issue date"

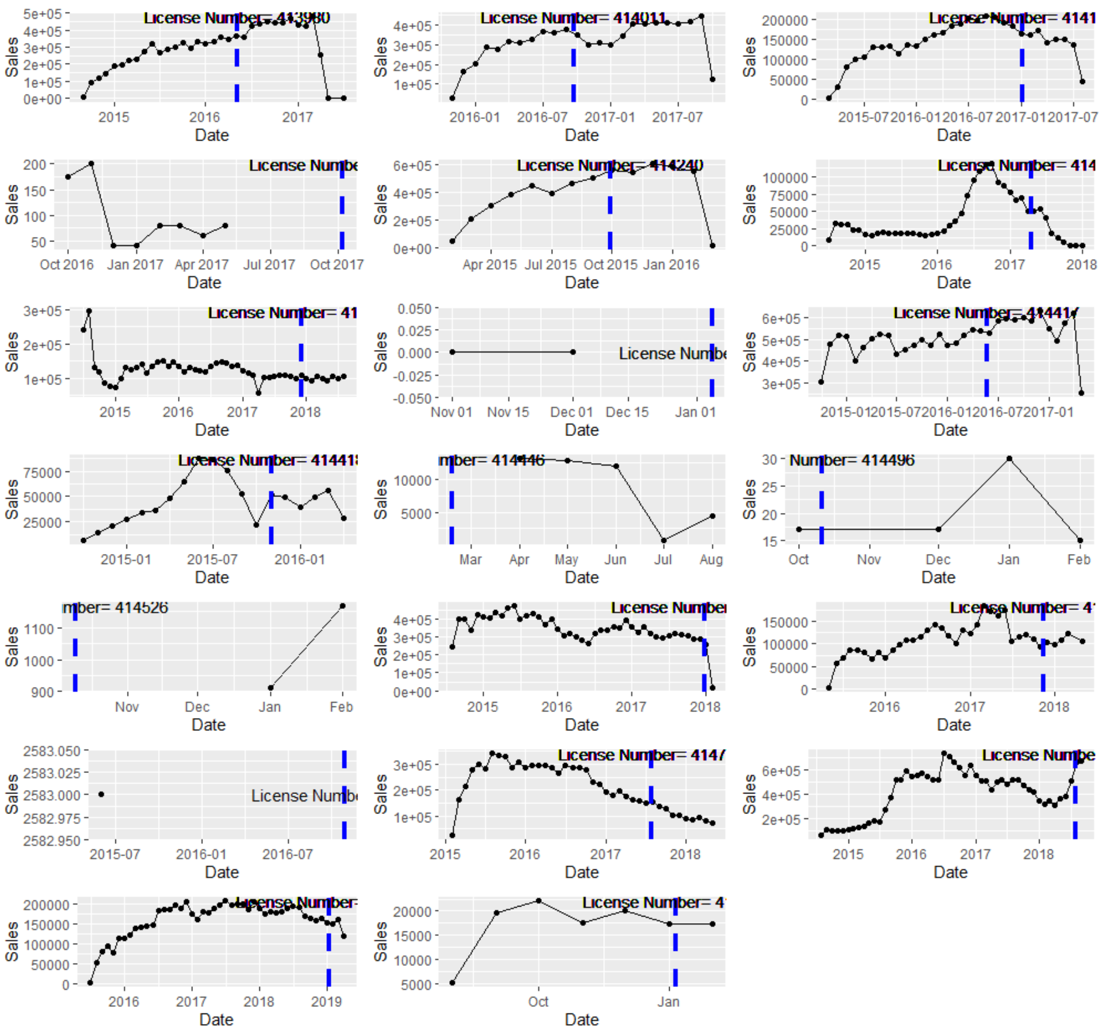


Figure. One dispensary with "Closed temporary", blue lines mark the license "Issue date"

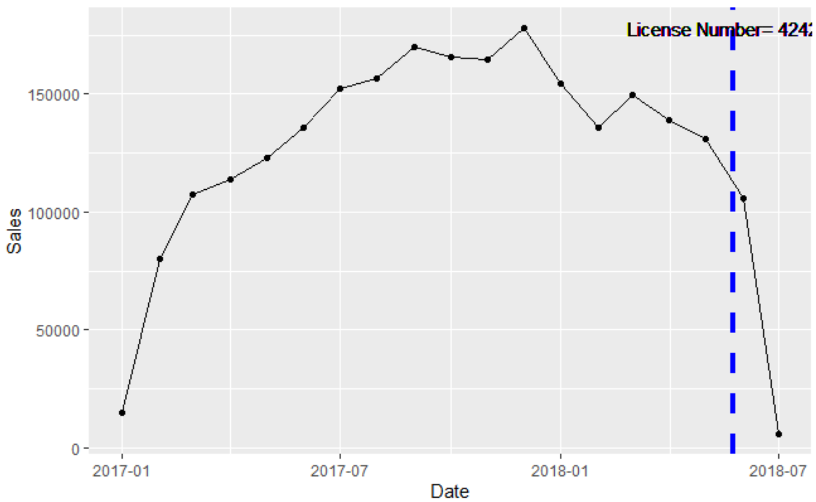


Figure. A sample of dispensaries with "pending issued" privilege status (n=19 in total), blue lines mark the license "Issue date"

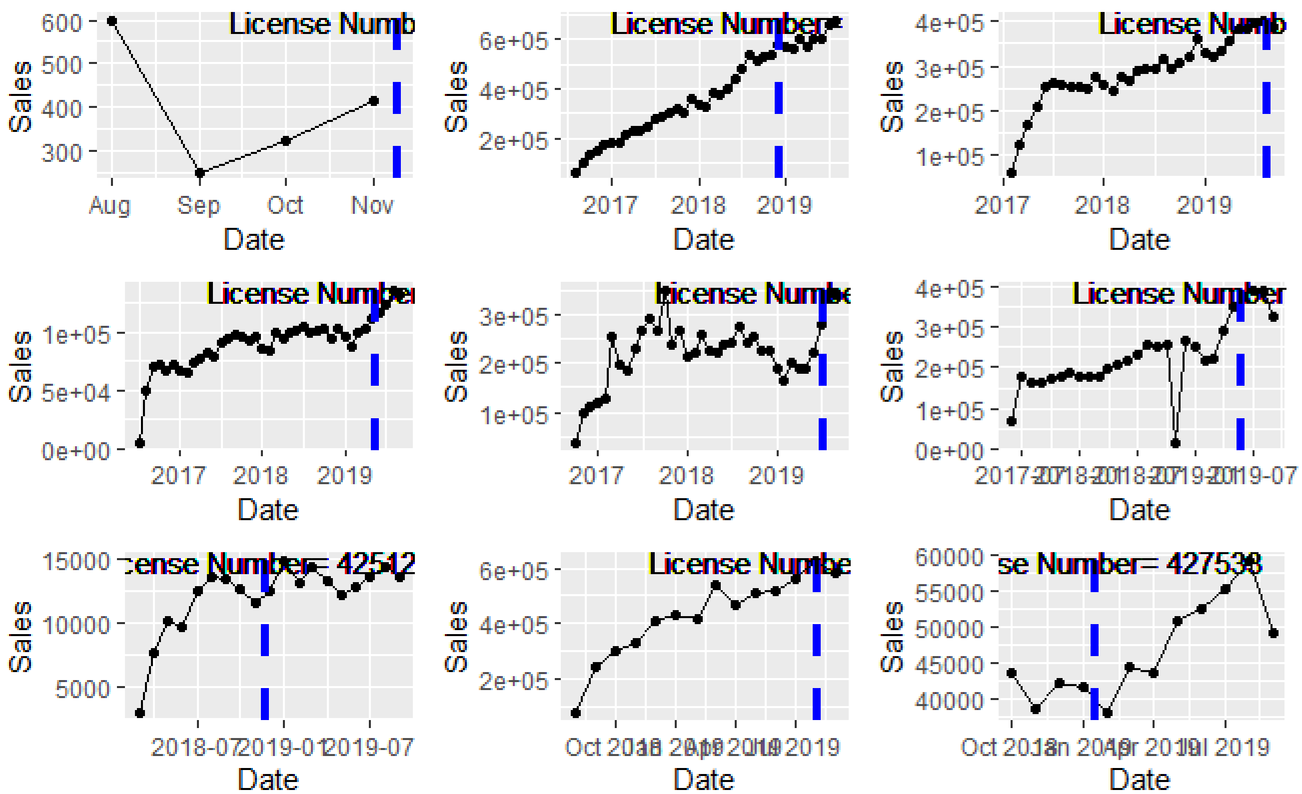
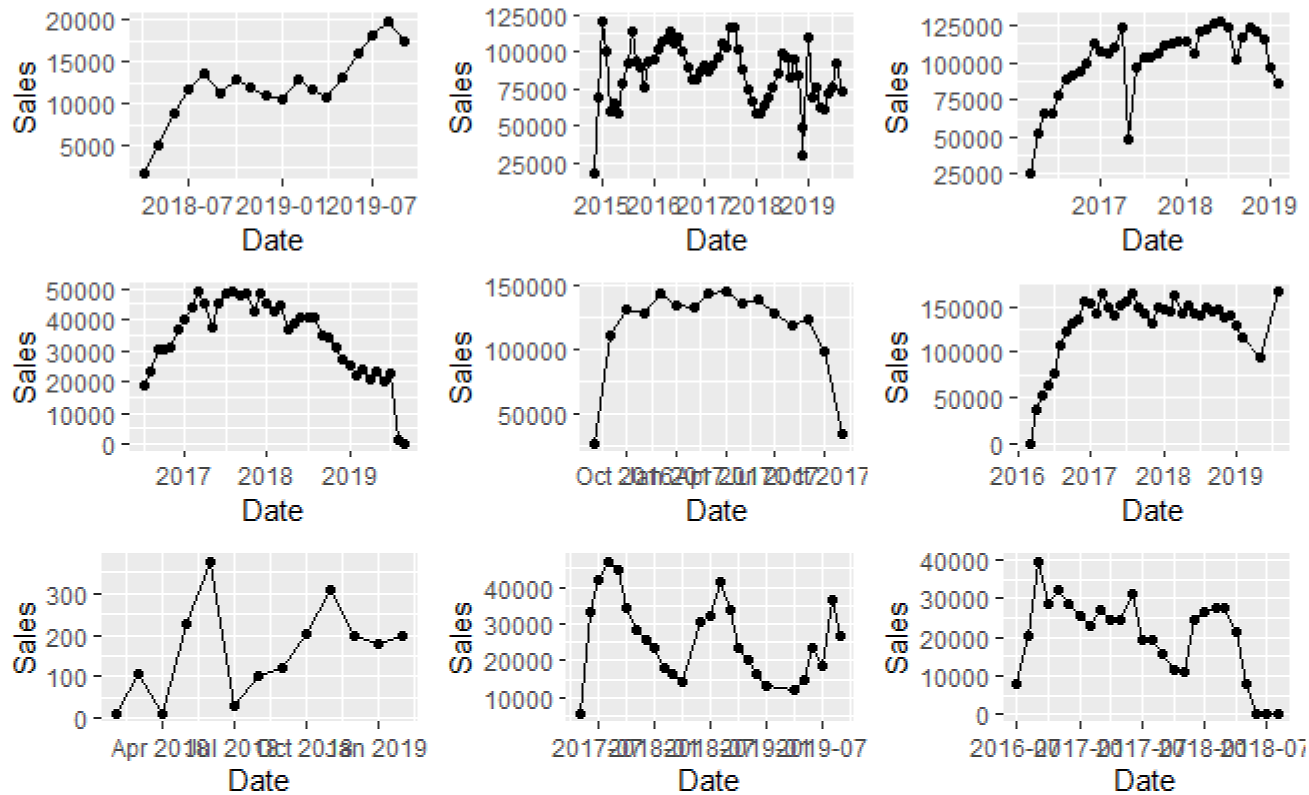


Figure. Dispensaries with "pending not issued" privilege status (n=9 in total)



5.1.5 *Covariates*

We included time-varying sociodemographic and economic variables in the model as described in the following table.

Table. Model variables

Variable	**Long Description**	**Method for inclusion in model**	**Dates of all available data**	**Dataset**
Outcome: Opioid dispensing	Long-term, acute, long-term high dose, new long-term opioid dispensing	Counts of persons using opioid	Q1 2012 – Q4 2018, quarter	Opioids
Population	Population offset for count variable model	Log transformed population	AHRF – 2012-2017, annual BREE – 2012-2019, annual	Opioids
Exposure: Cannabis total sales	Total sales of cannabis in $10K per 1000 population	Both stages, raw	July 2014 – September 2019, month	Sales
Instrument: Cannabis dispensary density	Count of active dispensaries per 1000 population	First stage, raw	July 2014 – September 2019, month	Licenses
Month	Fixed effect for quarter	Indicator variable	--	AHRF
County	Fixed effect for county	Indicator variable	--	AHRF
Age gender	Percent of population male or female and aged (<15, 15-19, 20-24, 25-44, 45-64, 65+)	Percent age (& gender), raw	2012-2017, annual	AHRF

Race	Percent white, percent non-white	Percent race, raw	2012-2017, annual	AHRF
Per capita income	Median per capita income	Raw	2012-2017, annual	AHRF
Household income	Median household income	Raw		
Unemployment	Percent of persons unemployed (population 16 years and over)	Percent unemployment, raw	2012-2018, annual	AHRF
Poverty	Percentage of persons in poverty	Percent poverty, raw	2012-2017, annual	AHRF
No health insurance (non-Medicare)	Percent of persons aged under 65 without with health insurance	Percent without health insurance, raw	2013-2017, annual	AHRF
Medicare	Percent Medicare prescription drug plan enrolled	Percent Medicare drug plan enrolled, raw	2012-2017	AHRF
Physician supply	Total count of active physicians per thousand population	Count of physicians, raw	2012-2017, annual	AHRF

Abbreviations: AHRF = Area Health Resource File

5.1.6 *Cannabis dispensary spatial data*

Distance is often used in modeling applications as an instrument as it is sufficient to explain exposure;[140] people who are closer to an exposure are more likely to be exposed and distance is not typically associated with outcomes. We evaluated distance from the center of each county's population density to the nearest cannabis dispensary, which did not necessarily need to be within county. We hypothesized that farther away dispensaries from the centers of population density would have lower levels of cannabis demand. We selected population density centers instead of county centroids because this is more a meaningful approximation of the distance an individual will travel.[141] In addition, it is unlikely that distance to dispensary impacts opioid dispensing other than through the causal pathway of interest.

We used the Geocoding Google application program interface (API) and the *ggmaps* R package to geocode the cannabis dispensaries from their given addresses. The resulting file was 546 rows of license number, dispensary name, and latitude and longitude coordinates. Of these rows, 11 were license numbers only, and do not have a given dispensary name or address, so we were not able to geocode.

We relied upon centroids of counties to generate distance- and time-related variables: Euclidean distance, driving distance, and driving time to dispensaries. We used publicly available data from the 2010 Census[142] which included coordinates of the population-weighted centroids of each county. To generate Euclidean distance in kilometers, we used the Distance Matrix Google API and the *sp* R package) command to estimate distances from centroids to each cannabis dispensary. The resulting file was 21294 rows (546 dispensaries for 39 counties). We then wrote a generic function to generate the minimum distance to a dispensary (in any county) for each county-month. The resulting dataset was 2468 rows.

To generate driving distance in kilometers and driving time in minutes, we used the Distance Matrix Google API and the "gmapsdistance" package in R. The resulting file was 21294 rows (546 dispensaries for 39 counties). We selected a single date and time to request driving time and distance data from the API despite the reality that driving distances and times vary with seasonality, day of the week, and time of day. Driving distance and time correspond to those estimated for a single date and time in the middle of the data range, Wednesday, February 1, 2017 at 1200H Pacific Standard Time (2000H Greenwich Mean Time). We then utilized the aforementioned function to generate the minimum driving distance and driving time for each county-month. We note that it is possible for a county-month to have a minimum driving time and distance that do not correspond to the same dispensary; however, this was typically not the case. Lastly, we generated these spatial data at the county-quarter level, aggregating over the distances and time values such that the quarters represent an average of the three corresponding monthly values.

5.1.7 *Retail license allotments*

We also reviewed data available from the LCB on the allotted number of licenses in WA jurisdictions.[139] We aggregated this data into counts allotted per county (a sum of allotments both in cities/towns and "at-large"). This data was added to the county-month level dataset containing sales and shops and varied depending on the date prior to and after a second round of licenses (see below). We also generated a variable that was the proportion of licenses utilized at a particular date. For example, if a county was allotted a maximum of 5 licenses, and had 4 active dispensaries, this value was 0.8. For further information, see 6.2.3.

5.1.8 *Integration of recreational and medical markets*

Several key changes occurred in the cannabis market during the time period of interest. These include a cannabis tax rate change (Q3 2015)[53], an increase in the number of available retail cannabis licenses (Q1 2016)[139], and the integration of medical and recreational retail markets (Q3 2016) as part of the Cannabis Patient Protection Act. Integration of cannabis markets dissolved the previous system in place for medical cannabis including closing collective gardens and shifting to award medical licenses to retail establishments. Thus, total cannabis sales in the period following this shift now reflect a subset of medical sales, and this issue extends to all of the post-Q2 2016 quarterly data by retail license used in this analysis. It does not appear to be possible to separate retail and medical sales at this time; however, these data may be available at the raw transaction level in state tracking systems.

Ultimately, this is only a problem in dispensaries that received a medical endorsement and began to sell medical product. Inclusion of a covariate that account for counts of dispensaries granted a medical endorsement may be possible; however, it appears that LCB provides data on current medical endorsements. In addition, this may be more of a problem in more densely populated counties such as King and Pierce which account for the largest proportion of medical cannabis sales (38% and 16% based on 2015 estimates).[143]

There may be some data to determine the proportion of total sales that medical cannabis comprises. Based on data prepared by the Department of Revenue, the sales that are exempt from sales tax due to being sales of medical cannabis only represent 1-2% of the total retail value.[144] This is in conflict with the estimate that medical cannabis made up 37% of the entire cannabis market in 2015[143]; however, this estimation was done on the data from the period prior to medical cannabis and under a differently structured system with different prices. This combined with the fact that there are very few issued medical cannabis licenses in Washington State relative to the potential size of the eligible population suggests that the integration of sales data will not heavily bias the results. A sensitivity analysis using the post-Q2 2016 data was not performed since it would half the available data.

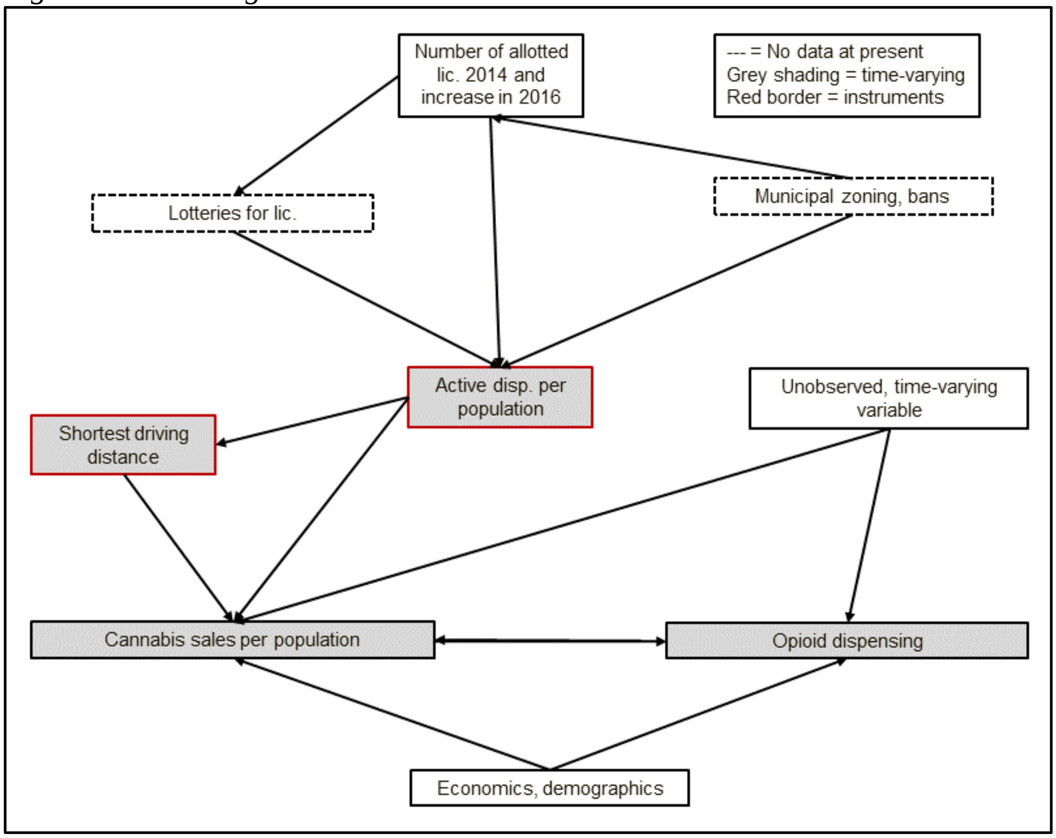
5.1.9 *Cannabis retail zoning*

Washington State cannabis retail zoning is evolving over time and may vary in the level of restrictions since jurisdictions are granted authority to regulate land usage. The Municipal Research Services Center (MRSC) collects information about cannabis regulation in Washington State.[80] One tool MRSC provides is an interactive map of the type of zoning ordinances which can display jurisdiction- or county-level status. Relevant to these analyses are jurisdiction-level ordinances that restrict the number of retail cannabis establishments. Unfortunately, MRSC could not provide a dataset with longitudinal changes in status. This type of tracking is also particularly complicated since ordinances differ widely in content and expiration and renewal dates. Figures of sales and dispensary density in the subset of states with some municipal ban over the study period are within 6.2.3.

Chapter 6. APPENDIX B. ADDITIONAL TABLES & FIGURES FOR ANALYSIS OF CANNABIS SALES AND OPIOID DISPENSING IN WASHINGTON STATE

6.1 CAUSAL MODEL

Figure. Causal diagram

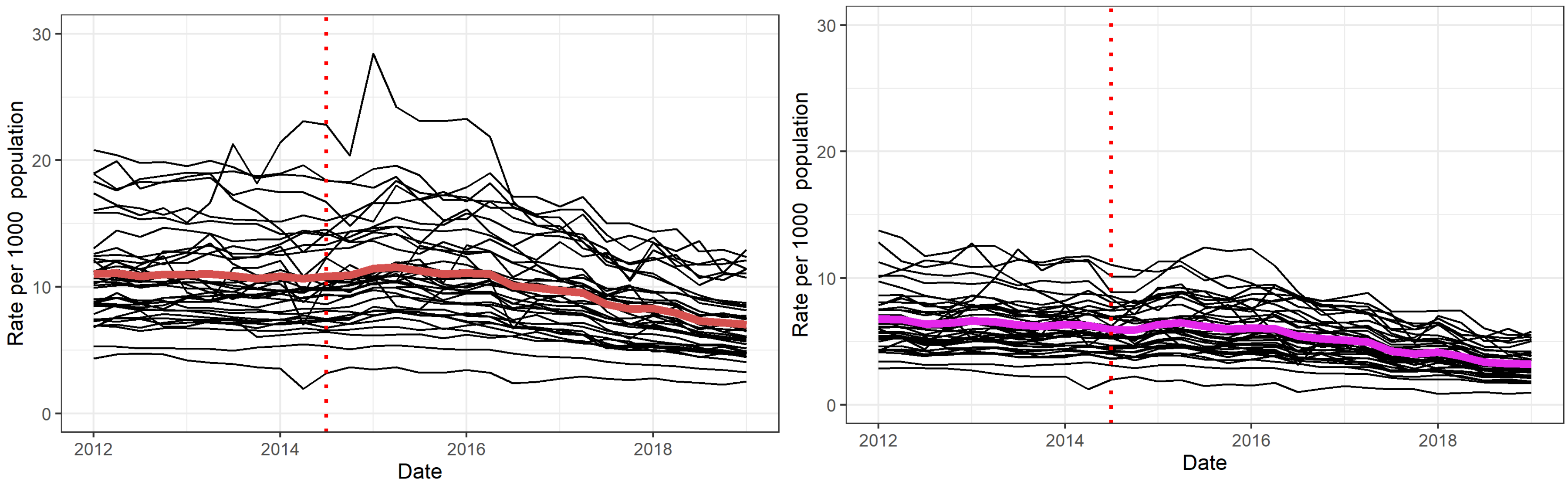


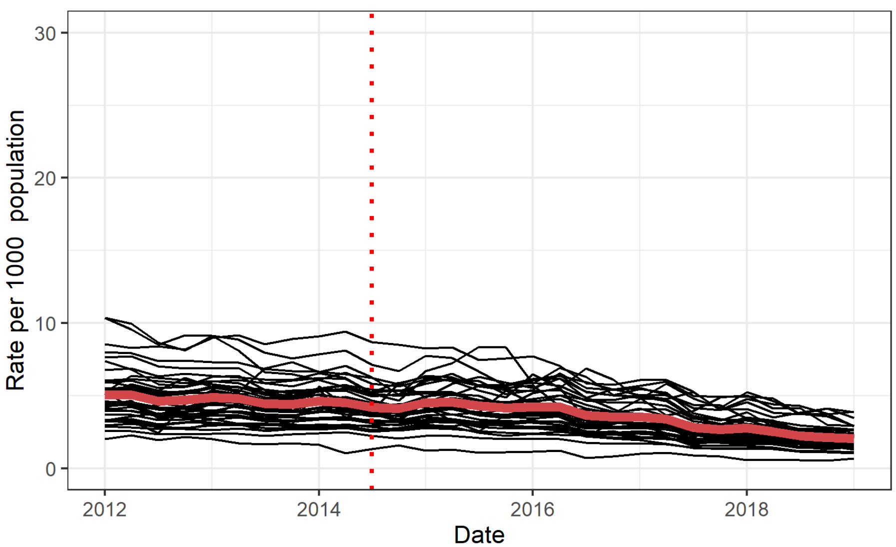
Abbreviations: disp = dispensary, lic = license

Notes: Municipal bans and zoning status around retail dispensaries are only reported via the Municipal Services Research Center and the zoning and ban status has changed over time. Municipal bans determined the increase in the number of allotted licenses in 2016. Data on lotteries for licenses in municipalities with greater applications than the number of allotted licenses is not publicly available; however, it is known that a lottery occurred within 95 municipalities.

6.2 ADDITIONAL OUTCOMES & ANALYSIS

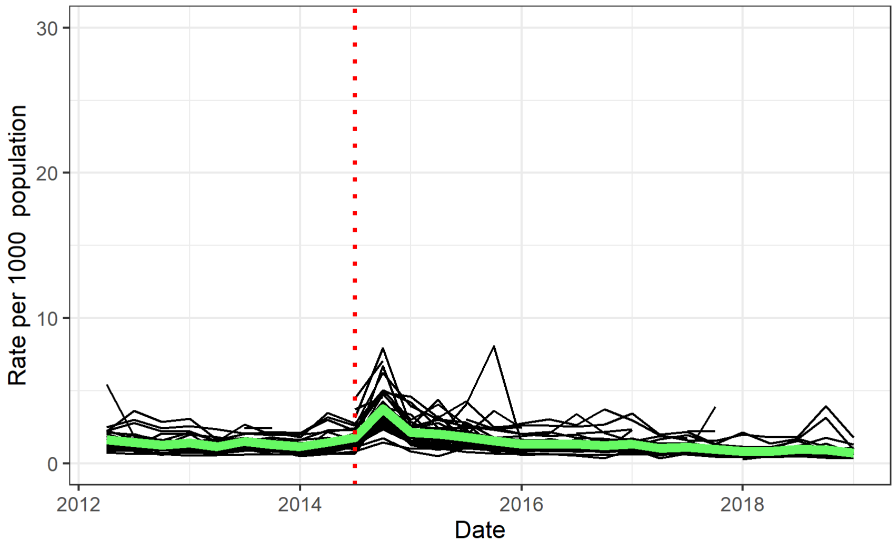
Figure. Changes in the rate of opioid dispensing in Washington State (2012-2018), high dose opioid outcomes





Abbreviations: MME = milligrams of morphine equivalent
Notes: Figures depict the rate of opioid dispensing across counties in Washington State for outcomes: long-term high dose 50 mme (upper left), long-term high dose 90 mme (upper right), and long-term high dose 120 mme (lower left). Dispensing outcomes were defined as: long-term high-dose = number of patients, per 1000 population, who have filled prescriptions for at least 60 days' supply of opioids during the quarter and whose prescriptions provided a dose of 50/90/120 mme/day or more, averaged over the quarter. Rates are age and gender adjusted. The solid-colored lines reflect the average, not-population adjusted rate. The dotted line reflects the timing of the first recreational cannabis dispensary opening in Washington State (2014-07-01).

Figure. Changes in the rate of new long-term opioid dispensing in Washington State (2012-2018)



Notes: The figure depicts the rate of opioid dispensing across counties in Washington State for new long-term opioid dispensing. This is defined as: new long-term = number of patients with long-term opioid prescriptions, per 1000 population, who were new opioid patients in the past quarter, and are long-term opioid patients (i.e., prescribed 60 or more days' supply) in the present quarter. Patients with no opioid prescriptions in the quarter prior to the previous quarter are excluded. Patients with tramadol prescriptions in the third and fourth quarters of 2014 were excluded as new opioid patients because of the possibility that they might have had long-term prescriptions. Rates are age and gender adjusted. The solid-colored line reflects the average, not-population adjusted rate. The dotted line reflects the timing of the first recreational cannabis dispensary opening in Washington State (2014-07-01). County-level rate data were missing for a number of county-quarters. Counties most likely to be missing data were Adams (n=1), Columbia (n=5), Ferry (n=3), Garfield (n=16), Lincoln (n=1), San Juan (n=2), Wahkiakum (n=14).

Table. Secondary outcomes: estimated effect of cannabis sales on the number of individuals dispensed long-term high dose and new long-term opioids in Washington State (2014-2017)

	IV. HD 50 MME dispensing		**V. HD 90 MME dispensing**		**VI. HD 120 MME dispensing**		**VII. New long-term dispensing**	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Outcome	1443	2203	791	1240	550	875	232	376
Population	183440	364999	183440	364999	183440	364999	183440	364999
Model	**Estimate**	**95%CI**	**Estimate**	**95%CI**	**Estimate**	**95%CI**	**Estimate**	**95%CI**
J. Naïve model controlling for population	**-163**	**[-235, -90]**	**-105**	**[-146, -63]**	**-79**	**[-109, -49]**	**-41**	**[-54, -27]**
K. Add clustering on county	-163	[-338, 13]	-105	[-213, 3]	-79	[-823, 65]	**-41**	**[-81, -1]**
L. Add fixed effect of time	-188	[-458, 81]	-108	[-2654, 48]	-76	[-188, 36]	-16	[-57, 26]
M. Add health insurance covariate	-262	[-530, 6]	-150	[-305, 5]	-106	[-218, 6]	-29	[-73, 15]
N. Add all covariates	-170	[-382, 42]	-92	[-212, 28]	-64	[-150, 22]	-23	[-63, 17]
O. Add county fixed effect	-4	[-38, 30]	-7	[-36, 22]	-7	[-31, 17]	-2	[-25, 21]
P. Add instrumental variable (2SLS)	43	[-25, 111]	39	[-18, 96]	32	[-15, 79]	39	[-22, 101]

Abbreviations: CI = confidence interval, HD= high dose, IV = instrumental variable, MME = milligrams of morphine equivalent, SD = standard deviation, 2SLS = two-stage least squares

Notes: Estimates are from subsequent linear models that are nested. All models from the second model onward include clustering on county. The interpretation of the estimate is for each $10K per 1000 population increase in cannabis sales, the change in the number of individuals dispensed opioids. Estimates that are bolded are statistically significant. Covariate adjusted models controlled for the following: proportion white, proportion living in poverty, proportion unemployed, median household income, median per capita income, proportion under age 65 that are uninsured, proportion of those eligible who are Medicare part D enrolled, and the number of active medical doctors per 1000 population.
*Confidence intervals from two stage models were generated from bootstrapped standard errors to account for uncertainty in two stages.

6.2.1 *Nonlinear models*

Table. Estimated effect of cannabis sales on the number of individuals dispensed opioids in Washington State (2014-2017), results from non-linear models

	I. Any opioid dispensing		**II. Short-term dispensing**		**III. Long-term opioid dispensing**	
	Mean	SD	Mean	SD	Mean	SD
Outcome	16684	29411	12678	23428	4007	6126
Population	183440	364999	183440	364999	183440	364999
Model	**Estimate**	**95%CI**	**Estimate**	**95%CI**	**Estimate**	**95%CI**
Linear models						
F. Add county fixed effect	81	[-220, 382]	79	[-176, 332]	3	[-52, 57]
G. Add instrumental variable 2SLS*	530	[-85,1147]	467	[-63,998]	64	[-56,183]
Negative binomial models						
H. Negative binomial model with fixed effects	76	[-55, 207]	85	[-0, 170]	-4	[-50, 42]
I. Negative binomial IV 2SRI*	-15	[-294, 264][1]	-35	[-253, 183][2]	-3	[-145, 138][3]

Abbreviations: CI = confidence interval, HD= high dose, IV = instrumental variable, MME = milligrams of morphine equivalent, SD = standard deviation, 2SLS = two-stage least squares, 2SRI = two-stage residual inclusion

Notes: The interpretation of the estimate is for each $10K per 1000 population increase in cannabis sales, the change in the number of individuals dispensed opioids. Estimates that are bolded are statistically significant. Covariate adjusted models controlled for the following: proportion white, proportion living in poverty, proportion unemployed, median household income, median per capita income, proportion under age 65 that are uninsured, proportion of those eligible who are Medicare part D enrolled, and the number of active medical doctors per 1000 population.*Normal-based confidence intervals from the two stage models were generated from bootstrapped standard errors to account for uncertainty in two stages.

[1]This non-linear two-stage model produced 575 non-convergences in 5000 bootstrap iterations. [2]This non-linear two-stage model produced 206 non-convergences in 5000 bootstrap iterations.[3]This non-linear two-stage model produced 368 non-convergences in 5000 bootstrap iterations.

Table. Secondary outcomes: estimated effect of cannabis sales on the number of individuals dispensed long-term high dose and new long-term opioids in Washington State (2014-2017), results from non-linear models

	IV. HD 50 MME dispensing		**V. HD 90 MME dispensing**		**VI. HD 120 MME dispensing**		**VII. New long-term dispensing**	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Outcome	1443	2203	791	1240	550	875	232	376
Population	183440	364999	183440	364999	183440	364999	183440	364999
Model	**Estimate**	**95%CI**	**Estimate**	**95%CI**	**Estimate**	**95%CI**	**Estimate**	**95%CI**
Linear models								
O. Add county fixed effect	-4	[-38, 30]	-7	[-36, 22]	-7	[-31, 17]	-2	[-25, 21]
P. Add instrumental variable 2SLS*	43	[-25, 111]	39	[-18, 96]	32	[-15, 79]	39	[-22, 101]
Negative binomial models								
Q. Negative binomial Model F	-12	[-33, 8]	**-17**	**[-32, -2]**	**-15**	**[-27, -3]**	1	[-8, 9]
R. Negative binomial IV 2SRI*	-21	[-91, 50][1]	-23	[-70, 21][2]	-22	[-62, 17][3]	3	[-24, 29][4]

Abbreviations: CI = confidence interval, HD= high dose, IV = instrumental variable, MME = milligrams of morphine equivalent, SD = standard deviation, 2SLS = two-stage least squares, 2SRI = two-stage residual inclusion

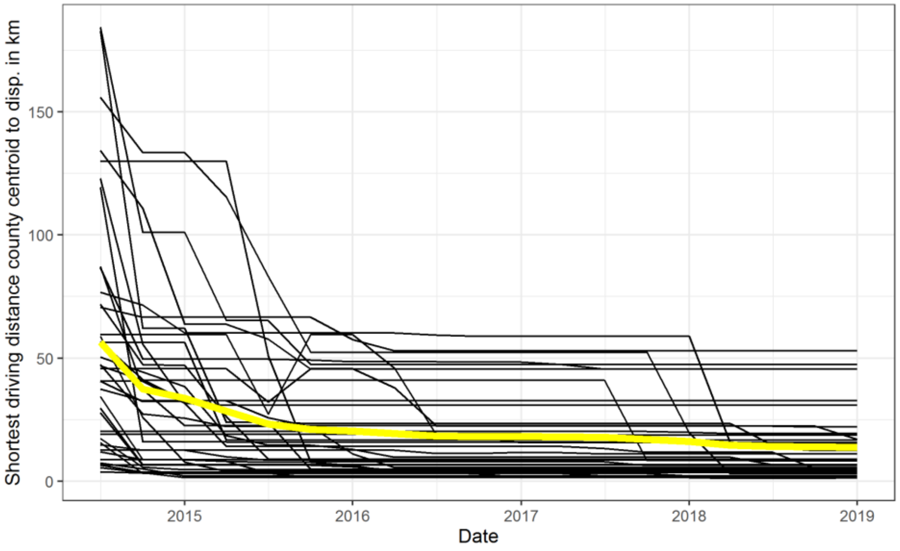
Notes: The interpretation of the estimate is for each $10K per 1000 population increase in cannabis sales, the change in the number of individuals dispensed opioids. Estimates that are bolded are statistically significant. Covariate adjusted models controlled for the following: proportion white, proportion living in poverty, proportion unemployed, median household income, median per capita income, proportion under age 65 that are uninsured, proportion of those eligible who are Medicare part D enrolled, and the number of active medical doctors per 1000 population.

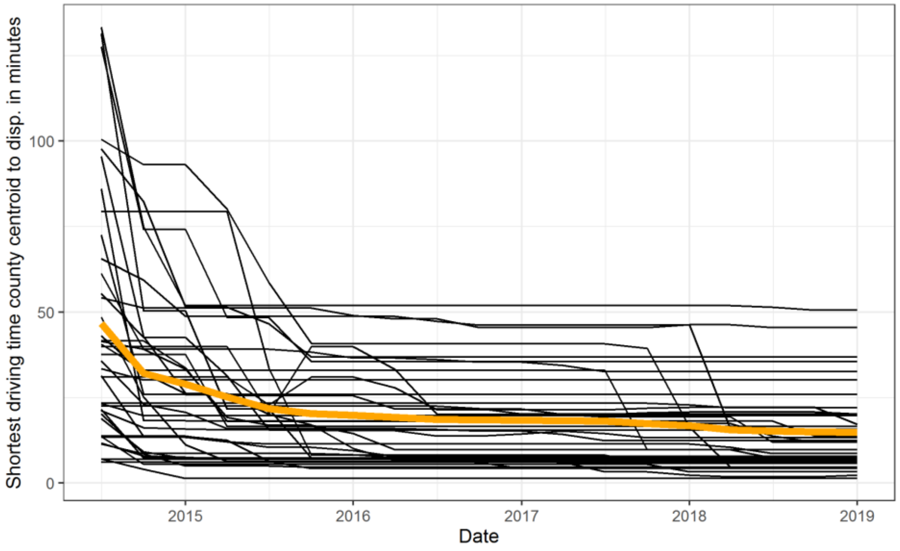
*Confidence intervals from the two stage models were generated from bootstrapped standard errors to account for uncertainty in two stages.

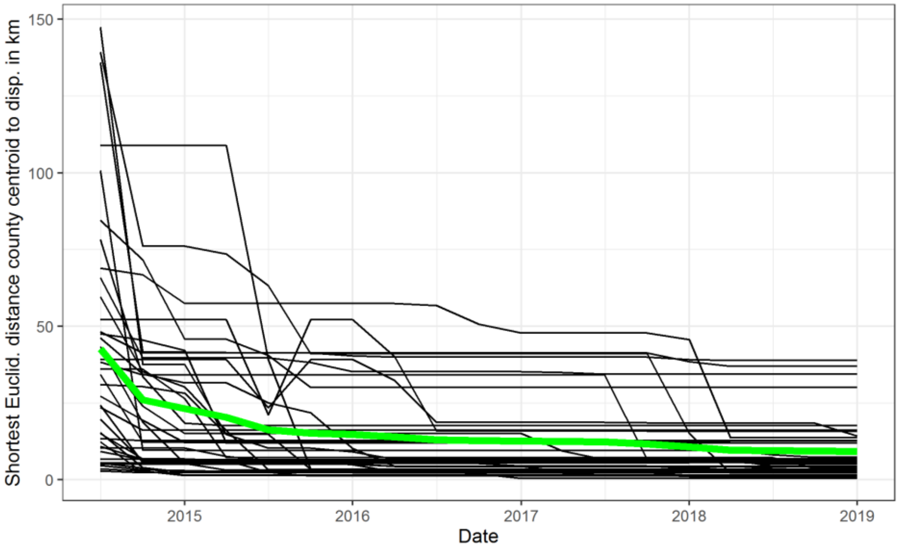
[1]This non-linear two-stage model produced 2045 non-convergences in 5000 bootstrap iterations. [2]This non-linear two-stage model produced 1355 non-convergences in 5000 bootstrap iterations. [3]This non-linear two-stage model produced 392 non-convergences in 5000 bootstrap iterations. [4]This non-linear two-stage model produced no non-convergences in 5000 bootstrap iterations.

6.2.2 *Access-related variables as potential instruments*

Figure. Changes in access to retail cannabis dispensaries in Washington State (2014-2018)







Notes: Figures depict cannabis retail dispensary access measures from the timing of the first dispensary opening (2014-07-01): driving distance (upper left), driving time (upper right), and Euclidean distance (lower left). Access measures were defined from the population-weighted county centroid to the nearest active dispensary in each quarter. Scales are not consistent across figures. The solid-colored lines reflect the average, not-population adjusted values.

Table. Follow-up (2017 Q4) retail cannabis dispensary access characteristics, across quintiles of the change in cannabis sales (n=39 counties) and overall in Washington State

Quantile of change in cannabis sales	**1**	**2**	**3**	**4**	**5**	**Overall**
Average difference in cannabis sales (Q4 2017 – Q3 2014), in $10K per 1000 population	0.51	2.03	2.81	3.43	5.20	2.95
Population	25555	86764	119290	521656	134579	178671
Euclidean distance (km)	26.3	17.0	5.7	3.0	5.8	11.7
Driving distance (km)	33.1	25.5	11.0	4.7	10.1	17.0
Driving time (minutes)	28.4	22.8	16.7	6.6	11.7	17.4

Table. Association of cannabis sales with cannabis with mean county-level driving distance to a dispensary in Washington State (2014-2017)

Model	**Estimate**	**95%CI**	**p-value**
Mean driving distance	-0.01	[-0.02, 0.003]	0.132
Adjusted R-squared	0.77	--	--
Partial R-squared	0.03	--	--
Robust F-test (1,38)	2.29	--	0.14
Test of endogeneity, F(1,38)	1.19	--	0.28

Abbreviation: CI = confidence interval

Notes: This first-stage linear model for use in two-stage models with instrumental variables included a fixed effect of time and county, clustering on county, as well as control for the following covariates: proportion white, proportion living in poverty, proportion unemployed, median household income, median per capita income, proportion under age 65 that are uninsured, proportion of those eligible who are Medicare part D enrolled, and the number of active medical doctors per 1000 population. Reported statistics account for county-level clustering.

Table. Association of cannabis sales with cannabis with the number of allotted licenses in Washington State (2014-2017)

Model	**Estimate**	**95%CI**	**p-value**
Number of allotted licenses	0.01	[-0.03, 0.05]	0.69
Adjusted R-squared	0.76	--	--
Partial R-squared	0.00	--	--
Robust F-test (1,38)	0.16	--	0.69
Test of endogeneity, F(1,38)	24.26	--	<0.001

Abbreviation: CI = confidence interval

Notes: This first-stage linear model for use in two-stage models with instrumental variables included a fixed effect of time and county, clustering on county, as well as control for the following covariates: proportion white, proportion living in poverty, proportion unemployed, median household income, median per capita income, proportion under age 65 that are uninsured, proportion of those eligible who are Medicare part D enrolled, and the number of active medical doctors per 1000 population. Reported statistics account for county-level clustering.

Table. Association of cannabis sales with cannabis with mean county-level driving distance to a dispensary and dispensary density in Washington State (2014-2017)

Model	**Estimate**	**95%CI**	**p-value**
Mean driving distance	-0.01	[-0.02, 0.00]	0.23
Number of shops per 1000 pop	14.43	[7.78, 21.08]	<0.01
Adjusted R-squared	0.81	--	--
Partial R-squared	0.20	--	--
Shea's adjusted partial R-squared	0.10	--	--
Robust F-test (1,38)	9.34	--	<0.001
Test of endogeneity, F(1,38)	2.14	--	0.15
Test of overidentification (Sargan)	3.29	--	0.07

Abbreviation: CI = confidence interval
Notes: This first-stage linear model for use in two-stage models with instrumental variables included a fixed effect of time and county, clustering on county, as well as control for the following covariates: proportion white, proportion living in poverty, proportion unemployed, median household income, median per capita income, proportion under age 65 that are uninsured, proportion of those eligible who are Medicare part D enrolled, and the number of active medical doctors per 1000 population. Reported statistics account for county-level clustering; however, we note that the Sargan test cannot accommodate county clustering.

6.2.3 *Licenses and Regional Bans*

Figure. Changes in proportion of active or pending cannabis retail licenses in Washington State (2014-2018)

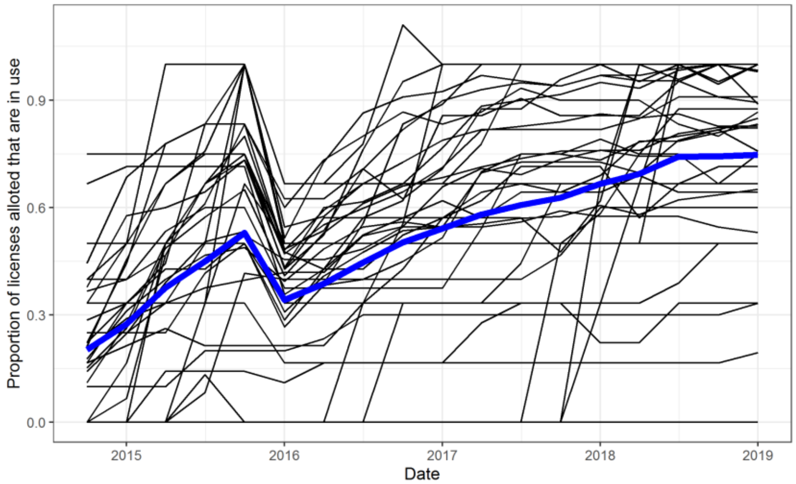


Figure. Allotted and active or pending cannabis retail licenses in Washington State (2014-2018)

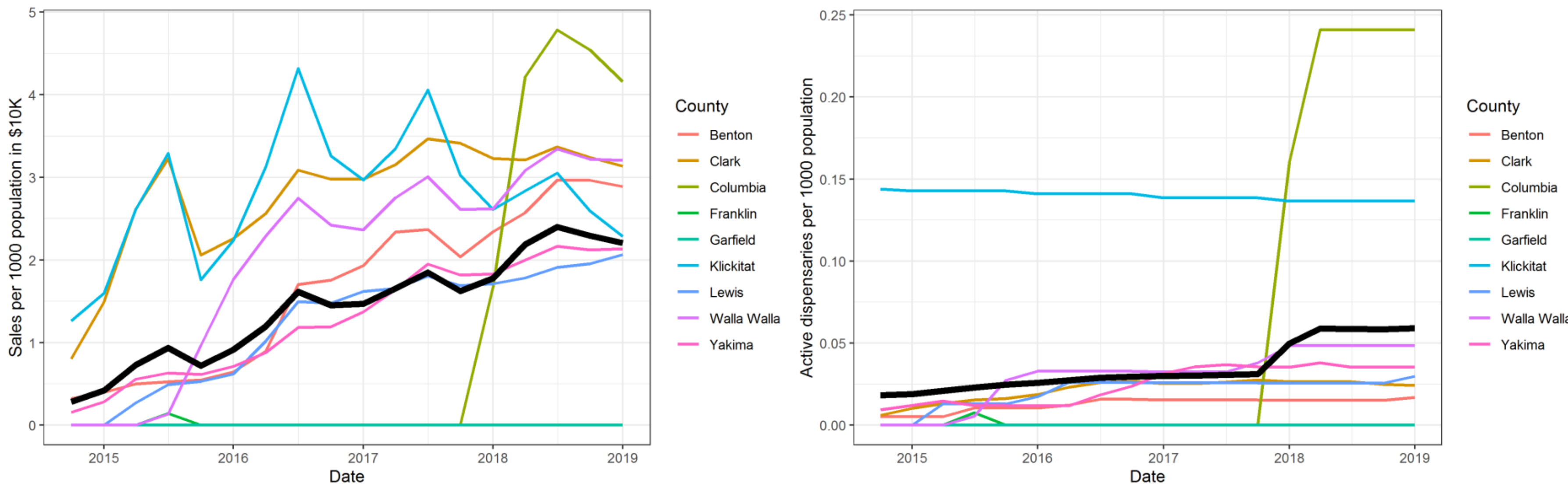
County	Average allotted licenses	Average proportion of active licenses	Average population
Adams	2.7	0.55	19703
Asotin	2.7	0.73	22214
Benton	10.0	0.25	192442
Chelan	7.4	0.78	76354
Clallam	8.9	0.73	73853
Clark	20.1	0.49	465312
Columbia	1.0	0.26	4099
Cowlitz	12.1	0.64	105576
Douglas	3.7	0.53	41046
Ferry	1.7	0.44	7731
Franklin	5.0	0.01	89661
Garfield	1.0	0.00	2218
Grant	9.9	0.58	95352
Grays Harbor	9.6	0.72	73164
Island	6.2	0.74	82472
Jefferson	6.2	0.80	31221
King	99.3	0.62	2123036
Kitsap	17.2	0.74	262881
Kittitas	5.4	0.70	44141
Klickitat	5.4	0.57	21471
Lewis	10.6	0.14	77342
Lincoln	2.7	0.22	10722
Mason	7.9	0.63	62941
Okanogan	7.2	0.59	42053
Pacific	2.7	0.89	21264
Pend Oreille	2.7	0.17	13362
Pierce	36.8	0.56	851024
San Juan	5.2	0.30	16455
Skagit	17.2	0.59	123337
Skamania	2.7	0.45	11628
Snohomish	57.4	0.49	780336
Spokane	28.8	0.82	497045
Stevens	6.2	0.64	44423
Thurston	18.9	0.81	274472
Wahkiakum	1.7	0.25	4031
Walla Walla	4.7	0.38	61126
Whatcom	25.1	0.70	214659
Whitman	6.2	0.54	48215
Yakima	14.0	0.45	252043

Allotted licenses available via: https://lcb.wa.gov/publications/Marijuana/MJ_Retail_Allocation_3-8-16.pdf

Table. Follow-up (2017 Q4) retail cannabis allotted and utilized licenses, across quintiles of the change in cannabis sales (n=39 counties) and overall in Washington State

Quantile of change in cannabis sales	**1**	**2**	**3**	**4**	**5**	**Overall**
Average difference in cannabis sales (Q4 2017 – Q3 2014), in $10K per 1000 population	0.51	2.03	2.81	3.43	5.20	2.95
Population	25555	86764	119290	521656	134579	178671
Allotted licenses	3.3	8.3	11.1	36.1	12.3	14.3
Proportion of allotted licenses used	0.2	0.6	0.7	0.8	0.9	0.6

Figure. Changes in cannabis sales per population and recreational cannabis dispensary density in Washington State (2014-2019) in counties with some form of municipal ban(s) during the study period



Notes: Figures depict the change in retail cannabis outcomes across counties in Washington State: sales per thousand population in $10K (upper left) and active dispensaries per thousand population (upper right). To be defined as an "active dispensary" in a given month, a dispensary must have had non-zero sales. The solid-colored black lines reflect the average, not-population adjusted values. Listed counties are those with some form of moratorium or ban on recreational cannabis dispensaries or sales during the study period.

Chapter 7. APPENDIX C. ADDITIONAL METHODS DETAIL FOR ANALYSIS OF CANNABIS POLICY AND USE OF MEDICATIONS FOR MENTAL HEALTH IN THE UNITED STATES

7.1 CANNABIS POLICY CHANGES

Table. Timing of cannabis policy changes

State	MC effective date	Active medical dispensaries date	Note	Reference for date of MC dispensaries	RC Effective Date	Active recreational dispensaries date	Reference for date of RC dispensaries
Alabama	0	0			0	0	
Alaska	1-Mar-99	0	Medical dispensaries not legally protected		24-Feb-15	Not allowed	
Arizona	1-Dec-10	1-Dec-12			0	0	
Arkansas	9-Nov-16	7-Aug-19		1	0	0	
California	1-Nov-96	1996			9-Nov-18	1-Jan-18	
Colorado	1-Jun-01	2005			10-Dec-12	1-Jan-14	
Connecticut	1-Oct-12	1-Aug-14			0	0	
Delaware	1-Jul-11	26-Jun-15			0	0	12
District of Columbia	27-Jul-10	1-Apr-13			26-Feb-15	Not allowed	
Florida	3-Jan-17	27-Jul-16		2	0	0	
Georgia	0	0			0	0	
Hawaii	1-Dec-00	8-Aug-17	Medical dispensaries not legally protected	3	0	0	13
Idaho	NA	0			0	0	
Illinois	1-Jan-14	1-Nov-15			1-Jan-20	1-Jan-20	
Indiana	0	0			0	0	14
Iowa	0	0			0	0	
Kansas	0	0			0	0	
Kentucky	0	0			0	0	
Louisiana	19-May-16	6-Aug-19		4	0	0	
Maine	1-Dec-99	1-Mar-11			30-Jan-17	9-Oct-20	15
Maryland	1-Jun-14	5-Jul-17			0	0	
Massachusetts	1-Jan-13	1-Jun-15			15-Dec-16	20-Nov-17	

Michigan	1-Dec-08	2009	Medical dispensaries not legally protected		6-Nov-18	1-Dec-19	
Minnesota	1-Jun-14	1-Jul-15			0	0	
Mississippi	0	0			0	0	
Missouri	6-Dec-18	0		5	0	0	
Montana	1-Nov-04	2009			0	0	
Nebraska	0	0			0	0	
Nevada	1-Oct-01	1-Dec-09			1-Jan-17	2-Jan-20	
New Hampshire	1-Aug-13	1-May-16			0	0	
New Jersey	1-Jul-10	1-Dec-12			0	0	
New Mexico	1-Jul-07	1-Jul-09			0	0	
New York	1-Jul-14	1-Jan-16			0	0	
North Carolina	0	0			0	0	
North Dakota	8-Nov-16	1-Mar-19		6	0	0	
Ohio	8-Sep-16	15-Jan-19		7	0	0	
Oklahoma	26-Jul-18	27-Jun-18		8	0	0	
Oregon	1-Dec-98	1-Jul-09			29-Mar-16	30-Sep-16	
Pennsylvania	12-May-16	14-Feb-18		9	0	0	
Rhode Island	1-Jan-06	1-Apr-13			0	0	
South Carolina	0	0			0	0	
South Dakota	0	0			0	0	
Tennessee	0	0			0	0	
Texas	0	0			0	0	
Utah	1-Dec-18	2-Mar-20		10	0	0	
Vermont	1-Jul-04	1-Jun-13			1-Jul-18	Not allowed	
Virginia	0	0			0	0	
Washington	1-Nov-98	2009	Medical dispensaries not legally protected		6-Dec-12	1-Jul-14	
West Virginia	1-Jul-19	0		11	0	0	
Wisconsin	0	0			0	0	

Wyoming	0	0			0	0	

Abbreviations: MC = medical cannabis, RC = recreational cannabis

Note: This table was adapted from data provided by Powell *et al.* 2015 and Shah *et al.* 2019. Recent changes were identified using the National Conference of State Legislatures (NCSL) State Cannabis Laws Tables, Weedmaps.com, and the Pro Con.org Table on Cannabis Legal Status. Additional information on the timing of dispensary opening was identified via the following media sources:

1. https://www.5newsonline.com/article/news/health/medical-marijuana-sales-50-million-arkansas/527-80450af7-e8d1-4ea5-bfbc-99cbb6785a0a
2. https://www.sun-sentinel.com/news/fl-ap-medical-marijuana-dispensary-20160726-story.html
3. https://www.cbsnews.com/news/hawaii-first-medical-marijuana-dispensary-maui-grown-therapies/
4. https://www.pbs.org/newshour/nation/louisiana-launching-medical-marijuana-after-years-of-waiting
5. https://www.bizjournals.com/stlouis/news/2020/08/03/when-missouri-dispensaries-will-begin-to-sell.html
6. https://www.mprnews.org/story/2019/03/01/medical-marijuana-first-debut-in-north-dakota
7. https://www.cleveland.com/open/2019/01/first-ohio-medical-marijuana-dispensary-opens-9-am-wednesday.html
8. https://ktul.com/news/local/first-oklahoma-medical-marijuana-clinic-opens-in-tulsa
9. https://www.phillymag.com/news/2018/02/14/medical-marijuana-dispensaries-pennsylvania/
10. https://abcnews.go.com/Health/wireStory/utahs-1st-medical-marijuana-dispensary-set-open-69337961
11. https://mjbizdaily.com/west-virginia-medical-marijuana-sales-start-delayed-until-2021-or-2022/
12. https://www.nbcchicago.com/news/local/history-made-first-legal-cannabis-sales-complete-as-dispensaries-open-in-illinois/2195119/
13. https://www.mlive.com/public-interest/2019/12/michigans-first-recreational-marijuana-customers-camped-outside-store-overnight.html
14. https://lasvegassun.com/news/2020/jan/02/marijuana-dispensary-opens-in-nevada-utah-border-c/
15. https://katu.com/news/local/this-dispensary-just-became-oregons-first-licensed-recreational-pot-retailer

7.2 STUDY SAMPLE

7.2.1 *Selection*

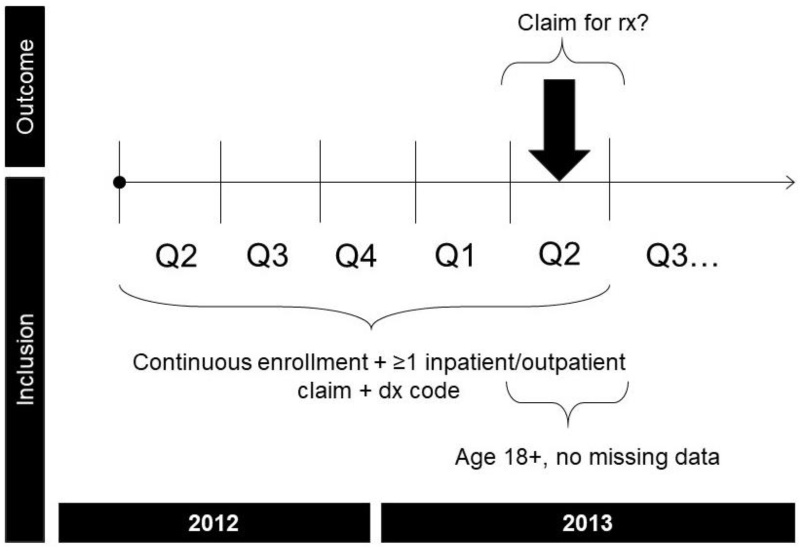


Figure. Example of the derivation of the study sample in a particular quarter

Table. Diagnosis codes of interest in diagnosis fields within Marketscan

ICD-9	ICD-10	Listing ICD-9	Listing ICD-10 (if different)	Category	Approximate ICD-10 to ICD-9	Approximate ICD-9 to ICD-10
30000	F419	Anxiety state, unspecified	Anxiety disorder, unspecified	Anxiety		
30001	F410	Panic disorder without agoraphobia	Panic disorder [episodic paroxysmal anxiety] without agoraphobia			
30002	F411	Generalized anxiety disorder				
30009	F418	Other anxiety states	Other specified anxiety disorders			F418
30009	F413	Other anxiety states	Other mixed anxiety disorders		30009	
29620	F329	Major depressive disorder, single episode – unspecified	Major depressive disorder, single episode, unspecified	Depression	29620 AND 311	F329
29621	F320	Major depressive affective disorder, single episode, mild				
29622	F321	Major depressive disorder, single episode – moderate				
29623	F322	Major depressive disorder, single episode – severe, without mention of psychotic behavior				
29624	F323	Major depressive affective disorder, single episode, severe, specified as with psychotic behavior	Major depressive disorder, single episode, severe with psychotic features		29624 AND 2980	F323
29625	F324	Major depressive affective disorder, single episode, in partial or unspecified remission				
29626	F325	Major depressive affective disorder, single episode, in full remission				
29630	F339	Major depressive affective disorder, recurrent episode, unspecified	Major depressive disorder, recurrent, unspecified			F339 AND F3340
29631	F330	Major depressive affective disorder, recurrent episode, mild				
29632	F331	Major depressive affective disorder, recurrent episode, moderate				
29633	F332	Major depressive affective disorder, recurrent episode, severe, without mention of psychotic behavior				
29634	F333	Major depressive affective disorder, recurrent episode, severe, specified as with psychotic behavior	Major depressive disorder, recurrent, severe with psychotic symptoms		29634 AND 2980	F333
29635	F3341	Major depressive affective disorder, recurrent episode, in partial or unspecified remission				
29636	F3342	Major depressive affective disorder, recurrent episode, in full remission				

2980	F333	Depressive type psychosis	Major depressive disorder, recurrent, severe with psychotic symptoms		29634 AND 2980	F323 AND F333
29630	F3340	Major depressive affective disorder, recurrent episode, unspecified	Major depressive disorder, recurrent, in remission, unspecified		29630	F339 AND F3340
2980	F323	Depressive type psychosis	Major depressive disorder, single episode, severe with psychotic features		19624 AND 2980	F323 AND F333
311	F329	Depressive disorder not elsewhere classified	Major depressive disorder, single episode, unspecified		29620 AND 311	F329
2720	E7800	Pure hypercholesterolemia	Pure hypercholesterolemia, unspecified (Effective October 2016)	Pure hypercholesterolemia	2720	E7800 AND 7801
2720	E7801	Pure hypercholesterolemia	Familial hypercholesterolemia (Effective October 2016)		2720	E7800 AND 7801
2720	E780	Pure hypercholesterolemia	Pure hypercholesterolemia (Effective October 2015 to September 2016)		2720	E7800 AND 7801

Abbreviations: ICD = International Classification of Diseases
Note: Not all codes of interest had perfect mapping from ICD-9 to ICD-10 and vice versa. Approximate mappings are listed in the final columns of the table. We used cross-walks available via https://www.hipaaspace.com/medical_billing/crosswalk.services/icd-10.to.icd-9.mapping/. When multiple alternative codes were indicated, we selected both codes. For example, ICD-10 F333 maps “single code-to-single code” to alternative #1 29634 and to alternative #2 2980.

Table. Enrollment and study samples (in millions), change in size across years

	Enrollment files	% Change	Our enrollment	% Change	PH Sample	% Change	Depression Sample	% Change	Anxiety Sample	% Change
# Enrollee-quarters			801,074,012		41,218,353		41,984,530		50,412,915	
2009	49.2									
2010	45.2	-8.13	104.50		6.0		4.6		4.1	
2011	52.2	15.49	107.11	2.50	5.7	-5.00	5.7	23.91	4.5	9.76
2012	53.1	1.72	124.70	16.42	6.4	12.28	5.9	3.51	6.2	37.78
2013	43.7	-17.70	96.69	-22.46	4.4	-31.25	4.6	-22.03	5	-19.35
2014	47.3	8.24	102.34	5.85	4.7	6.82	5.1	10.87	6.2	24.00
2015	28.3	-40.17	71.47	-30.17	3.2	-31.91	3.8	-25.49	4.9	-20.97
2016	27.9	-1.41	70.15	-1.85	3.1	-3.13	3.8	0.00	5.4	10.20
2017	26.1	-6.45	63.29	-9.78	2.6	-16.13	3.3	-13.16	5.1	-5.56
2018	27.1	3.83	60.84	-3.86	2.4	-7.69	3.5	6.06	5.4	5.88

Abbreviations: PH = pure hypercholesterolemia

Notes: The "Enrollment Files" column represents the Marketscan enrollment for each year with no exclusions/inclusions applied. The "Our enrollment" column represents the enrollment when we applied our inclusion/exclusion criteria (i.e., requiring a previous four quarters of continuous enrollment and enrollment in the given quarter).

7.2.2 *Enrollee counts*

Enrollment data within the Marketscan enrollment files are stored as indicators for months of enrollment. We translated this into quarters of enrollment. Each quarter within a year, the counts of individuals can increase or decrease as individuals are newly enrolled in or leave insurance plans. However, in most cases, individuals were typically enrolled for an entire calendar year. The study inclusion criteria require enrollment in the past four quarters and current quarter. This means that in a given quarter, an individual typically was enrolled continuously through the current year and previous year.

Based on annual enrollment files there are approximately 400M enrollee entries representing 146M enrollees across 2009 to 2018. Across years, there were distinct shifts in the sample size due to changes in the number of commercial claims data that Marketscan acquired and processed. This is particularly noteworthy across 2012/2013 (from 53M to 44M, 17% reduction) and 2014/2015 (from 47M to 28M, 40% reduction). Shifts in our enrollment sample and final samples reflected mostly similar declines (above Table) with some differences in magnitude. Including a fixed effect of year in models accounts for at least some of this potential effect.

There is limited publicly available information to understand the shifting sample of Marketscan. One future option would be to reweight the sample to the general population at each year. Marketscan does provide person-weights; however, these are available only at the region level. In order to derive state and demographic-specific weights, we could utilize the American Community Survey (ACS) or Medication Expenditure Panel Survey (MEPS) to anchor the samples to the general population with private insurance. Alternatively, very similar analyses could be undertaken using survey sampled data.

The differences in magnitude may be explained by methodological coding changes (i.e., ICD shift) and changes in the underlying population of enrollees with these diagnoses. Within annual datasets for outpatient claims, we identified enrollees with diagnosis codes of interest in DX1-DX4 fields. The switch from ICD-9 to ICD-10 occurred on October 1, 2015. We identified ICD-10 codes within 2015 data (expected) and ICD-9 codes within the 2016 data (not expected). As a result, we included all codes in the search within the datasets. However, it is possible that shifts in coding practices contribute to real differences in samples across 2015 and 2016. Counts may also increase/decrease due to real increases in disease prevalence over time. Also, there may be changes in the sample frame of enrollees with a particular diagnosis code. This may be attributed to shifting factors contributing to rates of diagnosis, for example, changes in diagnostic guidelines or reimbursement for particular codes.

7.3 Covariates

We utilized data from several sources to derive state-level covariates. An overview of the selected state-level covariates is shown in the below table. We used the Bureau of Economic Analysis (BEA) Interactive Data Tables to identify quarterly total per capital personal income. Density of medical doctors was identified using the Area Health Resource File (AHRF) 2018-2019 Access System. These data come from the American Community Survey (ACS). We extracted unemployment data from Bureau of Labor Statistics (BLS) using the Application Program Interface (API). These data were in the form as state-month, thus we averaged over three months sets to derive a quarterly measure.

Table. Selected state-level covariates

Dataset	**Level**	**Form**	**Note**	**Source**
Laws	State	Numeric	Quarter of policy change	Powell *et al.* 2015, Shah *et al.* 2019, online sources[1-4]
MSA and states	State	Codes	For coding purposes, from Marketscan (state)	BEA
Federal and nonfederal physicians	State-year (2010-2017)	Total active, requires population to calculate density	2010 is missing population; 2018 is missing for all data; Missing Puerto Rico	AHRF (ACS)
Unemployment	State-year (2010-2018)	Percentage	Missing Puerto Rico	BLS
Income 1	State-quarter	Numeric, per capita	Missing Puerto Pico	BEA
Income 2	MSA-year	Numeric, per capita	Also have population	BEA

Abbreviations: ACS = American Community Survey, AHRF = Area Health Resource File; BEA = Bureau of Economic Analysis; BLS = Bureau of Labor Statistics; MSA = metropolitan statistical area

Law information available via:

1. https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx
2. https://medicalmarijuana.procon.org/legal-medical-marijuana-states-and-dc/
3. https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx
4. https://weedmaps.com/learn/laws-and-regulations/

At the enrollee-level, we derived several covariates. The number of previous prescriptions was calculated from the sum of all claims in the past four quarters and the current quarter. A claim was considered duplicate if enrollee id, service date, and NDC number were the same. An enrollee's current CCI was derived based on both outpatient and inpatient claims with selected CCI diagnosis codes of interest in the past three quarters and current quarter. We further categorized CCI into CCI 0-1, 2, and 3+. Enrollees without previous prescription claims and without diagnosis codes were assigned zero for CCI and number of previous prescriptions.

Table. Component diagnosis codes for the Charlson Comorbidity Index

Diagnosis	**ICD-9 and ICD-10 Codes**	**Weight for calculating the CCI**
Myocardial infarction	'410','412', 'I21', 'I22','I252'	1
Congestive heart failure	'428', 'I43', 'I50', 'I099','I110','I132', 'I255', ‘I420', 'I425', 'I426', 'I427', 'I428', 'I429','P290'	1
Peripheral vascular disease	'441', '4439','7854','V434', 'I70', 'I71','I731', 'I738', 'I739', 'I771', 'I790', 'I792', 'K551','K558', 'K559','Z958', 'Z959'	1
Cerebrovascular disease	'430','431','432','433','434','435', '436','437','438', 'G45', 'G46', 'I60', 'I61', 'I62', 'I63', 'I64', 'I65','I66','I67','I68', 'I69', 'H340'	1
Dementia	'290', 'F00', 'F01', 'F02', 'G30', 'F051', 'G311'	1
Chronic pulmonary disease	'490','491','492','493','494','495','496','500','501','502','503','504','505','J40', 'J41', 'J42', 'J43', 'J44', 'J45','J46', 'J47', 'J60', 'J61', 'J62', 'J63', 'J64', 'J65', 'J66', 'J67', 'I278', 'I279', 'J684', 'J701','J703','5064'	1
Connective tissue disease (rheumatic)	'7100','7101','7104','7140','7141','7142', 'M05', 'M32','M33','M34', 'M06','M315', 'M351', 'M353', 'M360' '725', '71481'	1
Peptic ulcer disease	'531','532','533','534','K25', 'K26', 'K27', 'K28'	1
Mild liver disease	'5712','5715','5716','5714','B18', 'K73', 'K74', 'K700', 'K701', 'K702', 'K703', 'K709', 'K717', 'K713', 'K714', 'K715', 'K760', 'K762', 'K763', 'K764','K768','K769', 'Z944'	1
Diabetes without complication	'2500','2501','2502','2503','2507', 'E100', 'E101', 'E106', 'E108','E109', 'E110', 'E111', 'E116', 'E118', 'E119', 'E120', 'E121', 'E126', 'E129', 'E130', 'E131', 'E136', 'E138', 'E139', 'E140', 'E141', 'E146', 'E148', 'E149'	1
Diabetes with complications	'2504','2505','2506', 'E102', 'E103', 'E104', 'E105', 'E107', 'E112','E113', 'E114', 'E115', 'E117', 'E122', 'E123', 'E124', 'E125', 'E127', 'E132', 'E133', 'E134', 'E135', 'E137', 'E142', 'E143', 'E144', 'E145', 'E147'	2

Paraplegia and hemiplegia	'342', 'G81', 'G82', '3441', 'G041', 'G114', 'G801', 'G802', 'G830', 'G831', 'G832','G834','G839'	2
Renal disease	'582','583','585','586','588','N18','N19', 'N052','N053','N054','N055','N056','N057','N250','I120', 'I131','N032','N033','N034','N035', 'N036','N037','Z490','Z491','Z492', 'Z940','Z992'	2
Cancer	'140','141','142','143','144','145','146','147','148','149','150','151','152','153','154','155','156','157','158','159','160','161','162','163', '164','165','166','167','168','169','170','171','172','174','175','176','177', '178','179','190','191','192','193','194','195','196','197','198', '199','191','192','193','194','195','200','201','202','203','204','205','206','207','208','C00','C01','C02','C03','C04','C05','C06','C07','C08','C09','C10', 'C11', 'C12','C13','C14','C15','C16','C17','C18','C19','C20','C21','C22','C23','C24','C25','C26','C30','C31','C32','C33','C34','C37','C38','C39','C40', 'C41','C43','C45','C46','C47','C48','C49','C50','C51','C52','C53','C54', 'C55','C56','C57','C58','C60','C61','C62','C63','C64','C65','C66','C67', 'C68','C69','C70','C71','C72','C73','C74','C75','C76','C81','C82','C83', 'C84','C85','C88','C90','C91','C92','C93','C94','C95','C96','C97'	2
Moderate or severe liver disease	'5722','5723','5724','5725','5726','5727','5728', '4560','4561''K704','K711','K721','K729','K765','K766','K767','I850','I859','I864','I982', '45620','45621'	3
Metastatic carcinoma	'196','197','198', 'C77','C78','C79','C80', '1990','1991'	6
HIV/AIDS	'042','043','044', 'B20','B21','B22','B24'	6

Abbreviations: CCI = Charlson comorbidity index, ICD = International Classification of Diseases

7.4 Group-time average treatment effects for medical cannabis

7.4.1 *Limitations of traditional DID*

One key problem with our traditional DID approaches is that effect estimates from two-way fixed effects models give some weight to comparisons between newly treated units and those that have already been treated, along with desired comparisons of newly treated versus never treated and not-yet-treated units. In some scenarios, weights can be even negative which is problematic for overall effect estimation. Two-way fixed effects can thus lead to cases where treatment effects are negative overall but positive for individual units (or vice versa). In addition, these models are sensitive to group size, timing of treatment, and total time periods. Thus, we focused on the recently developed methods of Callaway & Sant'Anna (2020) [CS] to evaluate the robustness of the primary medical cannabis policy result for the outcome of antianxiety medication use in anxiety.

7.4.2 *Assumptions*

CS rely on several assumptions including stable treatment (i.e., treated units remain treated), no anticipation effects (or known effects), and parallel trends (or "pre-trends") where the average potential outcomes for a group treated at a given time and for a never treated groups would have followed parallel paths in all periods after treatment. CS breaks the average treatment effect in the treated into individual group-time treatment effects estimated with the never treated groups or not-yet-treated groups as counterfactuals. Importantly, CS does not impose any requirement of treatment effect heterogeneity across groups or time.

7.4.3 *Models*

We specified several models for medical cannabis policy using the group-time approach. The first was based on an unconditional assumption of parallel trends where we did not control for any covariates. We also specified a conditional model controlling for population, age, sex, density of physicians, income, and employment. Here we assumed that trends are parallel conditional on a set of pre-policy time-invariant characteristics. CS also derive "event study" type parameters which reflect averaging over group-time treatment effects for different lengths of an active medical cannabis policy. These are the analogue of dynamic treatment effects (i.e., lags and leads) in two-way fixed effects models where the effect estimates represent the effect of policies at different durations. Inspection of the magnitude and significance of the parameter estimates in the pre-policy period can provide support for “pre-trends” assumption.

We also included event study parameters that area an average treatment effect by duration of policy using a fixed set of states that have at least four quarters and 16 quarters of exposure. This approach was helpful to eliminate some problems due to heterogeneity and changing group composition over time, as well as evaluating the sensitivity to states that alter policies early in the study period. Lastly, we specified two forms of the model. The first used the states that never altered their medical cannabis policy for the counterfactual. The second incorporates the group of states prior to their policy change as well as the aforementioned group. These comparisons make slightly different assumptions, as noted in CS. While using not-yet-treated groups additionally as comparison units may improve inference, it also imposes restrictions on pre-policy trends for some groups, whereas the first form does not.

7.5 EVALUATING FIT IN SYNTHETIC CONTROL FOR RECREATIONAL CANNABIS ANALYSIS

We further evaluated the fit and robustness of the synthetic control results, specifically focusing on antianxiety medication use in enrollees with anxiety in Colorado.

7.5.1 *Donor states*

Based on best practices in synthetic control methods, predictor values for the treated state should fall between those for states within the donor pool. This issue can result in bias if there are nonlinear relationships that are strong between predictors and the outcome as demonstrated by Abadie et al.[117] In our case, predictors of antianxiety use in both Colorado and Washington were within ranges of those in the 24 donor pool states (data not shown).

7.5.2 *Predictor weights*

We utilized the default method for generating predictor weights, a regression-based method part of the *Synth* package. The optimal weights minimize the MSPE in the pre-policy period. For Colorado predictors, the lagged outcomes were the strongest predictors of the outcome, which is typical (table below). In the main model for Colorado, lagged outcomes were assigned approximately 20% each of the weight. The population and the proportion of the population with age between 30-50 were assigned the second highest weights (11% and 6%). Cross-validation methods for selecting predictor weights have been proposed by Abadie, Diamond, and Hainmueller (2015)[117] but optimal methods currently under study.

Table. Predictor weights for antianxiety use in Colorado

Predictor	Weight
Outcome Q1 2011	0.283
Outcome Q1 2012	0.204
Outcome Q1 2010	0.193
Age 30-50	0.105
Logged count of enrollees	0.058
Count of previous rx 60-180	0.039
Age 50+	0.027
Time since diagnosis 90-180	0.022
Unemployment	0.017

Income	0.016
CCI 2	0.015
CCI 3	0.013
Time since diagnosis 180+	0.004
Medical doctor density	0.003
Sex	0.000
Count of previous rx 180+	0.000

7.5.3 *Predictor selection*

We tested model sensitivity to the choice of outcome lags and predictors, looking at the RMSPE and fit in the pre-policy period, the synthetic state outcomes in the post-period, and the changes in donor states across models. The main model and the model selecting a different subset of quarters had the smallest RMSPE (table below), suggesting the best fit.

Pretreatment outcomes for synthetic states vary with the lagged outcome used in the model (figure below). As expected, the model containing no lagged outcomes and that with a single lagged outcome in quarter 6 tracked most poorly, though the synthetic control from all permutations of the model captured the downward trend preceding the policy change.

Choices about predictors impact the model RMSPE and outcomes because the weights change across models, particularly those that do not feature the same lagged quarters. For example, for antianxiety use in Colorado, Tennessee and Wyoming received high weights when lagged outcomes are considered in general but very low weights when lags are not considered. When no lags are considered, Michigan and Idaho were the most prominently weighted states, meaning that these states are similar on covariates of interest.

We did not evaluate sensitivity to different combinations of predictors because we preferred to prespecify these covariates. However, this is done in some cases and may produce improvements in the RMSPE and again change predictor weights and state weights. Removing all other (non-lagged) predictors increases the RMSPE, suggesting that these are indeed important covariates in the relationship of interest. In addition, nearly all states were assigned some weight, meaning that differentiating between a large subset of donor states was challenging.

Table. RMSPE for synthetic control models of Colorado with differing predictors and donor pool states

Model Number	**Model Description**	**RMSPE**
1	Main model: Q1,5,9 lagged outcome	0.00209
2	Q3,7,11 lagged outcome	0.00205
3	Q6 lagged outcome	0.00428
4	No lagged outcomes	0.00619
5	Average of lagged outcomes	0.00322
6	Only lagged outcomes	0.00315
7	Remove small states	0.00337

Abbreviations: Q = quarter, RMSPE = root means squared prediction error

Figure. Outcomes for synthetic Colorado with differing predictors and donor pool states

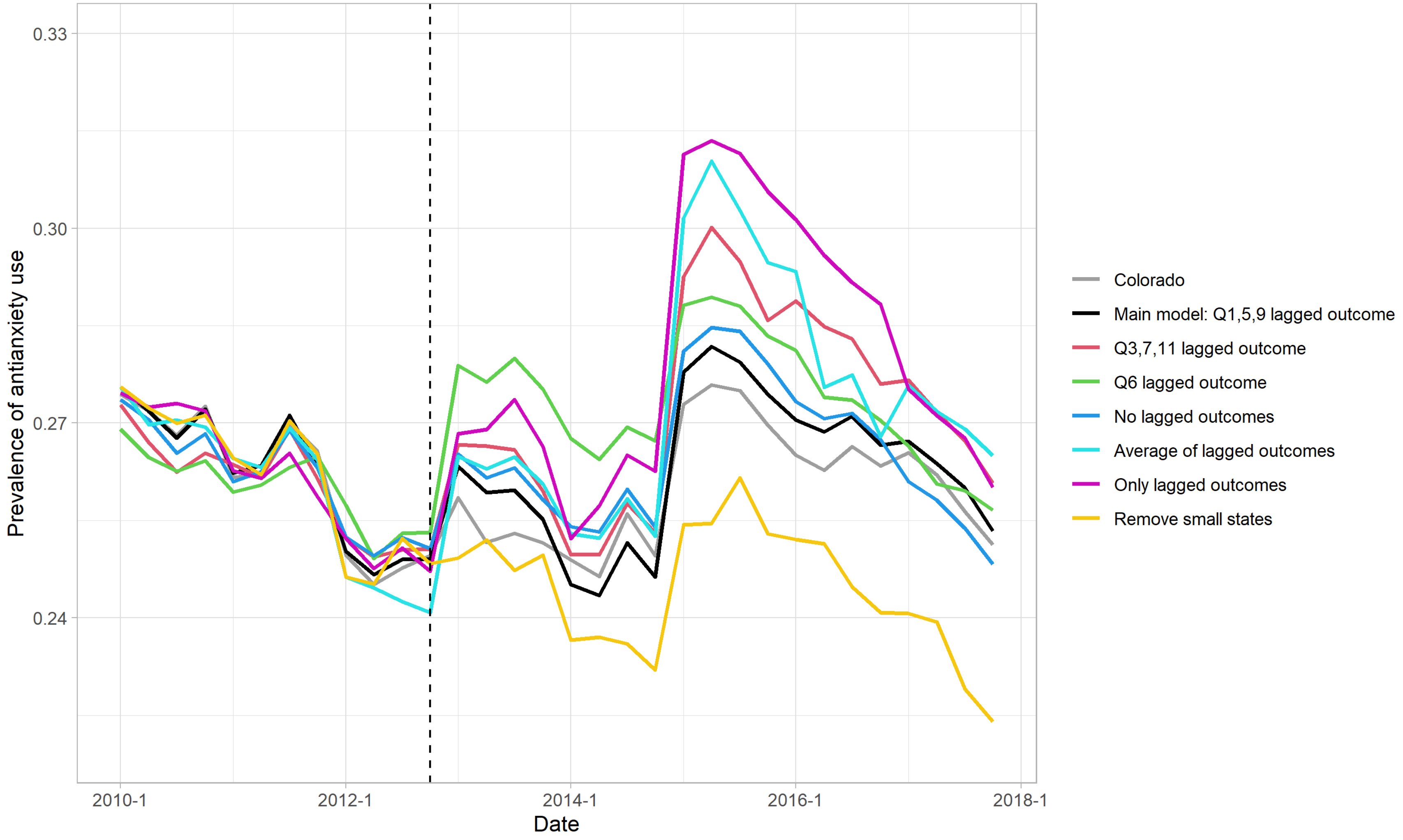


Table. State weights with differing predictors and donor pool states

State	Mod1 weight	Mod 2 weight	Mod 3 weight	Mod 4 weight	Mod 5 weight	Mod 6 weight
	Q1,5,9	**Q3,7,11**	**Q6**	**No lags**	**Average lags**	**Only lags Q1,5,9**
Alabama	0	0	0.073	0	0.002	0.022
California	0	0.155	0.184	0.002	0.065	0.017
Georgia	0.214	0	0	0.001	0.002	0.024
Hawaii	0	0	0.006	0.001	0.001	0.114
Idaho	0	0	0	0.213	0.002	0.017
Indiana	0	0	0	0	0	0.099
Iowa	0.026	0.1	0	0	0.002	0.067
Kansas	0	0.002	0	0	0.002	0.012
Kentucky	0	0	0	0	0	0.02
Michigan	0.168	0.013	0.003	0.319	0.097	0.013
Mississippi	0	0.109	0	0.2	0.002	0.008
Montana	0	0.002	0	0.001	0.004	0.008
Nebraska	0	0.035	0.243	0.082	0.009	0.013
New Mexico	0	0	0	0.001	0.001	0.012
North Carolina	0	0	0	0	0.001	0.015
Rhode Island	0	0	0.007	0.001	0.089	0.012
South Carolina	0	0	0	0	0	0.02
South Dakota	0	0	0	0.001	0	0.012
Tennessee	0.151	0.274	0.377	0	0.335	0.417
Texas	0	0	0	0.151	0.002	0.012
Vermont	0.006	0	0.001	0.002	0.002	0.014
Virginia	0.197	0.123	0	0.001	0.22	0.015
Wisconsin	0	0	0	0	0.001	0.014
Wyoming	0.237	0.187	0.105	0.023	0.159	0.021

Chapter 8. APPENDIX D. ADDITIONAL TABLES & FIGURES FOR ANALYSIS OF CANNABIS POLICY AND USE OF MEDICATIONS FOR MENTAL HEALTH IN THE UNITED STATES

Table. Average marginal effects of cannabis policy change on medication usage (2010-2017) from an enrollee-level model using a logistic specification and from state-level models removing states with small numbers of enrollees

	Antianxiety/anxiety		**Antidepressant/depression**		**Antihyperlipidemic/pure hypercholesterolemia**	
	Estimate (95%CI)	**SE**	**Estimate (95%CI)**	**SE**	**Estimate (95%CI)**	**SE**
Enrollee-level models	n=33,931,726		n=28,334,653		n=31,174,617	
Logistic specification	0.99 (-0.48, 2.46)	0.75	0.12 (-0.55, 0.79)	0.34	2.02 (-1.19, 5.23)	1.64
State-level models	n=1216		n=1216		n=1216	
Remove small states	0.27 (-0.79, 1.33)	0.20	-1.00 (-3.27, 1.27)	1.11	0.19 (-1.88, 2.26)	1.02

Abbreviations: CI = confidence interval, SE = standard error

Notes: Estimates (percentage points) are from logistic and linear models, respectively. In the logistic model, an individual's use of a medication was regressed as indicated in the model descriptions. Normal-based confidence intervals are given for the logistic model. Models included fixed effects of state and quarter. The demographic and economic covariate adjusted models controlled for the following enrollee-level characteristics: Age (18-29, 30-49, 50+), sex, Charlson Comorbidity (0-1,2, 3+), number of previous prescriptions (0-59, 60-180, 180+), time since most recent diagnosis (0-89, 90-179, 180+), and state-level characteristics: percent unemployment, median income, and the number of medical doctors per 1000 population. Coefficients are expressed as the average marginal effect of the medical cannabis policy change in percentage points. Estimates that are bolded are statistically significant at $p \leq 0.05$. Abbreviations: MC = medical cannabis, RC = recreational cannabis, SE = standard error

Table. Effect of medical cannabis policy change on antianxiety use in anxiety (2010-2017) from state-level models using methods of Callaway & Sant'Anna with never treated and not-yet-treated states as controls

	Unconditional model		Conditional model	
Effect parameter	**Estimate (95%CI)**	**SE**	**Estimate (95%CI)**	**SE**
Simple weighted average	-0.24 (-1.07, 0.59)	0.42	-1.14 (-3.42, 1.15)	1.17
Event study (aggregated)	-0.54 (-1.71, 0.63)	0.60	-2.35 (-6.17, 1.46)	1.95
Event study with balanced groups (4 quarters)	-0.18 (-0.62, 0.26)	0.22	-0.16 (-0.90, 0.57)	0.38
Event study with balanced groups (16 quarters)	0.05 (-1.14, 1.24)	0.61	-0.84 (-3.24, 1.56)	1.22

Abbreviations: CI = confidence interval, SE = standard error

Notes: Effect estimates (percentage points) are from models using methods of Callaway & Sant'Anna 2020 (CS). The simple weighted average is the weighted average of group-time treatment effects with the weights proportional to the group size. States without a policy change and states who have not yet changed their policy served as "never treated" and "not-yet-treated" controls, respectively, for states when they changed their medical cannabis policies. The "Event study"-type parameters reflect averaging over group time treatment effects for different lengths of an active medical cannabis policy. Event study-type parameters with balanced groups were estimated on the subset of states with a minimum length of exposure to medical policy (either at least 4 quarters or 16 quarters). Two models were specified: an unconditional model using no covariates, and a conditional model using covariates measured at a single pre-policy timepoint. Because the covariates are time-varying in the main difference-in-differences model, an average is used for CS models. Baseline covariates included the log of the count of enrollees, average levels of age (18-29, 30-49, 50+) and sex, and state-level characteristics: percent unemployment, median income, and the number of medical doctors per 1000 population.

Table. Effect of medical cannabis policy change on antidepressant use in depression (2010-2017) from state-level models using methods of Callaway & Sant'Anna with never treated and not-yet-treated states as controls

	Unconditional model		**Conditional model**	
Effect parameter	**Estimate (95%CI)**	**SE**	**Estimate (95%CI)**	**SE**
Simple weighted average	-1.24 (-3.16, 0.69)	0.98	-1.09 (-4.85, 2.66)	1.92
Event study (aggregated)	-1.85 (-4.37, 0.66)	1.28	-2.05 (-7.14, 3.04)	2.60
Event study with balanced groups (4 quarters)	-0.86 (-1.88, 0.17)	0.52	-0.61 (-2.34, 1.11)	0.88
Event study with balanced groups (16 quarters)	-0.33 (-3.51, 2.84)	1.62	-0.24 (-4.19, 3.70)	2.01

Abbreviations: CI = confidence interval, SE = standard error

Notes: Effect estimates (percentage points) are from models using methods of Callaway & Sant'Anna 2020 (CS). The simple weighted average is the weighted average of group-time treatment effects with the weights proportional to the group size. States without a policy change and states who have not yet changed their policy served as "never treated" and "not-yet-treated" controls, respectively, for states when they changed their medical cannabis policies. The "Event study"-type parameters reflect averaging over group time treatment effects for different lengths of an active medical cannabis policy. Event study-type parameters with balanced groups were estimated on the subset of states with a minimum length of exposure to medical policy (either at least 4 quarters or 16 quarters). Two models were specified: an unconditional model using no covariates, and a conditional model using covariates measured at a single pre-policy timepoint. Because the covariates are time-varying in the main difference-in-differences model, an average is used for CS models. Baseline covariates included the log of the count of enrollees, average levels of age (18-29, 30-49, 50+) and sex, and state-level characteristics: percent unemployment, median income, and the number of medical doctors per 1000 population.

Table. Average state-level prescription count and days supplied for several therapeutic classes from the larger sample of individuals with employer-sponsored insurance

	Mean total days supplied (SD) per quarter	**Mean days supplied per enrollee quarter**	**Mean total prescriptions (SD) per quarter**	**Mean prescriptions per 1000 enrollees (SD) per quarter**
Antihyperlipidemic	3907103 (4747427)	6.31 (1.48)	78329 (98424)	122.6 (27.85)
Antidepressant	4050441 (4392189)	7.3 (2.08)	98043 (108336)	172.89 (44.96)
Opiate agonist	860675 (1062620)	1.38 (0.54)	60680 (75565)	99.04 (32.49)
Opiate partial agonist	49662 (55208)	0.09 (0.06)	2176 (2399)	4.17 (2.87)
Barbiturate	9847 (12864)	0.02 (0.01)	270 (351)	0.42 (0.18)
Benzodiazepine	726392 (878782)	1.15 (0.37)	28207 (33778)	45.43 (12.02)
Other ASH	697300 (869591)	1.18 (0.31)	22104 (27450)	37.22 (10.03)

Abbreviations: ASH = anxiolytic sedative hypnotic, SD = standard deviation

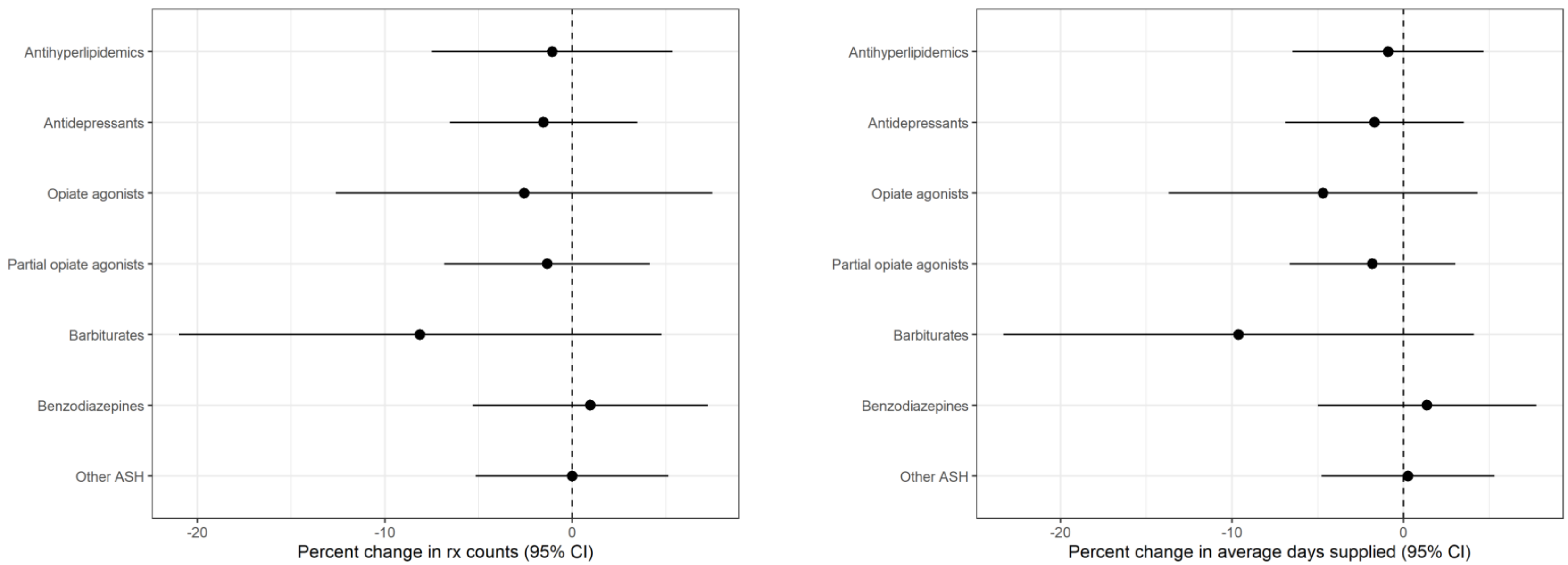


Figure. Effect of medical cannabis policy change on state-level prescription counts and total days supplied, in the larger sample of individuals with employer-sponsored insurance, secondary analysis

Notes: Plotted estimates are from separate log linear models of counts and days supplied per enrollee for each medication class. All models were adjusted for the presence of a recreational cannabis policy. Demographic and economic covariate adjusted models controlled for average levels of the following aggregated enrollee characteristics: proportion in age groups (18-29, 30-49, 50+), sex, employment status, the natural log of the number of enrollees, and state-level characteristics: percent unemployment, median income, and the number of medical doctors per 1000 population. Estimates are expressed as the percent changes in outcomes given a medical cannabis policy change. Abbreviations: CI = confidence interval

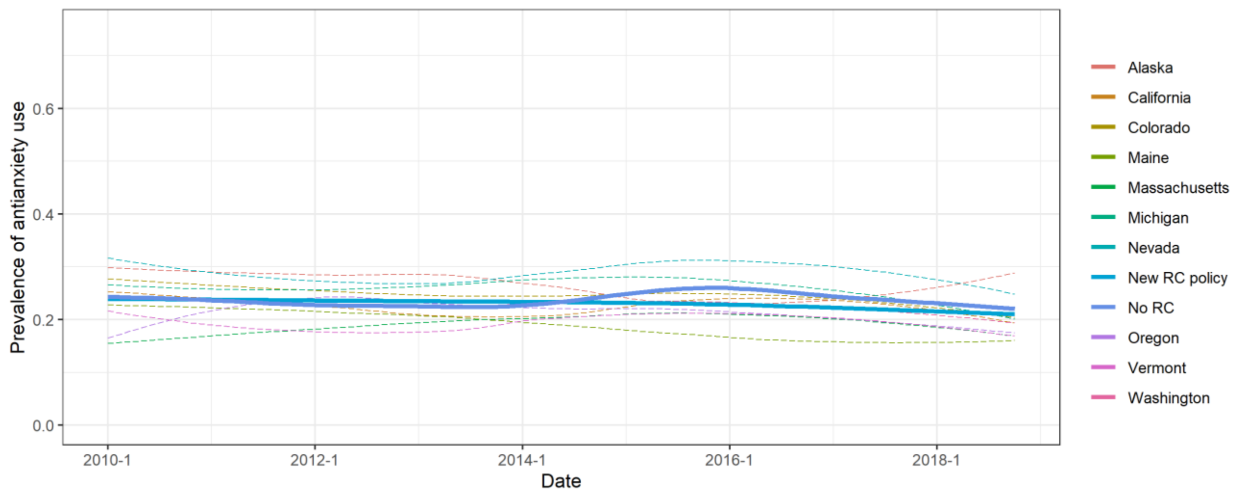


Figure. Smoothed prevalence of antianxiety use among enrollees with anxiety within US states, by recreational cannabis policy status and in individual states with recreational policy change in 2010-2018

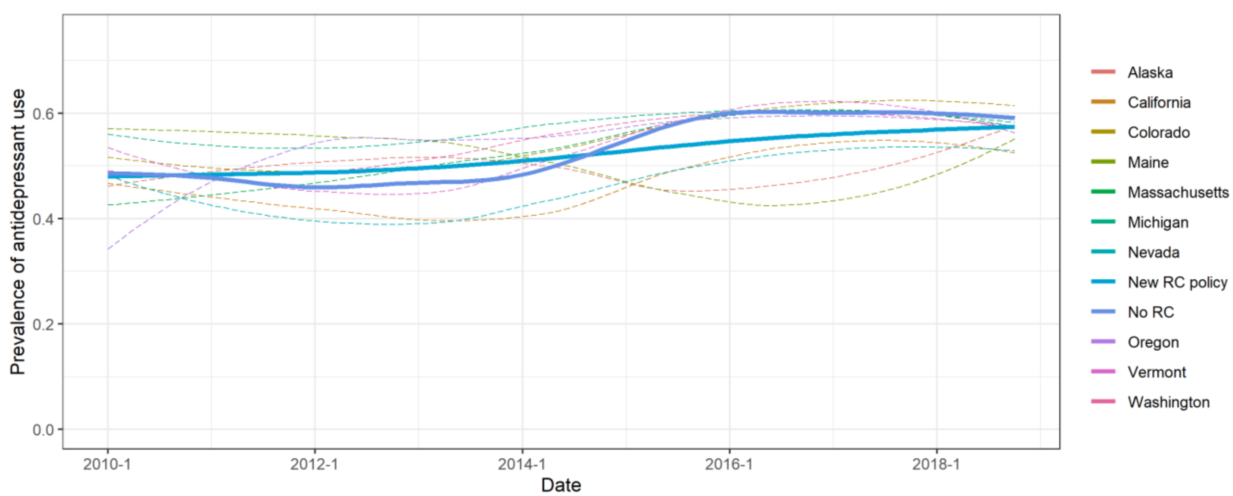


Figure. Smoothed prevalence of antidepressant use among enrollees with depression within US states, by recreational cannabis policy status and in individual states with recreational policy change in 2010-2018

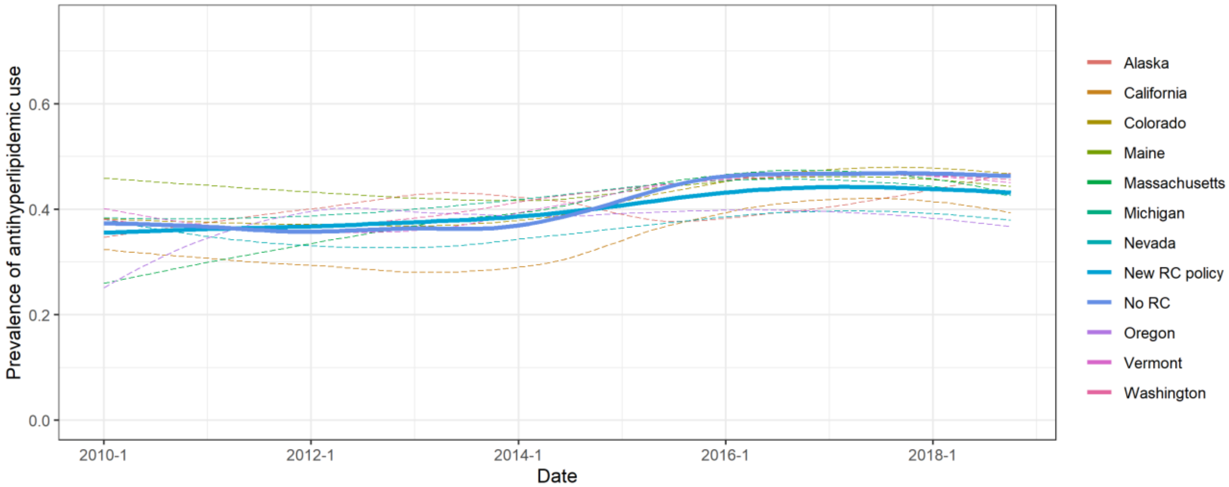


Figure. Smoothed prevalence of antihyperlipidemic class use among enrollees with pure hypercholesterolemia within US states, by recreational cannabis policy status and in individual states with recreational policy change in 2010-2018

Notes: In the above figures, curves represent LOESS smoothed state-level quarterly prevalence over time. Trends are greatly impacted by the sample size within each state-quarterly sample. Plotted curves represent locally estimated scatterplot smoothed state-quarterly prevalence over time. Thicker lines indicate averages over groups of states defined by medical cannabis status that are unadjusted for counts of individuals. "New RC policy" consists of the 10 states with a recreational policy change between 2010 and 2018, "No RC" the 41 states with no recreational cannabis. Dashed lines represent the individual states within the "New RC" group. Abbreviations: RC = recreational cannabis

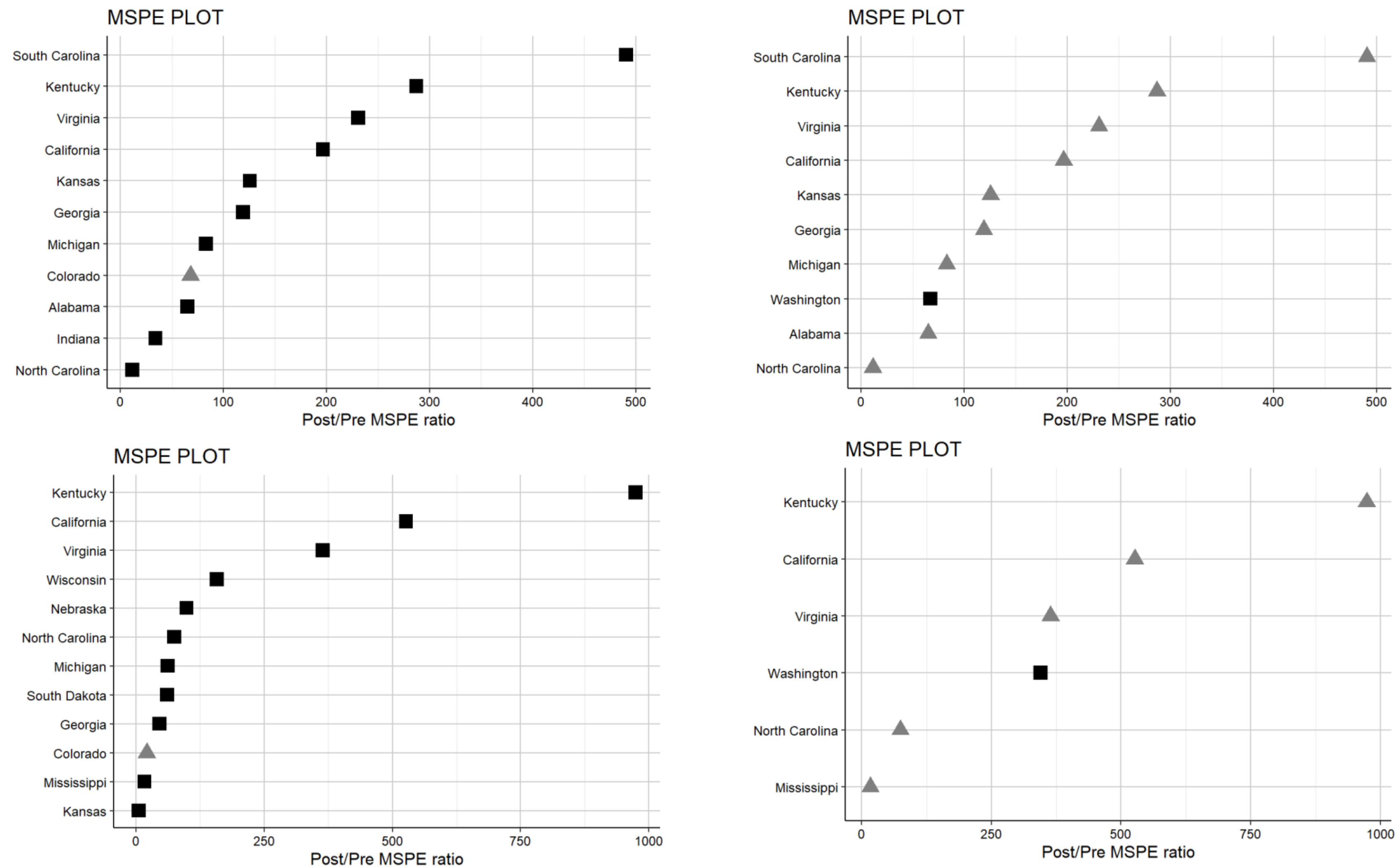


Figure. Mean squared prediction error ratios from placebo test models evaluating the effect of recreational cannabis dispensary opening on medication use outcomes from state-level placebo models using a synthetic control modelling approach

Notes: In the above figure, the top panel represents the synthetic control model-based estimates of post- to pre-policy mean square prediction error. The top panel reflects antianxiety use in anxiety and the bottom panel antidepressant use in depression. High ratios are indicative of large treatment effects.

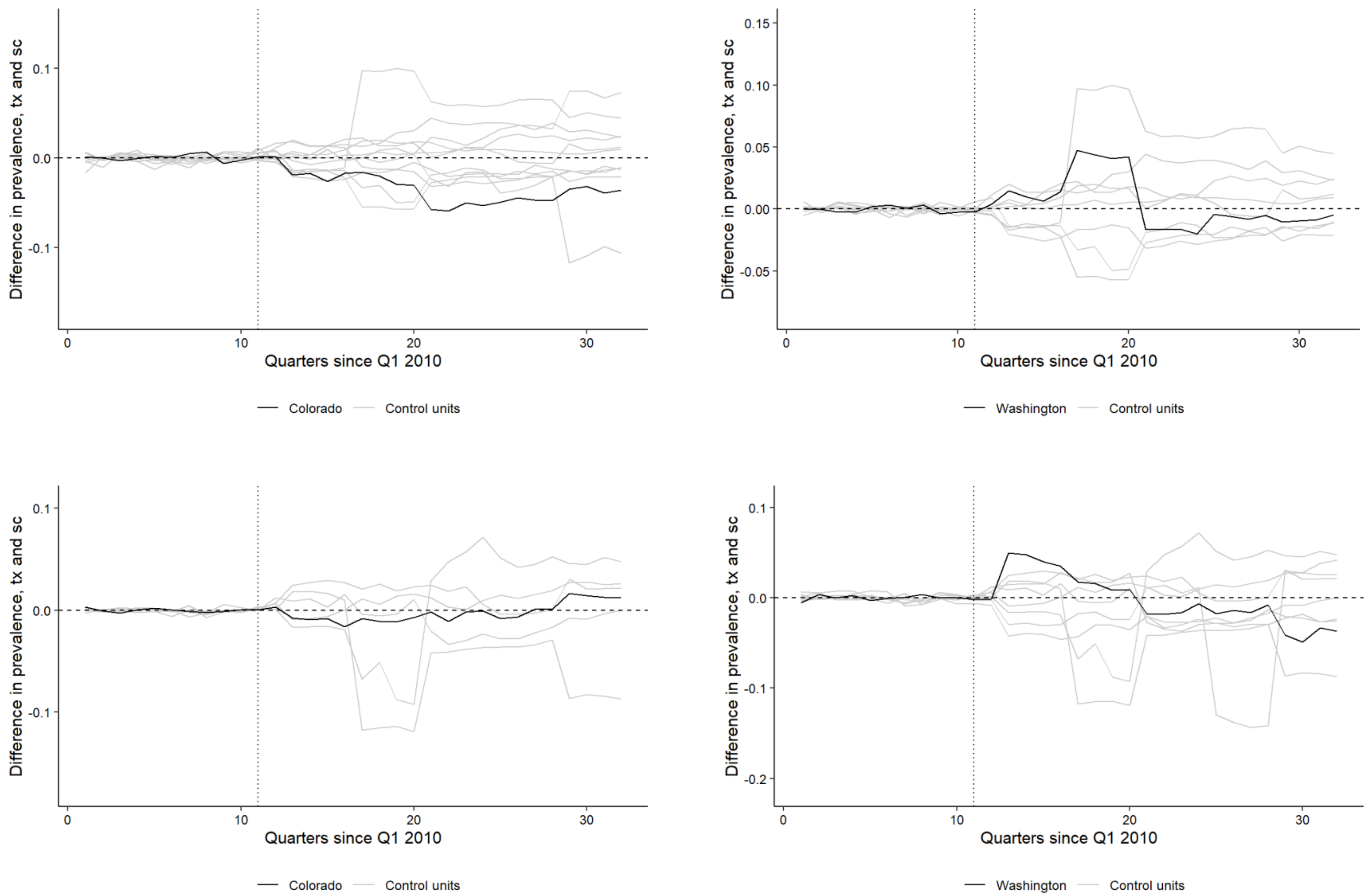
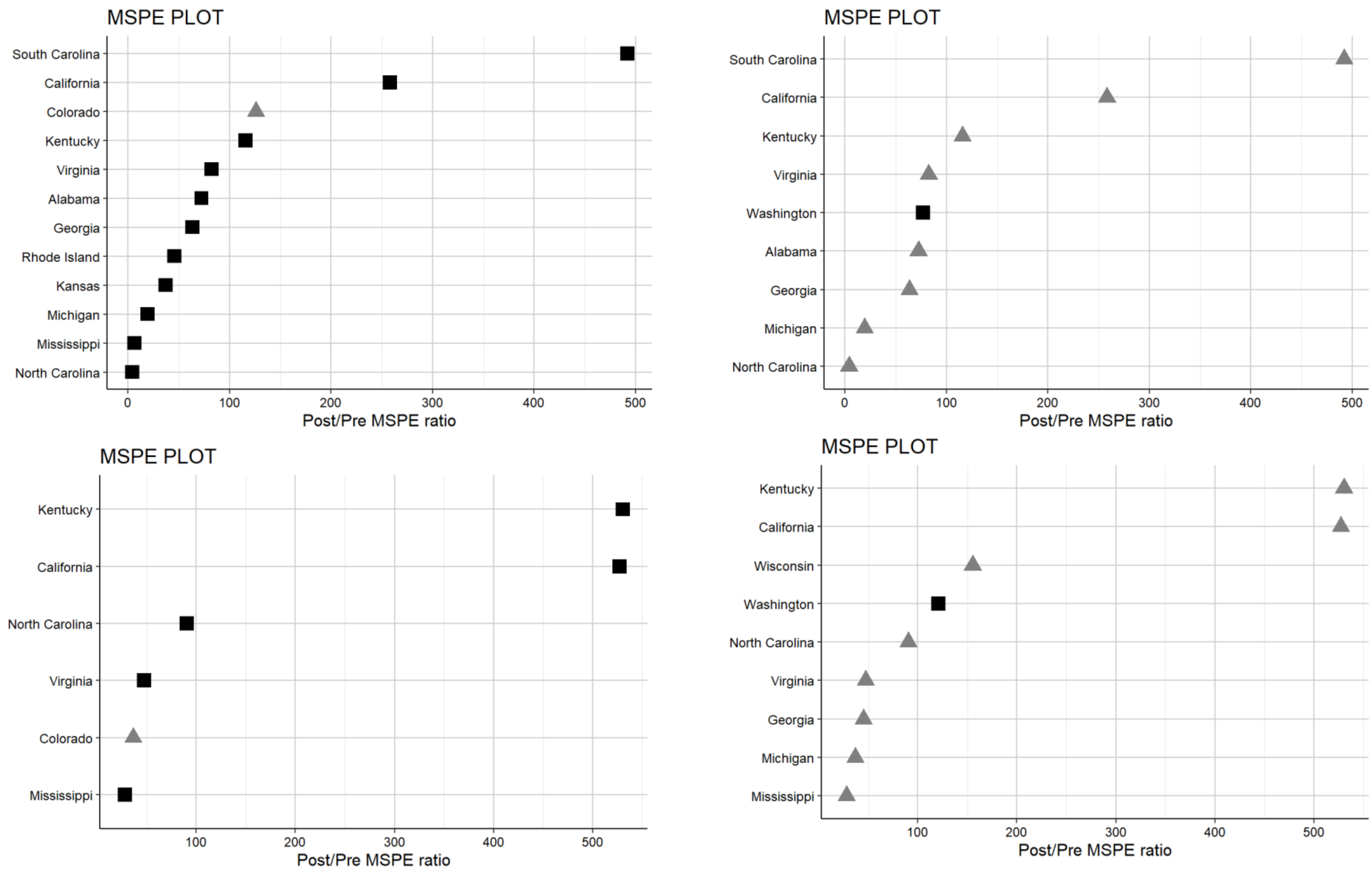


Figure. Effect of recreational cannabis policy change on the prevalence of medication use outcomes from state-level models using a synthetic control approach and removing states with small samples of enrollees from the donor pool

Notes: In the above figure, the top panel represents the treatment effects on antianxiety use in anxiety and the bottom panel antidepressant use in depression. Estimates were derived from synthetic control models. Solid black lines are treated states Colorado (left) and Washington (right). Grey lines reflect placebos for donor pool states.



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Notes: In the above figure, the top panel represents the synthetic control model-based estimates of post- to pre-policy mean square prediction error. The top panel reflects antianxiety use in anxiety and the bottom panel antidepressant use in depression. High ratios are indicative of large treatment effects.

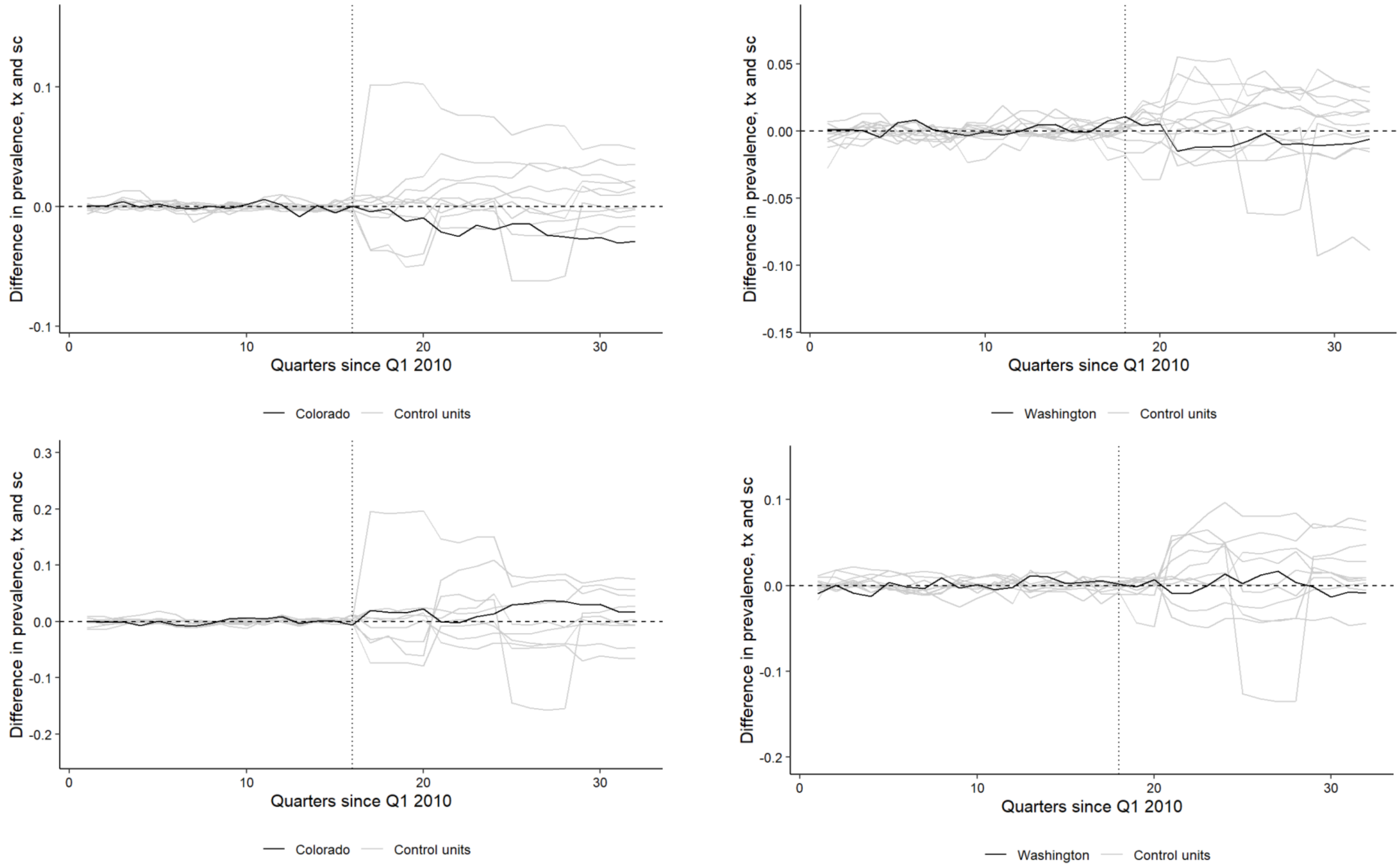

Figure. Effect of recreational cannabis dispensary opening on the prevalence of medication use outcomes from state-level models using a synthetic control approach

Notes: In the above figure, the top panel represents the treatment effects on antianxiety use in anxiety and the bottom panel antidepressant use in depression. Estimates were derived from synthetic control models. Solid black lines are treated states Colorado (left) and Washington (right). Grey lines reflect placebos for donor pool states.

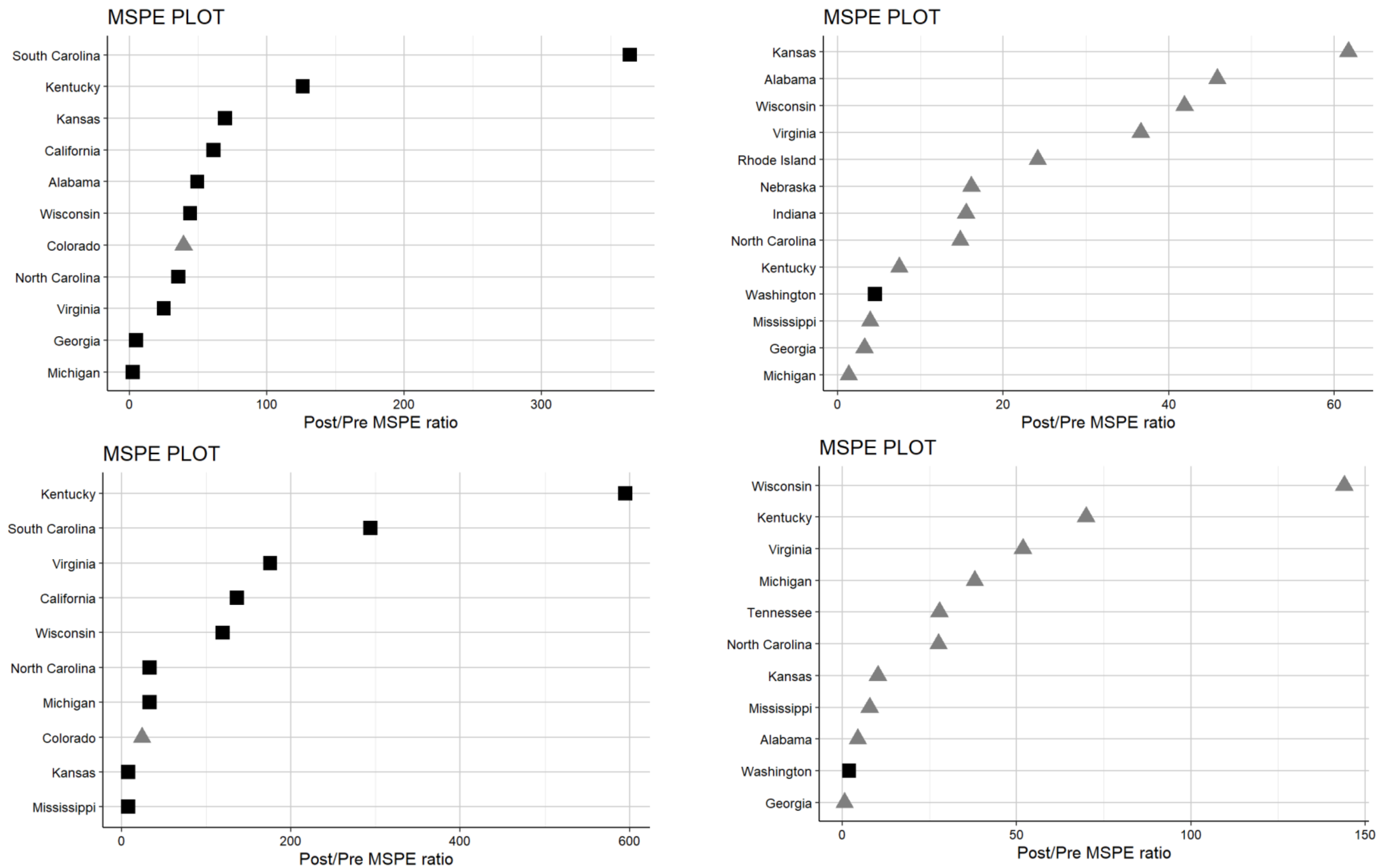

Figure. Mean squared prediction error ratios from placebo test models evaluating the effect of recreational cannabis dispensary opening on medication use outcomes from state-level placebo models using a synthetic control modelling approach

Notes: In the above figure, the top panel represents the synthetic control model-based estimates of post- to pre-policy mean square prediction error. The top panel reflects antianxiety use in anxiety and the bottom panel antidepressant use in depression. High ratios are indicative of large treatment effects.

VITA

Lauren Strand, MS, PhD previously got her MS in epidemiology within the UW School of Public Health. Her main research interests are in drug policy, mental health, and therapeutics used in neurology, and her work draws methods from pharmacoepidemiology, econometrics, economic evaluation, and policy evaluation. She has served as a teaching assistant for courses in health economics, economic evaluation and health technology assessment, programming, and epidemiology. During her PhD program, Lauren completed a Fellowship with the Washington Research Foundation focusing on early phase health technology assessment and she was awarded the 2019-2020 Magnuson Scholarship for the School of Pharmacy. She has previously worked in Health Economics & Outcomes Research consulting and currently holds a position as a Research Scientist at Myriad Genetics.