**Using Policy and Innovation to Improve Life-Saving Access to Naloxone**


**Abstract:**

Naloxone is a life-saving medication which helps reverse the effects of an opioid overdose. Improving naloxone access is a central pillar of the federal response to the worsening opioid crisis in the United States. Existing studies have evaluated the effects of state naloxone access laws, such as standing/protocol orders and prescriptive authority laws, which permit naloxone to be dispensed by pharmacies directly to consumers without a patient-specific prescription. However, this literature has ignored the role of pharmaceutical innovations like Narcan. Narcan, introduced to the marketplace in February 2016, is a naloxone nasal spray that permits laypersons to successfully administer the drug without training. We test the hypotheses that naloxone access laws alone increased the distribution of naloxone prior to Narcan, and that the introduction of Narcan further expanded naloxone's distribution and its life-saving impacts. We use a robust difference-in-differences method to analyze cross-state variation in the adoption of naloxone access laws and their timing relative to Narcan's introduction. We show that states with naloxone access laws permitting pharmacists to dispense to consumers experienced substantially greater naloxone dispensing after Narcan's introduction, effects that far outpaced the independent effects of naloxone access laws. We also find that while these naloxone access laws did not reduce non-synthetic, opioid-related overdose mortality rates on their own, once Narcan was introduced these mortality rates significantly declined. These findings indicate the important interaction of innovation and policy, and raise concerns about availability and pricing of naloxone nasal spray now that the U.S. has allowed for over-the-counter sales.



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∗ We would like to thank our colleagues Rosanna Smart, Bradley Stein, and Corey Davis for useful insights about the policy data. We received especially helpful feedback from our discussants Thanh Lu as well as participants at the American Economic Association Annual Meeting (2023), Southeastern Health Economics Study Group Conference, and the NYU Center for Opioid Policy & Epidemiology. Any opinions and conclusions expressed herein are those of the authors and do not necessarily represent the views of any affiliate. All results have been reviewed to ensure that no confidential information is disclosed. Financial support for this research from the CDC (R01CE02999) is gratefully acknowledged.

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## I. Introduction

Pharmaceutical and medical device innovations have played a crucial role in life expectancy increases in the United States over the past few decades (Lichtenberg 2013). Recent estimates suggest that 35% of the 3.3 year increase in life expectancy in the United States among all residents between 1990- 2015 was due to pharmaceutical innovation, driven largely by pharmaceuticals targeting heart disease (Buxbaum, Chernew et al. 2020). Medical devices have also increased life expectancy, like the EpiPen that has resulted in lower risk of hospitalization and fatality due to anaphylaxis (Ma, Danoff et al. 2014). In nearly all cases, the research and development costs of these innovations are far outweighed by the benefits (Cutler and McClellan 2001). However, some innovations have increased mortality. Oxycontin, for example, represented a technological advancement through its extended-release formulation of oxycodone that became a major driver of U.S. drug overdose deaths, due in large part because of Purdue Pharma's aggressive marketing of the drug (Cutler and Glaeser 2021, Alpert, Evans et al. 2022). Opioid-related mortality today is a major contributor to the recent declines in U.S. life expectancy (Dyer 2018, Woolf and Schoomaker 2019).

A central pillar of the federal response to the opioid crisis is to improve access to naloxone (EOPOTUS 2016, ASPE 2021, Houser 2022). Naloxone is a lifesaving medication which helps reverse the effects of an opioid overdose. It was first approved for use in the United States in 1971, however its uptake had been slow until recently. Administering naloxone typically involved injecting it into the person overdosing, an act which required extensive training. Laypersons were generally unable to provide needed care in the moment, so naloxone administration was typically reserved for first responders, medical personnel, and trained bystanders. However, in November 2015, Narcan Nasal Spray became the first FDA-approved naloxone product for intranasal administration. This medical device represented a landmark innovation by reducing the barrier to administering naloxone, thus broadening naloxone's potential use by untrained laypeople. While intranasal formulations were available prior to Narcan, these products still required training and were generally only available to local

community-based groups. In contrast, Narcan nasal spray requires no assembly, no training, and delivers a consistent, approved dose (NIDA 2017). Generic versions became available in 2021.

By changing the route of administration from injection requiring training to a nasal spray requiring no training,[1] Narcan made naloxone more broadly accessible to the public and expanded the probability that a person overdosing could be saved by a bystander. However, the barrier to administration is not the only barrier individuals face in receiving naloxone. An increasing number of naloxone access laws (NALs) have focused on reducing the barriers to dispensing naloxone. These state policies have spurred a number of studies exploring their role in naloxone claims and overdose mortality (Gertner, Domino et al. 2018, Lambdin, Davis et al. 2018, Xu, Davis et al. 2018, Abouk, Pacula et al. 2019, Sohn, Talbert et al. 2019). This literature has generally ignored the role of Narcan and its potentially important interaction with NALs.

In this paper, we study the interaction of policy and innovation in promoting harm reduction strategies to fight the rise in opioid overdose deaths. To do so, we examine three experimental settings: (1) early NALs adopted in 2010-2015, prior to Narcan's introduction; (2) Narcan's introduction in states with existing NALs; and (3) NALs adopted in 2016-2019, after Narcan's introduction. Focusing on the early period prior to the introduction of Narcan, we identify the impacts of the staggered adoption of dispensing NALs alone, without Narcan. Then, following FDA approval in November 2015, Narcan was introduced nationwide in February 2016. Once approved, the distribution of Narcan varied substantially across states, due to variation in state laws related to prescribing and dispensing. In states without dispensing NALs, physicians were required to prescribe naloxone to the specific patient in need, while states with dispensing NALs (i.e. standing/protocol orders and prescriptive authority laws) facilitated the distribution of naloxone directly from a pharmacy without a prescription to any individual in a position to save a life (Rees, Sabia et al. 2019, Smart, Pardo et al. 2021). Studying the effects of NALs enacted after Narcan's introduction between 2016-2019 identifies a similar interactive effect of policy and innovation. While previous studies have examined NALs, we are aware of no other study that has examined the combination of policy and pharmaceutical innovation.

[1] While Narcan requires no training to administer, education about the drug may be important. For instance, because the effects of Narcan only last 30-90 minutes and opioids can stay in the body much longer than that, it is important to seek out medical help even if the person who overdosed has revived (NIDA 2017).

We use the Borusyak, Jaravel et al. (2021) robust difference-in-differences method to estimate the impacts of NALs and Narcan in the three experimental settings. This approach leverages the differential timing of state policy adoption, estimates counterfactuals using control observations, and compares "imputed" outcomes to observed outcomes in order to estimate treatment effects. This robust difference-in-differences method is robust to heterogeneity across groups and periods when treatment adoption is staggered. In addition, the imputation method is robust to treatment heterogeneity due to covariates (Caetano, Callaway et al. 2022, Powell 2023).

The literature has suggested that NALs independently increase naloxone dispensing. Using pharmacy-level data from Symphony Health, our evidence confirms previous studies showing that states' staggered adoption of NALs between 2010-2015 (before Narcan) produced statistically significant increases in naloxone dispensing: 1.41 additional claims per 100,000 state residents. However, we also find that naloxone dispensing in those same states increased even more after Narcan was introduced in 2016: 9.20 additional claims per 100,000 residents. The juxtaposition of these effects suggests an independent role for the pharmaceutical innovation of Narcan. We find that Narcan quickly became the most dispensed naloxone brand such that by the end of 2016 naloxone distribution was 2.5 times higher in states that implemented a dispensing NAL. Furthermore, we show that NALs enacted after Narcan's 2016 introduction expanded naloxone dispensing even more: 12.31 additional claims per 100,000 residents. Together, the evidence indicates that much of the overall impact of NALs on naloxone distribution occurred after the introduction of Narcan.

After quantifying the differential effects of dispensing NALs and Narcan on the distribution of naloxone via pharmacies, we study the downstream effects on overdose death rates. Evidence of the mortality impacts of NALs is mixed (Smart, Pardo et al. 2021) with some studies showing large decreases (McClellan, Lambdin et al. 2018, Abouk, Pacula et al. 2019, Rees, Sabia et al. 2019) and others showing no evidence of mortality effects (Pardo 2017). Other research even suggests that naloxone access produces a moral hazard effect, leading to higher rates of opioid-related overdose mortality (Erfanian, Grossman et al. 2019) or increased opioid-related hospitalizations (Doleac and Mukherjee 2022). However, this literature does not distinguish between pre-Narcan and post-Narcan periods. Our approach examining the role of Narcan's introduction provides clarity to the mixed existing evidence. During the pre-Narcan,

2010-2015 period, we observe no evidence that the adoption of dispensing NALs significantly altered the rate of non-synthetic, opioid-related overdose mortality (this measure excludes synthetic opioids such as fentanyl). However, we find that once Narcan was introduced in early 2016, the same states that adopted dispensing NALs between 2010-2015 experienced significant reductions in the rate of non-synthetic, opioid-related overdose mortality. We also find that states that adopted dispensing NALs after Narcan's introduction experienced similarly large and significant reductions in the rate of opioid-related overdose mortality. When we consider the possible differential impacts by sex, race, and age, we find consistent results demonstrating that the introduction of Narcan enabled states with dispensing NALs to bend the opioid mortality curve for each demographic group. However, we do find that Narcan combined with dispensing NAL had a larger impact on non-synthetic, opioid-related overdose mortality rates among men than among women, and on those middle aged (25-44 years and 45-64 years) as compared to younger individuals or older adults. Importantly, we find that Narcan's introduction only significantly reduced non-synthetic, opioid-related overdose mortality rates among non-Hispanic Whites.

In light of our differential effect sizes across demographic groups, we sought to understand what barriers might be contributing to differential access to naloxone beyond state laws. We first consider geographic characteristics and find that counties in the top quartiles of Black and Hispanic populations experienced no significant increase in naloxone dispensing following the adoption of NALs and the introduction of Narcan. Similarly, we find that the adoption of NALs and the introduction of Narcan did not significantly affect naloxone dispensing in rural counties or counties in the top quartile of poverty. Next, we examine how the types of pharmacies in areas affect naloxone dispensing. Research has shown that chain pharmacies, such as CVS and Walgreens, are much more likely to stock naloxone than independent pharmacies (Lai, Friedson et al. 2022). Echoing this, we find that counties without chain pharmacies experienced no significant increase in naloxone dispensing following the adoption of NALs and the introduction of Narcan.

Finally, we examine the role of cost as a barrier to distribution, which is particularly important in light of the March 2023 announcement by the U.S. Food and Drug Administration to allow Narcan to be sold over-the-counter without a prescription (FDA 2023). While this

change may further broaden access, many insurance companies do not provide coverage for drugs sold over the counter, and hence the decision could change the price consumers face for Narcan. We find in our time period examined that the increase in naloxone distribution caused by NALs and Narcan was concentrated among Medicaid and Medicare beneficiaries, who, according to prior research, faced the lowest out-of-pocket costs throughout the period (Peet, Powell et al. 2022). We find similar results when examining the effects of NALs and Narcan by range of out-of-pocket costs: NALs and Narcan increased naloxone dispensing most among consumers that faced the lowest out-of-pocket costs ($0-$10), with successively smaller effects seen among those paying $10-$25, $25-$50, and $50+.

The conclusions of this paper suggest a larger role for harm reduction strategies in combatting the worst impacts of the opioid crisis. The literature has suggested that supply-side interventions often exacerbate overdose rates (Meinhofer 2018, Kim 2021, Powell and Pacula 2021). Demand-side interventions, including increasing access to treatment, particularly medications for opioid use disorder, have recently received more attention and funding, but these rely on people being able to seek treatment. People are able to seek treatment if the harm caused by overdoses is reduced. Our results demonstrate that pharmaceutical innovations combined with harm reduction policies can save lives before people agree to treatment. However, we also find that the administration of naloxone is not the only relevant barrier. While NALs and Narcan dramatically increased naloxone dispensing among those covered by Medicare and Medicaid that face low out-of-pocket costs, we find that the impacts of NALs and Narcan are muted among consumers that face higher out-of-pocket costs. Additionally, we find that structural barriers tied to geography as counties with high Black and Hispanic populations and high poverty counties did not experience significant increases in naloxone dispensing following the adoption of NALs and the introduction of Narcan. Furthermore, the adoption of NALs and the introduction of Narcan did not significantly increase naloxone dispensing in counties without chain pharmacies (predominantly rural). These other barriers to access caused the reductions in overdose mortalities to be unevenly distributed, suggesting the need for further efforts to enhance access to this life-saving drug.

## II. Background

### *Naloxone Access Laws*

Opioid overdoses occur when a person takes a lethal or toxic amount of a regulated prescription opioid, such as oxycodone, morphine, and tramadol, or an illicitly obtained opioid, including heroin and illicitly-manufactured fentanyl. Overdoses can cause respiratory depression and/or hypoxia, potentially leading to death. Naloxone is an opioid antagonist with no potential for abuse that reverses the effects of an opioid overdose. Naloxone hydrochloride was developed in the 1960's and approved by the FDA in 1971. Naloxone works by competing for opioid receptor sites in the central nervous system, thus blocking the effects of opioids (Keegan and Dey 2017). Once administered, naloxone takes two to three minutes for its effect to be felt.

In recent decades various types of policies have been implemented by states in an effort to mitigate the opioid crisis. Modern day prescription drug monitoring programs (PDMPs) started being implemented in the early 2000s as a way to track prescribing and dispensing of controlled drugs, helping to avoid inappropriate prescribing and limit the supply of opioids to those seeking excess access through doctor shopping and pharmacy shopping (Grecu, Dave et al. 2019). More rigid supply reduction laws began getting adopted starting in 2010, with pain clinic regulations (often referred to "pill mill laws") (Rutkow, Chang et al. 2015, Axeen et al. 2021), and policies limiting the number of days supply that could be dispensed for new prescriptions for opioids to 3- or 7-days supply (Davis, Lieberman et al. 2019, Cramer, Gunaseelan et al. 2021, Sacks, Hollingsworth et al. 2021). These policies differ in focus from harm reduction policies such as naloxone access laws ("NALs") and Good Samaritan laws.

Traditionally, naloxone has been available only following a prescription from a medical provider and only to the patient for whom the provider writes the prescription. However, opioid overdose victims face a number of barriers to obtaining clinical or professional care (Bowles 2017). Moreover, most witnesses to drug overdoses are individuals engaging in the same risky behavior (Tobin, Davey et al. 2005). In this study we examine a group of laws that we term "dispensing NALs." While NALs take different forms,[2] the objective of dispensing NALs is to make it easier to distribute naloxone to any individual in a position to save a life and thereby reduce the harm associated with excess consumption of these highly addictive substances, notably fatal opioid overdose (Rees, Sabia et al. 2019, Smart, Pardo et al. 2021).

[2] For information on the various categories of NALs, see Davis, C. and D. Carr (2017). "State legal innovations to encourage naloxone dispensing." Journal of the American Pharmacists Association **57**(2): S180-S184.

Non-patient specific standing orders or protocol orders are one type of dispensing NAL. Standing orders enable pharmacists to dispense naloxone to any person meeting predetermined criteria, including to "third parties" or bystanders that are not in need of opioid overdose reversal. Similarly, protocol orders allow pharmacists to dispense to anyone without a prescription but requires that the pharmacist have a physician approved protocol (either from a physician, a medical board, or other state agency reflecting a medical opinion).

The other type of dispensing NAL that we consider in this study is prescriptive authority. Prescriptive authority laws go a step further than either standing orders or protocol orders, in that they expand the pharmacist's scope of practice allowing them to directly prescribe and distribute naloxone themselves.

Figure 1 shows the timing of implementation of dispensing NALs by state. Illinois was the first state to implement a dispensing NAL (a non-patient specific standing order) in 2010. Table 1 separates non-patient specific standing/ protocol orders (grouped together due to their similarity in practice) and prescriptive authority laws and describes the timing of their implementation up through 2016, the point at which Narcan became available in the marketplace.

The existing research on NALs is mixed (Smart, Pardo et al. 2021). On one hand, analyses of the effects of NALs on naloxone distribution show positive and generally significant effects that vary by NAL type (Gertner, Domino et al. 2018, Lambdin, Davis et al. 2018, Xu, Davis et al. 2018, Abouk, Pacula et al. 2019, Sohn, Talbert et al. 2019). On the other hand, studies of the effects of NALs on opioid-related overdose mortality range from evidence that NALs reduce the rate of mortality by 9-15% (McClellan, Lambdin et al. 2018, Rees, Sabia et al. 2019), to evidence of moral hazard with NALs leading to higher rates of opioid-related overdose mortality (Erfanian, Grossman et al. 2019) or increased opioid-related hospitalizations (Doleac and Mukherjee 2022). Within this range are studies showing that only certain NAL types reduce the rate of opioid-related overdose mortality (Abouk, Pacula et al. 2019). Other studies indicate that NALs lead to higher rates of opioid-related emergency room visits (Blanchard, Weiss et al. 2018, Abouk, Pacula et al. 2019) along with higher rates of opioid-related theft (Doleac and Mukherjee 2022).

***Narcan***

While NALs have been shown to increase naloxone dispensing (Gertner, Domino et al. 2018, Lambdin, Davis et al. 2018, Xu, Davis et al. 2018, Abouk, Pacula et al. 2019, Sohn, Talbert et al. 2019), overdose victims face other barriers to actually using naloxone. The original version of naloxone approved by the FDA in 1971 is administered intravenously with doses ranging from 0.4 mg to 2 mg. Its intramuscular injection required administration by medical professionals, trained emergency medical service providers, or other individuals trained to administer naloxone (Keegan and Dey 2017). So, even if naloxone dispensing increases, the method of administration may continue to act as a barrier to naloxone use because opioid overdose victims and their observers may fear calling authorities out of risk of being arrested for possession drug paraphernalia, such as the syringe used to administer the dose, if not drug possession/ use itself (Tobin, Davey et al. 2005, Bowles 2017).

Recent pharmaceutical innovations have attempted to address the administration barrier. In 2014, kaléo Pharmaceuticals introduced Evzio, an auto-injector and the first naloxone product designed for layperson administration (Beletsky 2015). However, Evzio's lack of impact highlights a different barrier to the use of naloxone: cost. Evzio's average out-of-pocket costs were over 4 times higher than generic naloxone among insured patients, and over 16 times higher than generic naloxone among uninsured individuals (Peet, Powell et al. 2022). These high out-of-pocket costs for Evzio limited its distribution while on the market and ultimately led to it being discontinued in 2020 (Peet, Powell et al. 2022). However, around the same time Evzio was introduced, the National Institute of Drug Abuse funded Adapt Pharma and Opiant Pharma to develop another formulation of naloxone that could be administered by laypersons. This collaboration led to the development of an intranasal formulation of naloxone called Narcan. Narcan was approved by FDA in November 2015 and launched in February 2016. The product is simple, painless, can easily be administered by overdose witnesses, delivers greater bioavailability than intramuscular forms, and rapidly produces therapeutic effects (Keegan and Dey 2017). In contrast to Evzio, Narcan was also affordable, with average out-of-pocket costs similar to generic naloxone. In its first year on the market Narcan became the dominant brand of naloxone (see Figure 2).

The barriers addressed jointly by both dispensing NALs and Narcan form the hypotheses of this study. We first hypothesize that dispensing NALs prior to 2016 increased naloxone

distribution by relaxing the prescription requirements. Our second hypothesis is that the introduction of Narcan further expanded naloxone distribution in states with dispensing NALs by removing the administration barrier. Moreover, we hypothesize that the easier administration offered by the introduction of Narcan reduced the rate of non-synthetic, opioid-related overdose mortality. We examine the combined effects of NALs and Narcan in two types of states: 1) states that had NALs in place prior to Narcan's introduction in early 2016, and 2) states that adopted NALs after Narcan's introduction.

## III. Data

We analyze the impacts of NALs and the combined impacts of NALs and Narcan using various data sources. First, we use pharmacy prescription claims data to describe naloxone dispensing. Second, we use vital statistics mortality data to describe non-synthetic, opioid-related overdose mortality rates. Third, we use a policy database detailing the timing of state (and District of Columbia) NALs. We also use additional data that describe population characteristics. Each data source describes the years 2010-2019, however, our analyses will focus on two different periods within this timeframe. To examine the impacts of NALs implemented prior to Narcan we will examine the 2010 to 2015 period. To examine the combined impacts of NALs and Narcan we will focus on the 2016 to 2019 period.

### *Pharmacy Prescription Claims Data*

Our prescription claims data describing naloxone dispensing across retail pharmacies in the U.S. comes from Symphony Health. Symphony Health is a health technology company which compiles retail pharmacy prescription claims from all payers – private insurance, Medicare, Medicaid, other public assistance programs (VA/Tricare), as well as the uninsured. Our extract of the Symphony Health data describes a 72% sample of U.S. retail pharmacies and approximately 90% of prescriptions filled in those pharmacies between 2010 and 2019. Our extract of the Symphony Health data is geographically identified at the 3-digit zip code level. We crosswalk these 3-digit zip codes to counties and states. The Symphony data is also disaggregated by year, quarter, dosage, payer type, and drug brand (generic naloxone, Evzio, and Narcan). During the 2010-2019 period the drug brand is equivalent to the administration method: injection of generic naloxone, auto-injection of Evzio, and intranasal Narcan.

We use the Symphony Health data to measure naloxone dispensing: the number of naloxone claims in a state or county and year-quarter, and we scale it by the state's or county's population multiplied by 100,000. We also calculate the same measure of naloxone dispensing by payer. Each state's overall population is determined using Surveillance, Epidemiology, and End Results Program (SEER) data. Each state's number of beneficiaries by payer type is determined using Kaiser Family Foundation (KFF) data.

Figure 2 shows the national trend in naloxone dispensing per capita between 2010 and 2019 by drug brand. Prior to 2014 less than 1 claim of naloxone (total across all brands) was dispensed per 100,000 residents. Naloxone distribution first began to increase in 2015, coinciding with the introduction of dispensing NALs in many states. However, naloxone distribution began to increase exponentially with the introduction of Narcan in 2016. The by-drug breakdown in naloxone claims rate shows that by the second quarter of 2016 Narcan was the dominant form of naloxone. Since that time, claims of Narcan have continued to dwarf both Evzio and generic naloxone.

***Mortality Data***

To measure opioid-related overdose mortality we use the Centers for Disease Control and Prevention (CDC) National Vital Statistics System (NVSS) Multiple Cause of Death mortality files from 2010 to 2019. These data represent a census of deaths in the United States. Specifically, we use a restricted-use version of the NVSS data that contains state and county of residence identifiers. Opioid-related overdose mortalities are categorized according to International Classification of Diseases, Tenth Revision (ICD-10) coding. We include overdose mortalities coded as unintentional (X40-X44), suicide (X60-X64), homicide (X85), or of undetermined intent (Y10-Y14). Our main overdose outcome of interest is the rate of mortality involving natural/semisynthetic opioids (e.g., OxyContin) and/or heroin and excluding synthetic opioids (e.g., fentanyl). We exclude fentanyl from the overdoses of interest because, while naloxone can treat a fentanyl overdose, fentanyl is substantially stronger than natural/semisynthetic opioids or heroin. Relative to morphine, OxyContin and other natural/semisynthetic opioids are 1.5 times stronger, and heroin is 2 to 5 times stronger. In contrast, fentanyl is 50 to 100 times stronger than morphine (Keating and Granados 2017). Consequently, overdoses involving fentanyl require higher and/or multiple doses of naloxone

delivered rapidly to overdose victims and may also require the use of defibrillators (Moss and Carlo 2019). Overdoses mortalities involving natural/semisynthetic opioids and/or heroin are indicated by the following ICD-10 codes: T40.1 (heroin), and T40.2 (natural/semisynthetic opioids). Among these overdoses, we exclude those that also involve T40.4, or synthetic opioids (e.g., fentanyl) other than methadone.

However, we also separately examine overdoses involving synthetic opioids (e.g., fentanyl) other than methadone (T40.4). Furthermore, as placebo outcome tests, we also examine overdose deaths related to non-opioid substances that cannot be reversed by naloxone. We categorize these placebo outcomes into: (1) those involving cocaine (T40.5), and (2) those involving any other substance(s) except natural/semisynthetic opioids (T40.2) or heroin (T40.1). We scale each of these measures of the rate of overdose mortality involving opioids and non-opioids by the state's population multiplied by 100,000. Each state's overall population is determined using data from the Surveillance, Epidemiology, and End Results Program (SEER).

Figure 3 shows the 2010-2019 national trend in our outcome of interest, the rate of overdose mortality involving non-synthetic opioids, and contrasts this trend with the overall trend in overdose mortality involving any opioid. Both the rate of overdose mortality involving any opioids and the rate of overdose mortality involving non-synthetic opioids increased up to 2016. However, after 2016, the rate of overdose mortality involving any opioids continued to increase, while the rate of overdose mortality involving non-synthetic opioids began to decline.

***Naloxone Access Laws Data***

We use the RAND Opioid Policy Tools and Information Center (OPTIC) policy database to construct the treatment variables of interest. The OPTIC policy database is a comprehensive repository of the details and timing of state (and District of Columbia) policies related to opioid prescribing. OPTIC identifies existing data from sources on state policies including (but not limited to) the National Alliance for Model State Drug Laws, the National Conference of State Legislatures, the Prescription Drug Abuse Policy Surveillance System (PDAPs) and the PDMP Training and Technical Assistance Center. The OPTIC research team then reviews the definitions of the policy being tracked in each source as well as the dates of policy enactment and adoption, to better understand where there is variation across sources and what the reason for that variation is. OPTIC then extracts from the investigation of original data feeding these

sources a consistently defined policy across all states with accurate effectiveness dates that are relevant for analysts seeking to understand the impact of the policy (once implemented) on opioid outcomes.

The main policy variables of interest are: (1) an indicator of when a dispensing NAL (either non-patient specific standing/protocol order or prescriptive authority) was adopted in a state; and (2) an indicator of states that had a dispensing NAL in place prior to or simultaneous with Narcan's introduction. Furthermore, we separately assess the impact of dispensing NALs prior to Narcan's introduction and afterwards. While the FDA approved Narcan in November 2015 we do not observe any Narcan claims nationally until Narcan was introduced in the marketplace during the first quarter of 2016. Thus, for the analysis, we consider Narcan's introduction to be the first quarter of 2016. We also use OPTIC to describe other policies such as Good Samaritan laws (which limit the legal liability of individuals who help overdose victims) (Davis and Carr 2017), and state Medicaid expansion under the Affordable Care Act. In certain models, we will condition on these time-varying measures of state policies that may independently predict naloxone distribution and the rate of non-synthetic, opioid-related mortality.

Table 1 lists the states that had either non-patient specific standing/protocol orders or pharmacist prescriptive authority NALs in place prior to Narcan's introduction and the timing of their adoption prior to 2016. Thirty-six states had either a non-patient specific standing/protocol order or prescriptive authority NALs in place prior to or simultaneous with Narcan's introduction. Among these 36 states, the vast majority (33) had adopted non-patient specific standing/protocol orders, rather than prescriptive authority policies. Only three states (Connecticut, Idaho, and New Mexico) adopted prescriptive authority NALs prior to the first quarter of 2016. Seven states that adopted non-patient specific standing/protocol orders prior to Narcan's introduction later adopted prescriptive authority NALs; two states that adopted prescriptive authority NALs later implemented non-patient specific standing/protocol orders. Just over half (18) of the states with non-patient specific standing/protocol orders or prescriptive authority NALs adopted these policies during 2015.

***Summary Statistics***

Table 2 provides summary statistics comparing the characteristics of states with and without dispensing NALs (i.e., either non-patient specific standing/protocol orders or prescriptive authority policies) prior to Narcan's introduction. The first comparisons are of outcomes, specifically naloxone claims rates and non-synthetic, opioid-related mortality rates. The rate of naloxone claims for states with any type of dispensing NAL prior to Narcan was, in aggregate, 3.53 times higher of than the naloxone claims rate in states without a dispensing NAL before 2016. This difference is consistent with the result that NALs alone increased naloxone dispensing. However, the rates of overdose mortality involving non-synthetic, opioids in states with and without a dispensing NAL before 2016 were not significantly different.

We also use data from SEER and KFF to compare select demographic characteristics of states with and without a dispensing NAL before Narcan's introduction. States that implemented a dispensing NAL prior to 2016 had, on average, significantly larger populations than states without. States without a dispensing NAL before 2016 had smaller Black and Hispanic populations and greater non-Hispanic white populations than states that implemented either NAL before 2016. While the age distributions of each group of states were comparable, states without a dispensing NAL before 2016 had larger populations of 0-24 and 25-44 year old individuals. Finally, while each group of states had comparable distributions of Medicare and uninsured populations, states without a dispensing NAL before 2016 had higher proportions of their populations covered by private and other public insurance while states with a dispensing NAL before 2016 had a higher proportion of their population covered by Medicaid. The differences between these two groups of states are small in magnitude but motivate the use of methods which account for pre-existing differences.

Figure 4 displays the 2010-2015 naloxone dispensing trends in states with and without a dispensing NAL before Narcan's introduction. As previously noted, states without a dispensing NAL before 2016 had, on average, lower naloxone claims rates. This difference in naloxone dispensing between states with and without a dispensing NAL before 2016 suggests that the adoption of NALs may have had an impact on naloxone dispensing. While the rate of naloxone claims in each group of states differ, during the four quarters immediately preceding Narcan's introduction in 2016, states with and without a dispensing NAL before 2016 experienced approximately parallel trends. Figure 5 shows 2010-2015 trends in non-synthetic, opioid-related

overdose mortality rates among states with and without a dispensing NAL before Narcan's introduction. Throughout the 2010-2015 period the rates are approximately equivalent and parallel.

## IV. Empirical Strategy

We employ a robust difference-in-differences approach to estimate both static and dynamic effects of dispensing NALs and Narcan's introduction on naloxone distribution and non-synthetic, opioid-related mortality rates. Specifically, we employ the Borusyak, Jaravel et al. (2021) imputation difference-in-differences (IDiD) method.

The IDiD method is robust to heterogeneity across groups and periods when treatment adoption is staggered. It is also robust to covariate-related treatment heterogeneity. The Borusyak, Jaravel et al. (2021) IDiD method identifies the overall average effect of the treatment on the treated (ATT) in two stages. In the first stage, IDiD regresses the outcome on group and period fixed effects (as well as covariates) using the subsample of untreated observations. With these estimates, IDiD constructs counterfactuals for the entire sample. We model untreated outcomes as:

$$Y_{it}(0) = \lambda_i + \gamma_t + \delta X'_{it} + \varepsilon_{it} \quad (1)$$

$Y_{it}(0)$ denotes the outcome of interest, either naloxone claims rate or non-synthetic, opioid-related mortality rate (both scaled per 100,000 population) for state (or county) *i* at time *t*. Each of our models use quarter of the year as the temporal unit of analysis, or $t$. Using quarter of the year yields less noisy measures than months, but also allow us to look more precisely at the timing of the introduction of dispensing NALs and Narcan than annual units. While state boundaries likely do not appropriately define naloxone distribution markets, NALs are implemented at the state-level and performing state-level analysis should not induce bias. The specification above includes state and time fixed effects as well as a vector of time- and state-varying covariates, discussed more below.

As described, we examine the impact of NALs and Narcan in three experimental settings: (1) NALs adopted in 2010-2015, prior to Narcan's introduction; (2) Narcan's introduction in states with existing NALs; and (3) NALs adopted in 2016-2019, after Narcan's introduction. First, we estimate the first stage using controls during the 2010-2015 period and construct one

counterfactual that is used to examine both experimental settings (1) and (2). This way, any effect of NALs produced as a result of NALs adopted prior to Narcan's introduction (experimental setting 1) will be reflected in the pre-treatment estimates of trends prior to Narcan's introduction in states with NALs (experimental setting 2). Then, to analyze experimental setting (3), we use controls during the 2016-2019 period and construct a separate counterfactual. This counterfactual describes the outcomes without NALs but reflects Narcan's introduction in all states and time periods.

The second stage calculates the effects of NALs and Narcan as the difference between the observed outcome and the counterfactuals. ATT are then defined as the population-weighted averages of the difference between the observed outcome and predicted counterfactual: $Y_{it} - \hat{Y}_{it}(0)$. We present these estimates as static for the entire post-period and dynamic by time-relative-to-treatment (in quarter of the year terms). The dynamic estimates include a description of any pre-existing trends prior to treatment not captured by state and time fixed effects as well as any additional covariates included in the model.

Our estimates are population weighted and the standard errors are adjusted for clustering at the state level. The base model, denoted IDiD, includes only state and time fixed effects. We also explore models in which $X_{it}$ includes time-varying policy indicators (e.g., Medicaid expansion, Good Samaritan laws) which we denote as +Policy. We also estimate models in which  includes control variables selected by post-double selection LASSO (Belloni, Chen et al. 2012) from among a wide selection of policy indicators, demographic characteristics, rates of OxyContin misuse prior to reformulation (2004-2009),[3] and interactions of those covariates with "ever treated" and, separately, time indicators. This model is denoted as +LASSO.

## V. Main Results

Our main results describe the effects of NALs and Narcan in the 3 experimental settings: (1) dispensing NALs implemented before 2016; (2) Narcan's introduction in states with existing

[3] OxyContin has been implicated as a key driver of the opioid epidemic (Kolodny et al., 2015) and recent work concludes that its introduction explains a significant share of the growth in overdoses since 1996 (Alpert et al., 2022).

NALs; and (3) dispensing NALs implemented after Narcan's introduction. We explore these effects on both naloxone claims and the rate of non-synthetic, opioid-related overdose mortality.

***Naloxone Claims***

First, consider the static effects on naloxone claims rates described in the top panel of Table 3. The staggered adoption of dispensing NALs prior to 2016 is shown to significantly increase the rate of naloxone claims in each model. The estimates of changes to naloxone dispensing range from 1.26 additional claims per 100,000 residents (+Policy), to 1.41 additional claims per 100,000 residents (IDiD and +LASSO model). Each of these estimates are significant at the 5% level, and they do not significantly differ across models. However, the effects of dispensing NALs alone are substantially smaller than when dispensing NALs are combined with Narcan. Narcan's introduction in states with existing dispensing NALs is estimated to increase naloxone dispensing by between 9.05 (+Policy, significant at the 1% level) and 9.20 claims per 100,000 residents (IDiD and +LASSO, significant at the 1% level). Furthermore, states that adopted naloxone laws after the introduction of Narcan experienced an even larger increase in naloxone dispensing. Compared to never and not-yet treated units, the adoption of dispensing NALs after Narcan's introduction increased naloxone dispensing by between 12.31 (IDiD and +Policy, significant at the 1% level) and 12.73 (+ LASSO, significant at the 1% level) additional claims per 100,000. Note that these estimates do not significantly differ across models. The results imply that the growth in naloxone dispensing that resulted from Narcan's introduction in states with dispensing NALs was 6 to 10 times higher than the growth produced by dispensing NALs alone.

Figure 6 shows the dynamic effects of dispensing NALs and Narcan on naloxone claims rates. First, the dynamic effects of dispensing NALs introduced prior to 2016 are shown in the top left panel. In these states, naloxone claims rate immediately grew by 0.67 claims per 100,000 in the quarter of dispensing NAL adoption (Q0). While not statistically significant in Q0-Q2, the effects were significant at the 10% level in Q3 (0.75). In Q4 the effect is significant at the 5% level (2.13) and between Q4 and Q7 the impacts on naloxone dispensing essentially plateau before declining slightly in Q8. Next, the top right panel shows the dynamic effects of Narcan's introduction in states that had pre-existing dispensing NALs. First note that the pre-trends reflect a relatively small increase. However, the pre-trends are quickly dwarfed by the effects of

Narcan's introduction. Narcan's introduction led to an immediate increase in naloxone dispensing vis-à-vis states that did not have these laws, and the effect only grew with time. By Q1, 3.99 additional naloxone claims per 100,000 (significant at the 5% level) were dispensed; this grew to 11.49 additional claims per 100,000 in Q5, and more than 16 additional claims per 100,000 in each of the remaining quarters, Q6-Q8. Finally, the bottom panel shows the dynamic effects of dispensing NALs adopted after Narcan's introduction. Compared to never and not-yet treated units, states that adopted dispensing NALs after the introduction of Narcan (AK, AZ, DC, FL, HI, IA, KS, MI, MO, MT, SD, UT, WV, WY) experienced an even larger increase over time. From Q0-Q2 the effect sizes are similar, but with greater uncertainty, than the estimates of Narcan's introduction in states with dispensing NALs. Then in Q3 we observe the first statistically significant (5% level) effect, an additional 8.21 naloxone claims per 100,000. And this continuously grows until reaching 26.75 additional claims per 100,000 in Q8.

***Non-synthetic, Opioid-Related Overdose Mortality Rates***

We next examine the downstream effects of NALs and Narcan on overdose death rates. First, consider the effects of NALs adopted prior to Narcan's introduction. The second panel of Table 3 shows that before Narcan's introduction NALs did not significantly change the rate of non-synthetic, opioid-related mortality. This means that while, as discussed, dispensing NALs adopted prior to Narcan's introduction significantly increased naloxone distribution, the increase in naloxone access did not translate into fewer lives lost during the 2010-2015 period. However, with the introduction of Narcan, we do see an immediate reduction in non-synthetic, opioid-related mortality rates in states that had pre-existing dispensing NALs. Narcan's introduction in these states reduced the rate of non-synthetic opioid-related mortality by between -0.15 to -0.22 per 100,000 (significant at the 5% level). Then, states that adopted naloxone laws after the introduction of Narcan experienced an even larger reduction in non-synthetic, opioid-related mortality. The adoption of dispensing NALs after Narcan's introduction reduced non-synthetic, opioid-related mortality by between -0.58 (+ LASSO, significant at the 1% level) and -0.62 (IDiD and + Policy, significant at the 1% level) per 100,000. The estimates do not significantly differ across models.

We next examine the dynamic effects of dispensing NALs and Narcan on non-synthetic, opioid-related mortality rates in Figure 7. First, the dynamic effects of dispensing NALs

introduced prior to 2016 are shown in the top left panel. In these states, the rate of non-synthetic, opioid-related mortality declines slightly following the adoption of dispensing NALs. Between Q0-Q3 NALs are shown to reduce the rate of non-synthetic, opioid-related mortality by between -0.10 and -0.18 per 100,000, but the effects are not statistically significant at the 5% level until Q4. Between Q4-Q8 the estimates are relatively stable, reflecting a reduction in non-synthetic, opioid-related mortality by between -0.15 and -0.25 per 100,000.

Next, the top right panel of Figure 7 shows the dynamic effects of Narcan's introduction in states with dispensing NALs. These results show that while Narcan's introduction eventually produced significant reductions in the rate of non-synthetic, opioid-related mortality, the effects are not immediately observed. Each of the estimates in Q0-Q1 are not statistically significant at the 5% level. In Q2 we observe a significant reduction in the crude rate (-0.14 per 100,000, significant at the 5% level). Subsequently, the largest reductions are observed in Q3 (-0.25 per 100,000), Q7 (-0.39 per 100,000), and Q8 (-0.48 per 100,000), and each are significant at the 5% level.

Finally, we examine the dynamic effects of dispensing NALs adopted after Narcan's introduction (bottom panel of Figure 7). In this case, the impacts are immediately significant. In the same quarter that dispensing NALs are adopted, the rate of non-synthetic, opioid-related mortality is reduced by -0.41 per 100,000 (significant at the 5% level). Each of the subsequent dynamic effect estimates are statistically significant (at either the 5% or 1% level) and continuously grow in magnitude until Q8. In Q8 dispensing NALs adopted after Narcan's introduction are estimated to reduce the rate of non-synthetic, opioid-related mortality by -0.91 per 100,000.

***Synthetic Opioids***

We also examine the effects of dispensing NALs and Narcan on the rates of synthetic opioid (e.g., fentanyl) overdose mortality. These results are presented in Table 4. Hypothetically, while naloxone could effectively counter an overdose involving synthetic opioids, fentanyl and its analogues are so powerful (33 to 66 times stronger than natural/semisynthetic opioids, and 10 to 20 times stronger than heroin) (Keating and Granados 2017) that a single dose of naloxone is insufficient to prevent complete collapse. One dose of naloxone simply buys a little bit of a time. Instead, treatment of overdoses involving fentanyl generally require higher and/or multiple doses

delivered rapidly (Moss and Carlo 2019). Indeed, our results suggest that even the innovation of Narcan in combination with NAL laws is insufficient to reduce the rate of overdose mortality involving synthetic opioids during the period evaluated. This is important because fentanyl is a major driver of the current phase of the opioid crisis.

***Placebo Outcomes***

Since naloxone only reverses the effects of opioid-related overdoses, non-opioid overdoses should be unaffected by greater access to naloxone (NALs) or easier forms of administration (Narcan). Thus, non-opioid overdoses can serve as placebo outcomes enabling us to determine whether the results presented up to this point may be driven by some other, co-occurring mechanism(s). In Table 5 we examine the impact of NAL laws with and without Narcan on rates of overdose mortality involving (1) cocaine (top panel), and (2) any other substances except natural/semisynthetic opioids and/or heroin (bottom panel). The results show no relationship between these mortality rates and (1) the adoption of dispensing NALs prior to 2016, (2) Narcan's introduction in states with dispensing NALs, or (3) dispensing NALs adopted after Narcan. So, although we know that fentanyl has been bleeding into the supply of other drugs sold on the illegal market, neither NAL laws nor the introduction of Narcan has influenced rates of mortality for other drugs. This result reinforces both our null effect findings for synthetic opioids shown in Table 4, and provides compelling evidence that our main findings presented in Table 3 are in fact real and being driven by the introduction of an innovative delivery mechanism of naloxone – Narcan.

**VI. Heterogeneity**

The results presented up to this point establish that the pharmaceutical innovation of Narcan catalyzed naloxone access laws to increase distribution and to more effectively reduce non-synthetic, opioid-related mortality rates. We next consider heterogeneity in our findings.

We first examine heterogeneity in the responsiveness of non-synthetic opioid-related mortality. Table 6 shows the results by sex, race/ethnicity, and age. First, consider the differences by sex. We observe no significant, sex-specific effects of dispensing NALs adopted prior to 2016. However, once Narcan is introduced, the rates of both male and female non-synthetic, opioid-related mortality begin to decline and the effect is much larger among males:

between -0.26 (IDiD and +LASSO, not statistically significant) to -0.42 (+Policy, significant at the 10% level) per 100,000 among males compared to between -0.05 (IDiD and +LASSO, not statistically significant) to -0.07 (+Policy, not statistically significant) per 100,000 among females. Then, the adoption of dispensing NALs after Narcan's introduction further magnified the reduction in non-synthetic, opioid-related mortality among both males and females, and the disparity persisted. Among males, the adoption of dispensing NALs after Narcan's introduction reduced the rate of non-synthetic, opioid-related mortality by between -0.77 (+ Policy, significant at the 5% level) and -0.87 (IDiD and +LASSO, significant at the 1% level) per 100,000. In contrast, the adoption of dispensing NALs after Narcan's introduction reduced the rate of non-synthetic, opioid-related mortality among females by approximately -0.38 (significant at the 1% level).

Next, consider the differences by race/ethnicity. First, we observe no significant effects of dispensing NALs adopted prior to 2016 among any racial/ethnic group. Similarly, we observe no statistically significant effects of Narcan's introduction in states with dispensing NALs. However, in the 2016-2019 period after Narcan's introduction we observe statistically significantly effects of dispensing NALs, but only among non-Hispanic Whites. Dispensing NALs adopted after Narcan's introduction are shown to significantly reduce the rate of non-synthetic, opioid-related mortality by -0.56 per 100,000 among non-Hispanic Whites. While the point estimates for Hispanics and other races/ethnicities are suggestive of reductions in the rate of non-synthetic, opioid-related mortality, they are not statistically significant. On the other hand, the point estimates for non-Hispanic Blacks, while not significantly different from zero, suggest that non-synthetic, opioid-related mortality rates continued to rise after Narcan's introduction and the adoption of dispensing NALs.

Finally, consider the differences by age group. Here, we do observe significant effects of dispensing NALs adopted prior to 2016, but only in the age 65+ group: -0.17 per 100,000 (significant at the 90% level). Dispensing NALs adopted prior to 2016 did not produce significant effects among any other age group, but the largest in magnitude point estimate is observed among those age 45-64. This pattern is observed in each of the 3 experimental settings. Among those age 45-64, the impacts of Narcan's introduction in states with pre-existing dispensing NALs and NALs adopted after Narcan's introduction are largest in magnitude.

Narcan's introduction in state with pre-existing dispensing NALs is shown to reduce the rate of non-synthetic, opioid-related mortality among those age 45-64 by between -0.52 (IDiD and +LASSO, not statistically significant) and -0.74 (+Policy, significant at the 10% level) per 100,000. Also, dispensing NALs adopted after Narcan reduced the rate of non-synthetic, opioid-related mortality among those age 45-64 by between -1.15 (IDiD and + LASSO) and -1.19 (+ Policy) per 100,000 (significant at the 99% level). The age 25-44 group experienced the second largest reduction in the rate of non-synthetic, opioid-related mortality: between -0.82 (+Policy, significant at the 5% level) and -0.88 (IDiD and +LASSO, significant at the 99% level) per 100,000 following the adoption of dispensing NALs after Narcan.

The differential impacts of NALs and Narcan on the rates of non-synthetic opioid-related mortality by sex, race/ethnicity, and age raises an important question about equitable access to this life-saving drug. While the prescription claims data do not adequately describe the patient's demographics, we can consider whether distribution of naloxone is lower or higher in communities with different population characteristics. Table 7 presents findings on naloxone distribution by county population characteristics. While previous results use state-level analysis, to explore heterogeneity, here we employ county-level data and conduct the analysis at the county level. These results describe geographic disparities in naloxone access by county racial/ethnic characteristics, county socioeconomic characteristics, county urban/rural status, and the presence or lack of chain pharmacies in counties. We first compare the effects of NALs and Narcan in the counties with highest quartile of non-Hispanic Black population to other counties. These results indicate that the adoption of NALs and the introduction of Narcan did not significantly increase the distribution of naloxone in counties with the highest non-Hispanic Black populations. Similarly, we find that the adoption of NALs and the introduction of Narcan did not significantly increase the distribution of naloxone in counties with the highest Hispanic populations. High poverty counties also did not experience an increase in naloxone distribution after the adoption of NALs and the introduction of Narcan. Furthermore, while NALs and Narcan significantly increased naloxone distribution in urban counties, rural counties saw no significant change in naloxone access. We also show a stark divide between counties with and without a chain pharmacy. Our results reflect this difference in naloxone stocking patterns reported elsewhere (Lai, Friedson et al. 2022), showing that counties with chain pharmacies experienced a significant increase in naloxone distribution following the adoption of NALs and

the introduction of Narcan, while counties without chain pharmacies (which are predominantly rural) did not experience a significant increase in naloxone distribution.

Differences identified across counties with specific characteristics may simply reflect lower rates of insurance or greater public insurance in specific areas, and research has already shown that insurance status plays an important role in access to naloxone (Murphy, Morgan et al. 2019, Peet, Powell et al. 2022). Table 8 shows the payer-specific effects of NALs and Narcan. First, we observe that dispensing NALs adopted prior to 2016 significantly increase naloxone dispensing among Medicare beneficiaries (from 2.35 to 2.51 additional claims per 100,000, significant at the 1% level). Similarly, dispensing NALs adopted prior to 2016 significantly increase naloxone dispensing among Medicaid beneficiaries (from 1.91 to 2.04 additional claims per 100,000, significant at the 10% level), and privately insured individuals (from 0.54 to 0.61 additional claims per 100,000, significant at the 5% and 1% levels). While we observe no statistically significant effects on claims made to other public assistance (e.g., Veterans Affairs) payers, dispensing NALs adopted prior to 2016 significantly expanded naloxone access among uninsured individuals: between 2.48 (+Policy, significant at the 10% level) and 3.04 (IDiD and +LASSO, significant at the 5% level) additional claims per 100,000.

However, while the benefits of NALs are magnified by the introduction of Narcan among those covered by private insurance, Medicare, or Medicaid, naloxone access among the uninsured is not substantially expanded by the introduction of Narcan. In contrast, once Narcan is introduced, private, Medicare, and Medicaid claims rates increase even more than after dispensing NALs were adopted in states prior to 2016. Narcan's introduction increased the effects of dispensing NALs on uninsured claims rate from between 2.48 to 3.04 additional claims per 100,000 prior to Narcan, to 3.9 additional claims per 100,000 (significant at the 99% level) following Narcan's introduction. In contrast, Narcan's introduction led to 14.3 additional naloxone claims per 100,000 (significant at the 1% level) among Medicare beneficiaries and 12.6 additional naloxone claims per 100,000 (significant at the 1% level) among Medicaid beneficiaries. Finally, dispensing NALs adopted after Narcan further expanded naloxone distribution, particularly among Medicare and Medicaid beneficiaries. Dispensing NALs adopted after Narcan led to 25.7 additional claims per 100,000 (significant at the 99% level) among Medicare beneficiaries, and between 21.3 and 22.4 additional claims per 100,000 (significant at

the 99% level) among Medicaid beneficiaries. In contrast, the effects of dispensing NALs adopted after Narcan do not differ substantially from the estimated effects of NALs prior to Narcan among uninsured individuals.

These payer-specific findings suggest that out-of-pocket costs may modify the effects of dispensing NALs and Narcan. To examine this further, we consider heterogeneity in naloxone distribution by range of out-of-pocket costs and display these results in Table 9. In each of the 4 ranges of out-of-pocket costs ($0-$10, $10-$25, $25-$50, and $50+) we observed the same gradient across experimental settings: the smallest effects for dispensing NALs adopted prior to 2016, medium-sized effects of Narcan's introduction in states with dispensing NALs, and the largest effects for NALs adopted after Narcan's introduction. However, we also see substantial differences across out-of-pocket cost ranges indicating that the impacts of NALs and Narcan on naloxone distribution decreased as the out-of-pocket costs faced by consumers increased. We observe that naloxone claims increased most among consumers facing the lowest out-of-pocket costs ($0-$10): from 0.69 (+Policy, significant at the 10% level) to 0.77 (IDiD and +LASSO, significant at the 5% level) per 100,000 for NALs prior to 2016; approximately 3.6 (significant at the 1% level) per 100,000 for Narcan's introduction in states with pre-existing NALs; and from 5.8 (IDiD and +Policy, significant at the 1% level) to 6.1 (+LASSO, significant at the 1% level) per 100,000 for NALs after Narcan's introduction. The second largest effects of NALs and Narcan occurred among consumers facing the next lowest out-of-pocket costs ($10-$25): approximately 0.2 (significant at the 5% level) per 100,000 for NALs prior to 2016; approximately 1.51 (significant at the 5% level) per 100,000 for Narcan's introduction in NAL states; and from 3.57 (IDiD and +Policy, significant at the 1% level) to 3.74 (+LASSO, significant at the 1% level) per 100,000 for NALs after Narcan's introduction. The adoption of NALs and the introduction of Narcan had less of an effect among consumers that faced out-of-pocket costs between $25-$50: approximately 0.1 (significant at the 10% level) per 100,000 for NALs prior to 2016; approximately 0.93 (significant at the 1% level) per 100,000 for Narcan's introduction in NAL states; and from 1.40 (+LASSO, significant at the 1% level) to 1.48 (IDiD and +Policy, significant at the 1% level) per 100,000 for NALs after Narcan's introduction. And NALs and Narcan generally caused naloxone distribution to increase least among consumers facing out-of-pocket costs greater than $50: from 0.18 (+Policy, significant at the 5% level) to 0.19 (IDiD and +LASSO, significant at the 1% level) per 100,000 for NALs prior to 2016; from

0.28 (+Policy, significant at the 1% level) to 0.29 (IDiD and +LASSO, significant at the 1% level) per 100,000 for Narcan's introduction in NAL states; and from 0.44 (IDiD and +Policy, significant at the 1% level) to 0.46 (+LASSO, significant at the 1% level) per 100,000 for NALs adopted after Narcan's introduction.

## VII. Discussion and Conclusions

The opioid crisis claims 1.6 million years of life annually in the United States, exceeding the burden attributable to homicides, hypertension, HIV/AIDS, and pneumonia (Gomes, Tadrous et al. 2018). The crisis continues unabated with overdose deaths reaching record highs in 2021 (CDC 2022). An important tool in combatting the opioid crisis is naloxone. To increase access to this potentially lifesaving drug, states have increasingly implemented dispensing naloxone access laws such as non-patient specific standing/protocol orders, and prescriptive authority policies. The intent of each dispensing NAL is to eliminate the need for each potential or actual overdose victim to obtain a prescription from their healthcare provider. Instead, potential or actual overdose victims as well as other potential witnesses can obtain naloxone, as needed, directly from pharmacists. A large literature has examined the impacts of NALs and generally shown that they cause naloxone distribution to increase (Smart, Pardo et al. 2021).

However, obtaining naloxone is not the only relevant barrier faced by potential or actual overdose victims. Training on how to safely administer safely was also needed, and most formulations of naloxone prior to Narcan could only be administered by medical professionals, emergency medical service providers, or other trained individuals (Keegan and Dey 2017). Injection naloxone and the training required to deliver it acts as a barrier because potential overdose bystanders or witnesses may fear having to call authorities to administer it due to their own risk of arrest (Bowles 2017). Narcan, an FDA-approved naloxone nasal spray, overcomes this barrier permitting laypersons to successfully administer the drug on their own without specialized training.

We provide evidence that dispensing NALs alone increased naloxone distribution in some communities, but that Narcan's introduction greatly expanded naloxone distribution even in states with existing dispensing NALs. Using the Borusyak, Jaravel et al. (2021) difference-in-differences method that is robust to heterogeneity across groups and periods when treatment adoption is staggered, we show that NALs alone significantly increased naloxone dispensing by

between 1.26 to 1.41 additional claims per 100,000. Then, when Narcan was introduced in states with prior NALs, naloxone dispensing significantly increased by between 9.05 and 9.20 additional claims per 100,000. States that adopted NAL laws after the introduction of Narcan experienced even larger increases in naloxone dispensing: between 12.31 and 12.73 additional claims per 100,000. These results indicate that Narcan was an important innovation that increased the effectiveness of dispensing NALs ensuring that naloxone could be accessed by lay people to avert fatal overdoses involving non-synthetic opioids.

Whether naloxone was used to successfully avert fatal overdoses is another question that our study addresses. Up to this point, researchers have generated mixed evidence of the effects of NALs on overdose mortality rates. Previous evidence ranges from large decreases in overdose mortality rates (McClellan, Lambdin et al. 2018, Abouk, Pacula et al. 2019, Rees, Sabia et al. 2019), to null effects (Pardo 2017), as well as moral hazard effects with increased overdose mortality rates (Erfanian, Grossman et al. 2019, Doleac and Mukherjee 2022). Our analysis of the mortality effects of dispensing NALs alone indicate that increased naloxone distribution does not necessarily translate to significant declines in non-synthetic, opioid-related overdose mortality rates. However, we show that once Narcan was introduced, offering effective means of administering proper doses without special training, greater distribution of naloxone began to translate into significant reductions in the rates of non-synthetic, opioid-related mortality. These results indicate that while expanding naloxone access is important, the pharmaceutical innovation of Narcan was also critical to provide easier administration by laypersons and knowledge about naloxone use in order to reduce mortality.

However, our results also indicate substantial heterogeneity in the populations that experienced greater access to naloxone and its harm reduction benefits following the adoption of NALs and the introduction of Narcan. We find significant differences in the mortality effects of NALs and Narcan by sex (larger reductions among men than women) and by age (larger reductions for adults ages 45-64 and 25-44 compared to younger or older individuals). Additionally, we find that non-Hispanic Whites experienced the largest reductions in mortality rates from NALs and Narcan. This racial/ethnic disparity is a downstream impact of our county heterogeneity results which demonstrate that the increase in naloxone access caused by the adoption of NALs and the introduction of Narcan was concentrated outside of counties with high

non-Hispanic Black and Hispanic populations. Additionally, our results demonstrate that the adoption of NALs and the introduction of Narcan did not significantly increase naloxone access in high poverty counties, rural counties, and or counties without chain (e.g., CVS, Walgreens) pharmacies. Another important remaining barrier to naloxone access is cost. While dispensing NALs significantly increased naloxone distribution among uninsured individuals, the introduction of Narcan led to substantially greater distribution among Medicare and Medicaid beneficiaries. These results are collaborated by our examination of heterogeneity across out-of-pocket costs. We show that dispensing NALs and Narcan produced the greatest increase in naloxone access among consumers that faced the lowest out-of-pocket costs.

The heterogeneous impacts of NALs and Narcan have important implications moving forward in grappling with the opioid crisis. The disparities across race/ethnicity suggest the importance of geography and other barriers to naloxone access that may be mitigating the impact of Narcan's technological innovation. Our results indicate that additional efforts are needed to expand naloxone access in areas with large populations of non-Hispanic Blacks and Hispanics, as well as rural and high poverty areas. Additionally, following FDA approval in March 2023, Narcan is now available over-the-counter (FDA 2023). While intended to expand access by allowing Narcan to be sold directly to consumers online or in drug stores, convenience stores, grocery stores and gas stations, the actual impact is unclear. While research documents variation in the willingness of pharmacists to dispense naloxone (Muzyk, Smothers et al. 2019), naloxone has been available without a prescription throughout the country for years because of non-patient specific standing orders or protocol orders and prescriptive authority laws in place in every state. The decision to make Narcan available over-the-counter now raises the importance of the out-of-pocket cost or price barrier in addition to geographic disparities in availability to the product. Our results demonstrate that the impacts of NALs and Narcan were muted at higher levels of out-of-pocket costs. The price of over-the-counter Narcan may be particularly impactful among Medicaid and Medicare beneficiaries that, up to this point, have faced the lowest out-of-pocket costs for naloxone (Peet, Powell et al. 2022), much lower than the $44.99 suggested retail price of over-the-counter Narcan (Emergent Biosolutions 2023).

Nevertheless, the results of this paper suggest a larger role for harm reduction strategies in combatting the worst impacts of the opioid crisis. The literature has suggested that supply-side

interventions often exacerbate overdose rates (Meinhofer 2018, Kim 2021, Powell and Pacula 2021). Demand-side interventions, including increasing access to treatment, particularly medications for opioid use disorder, have recently received more attention and funding, but these rely on people seeking treatment. Harm reduction policies, such as improving naloxone access and developing formulations that are easily administered, can save people from the fatal consequences of overdoses and enable them to seek treatment. However, harm reduction policies have also been criticized as producing moral hazard effects leading to null or increased rates of overdose mortality and other outcomes correlated with overdoses (e.g., crime) (Doleac and Mukherjee 2022). In contrast, our results indicate no moral hazard associated with expanded naloxone access. While our results show that policies that expanded naloxone access did not, on their own, save lives, when these policies were combined with easier methods of administration offered by the pharmaceutical innovation of Narcan, the rate of non-synthetic, opioid-related overdose mortality rates significantly declined.

However, this study has a few limitations which point to avenues for future research. First, while our focus is on pharmaceutical distribution of naloxone, potential and actual opioid-related overdose victims may also obtain naloxone from community-based organizations and first responders (Spector, Galletly et al. 2022). The lack of data on naloxone distribution through community-based organizations and first responders is mainly a threat to the interpretation of our results on non-synthetic, opioid-related overdose mortality rates. It could be the case that states that adopted dispensing NALs also simultaneously increased naloxone distribution through community-based organizations and first responders, thereby contributing to the effects we observe. However, because we observe significant increases in pharmacy-based naloxone distribution, any increase in naloxone distribution outside of pharmacies does not invalidate the connection between NALs, pharmacy-based naloxone distribution, and non-synthetic, opioid-related overdose mortality rates. Furthermore, because first responders and individuals serving at community-based organizations typically have training and extensive experience administering naloxone, Narcan would have represented a less meaningful innovation addressing the barrier to administer naloxone. Finally, the opioid crisis continues to evolve and is currently being driven by synthetic opioids (i.e., fentanyl). Our results indicate that NALs and Narcan did not significantly affect the rate of overdose mortality involving synthetic opioids. Given the lateness of the introduction of Narcan in the opioid crisis, and the general transition from heroin to

fentanyl in illicit markets, our evidence suggests that single doses of naloxone may be insufficient to fully offset the respiratory impact of the more potent opioids available in the market. This suggests that there may be additional information and other barriers to overcome in using naloxone to help save individuals from overdoses involving synthetic opioids. For instance, treatment of overdoses involving synthetic opioids may require multiple administrations or higher doses of naloxone repeated over time. Additional work is needed to better understand what additional efforts may be required to curb the latest evolution of the opioid crisis.

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## Tables:

**Table 1: Dispensing Naloxone Access Laws Prior to Narcan's Introduction**

| Non-patient specific standing/protocol orders | Prescriptive authority policies |
|---|---|
| Alabama (June 2015) | |
| Arkansas (July 2015) | |
| California (Jan 2014) | |
| Colorado (Apr 2015)* | |
| | Connecticut (June 2015)* |
| Delaware (Aug 2014) | |
| Georgia (Apr 2014) | |
| | Idaho (July 2015) |
| Illinois (Jan 2010) | |
| Indiana (Apr 2015) | |
| Kentucky (June 2013) | |
| Louisiana (Aug 2015) | |
| Maine (Oct 2015)* | |
| Maryland (Oct 2015) | |
| Massachusetts (July 2014) | |
| Minnesota (May 2014)* | |
| Mississippi (July 2015) | |
| Nevada (Oct 2015) | |
| New Hampshire (June 2015) | |
| New Jersey (July 2013) | |
| | New Mexico (March 2014)* |
| New York (June 2014) | |
| North Carolina (Apr 2013) | |
| North Dakota (Aug 2015)* | |
| Ohio (July 2015) | |
| Oklahoma (Nov 2014)* | |
| Oregon (July 2013)* | |
| Pennsylvania (Dec 2014) | |
| Rhode Island (Mar 2014) | |
| South Carolina (June 2015) | |
| Tennessee (July 2014) | |
| Texas (Sept 2015) | |
| Vermont (July 2013)* | |
| Virginia (Apr 2015) | |
| Washington (July 2015) | |
| Wisconsin (Apr 2014) | |

* - indicates states that later adopted the alternative policy. States that adopted non-patient-specific standing/protocol orders or prescriptive authority policies after Narcan's introduction to the marketplace in February 2016 are: Alaska, Arizona, District of Columbia, Florida, Hawaii, Iowa, Kansas, Michigan, Missouri, Montana, South Dakota, Utah, West Virginia, Wyoming. States that, to date, have not adopted either type of policy are: Nebraska.

**Table 2: Summary Statistics**

| | All states | States *with* either NAL in place prior to 2016 | States *without* either NAL in place prior to 2016 | Test of equality of means | Data source |
|---|---|---|---|---|---|
| ***Outcomes (in per 100k rates):*** | | | | | |
| Naloxone claims | 0.42 | 0.53 | 0.15 | 0.00 | Symphony, 2010-2015 |
| Non-synthetic, opioid-related mortalities | 1.52 | 1.49 | 1.59 | 0.10 | NVSS, 2010-2015 |
| ***Demographic characteristics:*** | | | | | |
| Population (mean) | 6,176,384 | 7,089,389 | 3,985,174 | 0.00 | SEER, 2010-2015 |
| Sex (%) | | | | | |
| Male | 49.36% | 49.18% | 49.79% | 0.00 | SEER, 2010-2015 |
| Female | 50.64% | 50.82% | 50.21% | 0.00 | SEER, 2010-2015 |
| Race/ethnicity (%) | | | | | |
| White | 70.88% | 70.40% | 72.02% | 0.11 | SEER, 2010-2015 |
| Black | 11.54% | 12.80% | 8.51% | 0.00 | SEER, 2010-2015 |
| Hispanic | 11.06% | 11.65% | 9.63% | 0.00 | SEER, 2010-2015 |
| Other | 6.52% | 5.13% | 9.84% | 0.00 | SEER, 2010-2015 |
| Age (%) | | | | | |
| 0-24 years | 33.19% | 32.99% | 33.68% | 0.00 | SEER, 2010-2015 |
| 25-44 years | 26.02% | 25.95% | 26.22% | 0.02 | SEER, 2010-2015 |
| 45-64 years | 26.61% | 26.90% | 25.91% | 0.00 | SEER, 2010-2015 |
| 65+ years | 14.17% | 14.16% | 14.19% | 0.80 | SEER, 2010-2015 |
| Insured (%) | | | | | |
| Private | 54.52% | 54.21% | 55.26% | 0.00 | KFF, 2010-2015 |
| Medicaid | 17.75% | 18.23% | 16.59% | 0.00 | KFF, 2010-2015 |
| Medicare | 12.78% | 12.77% | 12.78% | 0.92 | KFF, 2010-2015 |
| Other public assistance | 2.34% | 2.15% | 2.81% | 0.00 | KFF, 2010-2015 |
| Uninsured | 12.61% | 12.64% | 12.55% | 0.75 | KFF, 2010-2015 |
| ***Number of states:*** | 51 | 36 | 15 | | |

Notes: State-level observations. Outcome means are weighted by state population over the 2010-2015 period. The first mortality rate is crude, non-age-adjusted (per 100,000). The second mortality rate is age-adjusted (per 100,000). Column 4 shows the p-value from a test of equality of means comparing states with and without either dispensin NAL in place prior to 2016

**Table 3: Static Average Treatment Effect of the Treatment on the Treated**

| | Claims Rate (per 100k) | | |
|---|---|---|---|
| | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | 1.410*** | 1.256** | 1.410*** |
| | (0.540) | (0.533) | (0.540) |
| Narcan + naloxone access law | 9.195*** | 9.052*** | 9.195*** |
| | (1.763) | (1.767) | (1.763) |
| Naloxone access law (after 2016) | 12.305*** | 12.305*** | 12.731*** |
| | (2.593) | (2.592) | (2.583) |
| Method | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes |

| | Non-Synthetic, Opioid-Related Mortality Rate (per 100k) | | |
|---|---|---|---|
| | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | -0.004 | -0.085 | -0.014 |
| | (0.079) | (0.092) | (0.074) |
| Narcan + naloxone access law | -0.152** | -0.220*** | -0.150** |
| | (0.074) | (0.077) | (0.075) |
| Naloxone access law (after 2016) | -0.621*** | -0.621*** | -0.582*** |
| | (0.194) | (0.194) | (0.209) |
| Method | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes |

Notes: *** 1% significance, ** 5% significance, * 10% significance. For "naloxone access law (prior to 2016)" estimates, N = 1,250. For "Narcan + naloxone access law" estimates, N = 663. For "Naloxone access law (after 2016)" estimates, N=182. All models include group (e.g., state) and period (e.g., quarter) fixed effects. All estimates are weighted by state population. All standard errors are clustered at the state level. Panel B displays effects on crude mortality rates, while Panel C displays effects on direct, age-adjusted mortality rates. Age-adjusted rates are calculated by applying age-specific mortality rates to the 2000 US standard population age distribution. Model (1) uses the difference-in-differences imputation (IDiD) method of Borusyak, Jaravel, and Spiess (2021) without additional control variables. Model (2) adds time-varying policy control variables (+ Policy). Model (3) includes time-varying control variables determined by post-double selection LASSO (+ LASSO).

**Table 4: Synthetic Opioid (e.g. Fentanyl) Overdose Mortality**

| | Synthetic Opioid (e.g. Fentanyl) Overdose Mortality Rate (per 100k) | | |
|---|---|---|---|
| | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | 0.211 | 0.151 | 0.211 |
| | (0.140) | (0.147) | (0.140) |
| Narcan + naloxone access law | 0.351 | 0.339 | 0.351 |
| | (0.450) | (0.449) | (0.449) |
| Naloxone access law (after 2016) | 0.162 | 0.162 | 0.139 |
| | (0.319) | (0.319) | (0.291) |
| Method | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes |

Notes: All outcomes are crude, non-age-adjusted mortality rates. *** 1% significance, ** 5% significance, * 10% significance. For "naloxone access law (prior to 2016)" estimates, N = 1,250. For "Narcan + naloxone access law" estimates, N = 663. For "Naloxone access law (after 2016)" estimates, N=182. All models include group (e.g., state) and period (e.g., quarter) fixed effects. All estimates are weighted by state population. All standard errors are clustered at the state level. Estimates here reflect crude mortality rates (per 100,000). Model (1) uses the difference-in-differences imputation (IDiD) method of Borusyak, Jaravel, and Spiess (2021) without additional control variables. Model (2) adds time-varying policy control variables (+ Policy). Model (3) includes time-varying control variables determined by post-double selection LASSO (+ LASSO).

**Table 5: Placebo Outcomes**

| | Cocaine (Non-Exclusive) Overdose Mortality Rate (per 100k) | | |
|---|---|---|---|
| | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | 0.0834** | 0.061* | 0.040 |
| | (0.037) | (0.032) | (0.036) |
| Narcan + naloxone access law | 0.103 | 0.101 | 0.103 |
| | (0.247) | (0.248) | (0.246) |
| Naloxone access law (after 2016) | -0.029 | -0.029 | -0.161 |
| | (0.140) | (0.139) | (0.175) |
| Method | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes |
| | **Overdose Mortalities Not Involving Natural/Semi-Synthetic Opioids and/or Heroin (per 100k)** | | |
| | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | -0.042 | -0.074 | -0.042 |
| | (0.078) | (0.092) | (0.078) |
| Narcan + naloxone access law | 0.478 | 0.465 | 0.478 |
| | (0.330) | (0.330) | (0.330) |
| Naloxone access law (after 2016) | 0.226 | 0.226 | 0.053 |
| | (0.261) | (0.261) | (0.259) |
| Method | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes |

Notes: All outcomes are crude, non-age-adjusted mortality rates. *** 1% significance, ** 5% significance, * 10% significance. For "naloxone access law (prior to 2016)" estimates, N = 1,250. For "Narcan + naloxone access law" estimates, N = 663. For "Naloxone access law (after 2016)" estimates, N=182. All models include group (e.g., state) and period (e.g., quarter) fixed effects. All estimates are weighted by state population. All standard errors are clustered at the state level. Estimates here reflect crude mortality rates (per 100,000). Model (1) uses the difference-in-differences imputation (IDiD) method of Borusyak, Jaravel, and Spiess (2021) without additional control variables. Model (2) adds time-varying policy control variables (+ Policy). Model (3) includes time-varying control variables determined by post-double selection LASSO (+ LASSO).

**Table 6: Non-Synthetic Opioid-Related Overdose Mortality Heterogeneity**

| | Male (per 100k) | | | Female (per 100k) | | |
|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | -0.051 | -0.189 | -0.189 | 0.043 | 0.015 | 0.015 |
| | (0.115) | (0.143) | (0.143) | (0.066) | (0.072) | (0.072) |
| Narcan + naloxone access law | -0.261 | -0.420* | -0.255 | -0.051 | -0.074 | -0.051 |
| | (0.218) | (0.217) | (0.218) | (0.119) | (0.118) | (0.119) |
| Naloxone access law (after 2016) | -0.870*** | -0.772** | -0.870*** | -0.386*** | -0.375*** | -0.386*** |
| | (0.332) | (0.329) | (0.332) | (0.104) | (0.104) | (0.103) |
| Method | IDiD | + Policy | + LASSO | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes | No | Yes | Yes |

| | Non-Hispanic White (per 100k) | | | Non-Hispanic Black (per 100k) | | |
|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | 0.056 | -0.006 | -0.006 | -0.232 | -0.326 | -0.326 |
| | (0.087) | (0.099) | (0.099) | (0.256) | (0.311) | (0.311) |
| Narcan + naloxone access law | -0.112 | -0.156 | -0.1112 | -0.040 | -0.125 | -0.040 |
| | (0.221) | (0.220) | (0.221) | (0.319) | (0.319) | (0.319) |
| Naloxone access law (after 2016) | -0.564*** | -0.559*** | -0.564*** | 0.453 | 0.497 | 0.453 |
| | (0.191) | (0.175) | (0.190) | (1.050) | (1.163) | (1.047) |
| Method | IDiD | + Policy | + LASSO | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes | No | Yes | Yes |

| | Hispanic (per 100k) | | | Other Race/Ethnicity (per 100k) | | |
|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | -0.052 | -0.083 | -0.083 | -0.287 | -0.222 | -0.222 |
| | (0.120) | (0.157) | (0.157) | (0.227) | (0.191) | (0.191) |
| Narcan + naloxone access law | -0.079 | -0.124 | -0.079 | -0.225 | -0.185 | -0.225 |
| | (0.167) | (0.169) | (0.167) | (0.305) | (0.305) | (0.305) |
| Naloxone access law (after 2016) | -0.373 | -0.235 | -0.373 | -0.486 | -0.353 | -0.486 |
| | (0.291) | (0.256) | (0.291) | (0.377) | (0.385) | (0.377) |
| Method | IDiD | + Policy | + LASSO | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes | No | Yes | Yes |

| | Age 0-24 (per 100k) | | | Age 25-44 (per 100k) | | |
|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | -0.022 | -0.029 | -0.029 | 0.232 | 0.164 | 0.164 |
| | (0.036) | (0.033) | (0.033) | (0.148) | (0.192) | (0.192) |
| Narcan + naloxone access law | -0.110 | -0.114 | -0.110 | -0.036 | -0.079 | -0.036 |
| | (0.079) | (0.079) | (0.079) | (0.319) | (0.321) | (0.319) |
| Naloxone access law (after 2016) | -0.287*** | -0.268*** | -0.287*** | -0.878*** | -0.817** | -0.878*** |
| | (0.082) | (0.078) | (0.082) | (0.326) | (0.337) | (0.325) |
| Method | IDiD | + Policy | + LASSO | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes | No | Yes | Yes |

| | Age 45-64 (per 100k) | | | Age 65+ (per 100k) | | |
|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | -0.204 | -0.412 | -0.412 | -0.085 | -0.169* | -0.169* |
| | (0.225) | (0.280) | (0.280) | (0.057) | (0.096) | (0.096) |
| Narcan + naloxone access law | -0.521 | -0.737* | -0.521 | -0.072 | -0.161 | -0.072 |
| | (0.333) | (0.313) | (0.333) | (0.105) | (0.116) | (0.105) |
| Naloxone access law (after 2016) | -1.150*** | -1.192*** | -1.150*** | -0.133 | -0.096 | -0.133 |
| | (0.364) | (0.413) | (0.364) | (0.185) | (0.211) | (0.185) |
| Method | IDiD | + Policy | + LASSO | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes | No | Yes | Yes |

Notes: All outcomes are crude, non-age-adjusted mortality rates. *** 1% significance, ** 5% significance, * 10% significance. For "naloxone access law (prior to 2016)" estimates, N = 1,250. For "Narcan + naloxone access law" estimates, N = 663. For "Naloxone access law (after 2016)" estimates, N=182. All models include group (e.g., state) and period (e.g., quarter) fixed effects. All estimates are weighted by state population. All standard errors are clustered at the state level. Estimates here reflect crude mortality rates (per 100,000). Model (1) uses the difference-in-differences imputation (IDiD) method of Borusyak, Jaravel, and Spiess (2021) without additional control variables. Model (2) adds time-varying policy control variables (+ Policy). Model (3) includes time-varying control variables determined by post-double selection LASSO (+ LASSO).

**Table 7: Heterogeneity by County Characteristics**

| | County Population: Top Quartile Non-Hispanic Black Claims Rate (per 100k) | | | County Population: Lower Quartiles Non-Hispanic Black Claims Rate (per 100k) | | |
|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | -0.041 | -0.027 | -0.027 | 0.853** | 0.733* | 0.733* |
| | (0.056) | (0.056) | (0.056) | (0.402) | (0.405) | (0.405) |
| Narcan + naloxone access law | 0.109 | 0.165 | 0.113 | 2.815* | 2.826* | 3.111** |
| | (0.743) | (0.665) | (0.742) | (1.564) | (1.558) | (1.444) |
| Naloxone access law (after 2016) | -0.988*** | -0.988*** | -0.988*** | 3.280*** | 3.280*** | 3.260*** |
| | (0.141) | (0.140) | (0.140) | (1.248) | (1.248) | (1.252) |
| Method | IDiD | + Policy | + LASSO | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes | No | Yes | Yes |

| | County Population: Top Quartile Hispanic Claims Rate (per 100k) | | | County Population: Lower Quartiles Hispanic Claims Rate (per 100k) | | |
|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | -0.038 | -0.049 | -0.049 | 1.080** | 0.954** | 0.808* |
| | (0.089) | (0.088) | (0.088) | (0.429) | (0.450) | (0.464) |
| Narcan + naloxone access law | -0.077 | -0.059 | -0.111 | 2.099 | 2.131 | 2.434** |
| | (0.576) | (0.578) | (0.573) | (1.329) | (1.304) | (1.197) |
| Naloxone access law (after 2016) | 0.228 | 0.228 | 0.228 | 4.735*** | 4.735*** | 4.729*** |
| | (0.760) | (0.760) | (0.760) | (1.685) | (1.685) | (1.700) |
| Method | IDiD | + Policy | + LASSO | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes | No | Yes | Yes |

| | County Population: Top Quartile Poverty Claims Rate (per 100k) | | | County Population: Lower Quartiles Poverty Claims Rate (per 100k) | | |
|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | -0.339 | -0.337 | -0.337 | 0.933** | 0.819** | 0.819** |
| | (0.039) | (0.037) | (0.037) | (0.394) | (0.403) | (0.403) |
| Narcan + naloxone access law | 0.287 | 0.297 | 0.291 | 0.527 | 0.561 | 0.793 |
| | (0.316) | (0.312) | (0.315) | (1.259) | (1.231) | (1.182) |
| Naloxone access law (after 2016) | -0.816 | -0.816 | -0.816 | 4.488*** | 4.488*** | 4.479*** |
| | (0.919) | (0.919) | (0.919) | (1.732) | (1.732) | (1.744) |
| Method | IDiD | + Policy | + LASSO | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes | No | Yes | Yes |

| | Rural County Claims Rate (per 100k) | | | Urban County Claims Rate (per 100k) | | |
|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | 0.631 | 0.618 | 0.618 | 0.904** | 0.803** | 0.803** |
| | (0.429) | (0.430) | (0.430) | (0.373) | (0.380) | (0.380) |
| Narcan + naloxone access law | 0.057 | 0.053 | 0.057 | -1.215 | -1.152 | -1.215 |
| | (1.030) | (1.041) | (1.027) | (2.645) | (2.517) | (2.638) |
| Naloxone access law (after 2016) | 1.086 | 1.086 | 1.098 | 5.013*** | 5.013*** | 5.959*** |
| | (0.749) | (0.749) | (0.740) | (0.846) | (0.846) | (0.609) |
| Method | IDiD | + Policy | + LASSO | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes | No | Yes | Yes |

| | County Lacks Chain Pharmacies Claims Rate (per 100k) | | | County Has Chain Pharmacies Claims Rate (per 100k) | | |
|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | 0.072 | 0.072 | 0.072 | 0.780** | 0.684* | 0.684* |
| | (0.058) | (0.058) | (0.058) | (0.365) | (0.367) | (0.367) |
| Narcan + naloxone access law | -2.046 | -2.062 | -2.046 | 0.393 | 0.410 | 0.393 |
| | (2.318) | (2.337) | (2.314) | (1.062) | (1.039) | (1.060) |
| Naloxone access law (after 2016) | -2.359 | -2.359 | -2.405 | 2.924*** | 2.924*** | 3.008*** |
| | (2.581) | (2.581) | (2.743) | (0.742) | (0.742) | (0.718) |
| Method | IDiD | + Policy | + LASSO | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes | No | Yes | Yes |

Notes: *** 1% significance, ** 5% significance, * 10% significance. All models include group (e.g., county) and period (e.g., quarter) fixed effects. All estimates are weighted by county population. All standard errors are clustered at the county level. Model (1) uses the difference-in-differences imputation (IDiD) method of Borusyak, Jaravel, and Spiess (2021) without additional control variables. Model (2) adds time-varying policy control variables (+ Policy). Model (3) includes time-varying control variables determined by post-double selection LASSO (+ LASSO).

**Table 8: Payer Heterogeneity**

| | Private Insurance Claims Rate (per 100k) | | | Other Public Assistance Claims Rate (per 100k) | | |
|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | 0.613*** | 0.536** | 0.613*** | 1.435 | 0.181 | 1.435 |
| | (0.231) | (0.234) | (0.231) | (4.241) | (4.551) | (4.240) |
| Narcan + naloxone access law | 3.818*** | 3.843*** | 3.818*** | -4.909 | -5.373 | -4.909 |
| | (1.147) | (1.143) | (1.146) | (7.428) | (7.578) | (7.419) |
| Naloxone access law (after 2016) | 6.598*** | 6.598*** | 6.767*** | -16.235 | -16.235 | -16.022 |
| | (1.546) | (1.545) | (1.561) | (14.672) | (14.671) | (14.653) |
| Method | IDiD | + Policy | + LASSO | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes | No | Yes | Yes |

| | Medicare Claims Rate (per 100k) | | | Uninsured Claims Rate (per 100k) | | |
|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | 2.513*** | 2.354*** | 2.513*** | 3.043** | 2.478* | 3.043** |
| | (0.759) | (0.777) | (0.759) | (1.331) | (1.275) | (1.331) |
| Narcan + naloxone access law | 12.634*** | 12.606*** | 12.634*** | 3.971*** | 3.957*** | 3.971*** |
| | (3.833) | (3.819) | (3.832) | (1.120) | (1.121) | (1.120) |
| Naloxone access law (after 2016) | 25.738*** | 25.738*** | 26.779*** | 2.890* | 2.890* | 3.148* |
| | (5.553) | (5.551) | (5.529) | (1.741) | (1.741) | (1.685) |
| Method | IDiD | + Policy | + LASSO | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes | No | Yes | Yes |

| | Medicaid Claims Rate (per 100k) | | |
|---|---|---|---|
| | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | 2.036* | 1.907* | 2.036* |
| | (1.104) | (1.081) | (1.104) |
| Narcan + naloxone access law | 14.369*** | 14.313*** | 14.369*** |
| | (3.679) | (3.666) | (3.679) |
| Naloxone access law (after 2016) | 21.295*** | 21.295*** | 22.439*** |
| | (5.386) | (5.386) | (5.341) |
| Method | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes |

Notes: *** 1% significance, ** 5% significance, * 10% significance. For "naloxone access law (prior to 2016)" estimates, N = 1,250. For "Narcan + naloxone access law" estimates, N = 663. For "Naloxone access law (after 2016)" estimates, N=182. All models include group (e.g., state) and period (e.g., quarter) fixed effects. All estimates are weighted by state population. All standard errors are clustered at the state level. Model (1) uses the difference-in-differences imputation (IDiD) method of Borusyak, Jaravel, and Spiess (2021) without additional control variables. Model (2) adds time-varying policy control variables (+ Policy). Model (3) includes time-varying control variables determined by post-double selection LASSO (+ LASSO).

**Table 9: Heterogeneity by Out-of-Pocket Costs**

| | OOP Cost Range: $0-$10 Claims Rate (per 100k) | | | OOP Cost Range: $25-$50 Claims Rate (per 100k) | | |
|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | 0.767** | 0.690* | 0.767** | 0.107* | 0.091 | 0.107* |
| | (0.360) | (0.356) | (0.360) | (0.056) | (0.058) | (0.056) |
| Narcan + naloxone access law | 3.589*** | 3.5741*** | 3.589*** | 0.931*** | 0.932*** | 0.931*** |
| | (0.990) | (0.986) | (0.989) | (0.297) | (0.298) | (0.297) |
| Naloxone access law (after 2016) | 5.783*** | 5.783*** | 6.100*** | 1.475*** | 1.475*** | 1.402*** |
| | (1.685) | (1.684) | (1.681) | (0.357) | (0.357) | (0.363) |
| Method | IDiD | + Policy | + LASSO | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes | No | Yes | Yes |

| | OOP Cost Range: $10-$25 Claims Rate (per 100k) | | | OOP Cost Range: $50+ Claims Rate (per 100k) | | |
|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) |
| Naloxone access law (prior to 2016) | 0.221** | 0.202** | 0.221** | 0.194*** | 0.177** | 0.194*** |
| | (0.099) | (0.101) | (0.099) | (0.070) | (0.069) | (0.070) |
| Narcan + naloxone access law | 1.506** | 1.517** | 1.506** | 0.290*** | 0.277*** | 0.290*** |
| | (0.624) | (0.622) | (0.624) | (0.097) | (0.101) | (0.097) |
| Naloxone access law (after 2016) | 3.569*** | 3.569*** | 3.736*** | 0.435*** | 0.435*** | 0.458*** |
| | (0.785) | (0.784) | (0.794) | (0.088) | (0.088) | (0.086) |
| Method | IDiD | + Policy | + LASSO | IDiD | + Policy | + LASSO |
| Other controls | No | Yes | Yes | No | Yes | Yes |

Notes: *** 1% significance, ** 5% significance, * 10% significance. All models include group (e.g., state) and period (e.g., quarter) fixed effects. All estimates are weighted by state population. All standard errors are clustered at the state level. Model (1) uses the difference-in-differences imputation (IDiD) method of Borusyak, Jaravel, and Spiess (2021) without additional control variables. Model (2) adds time-varying policy control variables (+ Policy). Model (3) includes time-varying control variables determined by post-double selection LASSO (+ LASSO).

**Figures:**

Figure 1: Timing of state adoption of either dispensing naloxone access law (non-patient specific standing/protocol orders, or prescriptive authority)

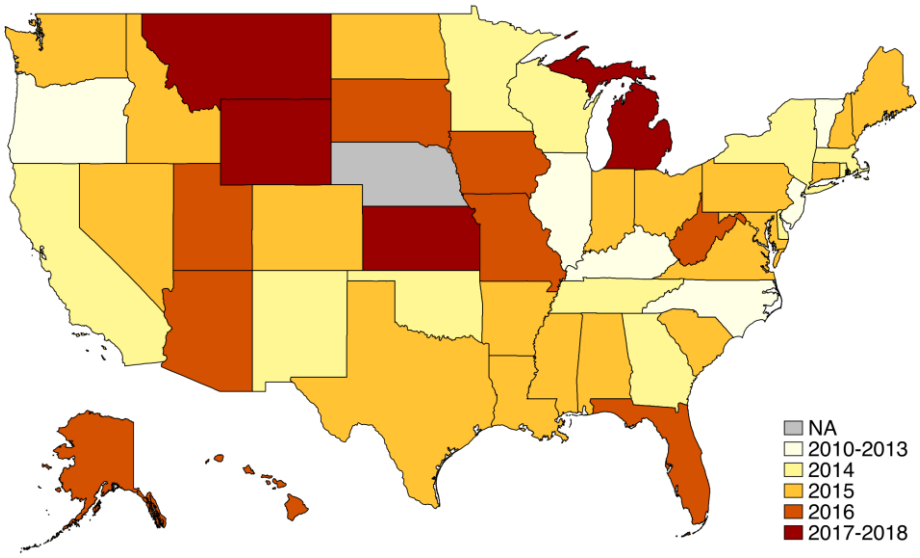



Figure 2: National trends in quarterly naloxone dispensing rate (per 100,000) via retail pharmacies by drug brand (Evzio, generic, and Narcan)

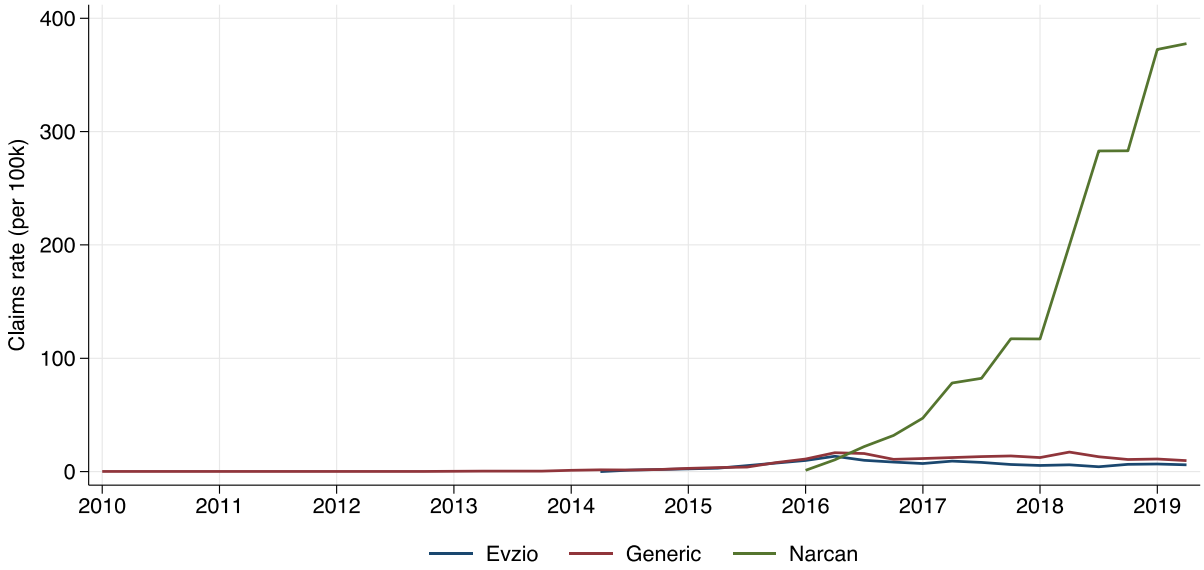


Figure 3: National trends in quarterly overdose mortality rates involving any opioids (blue), and involving natural/semisynthetic opioids and/or heroin but excluding mortalities involving fentanyl

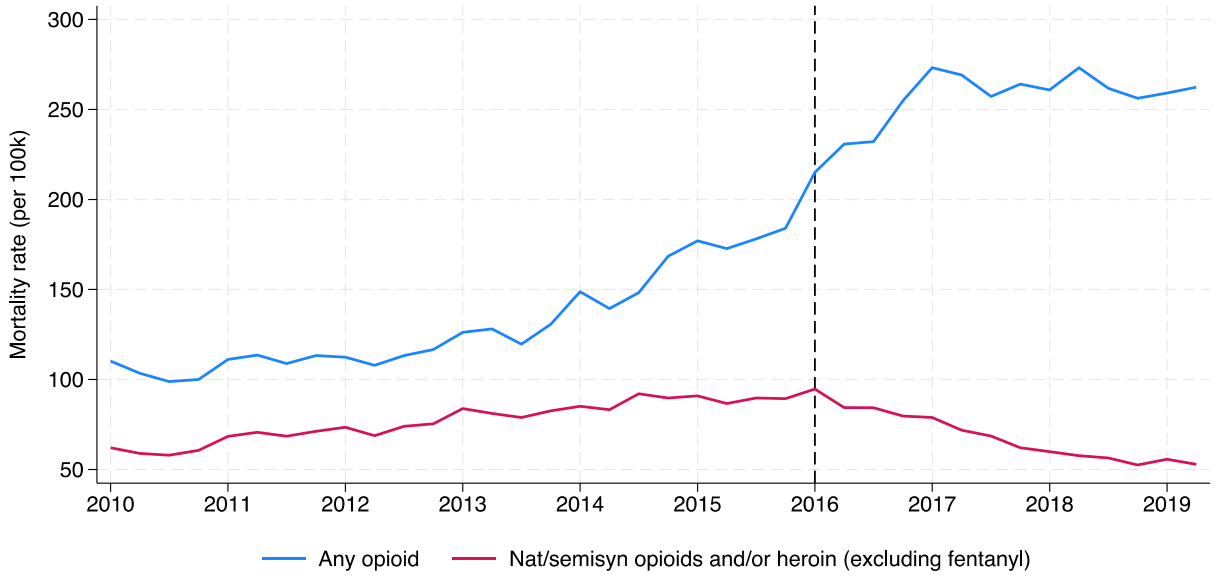



Figure 4: Trends in quarterly naloxone dispensing by dispensing naloxone access law status prior to Narcan's introduction

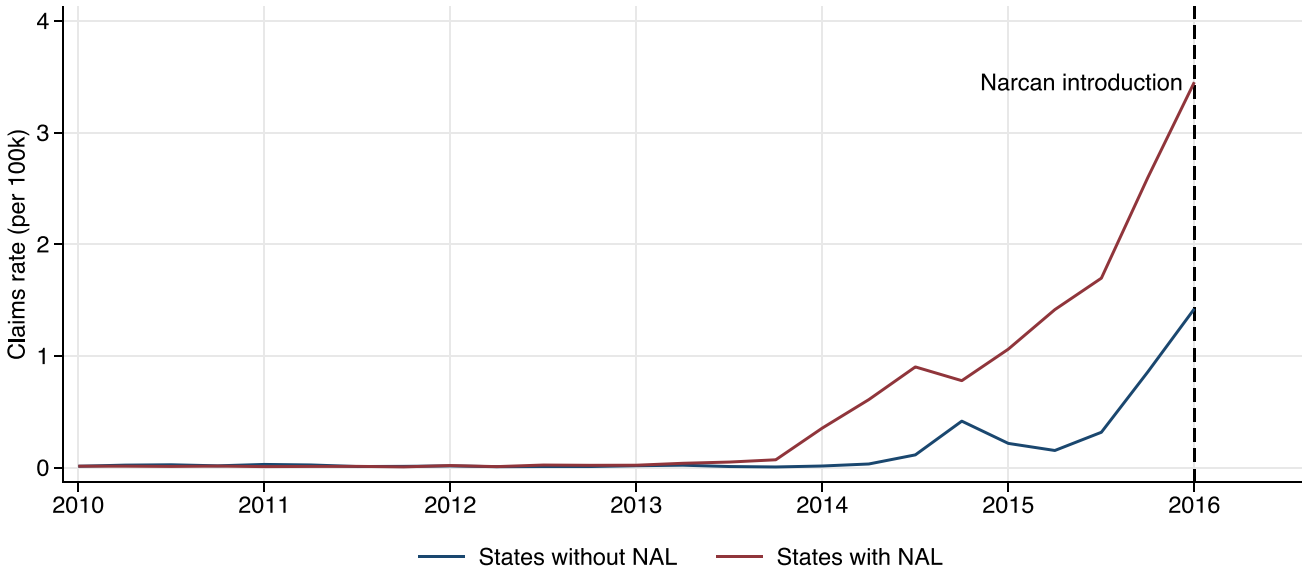
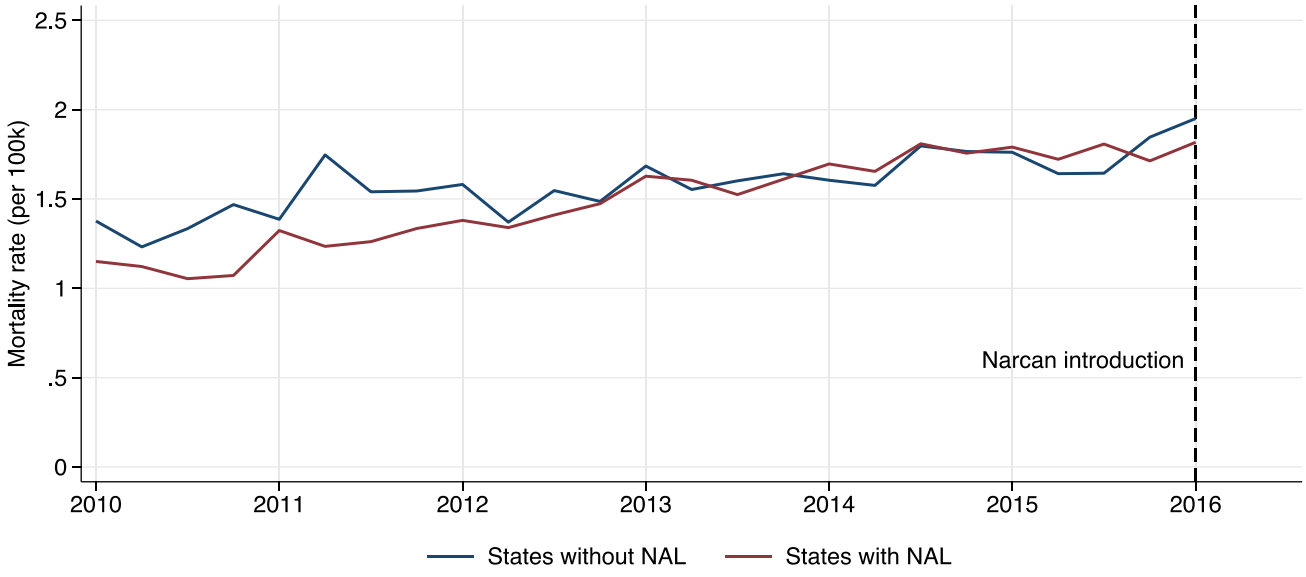


Figure 5: Trends in quarterly non-synthetic, opioid-related overdose mortality rates by dispensing naloxone access law status prior to Narcan's introduction




States with NAL prior to Narcan introduction:
AL, AR, CA, CO, CT, DE, GA, ID, IL, IN, KY, LA, ME, MD, MA, MN, MS, NV, NH, NJ, NM, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VT, VA, WA, WI

Figure 6: Naloxone distribution effects: (top left) dispensing NALs prior to 2016; (top right) Narcan's introduction in states with existing dispensing NALs; and (bottom) dispensing NALs adopted after Narcan's introduction

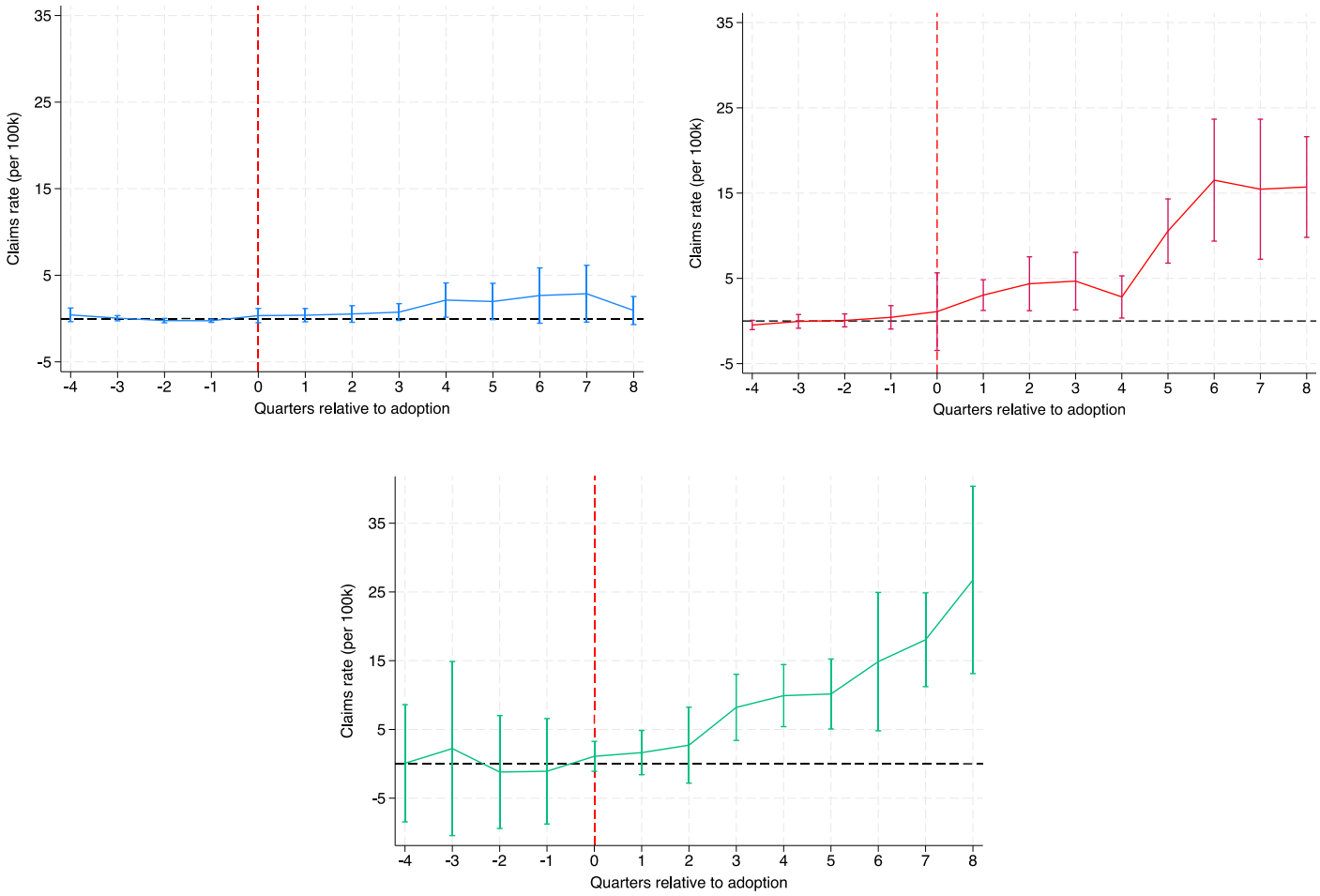


Figure 7: Effects on non-synthetic, opioid-related mortality rates: (top left) dispensing NALs prior to 2016; (top right) Narcan's introduction in states with existing dispensing NALs; and (bottom) dispensing NALs adopted after Narcan's introduction

