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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, including those that permit naloxone to be dispensed by pharmacies directly to consumers. 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 first test the hypothesis that naloxone access laws alone increased the distribution of naloxone prior to Narcan, followed by testing the hypothesis that the introduction of Narcan further expanded naloxone's distribution and its life-saving impacts. We analyze cross-state variation in the adoption of naloxone access laws and their timing relative to Narcan's introduction. We find 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 the laws themselves. We also find that while these naloxone access laws did not reduce non-synthetic opioid-related mortality rates on their own, once Narcan was introduced, these mortality rates significantly declined. These findings indicate the important interaction of innovation and policy.

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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 between 1990-2015 was due to pharmaceutical innovation, driven largely by pharmaceuticals targeting heart disease (Buxbaum et al., 2020). Medical devices have also increased life expectancy, such as the EpiPen, resulting in lower risk of hospitalization and fatality due to anaphylaxis (Fromer, 2016). In nearly all cases, the benefits of these innovations far outweigh the research and development costs (Cutler & McClellan, 2001). However, some innovations have increased mortality. OxyContin 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 (Alpert et al., 2022; Cutler & Glaeser, 2021). Opioid-related mortality has been a major contributor to recent declines in U.S. life expectancy (Woolf & Schoomaker, 2019).

A central pillar of the federal response to the opioid crisis is to improve access to naloxone (Haffajee et al., 2021). 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 has been slow until recently. A presumed primary barrier to distribution and uptake of naloxone has been the legal consequences associated with possessing and/or dispensing naloxone. An increasing number of states have adopted naloxone access laws (NALs) since 2010 in an effort to reduce those legal barriers, and considerable research attention has been given to evaluating their effects on fatal and nonfatal overdoses (Abouk et al., 2019; Rees et al., 2019; Sohn et al., 2019; Doleac and Mukherjee, 2022; Smart et al., 2024).

However, another potential barrier to uptake has been overlooked when considering the impact of these NAL policies: the complexity of administering naloxone. Naloxone, until February 2016, was administered via injection.[1] Someone interested in using naloxone to save lives had to become trained on how to transfer the proper dose from a vile into a clean needle syringe, how to identify the correct part of the body to inject the needle, and how to make sure

[1] Prior to Narcan, some community organizations distributed nasal spray formulations of naloxone, but these were not sold at pharmacies.

that all the medication is extracted from the syringe in a single shot. Given the preparation and skill required, 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 barriers to administering naloxone via a needle, thus broadening naloxone's potential use by untrained laypeople.[2] Narcan nasal spray was the first formulation requiring no assembly, no training, and no needle (NIDA, 2017). Following FDA approval, Narcan became available in the first quarter of 2016 with a prescription; generic versions became available in 2021, and in March 2023 the FDA allowed Narcan to be sold without a prescription.

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" (i.e. standing/protocol orders and prescriptive authority laws) alone, without Narcan. We focus on these policies given that the literature has previously found them to meaningfully improve naloxone access through pharmacies (Abouk et al., 2019; Smart et al., 2024).[3] Once Narcan was approved, its distribution varied substantially across states, due to variation in the existing state legal infrastructure 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 facilitated the distribution of naloxone directly from a pharmacy without a prescription to any individual in a position to save a life. Studying the effects of dispensing NALs enacted after Narcan's introduction between 2016-2019 identifies a similar interactive effect of policy and innovation.

While previous studies have examined dispensing NALs, we are unaware of any other study that has examined the combination of policy and pharmaceutical innovation in this context.

[2] While a pre-filled injectable formulation was available prior to Narcan in 2014, it was more than 4 times as expensive as generic naloxone for people with insurance, making cost a prohibitive barrier to its distribution.
[3] This literature has found that non-dispensing NALs (i.e. those that require a patient-specific prescription to obtain naloxone through a pharmacy) have little impact on naloxone pharmacy dispensing (Smart et al., 2024).

The specific role of pharmaceutical innovation is important in this context as it has implications regarding the market viability of specific naloxone products, which the FDA now allows to be sold over-the-counter. More generally, this study demonstrates the vulnerability to estimating policy effects in dynamic environments where factors outside of the policy can impact policy effectiveness in the real-world. This study identifies and operationalizes a critical source of treatment heterogeneity, which has been previously ignored. This source of heterogeneity almost entirely explains the main policy impacts studied in the literature.

We use the Borusyak et al. (2024) robust difference-in-differences method to estimate the impacts of dispensing NALs and Narcan in each of 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 difference-in-differences method is robust to heterogeneity across groups and periods when treatment adoption is staggered and when treatment heterogeneity is related to covariates (Caetano et al., 2022; Powell, 2023).

The literature has suggested that dispensing NALs independently increase naloxone dispensing. Using pharmacy-level data from Symphony Health, our evidence confirms previous studies showing that states' staggered adoption of dispensing NALs between 2010-2015 (before Narcan) produced statistically significant increases in naloxone dispensing: 1.41 additional claims per 100,000 state residents. However, we 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 important, independent role for the pharmaceutical innovation of Narcan. 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 had implemented a dispensing NAL. Furthermore, we show that dispensing NALs enacted after Narcan's 2016 introduction expanded naloxone dispensing more than dispensing NAL policies adopted prior to Narcan. Together, the evidence indicates that much of the overall impact of NALs on naloxone distribution occurred after the introduction of Narcan. We observe little evidence that our findings are driven by pre-existing trends. In addition, the effects cannot be explained by dispensing NALs improving naloxone access more effectively over time independent of Narcan's introduction.

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 dispensing NALs is mixed (Smart et al., 2021). However, this literature does not distinguish between pre-Narcan and post-Narcan periods. Our approach to examine the role of Narcan's introduction provides some clarity to the existing evidence. During the pre-Narcan period, we observe no evidence that the adoption of dispensing NALs significantly altered the rate of non-synthetic opioid-related mortality (age-adjusted, 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 relative reductions in the rate of non-synthetic opioid-related 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, particularly for certain demographic groups. Narcan combined with a 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. When studying mortality by race and ethnicity, we find that Narcan's introduction only significantly reduced non-synthetic opioid-related overdose mortality rates among non-Hispanic Whites.

In light of the differences in effect sizes across demographic groups, we seek 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 half of Black and Hispanic populations experienced smaller and often non-significant increases in naloxone dispensing following the adoption of dispensing NALs and the introduction of Narcan. Similarly, we find that the adoption of dispensing NALs and the introduction of Narcan exerted smaller and often non-significant effects on naloxone dispensing in rural counties or counties in the top quartile of poverty.

We also examine the role of healthcare infrastructure in naloxone dispensing, specifically how the types of pharmacies (e.g., chain and non-chain) in counties 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 et al., 2022). Echoing this, we find that the adoption of dispensing NALs and the introduction of Narcan produced substantially larger increases in naloxone dispensing in counties with chain pharmacies.

Additionally, 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 that the increase in naloxone distribution caused by dispensing 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 et al., 2022; Jiang et al., 2024). We do not find that Narcan's introduction lowered the monetary costs associated with naloxone, but that utilization increased disproportionately for those with lower out-of-pocket expenses, consistent with important interactive effects though other explanations are also possible.

Finally, and as a complementary measure of the potential downstream impacts of greater naloxone access, we evaluate the effects of dispensing NALs and Narcan on opioid use disorder (OUD) treatment episodes. A goal of improved naloxone access is to not just save lives immediately but also to hopefully provide an opportunity for the affected individual to seek treatment and avoid a future overdose. Medication for OUD (MOUD) has been shown to reduce all-cause and opioid-related mortality among overdose survivors (Larochelle et al., 2018). We find that states' staggered adoption of dispensing NALs between 2010-2015 (pre-Narcan) did not significantly increase the rate of OUD treatment episodes. However, once Narcan was introduced in 2016, the rate of OUD treatment episodes significantly increased in states that adopted dispensing NALs between 2010-2015. These results suggest that greater access to naloxone contributed to the rise in OUD treatment episodes.

This paper makes three primary contributions. First, we document the empirical importance of Narcan as a share of total naloxone dispensed through pharmacies. Naloxone is typically studied in aggregate with less discussion about specific formulations. We use rich

pharmacy claims data to quantify Narcan's market share and uniquely rapid adoption after introduction.

Second, we are the first to explore the potential benefit from and role of innovation related to naloxone delivery in the context of the opioid crisis, and the interactive importance of the legal infrastructure to heighten these benefits. This contribution involves the introduction of a novel empirical strategy designed to test the relative importance of Narcan's introduction in states with pre-existing dispensing NALs permitting its widespread availability. With this approach, we are able to provide a clear explanation for the previous inconsistency in findings from the literature pertaining to the impact of state NAL laws on opioid-related mortality and demonstrate the contribution of harm reduction strategies uniquely. In demonstrating the contribution of harm reduction strategies, we show, via OUD treatment episodes, that greater naloxone access provides an opportunity for overdose survivors to seek treatment and avoid future overdoses.

Third, we provide new evidence that demonstrates how the structural barriers in access to health care through both law and infrastructure limit communities' ability to respond to the opioid crisis in a manner that is equitable for all impacted by it. Structural determinants, in addition to out-of-pocket costs, can impair efforts to prevent overdoses within some vulnerable groups experiencing greater harm and need to be factored into policy responses (Barnett et al., 2023).

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 rate growth (Meinhofer, 2018; Powell & Pacula, 2021; Maclean et al., 2022). Demand-side interventions, including increasing access to treatment, particularly MOUD, have recently received more attention and funding, but these interventions rely on people being able and willing to seek treatment. Our results demonstrate that pharmaceutical innovations combined with harm reduction policies can save lives and create opportunities for individuals to seek treatment. This finding will become increasingly relevant as technological innovations continue to improve. For example, the FDA approved an intranasal nalmefene formulation in May 2023 due to the relative ineffectiveness of naloxone in response to

overdoses involving fentanyl (Coffin et al., 2022). As these new technologies are deployed, many of the same considerations regarding how to quickly dispense them will be relevant.

However, our results also reveal that structural barriers tied to geography are important in understanding the recent shift in opioid related mortality from White to non-White individuals. Counties with high Black and Hispanic populations and high poverty did not experience significant increases in naloxone dispensing following the adoption of dispensing NALs and the introduction of Narcan. Furthermore, the adoption of dispensing NALs and the introduction of Narcan did not significantly increase naloxone dispensing in counties without chain pharmacies (predominantly rural). These barriers to naloxone access caused the reductions in overdose deaths to be unevenly distributed, suggesting the need for further efforts to enhance access to this life-saving drug. Further, we find evidence that cost remains an important potential barrier for some. While dispensing NALs and Narcan dramatically increased naloxone dispensing among those that face low out-of-pocket costs (i.e., Medicaid and Medicare beneficiaries), the impacts of dispensing NALs and Narcan are muted among consumers that typically face higher out-of-pocket costs.

II. Background

Naloxone and Opioid-Related Policies

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. Naloxone typically takes two to three minutes to take effect after its administration.

In recent decades, various types of policies have been implemented by states in an effort to reduce the supply of opioids and mitigate the opioid crisis (Powell & Pacula, 2017). 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 et al., 2019; Alpert et al. 2024). More rigid supply reduction laws began getting adopted starting in 2010, with pain clinic regulations (often referred to "pill mill laws") (Rutkow et al., 2015; Cerdá et al., 2021; Mizushima et al., 2024), and policies limiting the number of days supply that could be dispensed for new prescriptions for opioids to 3- or 7-days supply (Cramer et al., 2021; Sacks et al., 2021). These policies differ in focus from harm reduction policies such as naloxone access laws ("NALs") and Good Samaritan laws, in that the latter emphasize reducing harm associated with use rather than supply explicitly.

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 et al., 2005). Over time, state have tried to relax some of these legal barriers to improve pharmacy access to naloxone for potential bystanders, which is considered the most cost-efficient distribution method to reduce overdose deaths (Townsend et al., 2020). In this study, we examine a group of laws that we term "dispensing NALs." While NALs broadly take different forms,[4] the objective of dispensing NALs is to reduce the legal barriers 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 et al., 2019; Smart et al., 2021). NALs which still require patients to obtain a prescription from a physician or other medical professional do not appear to affect naloxone dispensing (Smart et al., 2024).

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 who may not be using the opioid themselves. Similarly, protocol orders allow pharmacists to dispense to anyone without a prescription but require that the pharmacist have a physician-approved protocol (either from a physician, a medical board, or other state agency reflecting a medical opinion). Prescriptive authority laws go a step further than either standing orders or protocol orders, in that they expand the pharmacist's

[4] For information on the various categories of NALs, see Davis & Carr (2017).

scope of practice, allowing them to directly prescribe and distribute naloxone themselves. We consider standing/protocol orders and prescriptive authority policies as "dispensing NALs" and study their independent impacts as well as their interactions with the introduction of Narcan.

Table 1 lists the timing of implementation of dispensing NALs before Narcan's introduction. Non-patient specific standing/protocol orders (grouped together due to their similarity in practice) and prescriptive authority laws are separated in Table 1. Illinois was the first state to implement a dispensing NAL (a non-patient specific standing order) in 2010. Appendix Figure A.1 visualizes the map of dispensing NAL implementation in each state.

The existing research on NALs is mixed (Smart 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 (Sohn et al., 2019). Smart et al. (2024), in particular, find that prescriptive authority policies are disproportionately effective in areas with physician shortages given that they eliminate the requirement to obtain a prescription from a physician. 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 et al., 2018; Rees et al., 2019) to evidence of no effect on opioid mortality and increased opioid-related emergency department visits (Doleac & Mukherjee, 2022).

Narcan

While NALs have been shown to increase naloxone dispensing (Abouk et al., 2019; Sohn et al., 2019), bystanders and potential overdose victims face other barriers to actually acquiring and using naloxone.[5] 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. So, even if naloxone dispensing increases, the method of administration may continue to act as a barrier to naloxone use due to the need for training and because opioid overdose victims and their observers may fear calling authorities out

[5] There are also concerns that people will not purchase naloxone because of the stigma associated with opioid use disorder (Barnett et al., 2023; Green et al., 2017; Jacobson & Powell 2024).

of risk of being arrested for possession drug paraphernalia, such as the syringe used to administer the dose, if not drug possession/use itself (Bowles, 2017; Tobin et al., 2005).

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. 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 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. 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 (FDA, 2023). The product is simple, painless, can easily be administered by overdose witnesses, delivers greater bioavailability than intramuscular forms, and rapidly produces therapeutic effects. In contrast to Evzio, Narcan was also affordable, with average out-of-pocket costs similar to generic naloxone (Peet et al., 2022). Figure 1 shows that Narcan rapidly became the dominant brand of naloxone, representing 62% of all naloxone dispensed through pharmacies within its first year.

The barriers addressed jointly by both dispensing NALs and the introduction of 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 mortality. We examine the combined effects of dispensing NALs and Narcan in two types of states: 1) states that had dispensing NALs in place prior to Narcan's introduction in early 2016, and 2) states that adopted dispensing NALs after Narcan's introduction.

III. Data

We analyze the impacts of dispensing NALs and the combined impacts of dispensing NALs and Narcan using several 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 mortality rates. Third, we use a policy database detailing the timing of state (and District of Columbia) dispensing 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 dispensing NALs implemented prior to Narcan we will examine the 2010 to 2015 period. To examine the combined impacts of dispensing 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. come 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 sample of U.S. retail pharmacies and approximately 77% of naloxone prescriptions filled in those pharmacies between 2010 and 2019. The data are geographically identified at the 3-digit zip code level, which we crosswalk to counties and states. The Symphony data are 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. 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 1 (referenced above) 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 several dispensing NALs. 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 already 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. 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 mortality 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 but 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. 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 (Amaducci et al., 2023). Fentanyl is 33 to 66 times stronger than natural/semisynthetic opioids, and 10 to 20 times stronger than heroin (Keating & Granados, 2017). Overdoses deaths 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.

We also separately examine overdoses involving synthetic opioids (e.g., fentanyl) other than methadone (T40.4). In addition, as placebo outcome tests, we 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 by the state's population and multiply by 100,000.

Appendix Figure A.2 shows the 2010-2019 national trend in 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 only non-synthetic opioids began to decline as fentanyl's prevalence increased.[6] We age-adjusted our overdose death rates, though results throughout this paper are not meaningfully different if we use unadjusted rates.

Policy 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 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. In this paper, we use the same policy coding studied in Smart et al. (2024) to categorize dispensing NALs.

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

[6] See Moore et al. (2024) for a recent discussion of the fentanyl crisis.

state; and (2) an indicator of states that had a dispensing NAL in place prior to or simultaneous with Narcan's introduction. We separately assess the impact of dispensing NALs prior to Narcan's introduction and afterwards. While the FDA approved Narcan in November 2015, it was not introduced to the marketplace until February 2016. For the analysis, we consider Narcan's introduction to be the first quarter of 2016. We also use OPTIC to describe other policies, specifically Good Samaritan laws (which limit the legal liability of individuals who help overdose victims) (Davis & 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.

Thirty-six states adopted either a non-patient specific standing/protocol order or prescriptive authority NAL prior to Narcan's introduction (see Table 1). Among these 36 states, the vast majority (33) 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 in 2015.

Opioid Use Disorder Treatment Episode Data

To measure OUD treatment episodes, we use the Treatment Episode Data Set (TEDS) for 2010-2019. This data set captures publicly and privately funded annual treatment episodes for individuals ages 12 and older receiving treatment in a state-registered substance abuse treatment facility. While all states are required to report to SAMHSA treatment episodes that are paid for through public funds in specialty treatment settings, states differ in their inclusion of privately-paid episodes as well as the types of facilities that are required to be registered. TEDS records up to three substances being used by an individual at the time of admission and the patient's DSM diagnosis. To study treatment episodes per 10,000, we identify all treatment episodes with a DSM diagnosis of "opioid dependence" or "opioid abuse." While TEDS is the most comprehensive source of national data on specialty substance use treatment, there are concerns

that the TEDS does not capture all sources of treatment and that there may be inconsistent reporting standard across states (Batts et al., 2014). However, it is unlikely that these factors changed disproportionately in states adopting NALs or systematically at the time of Narcan's introduction. To account for potential confounding changes in reporting, we also study the percent of OUD treatment episodes relative to all substance use treatment episodes.

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 the rates of naloxone claims, non-synthetic opioid-related mortality (age-adjusted), OUD treatment episodes, and the average out-of-pocket cost per claim. 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. Appendix Figure A.3 (top) expands on this comparison, showing the 2010-2015 naloxone dispensing trends in states with and without a dispensing NAL before Narcan's introduction.

Additionally, Table 2 describes the age-adjusted rates of overdose mortality involving non-synthetic opioids in states with and without a dispensing NAL before 2016. Comparing these two groups of states, the age-adjusted rates of overdose mortality involving non-synthetic, opioids in states without a dispensing NAL were significantly higher than in states with a dispensing NAL before 2016. Appendix Figure A.3 (bottom) expands on this comparison, showing trends in the 2010-2015 age-adjusted rates of overdose mortality involving non-synthetic, opioids in states with and without a dispensing NAL before Narcan's introduction. The trends show that the differences between states with and without a dispensing NAL were larger between 2010-2012, but between 2013-2015 the age-adjusted rates of overdose mortality involving non-synthetic opioids are approximately equivalent and parallel in the two groups of states.

Table 2 also shows that the rate of OUD treatment episodes among individuals with an opioid-use disorder differs between states with and without a dispensing NAL before 2016. The

rate of OUD treatment episodes in states with a dispensing NAL before 2016 is 1.73 times higher than the same rate in states without a dispensing NAL before 2016. Additionally, Table 2 describes the differences in the average out-of-pocket cost per claim paid by consumers in states with and without a dispensing NAL before 2016. Consumers in states without a dispensing NAL before 2016 paid approximately $4.50 more than consumers in states with a dispensing NAL before 2016, but the difference is not statistically significant.

We 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 a dispensing NAL before 2016. States without a dispensing NAL before 2016 had larger population shares 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 across states.

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 et al. (2024) imputation difference-in-differences (IDiD) method.[7]

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 et al. (2024) 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

[7] This "imputation approach" is also discussed in Gardner (2022).

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:

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

$Y_{it}(0)$ denotes the untreated outcome of interest for state (or county) *i* at time *t*. It is only observed for untreated observations. Our models for naloxone claims and overdose mortality 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. The treatment episode analysis uses year as the temporal unit due to the availability of the data. While state boundaries likely do not appropriately define naloxone distribution markets, NALs are implemented at the state-level and performing state-level analyses 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.

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. For experimental setting (1), the sample period is 2010-2015 and the first stage is estimated using observations without dispensing NALs.[8] For the experimental setting (2), we study 2010-2019. The treated group is comprised of states with a dispensing NAL at the beginning of 2016. Because we anticipate that NALs themselves potentially have independent effects on our outcomes (as tested in the first experimental setting), we do not want to consider the pre-Narcan observations with NALs as "untreated." Instead, we use only observations untreated by dispensing NALs to estimate the unit fixed effects, time fixed effects, and $\boldsymbol{\delta}$ when estimating equation 1. However, "treatment" is limited to states having a NAL at the beginning of 2016 interacted with post-2016 time periods. This approach holds the policy constant and uses only the interaction for identification. To avoid attenuating the estimates as the non-NAL states adopt NALs after Narcan, we drop observations that adopt a NAL after the first quarter of 2016 for this

[8] Smart et al. (2024) find that non-dispensing NALs have little impact on naloxone access and use them as part of the comparison (i.e., "untreated") group. We follow this approach.

setting. Note that the treated units in experimental setting (2) should have a differential pre-trend if NALs themselves have independent impacts on the outcomes. Given this, when evaluating pre-treatment estimates, we consider the pre-treatment differences from experimental setting (1) as the appropriate parallel trends test for both experimental settings (1) and (2).[9]

To analyze experimental setting (3), we study 2016-2019, limiting the sample to states without a NAL at the beginning of 2016. The untreated observations are those without NALs. The pre-treatment estimates operate as valid placebo estimates since we assume (and test) that adopting and non-adopting states in this sample had similar responses to Narcan's introduction prior to NAL adoption.

For each setting, the second stage calculates the effects of NALs and Narcan as the difference between the observed outcome and the estimated counterfactuals. We normalize the average difference across the year prior to treatment to zero.[10] 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 covariates included in the model. These are placebo estimates which provide a test for the appropriateness of the experiment. We note that pre-treatment estimates from an imputation approach are not necessarily comparable to the post-treatment estimates, but both sets of estimates provide important independent information (i.e., pre-period estimates help test the validity of the experiment while post-period estimates reflect the dynamic impacts of the policy). We provide estimates for 4 quarters prior to treatment and 8 quarters after treatment.[11]

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 (Medicaid expansion,

[9] As always, the parallel trends assumption cannot be perfectly tested so we must rely on pre-period placebo estimates. For experimental settings (1) and (2), we rely on the same pre-period estimates.
[10] The estimator naturally normalizes the average of the entire pre-period to zero. We re-normalize to 0 in the four quarters prior to treatment since our event studies show the 4 quarters prior to treatment. This re-normalization maintains a consistent normalization period across quarterly and annual outcomes while also visually focusing the pre-period assessment on systematic differences in *trends*.
[11] We do not "bin" the endpoints.

and Good Samaritan laws) which we denote as "+Policy." We also estimate models which include control variables selected by post-double selection LASSO (Belloni et al., 2012) from among a wide selection of policy indicators, demographic characteristics, rates of OxyContin misuse prior to reformulation (2004-2009),[12] and interactions of those covariates with "ever treated" and, separately, time indicators. This model is denoted as "+LASSO." The latter interactions guard against the confounding influences of: (1) covariates having different relationships for the treated and untreated observations, and (2) changes in these relationships over time. These sources of heterogeneity could potentially and problematically be assigned to the treatment effects. Permitting this heterogeneity during estimation reduces concerns about this type of confounding variation.

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 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 mortality. We also study treatment episodes in the first two experimental settings.

Naloxone Claims

First, we 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).[13] Each of these estimates are significant at the 5% level, and they do not meaningfully differ across models. 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

[12] The rate of OxyContin misuse prior to reformulation has been shown to be a strong predictor of growth in heroin deaths (Alpert et al., 2018) and overdose deaths since 2010 (Powell & Pacula, 2021). This variable is collinear with the state fixed effects, but the interactions with time fixed effects – the meaningful predictors in the reformulation literature – can be selected by LASSO.

[13] Note that in this case (and others in which the +LASSO results do not differ from the IDiD or +Policy results), the post-double selection LASSO method does not select any time-varying covariates.

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. 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.[14]

Figure 2 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. We observe little evidence of pre-existing trends.

Next, the top right panel shows the dynamic effects of Narcan's introduction in states that had pre-existing dispensing NALs. The pre-trends, as expected, reflect a relatively small increase due to NAL adoption. As discussed, we refer to the pre-period estimates from the top left panel as the valid pre-period placebo estimates for the Narcan experimental setting. 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 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,

[14] Since we are using non-NAL states as the comparison group, we cannot estimate the independent impact of Narcan on states without NALs.

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.

Overall, the results suggest an important role for Narcan as states with pre-existing NALs experienced a jump in claims beginning right after Narcan's introduction. If it were not Narcan's introduction, but rather a simple change in the effectiveness of the NAL laws being adopted, we would likely not have seen such a sudden jump in states with *pre-existing* NALs. However, these results do not preclude the possibility that dispensing NALs simply became more effective over time or exerted greater impact as the opioid crisis worsened, rather than being catalyzed by Narcan's introduction. To assess this possibility, we analyzed the effects of dispensing NALs by time of adoption prior to Narcan: pre-2014 (6 states), 2014 (11 states), early-2015 (Q1-Q2, 4 states), 2016 (9), and 2017 (5).[15] The results are presented in Appendix Figure A.4. The pre-Narcan results do not convey any systematic relationship between the adoption date and the effectiveness of the dispensing NALs. The 2014 dispensing NALs appear to have the largest effects on claims, followed by the pre-2014 dispensing NALs. The early-2015 dispensing NALs had little effect on claims. If more recent dispensing NALs were simply more effective, we would expect especially large effects for the early-2015 NALs. In the top right panel, we disaggregate the post-Narcan groups to illustrate similar heterogeneity. While the disaggregated estimates are imprecise, we observe growth in claims in both post-Narcan groups (2016 dispensing NALs and 2017 dispensing NALs).

Non-Synthetic Opioid-Related Overdose Mortality Rates

We next examine the downstream effects of dispensing NALs and Narcan on overdose death rates. First, we consider the effects of dispensing NALs adopted prior to Narcan's introduction. The second panel of Table 3 shows that before Narcan's introduction, dispensing NALs did not significantly change the age-adjusted rate of non-synthetic opioid-related mortality. This means that while, as discussed, dispensing NALs adopted prior to Narcan's

[15] We excluded late-2015 adopters to ensure that we had a meaningful number of post-adoption quarters to study prior to Narcan's adoption.

introduction modestly increased naloxone distribution, the increase in naloxone access did not translate into a significant reduction in the number of lives lost during the 2010-2015 period. However, with the introduction of Narcan, we estimate a marginally significant reduction in the age-adjusted rate of non-synthetic opioid-related mortality 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 -0.12 (+ Policy, not significant) to -0.14 (IDiD and + LASSO, significant at the 10% level) per 100,000. 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 -0.60 (+ Policy, significant at the 1% level) and -0.64 (IDiD and + LASSO, 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 3. 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-Q2 NALs are shown to reduce the rate of non-synthetic opioid-related mortality by between -0.10 and -0.14 per 100,000, but the effects are not statistically significant at the 5% level until Q3 (-0.18). 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 3 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 age-adjusted 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. Then, in Q2 we observe the first significant reduction in the age-adjusted rate of non-synthetic opioid-related mortality (-0.19 per 100,000, significant at the 5% level). Subsequently, the majority of the estimates are statistically significant at the 5% level.

Finally, we examine the dynamic effects of dispensing NALs adopted after Narcan's introduction (bottom panel of Figure 3). 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.

While the evidence points to the important, catalyzing role of Narcan, the precise mechanism is unclear. On the one hand, the larger mortality reductions that follow the introduction of Narcan may simply reflect the greater quantity of naloxone claims (as shown in the previous section). Alternatively, the larger mortality reductions that follow the introduction of Narcan may be due to *who* is purchasing Narcan. For instance, the results may also be explained if, compared to naloxone administered through injection, Narcan better enables layperson witnesses to administer naloxone to an overdose victim. As before, we also examine whether the results are driven by trends in the effectiveness of dispensing NALs. To do so, we repeat the analysis by time of dispensing NAL adoption and present the mortality results in Appendix Figure A.4. We do not observe evidence that dispensing NALs prior to Narcan become increasingly effective, while the 2016 and 2017 dispensing NALs both lead to larger reductions in mortality.

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 & Granados, 2017) that a single dose of naloxone is typically insufficient to prevent complete collapse. Instead, treatment of overdoses involving fentanyl generally require higher and/or multiple doses delivered rapidly (Amaducci et al., 2023). Indeed, our results suggest that even the innovation of Narcan in combination with dispensing NALs is insufficient to reduce the rate of overdose mortality involving synthetic opioids during the period evaluated. This result 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 (dispensing 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 Appendix Table A.1, we examine the impact of dispensing NALs with and without Narcan on rates of overdose mortality involving (1) cocaine (top panel), and (2) any 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, neither dispensing NALs nor the introduction of Narcan has influenced drug mortality rates involving drugs unaffected by naloxone's harm reduction potential. This result reinforces both our null effect findings for synthetic opioids shown in Table 4 and provides evidence that our main findings presented in Table 3 are being driven by the introduction of an innovative delivery mechanism of naloxone – Narcan.

Treatment Episodes

As a complementary measure of the downstream impacts of greater naloxone access, we study the effects of dispensing NALs and Narcan on OUD treatment episodes. Ideally, harm reduction strategies would work to save lives of individuals who experience an opioid overdose, thereby enabling them to seek treatment for their OUD. Consequently, if improvements in naloxone access work as hypothesized, fewer fatal overdoses would then lead some share of those saved to seek treatment. Using annual TEDS data from 2010-2019, we test this hypothesis by estimating our model for the first two experimental settings.[16]

Our results provide some evidence of increased OUD treatment episodes following the adoption of dispensing NALs and the introduction of Narcan (Table 5 and Figure 4). For pre-Narcan dispensing NALs, the average, static effects on the rate of treatment episodes (per 10,000) are between 4.17 (+ Policy and +LASSO, not significant) and 4.92 (IDiD, significant at the 10% level). Then, when Narcan is introduced, the rate of opioid treatment episodes (per

[16] Because the TEDS data is state-year and all post-Narcan dispensing NALs are adopted in 2016 or 2017, we are left with either 0 or 1 pre-treatment periods with which to estimate the third experimental setting.

10,000) in states with existing dispensing NALs grows to approximately 8.6 (statistically significant at the 10% level).[17] In order to assess whether these results are sensitive to systemic changes in reporting and other factors, we also examine the effects of dispensing NALs and Narcan on OUD treatment episodes as a percentage of all substance use treatment episodes. These results mirror the per capita rate of treatment episodes, suggesting that dispensing NALs increase the percentage of treatment episodes which are for opioids by 2.48 (+ Policy and +LASSO, not significant) to 2.69 (IDiD, significant at the 5% level) percentage points, and Narcan's introduction increases this to 5.2 percentage points (significant at the 5% level). The dynamic estimates in Figure 4 suggest an immediate effect following Narcan's introduction which grows in the following years. Overall, these results provide suggestive evidence of an increase in OUD treatment episodes resulting from the introduction of Narcan, which supports the idea that increasing naloxone access leads some of the individuals saved by naloxone to seek treatment.

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. We next consider heterogeneity in our findings.

Demographics and Geography

We first examine heterogeneity in the responsiveness of non-synthetic opioid-related mortality. Appendix Table A.2 shows results by sex, race/ethnicity, and age. First, we consider differences by sex. We observe no significant, sex-specific effects of dispensing NALs adopted prior to 2016. However, once Narcan is introduced, both male and female non-synthetic opioid-related mortality rates 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

[17] When interpreting the magnitude of the effects of dispensing NALs and Narcan on the rate of OUD treatment episodes, it is important to note the following: (1) TEDS data describe episodes, not individuals, and which may inflate the magnitude of the treatment episodes relative to deaths because individuals can seek treatment multiple times within a year; (2) TEDS is annual while our mortality estimates are quarterly; (3) OUD treatment episodes may also involve an individual's abuse of fentanyl, while our mortality results focus on the those related to prescription opioids and/or heroin.

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) per 100,000.

Next, we consider differences by race/ethnicity. First, we observe no significant effects of dispensing NALs adopted prior to 2016 among any racial/ethnic group. Similarly, while the estimates are negative, 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 White individuals. 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 the non-Hispanic White population. While the point estimates for Hispanic individuals and other races/ethnicities are suggestive of reductions in non-synthetic opioid-related mortality, they are not statistically significant. On the other hand, the point estimates for non-Hispanic Black individuals are positive though especially noisy.

We also consider differences by age group. Here, we 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 10% level). Dispensing NALs adopted prior to 2016 did not produce significant effects among any other age group, but the largest point estimate in magnitude 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 states 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 1% 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 1% 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. While our prescription claims data do not adequately describe patient demographics,[18] we can consider whether a county's demographic characteristics are associated with more or less distribution of naloxone. Appendix Table A.3 presents findings on naloxone distribution by county population characteristics, specifically race/ethnicity, poverty, and rurality. While the previous results use state-level analysis, to explore heterogeneity, here we conduct the analysis at the county level. We first compare the effects of NALs and Narcan in the counties in the top and bottom half of the distribution of share of the population that is non-Hispanic Black. These results indicate that while the introduction of Narcan in states with existing NALs significantly increased the distribution of naloxone in counties in the top half of non-Hispanic Black populations, generally, the impact of NALs and Narcan were concentrated and significantly larger in counties with smaller 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, while counties with smaller Hispanic populations saw large and significant increases in naloxone distribution. High poverty counties in states with existing NALs experienced increases in naloxone distribution once Narcan was introduced, but the effects of NALs and Narcan were concentrated in counties with lower rates of poverty. Similarly, while NALs and Narcan significantly increased naloxone distribution in rural counties beginning in 2016, the effects were significantly and meaningfully smaller than the increases in naloxone distribution observed in urban counties.

Additionally, Appendix Table A.3 shows how the effects of NALs and Narcan differ by the types of pharmacies found in counties. Naloxone can be difficult to find and many

[18] We observe claims by demographic characteristics, but there are large categories for "missing" given that demographic information is often imputed by Symphony Health using auxiliary information that is unavailable for large shares of the population.

pharmacies simply do not stock it (Eldridge et al., 2020; Lozo et al., 2019). However, chain pharmacies are much more likely to carry naloxone (Lai et al., 2022). Using data from the National Plan & Provider Enumeration System (NPPES) containing all pharmacies that accept Medicare or Medicaid, we geocoded each pharmacy, identifying the state and county of each. Using the name of the pharmacy in the NPPES data, we identified well-known chain pharmacies (e.g., CVS, Walgreens, Rite-Aid), as well as pharmacies of chain grocers (e.g., Walmart, Target, Kroger), pharmacies of health systems (e.g., Kaiser, Cigna), and smaller chain pharmacies (defined, following the literature standard, as more than 5 individual pharmacies, e.g. Nind et al., 2022). Remaining pharmacies are independent and comprise 32.6% of all pharmacies in our data (for 2010-2019), similar to the 34% reported by the 2021 National Community Pharmacists Association annual report (NCPA, 2021).[19] We estimate differential impacts by whether the county has a chain pharmacy or not. We find that counties with chain pharmacies experienced a significant increase in naloxone distribution following the introduction of Narcan, while counties without chain pharmacies (which are predominantly rural) experienced substantially smaller increases in naloxone distribution that were only significant for post-2016 NALs.

Insurance and Costs

Differences identified across counties with specific characteristics may simply reflect variation in insurance rates, and research has already shown that insurance status plays an important role in access to naloxone (Jiang et al., 2024; Peet et al., 2022). To explore this, we examine heterogeneity in the payer-specific effects of NALs and Narcan (Appendix Table A.4), using insurance information in our claims data and performing the analysis at the state level. 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). These NAL-specific results parallel similar findings in Smart et al. (2024). While we observe no statistically significant

[19] Note that the indicator of the presence of a chain pharmacy in the county is time-varying. However, in practice, counties infrequently change from having or not having a chain pharmacy in the study period (7.2% of counties).

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 with insurance coverage, 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 1% 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 1% level) among Medicare beneficiaries, and between 21.3 and 22.4 additional claims per 100,000 (significant at the 1% 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 mediate the effects of dispensing NALs and Narcan. To examine this further, we first examine whether the adoption of dispensing NALs and the introduction of Narcan led to any changes in the nominal out-of-pocket costs paid by consumers. Replacing naloxone claims rate with out-of-pocket costs per claim as the outcome, Appendix Table A.5 shows that while the point estimates suggest a decline in out-of-pocket costs beginning with Narcan's introduction, the estimates are imprecise and not statistically significant. This indicates that, on average, the adoption of NALs and the introduction of Narcan did not significantly alter the nominal out-of-pocket costs faced by consumers.

However, out-of-pocket costs may still represent a barrier to access for some consumers. We study claims based on the average out-of-pocket costs in a cell (3-digit zip code, year-quarter, dosage, payer type, and drug brand level) and display these results in Table 6. The motivation of this analysis is to study purchases at specific costs to the consumers. In each of 4 ranges of out-of-pocket costs ($0-$10, $10-$25, $25-$50, and $50+), we observe 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. 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.

The caveat with these results is that we do not observe out-of-pocket costs at the individual level. Instead, we observe claims and out-of-pocket costs in the Symphony Health data at the 3-digit zip code, year-quarter, dosage, payer type, and drug brand level. If the true, unobserved, individual-level data is left skewed then the out-of-pocket costs that we observe may underestimate the willingness to pay higher prices. However, the data that we observe is right skewed, suggesting that if the individual-level data is similarly skewed, our results actually overestimate the willingness to pay higher prices.

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 et al., 2018). 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 overdose victim or bystander to obtain a prescription from their healthcare provider. Instead, potential overdose victims as well as 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 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. 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. Moreover, bystanders will have much quicker response times.

We provide evidence that dispensing NALs alone increased naloxone distribution in some communities, but that Narcan's introduction greatly expanded naloxone distribution in states with existing dispensing NALs. We find that dispensing 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 dispensing NALs, naloxone dispensing significantly increased by between 9.05 and 9.20 additional claims per 100,000 in states with dispensing NALs. The relative increase in dispensing began immediately after Narcan's introduction and there is little evidence of any pre-introduction effect, suggesting that this differential effect was due to the availability of Narcan.

States that adopted dispensing 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. 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 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 dispensing NALs and the introduction of Narcan. We find significant differences in the mortality effects of dispensing 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 White individuals experienced the largest

reductions in mortality rates from dispensing 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 dispensing NALs and the introduction of Narcan was concentrated outside of counties with high Hispanic and non-Hispanic Black populations. Additionally, our results demonstrate that the adoption of dispensing NALs and the introduction of Narcan did not significantly increase naloxone access in high poverty counties, rural counties, and counties without chain pharmacies (e.g., CVS, Walgreens). 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 dispensing 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 non-Hispanic Black and Hispanic populations, 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. 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 dispensing 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 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; Powell & Pacula, 2021; Maclean et al., 2022). Demand-side interventions, including increasing access to treatment, particularly MOUD, have recently received more attention and funding, but these policies 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 such as crime (Doleac & Mukherjee, 2022). In contrast, our results indicate no moral hazard, at least in terms of overdose deaths. While our results show that dispensing NALs 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 mortality rates significantly declined. Moreover, our results suggest that dispensing NALs and Narcan also increase the rate of OUD treatment episodes, suggesting that harm reduction works as hypothesized, saving the lives of individuals that experience an opioid overdose and enabling them to seek treatment.

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 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 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 independent connections between NALs, pharmacy-based naloxone distribution, and non-synthetic opioid-related 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:					
Naloxone claims (per 100k)	0.42	0.53	0.15	0.00	Symphony, 2010-2015
Non-synthetic, opioid-related mortalities (per 100k)	1.53	1.50	1.61	0.05	NVSS, 2010-2015
Opioid use disorder treatment episodes (per 10k)	10.94	14.17	8.17	0.00	TEDS, 2010-2015
Out-of-pocket cost per claim	45.70	44.76	49.29	0.60	Symphony, 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 rate of non-synthetic, opioid-related mortality is age-adjusted (per 100,000). The rate of substance use treatment episodes is among the population of individuals with opioid-use disorder (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 Age-Adjusted Mortality Rate (per 100k)		
	(1)	(2)	(3)
Naloxone access law (prior to 2016)	0.005	-0.074	-0.074
	(0.080)	(0.094)	(0.094)
Narcan + naloxone access law	-0.144*	-0.122	-0.143*
	(0.074)	(0.077)	(0.075)
Naloxone access law (after 2016)	-0.635***	-0.602***	-0.635***
	(0.192)	(0.207)	(0.192)
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 direct age-adjusted mortality rates 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) Mortality

	Synthetic Opioid (e.g. Fentanyl) Age-Adjusted Mortality Rate (per 100k)		
	(1)	(2)	(3)
Naloxone access law (prior to 2016)	0.221	0.160	0.160
	(0.150)	(0.159)	(0.159)
Narcan + naloxone access law	0.473	0.375	0.473
	(0.297)	(0.292)	(0.297)
Naloxone access law (after 2016)	0.201	-0.054	0.201
	(0.339)	(0.257)	(0.338)
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 direct age-adjusted mortality rates (per 100,000) 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 5: Static Effects of NALs and Narcan on Treatment Admissions

	OUD Treatment Episodes (per 10k)		
	(1)	(2)	(3)
Naloxone access law (prior to 2016)	4.917*	4.172	4.172
	(2.930)	(3.111)	(3.111)
Narcan + naloxone access law	8.608*	8.572*	8.608*
	(5.090)	(5.186)	(5.090)
Naloxone access law (after 2016)			
Method	IDiD	+ Policy	+ LASSO
Other controls	No	Yes	Yes

	OUD Treatment Episodes Percent of All Admissions		
	(1)	(2)	(3)
Naloxone access law (prior to 2016)	2.685	2.484	2.484
	(2.660)	(3.224)	(3.224)
Narcan + naloxone access law	5.238**	5.221**	5.239**
	(2.597)	(2.630)	(2.597)
Naloxone access law (after 2016)			
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 = 287. For "Narcan + naloxone access law" estimates, N = 388. For "Naloxone access law (after 2016)" estimates, N=126. However, the effects of "Naloxone access law (after 2016)" cannot be estimated due to a lack of pre-treatment time periods (by year). All models include group (e.g., state) and period (e.g., year) fixed effects. All estimates are weighted by state population. All standard errors are clustered at the state level. Panel A displays effects on treatment admissions per 10,000 population. Panel B displays effects on treatment admissions per estimated OUD (see Krawczyck et al, 2022). 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: Heterogeneity by Out-of-Pocket Costs

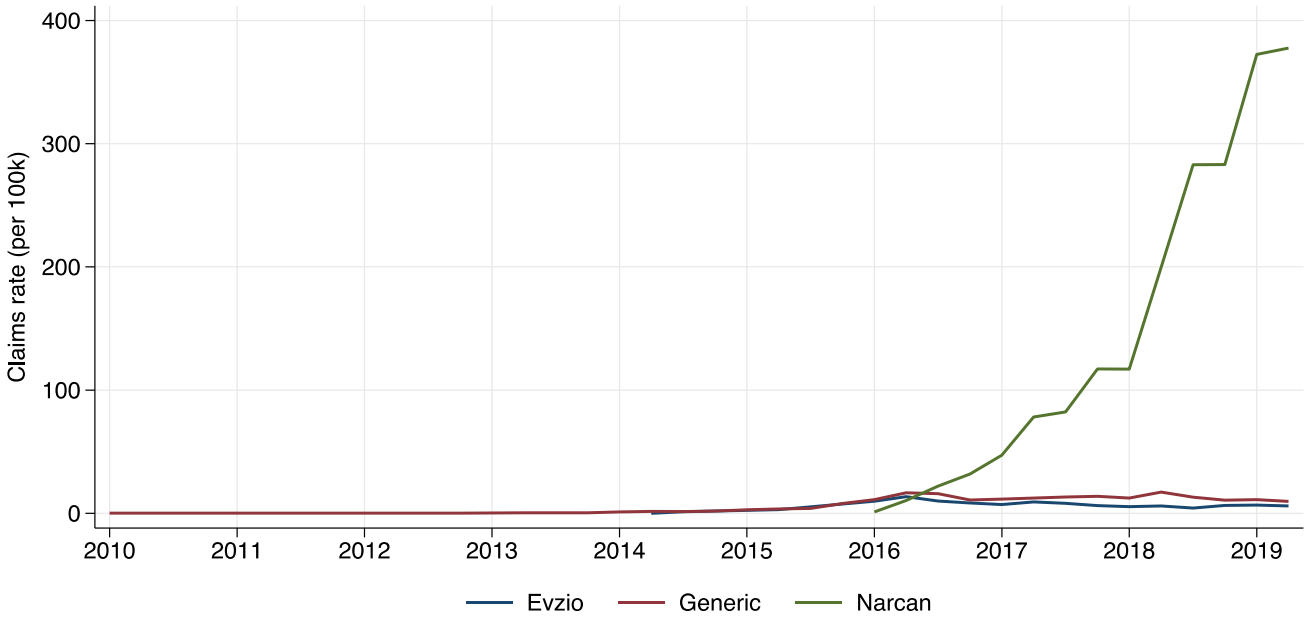
	OOP Cost Range: $0-$10 Claims Rate (per 100k)			OOP Cost Range: $25-$50 Claims Rate (per 100k)		
	(1)	(2)	(3)	(1)	(2)	(3)
Naloxone access law (prior to 2016)	0.767**	0.690*	0.767**	0.107*	0.091	0.107*
	(0.360)	(0.356)	(0.360)	(0.056)	(0.058)	(0.056)
Narcan + naloxone access law	3.589***	3.5741***	3.589***	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. 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 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).

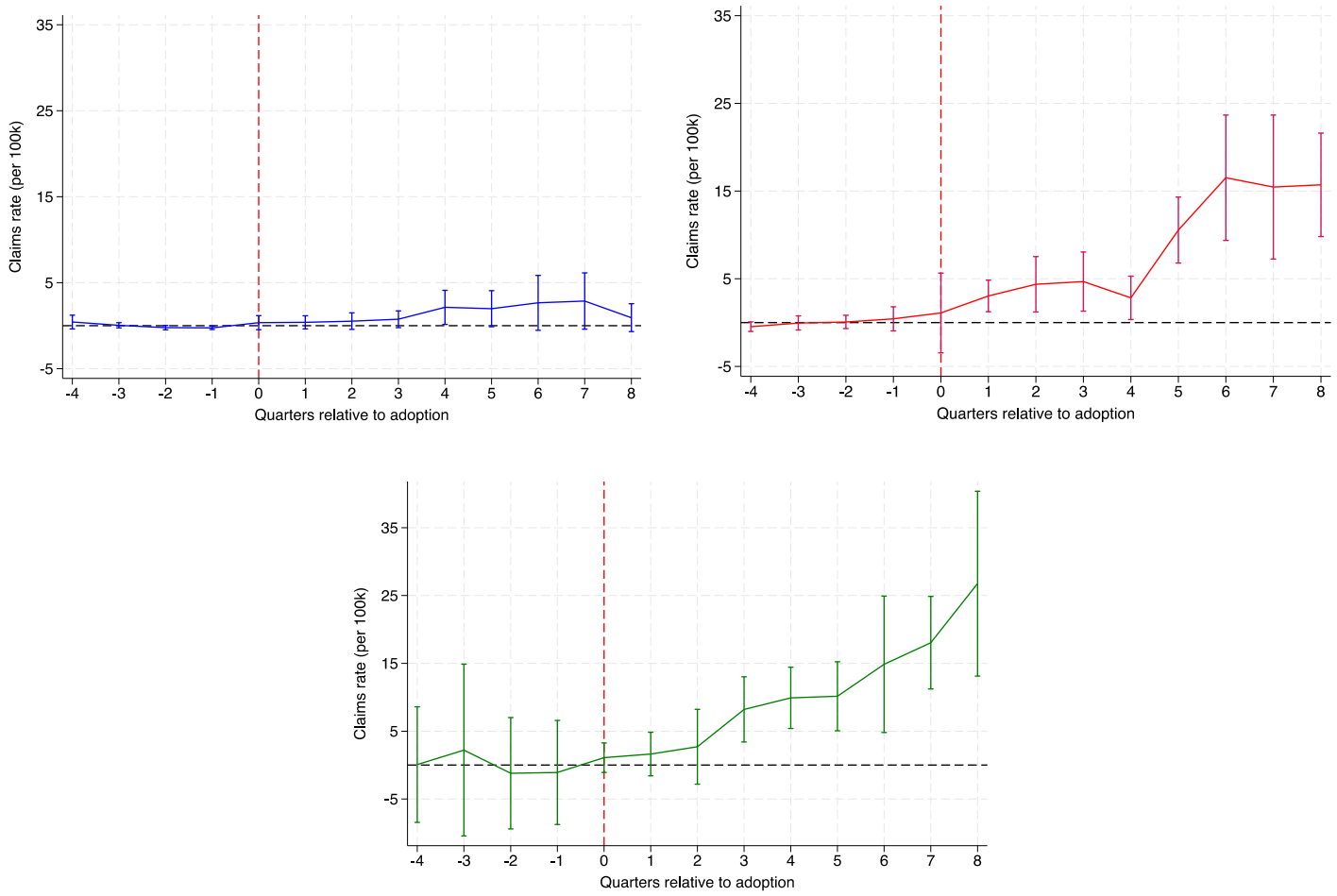
Figures:

Figure 1: National trends in quarterly naloxone dispensing rate (per 100,000) via retail pharmacies by drug brand (Evzio, generic, and Narcan)



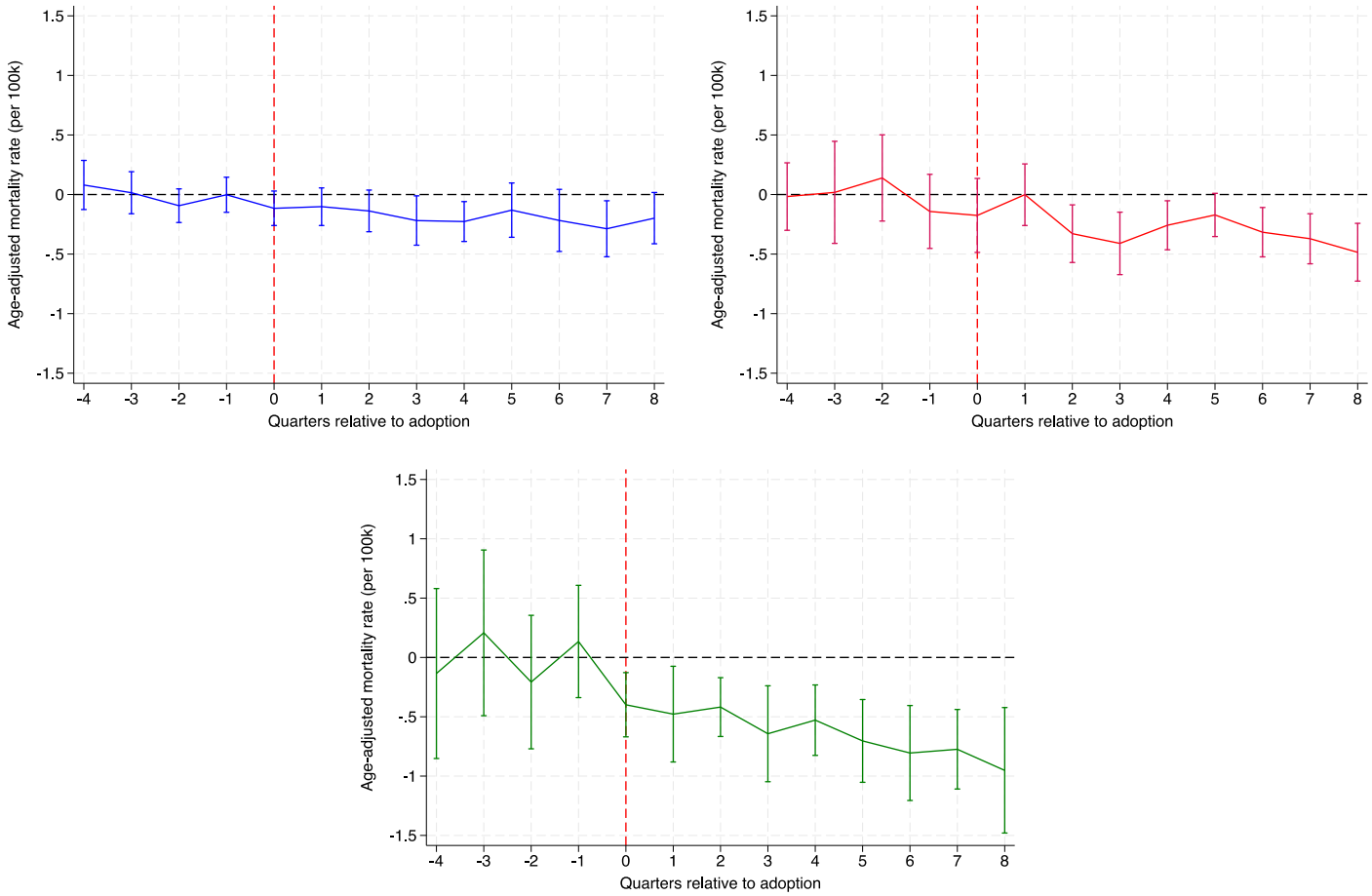
Source: Symphony Health Data

Figure 2: 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



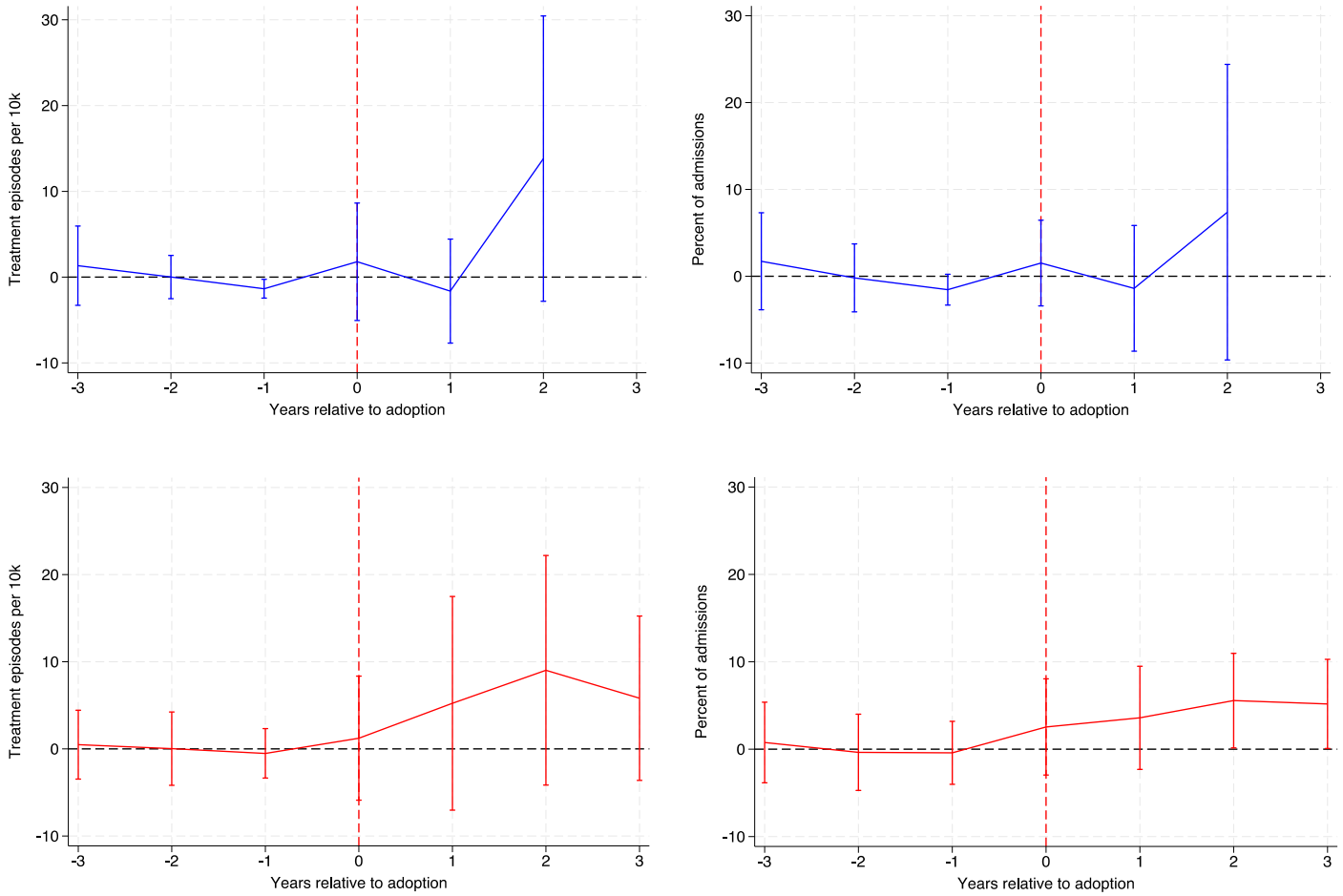
Notes: Estimates are from +LASSO models including group (e.g., state) and period (e.g., quarter) fixed effects as well as time-varying controls determined by post-double selection LASSO with 95% confidence intervals (adjusted for state-level clustering). All estimates are weighted by state population. 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.

Figure 3: Effects on non-synthetic opioid-related age-adjusted 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



Notes: Direct age-adjusted mortality rates are calculated by applying age-specific mortality rates to the 2000 US standard population age distribution. Estimates are from +LASSO models including group (e.g., state) and period (e.g., quarter) fixed effects, as well as time-varying controls determined by post-double selection LASSO with 95% confidence intervals (adjusted for state-level clustering). All estimates are weighted by state population. 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.

Figure 4: Effects on OUD treatment episodes: (top left) dispensing NALs prior to 2016 and admissions per 10,000; (top right) dispensing NALs prior to 2016 and percent of all treatment episodes; (bottom left) Narcan's introduction in states with existing dispensing NALs and admissions per 10,000; and (bottom right) Narcan's introduction in states with existing dispensing NALs and percent of all treatment episodes



Notes: Estimates are from +LASSO models including group (e.g., state) and period (e.g., quarter) fixed effects as well as time-varying controls determined by post-double selection LASSO with 95% confidence intervals (adjusted for state-level clustering). All estimates are weighted by state population. All standard errors are clustered at the state level. For "naloxone access law (prior to 2016)" estimates, N = 287. For "Narcan + naloxone access law" estimates, N = 388. Because the data are annual, providing only a small pre-period, we do not present results for the 2016-2019 adopters

Appendix Tables:

Table A.1: Placebo Outcomes

	Cocaine (Non-Exclusive) Age-Adjusted Mortality Rate (per 100k)		
	(1)	(2)	(3)
Naloxone access law (prior to 2016)	0.0834**	0.061*	0.061*
	(0.039)	(0.035)	(0.035)
Narcan + naloxone access law	0.119	0.125	0.119
	(0.080)	(0.081)	(0.080)
Naloxone access law (after 2016)	-0.037	0.169	-0.037
	(0.139)	(0.223)	(0.139)
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)	-0.041	-0.070	-0.070
	(0.081)	(0.096)	(0.096)
Narcan + naloxone access law	0.343	0.278	0.343
	(0.251)	(0.248)	(0.251)
Naloxone access law (after 2016)	0.242	0.432	0.242
	(0.275)	(0.291)	(0.274)
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 direct age-adjusted mortality rates (per 100,000) 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 A.2: 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	-0.111	-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 for each population group (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 A.3: Heterogeneity by County Characteristics

	County Pop: Top 50% Non-Hispanic Black Claims Rate (per 100k)			County Pop: Bottom 50% Non-Hispanic Black Claims Rate (per 100k)		
	(1)	(2)	(3)	(1)	(2)	(3)
Naloxone access law (prior to 2016)	0.065	0.023	-1.141	2.498*	2.375***	2.655*
	(0.467)	(0.623)	(1.198)	(1.476)	(1.480)	(1.472)
Narcan + naloxone access law	2.287***	2.287***	2.287***	13.632***	10.309***	13.632***
	(0.322)	(0.322)	(0.322)	(3.010)	(2.961)	(3.010)
Naloxone access law (after 2016)	2.173	1.730	1.173	16.512***	17.609***	16.512***
	(2.524)	(2.927)	(2.697)	(4.928)	(5.123)	(4.928)
Method	IDiD	+ Policy	+ LASSO	IDiD	+ Policy	+ LASSO
Other controls	No	Yes	Yes	No	Yes	Yes
	County Population: Top 50% Hispanic Claims Rate (per 100k)			**County Population: Bottom 50% Hispanic Claims Rate (per 100k)**		
	(1)	(2)	(3)	(1)	(2)	(3)
Naloxone access law (prior to 2016)	-0.103	-0.419	-1.104	0.682*	0.121	1.117
	(0.441)	(0.654)	(1.230)	(0.383)	(0.565)	(1.188)
Narcan + naloxone access law	1.909	1.880	1.909	12.160***	12.168***	12.168***
	(1.240)	(1.218)	(1.238)	(2.550)	(2.508)	(2.548)
Naloxone access law (after 2016)	3.225	4.705	4.705	14.636***	14.774***	14.636***
	(3.119)	(3.881)	(3.881)	(2.758)	(4.209)	(2.757)
Method	IDiD	+ Policy	+ LASSO	IDiD	+ Policy	+ LASSO
Other controls	No	Yes	Yes	No	Yes	Yes
	County Population: Top 50% Poverty Claims Rate (per 100k)			**County Population: Bottom 50% Poverty Claims Rate (per 100k)**		
	(1)	(2)	(3)	(1)	(2)	(3)
Naloxone access law (prior to 2016)	-0.105	-0.131	-0.208***	2.749***	2.494***	2.963**
	(0.077)	(0.092)	(0.078)	(0.510)	(0.643)	(1.388)
Narcan + naloxone access law	2.828*	2.784*	2.828*	17.388***	17.414***	17.414***
	(1.627)	(1.599)	(1.624)	(2.602)	(2.599)	(2.599)
Naloxone access law (after 2016)	0.523	0.564	0.518	16.747**	16.325**	17.473**
	(3.796)	(3.957)	(3.314)	(7.921)	(7.108)	(7.546)
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)	0.540	0.351	0.571	2.308	2.313	2.112
	(0.492)	(0.623)	(1.424)	(1.632)	(1.791)	(1.614)
Narcan + naloxone access law	5.897***	5.805***	5.897***	13.799***	13.662***	13.799***
	(2.094)	(2.057)	(2.090)	(3.656)	(3.590)	(3.647)
Naloxone access law (after 2016)	1.686***	1.686***	1.940***	18.182**	17.123**	18.182**
	(0.625)	(0.625)	(0.763)	(8.085)	(8.232)	(8.085)
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)	-0.046	-0.047	-0.105	1.526	1.384	1.844
	(0.102)	(0.097)	(0.113)	(1.504)	(1.628)	(1.348)
Narcan + naloxone access law	3.160	3.142	3.160	14.519***	14.371***	14.519***
	(3.108)	(3.054)	(3.103)	(2.257)	(2.218)	(2.253)
Naloxone access law (after 2016)	1.049***	1.917***	1.049***	13.578*	12.045***	13.578*
	(0.402)	(0.482)	(0.402)	(5.203)	(4.434)	(5.203)
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. For "naloxone access law (prior to 2016)" estimates, N = 75,900. For "Narcan + naloxone access law" estimates, N = 40,794. For "Naloxone access law (after 2016)" estimates, N=10,517. 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 A.4: 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 A.5: Out-of-Pocket Cost per Claim

	OOP Cost per Claim		
	(1)	(2)	(3)
Naloxone access law (prior to 2016)	17.127	17.917	17.127
	(12.423)	(12.360)	(12.423)
Narcan + naloxone access law	-5.137	-5.891	-5.137
	(12.420)	(12.029)	(12.420)
Naloxone access law (after 2016)	-8.383	-8.383	-9.875
	(10.558)	(10.558)	(10.053)
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).

Appendix Figures:

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

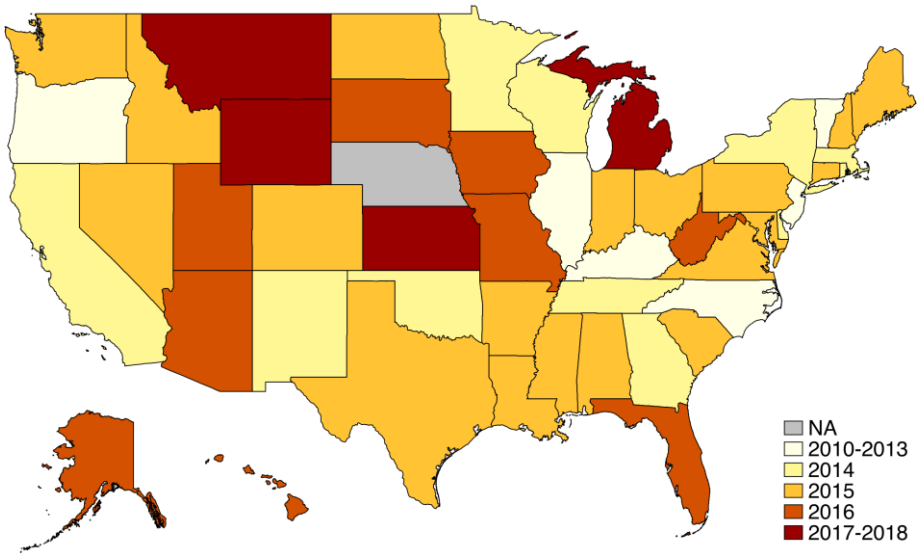


Figure A.2: National trends in quarterly overdose deaths involving any opioids (blue), and overdose mortalities involving either natural/semisynthetic opioids or heroin but excluding overdose deaths involving fentanyl

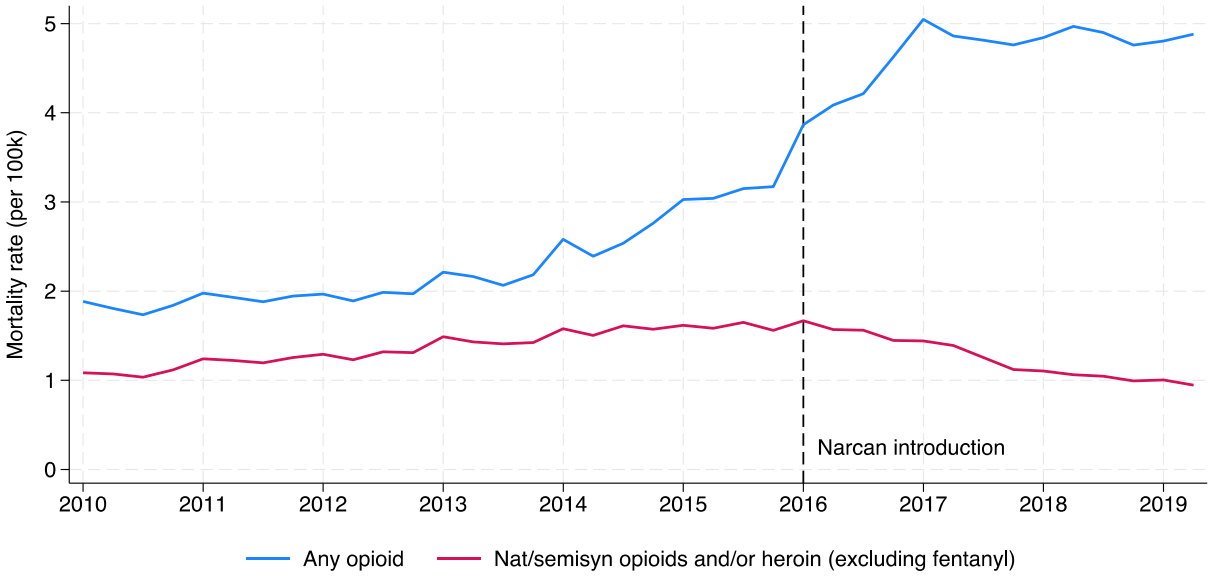
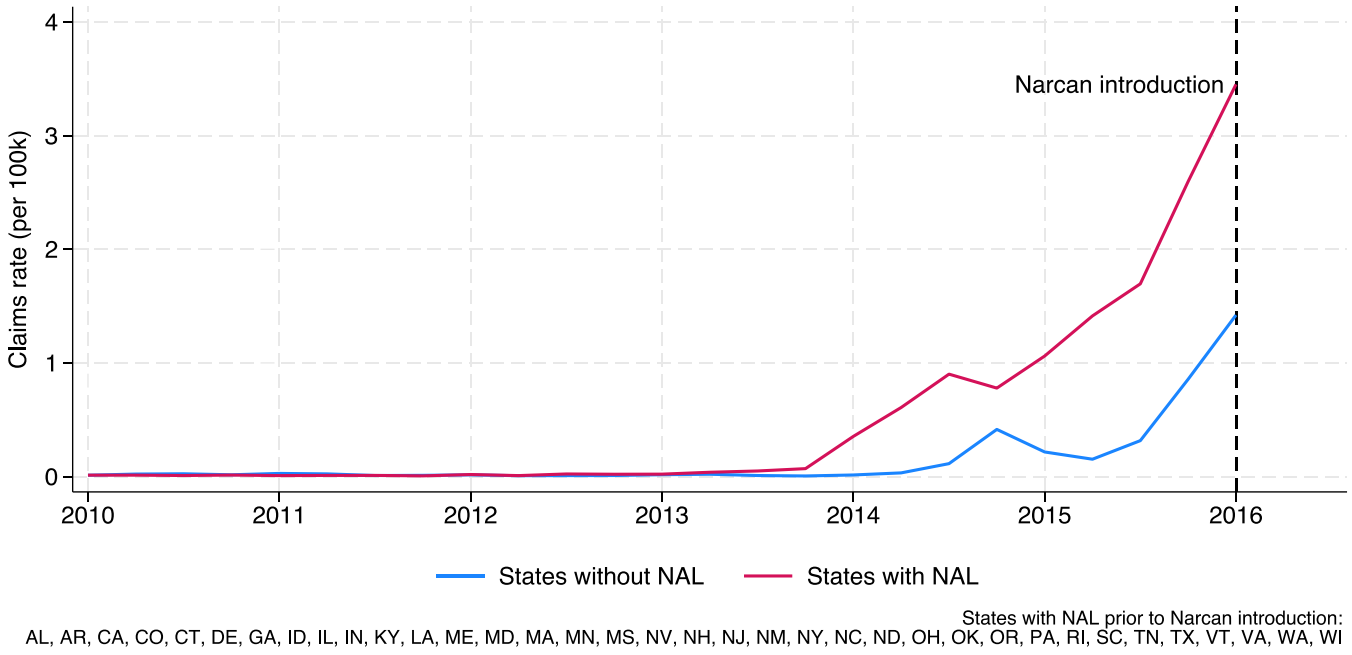
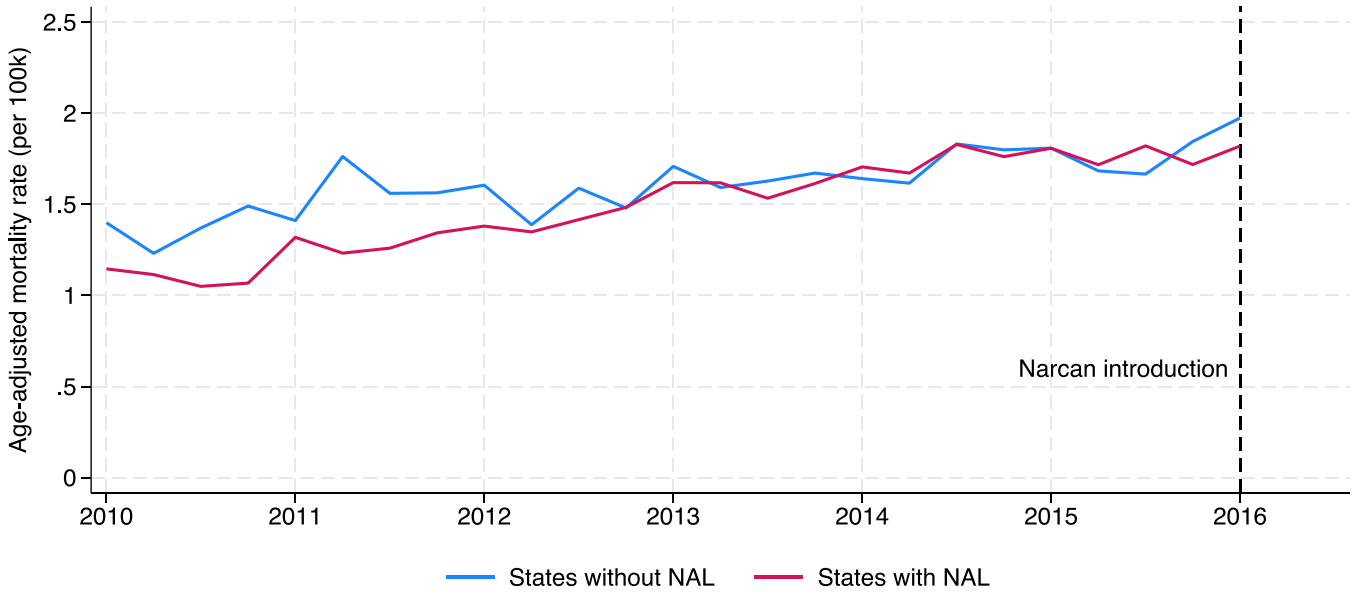


Figure A.3: Trends in (A, top) quarterly naloxone dispensing by dispensing naloxone access law status prior to Narcan's introduction; and (B, bottom) quarterly non-synthetic opioid-related mortality rates by dispensing naloxone access law status prior to Narcan's introduction

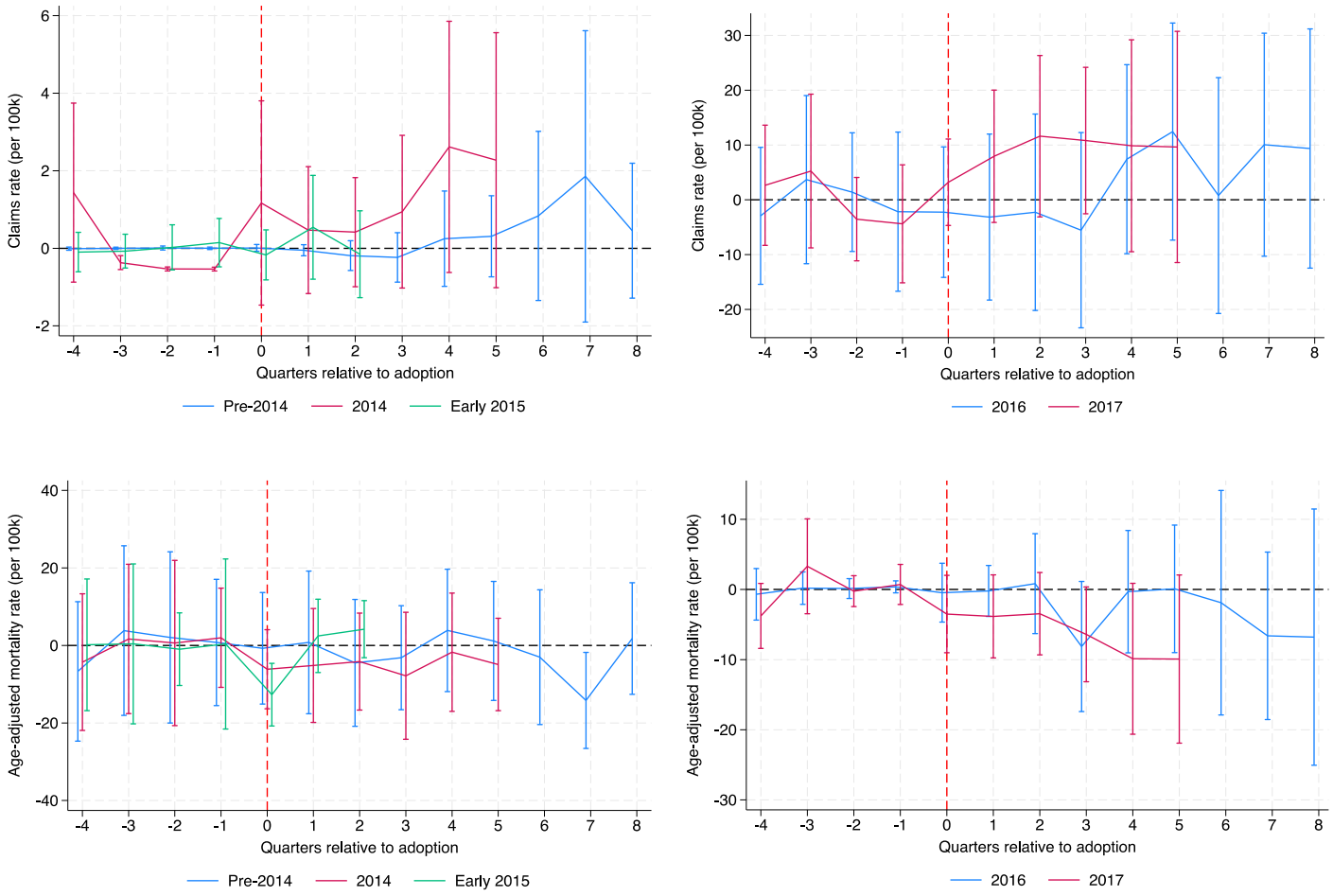


States with NAL prior to Narcan introduction:
AL, AR, CA, CO, CT, DE, GA, ID, IL, IN, KY, LA, ME, MD, MA, MN, MS, NV, NH, NJ, NM, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VT, VA, WA, WI



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 A.4: Effects of dispensing NALs by time of adoption: (top left) pre-Narcan, naloxone claims rate; (top right) post-Narcan, naloxone claims rate; (bottom left) pre-Narcan, non-synthetic opioid overdose mortality rate; (bottom right) post-Narcan, non-synthetic opioid overdose mortality rate



Notes: Estimates are from +LASSO models including group (e.g., state) and period (e.g., quarter) fixed effects as well as time-varying controls determined by post-double selection LASSO with 95% confidence intervals (adjusted for state-level clustering). All estimates are weighted by state population. For "Pre-2014" estimates, N = 1,124. For "2014" estimates, N = 1,103. For "Early 2015" estimates, N=1,054. For "2016" estimates, N=153. For "2017" estimates, N=88.