A Manufactured Tragedy: The Origins and Deep Ripples of the Opioid Epidemic

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Abstract

This paper studies the origins and consequences of the opioid epidemic. Drawing on unsealed records from state litigation against Purdue Pharma, we exploit detailed features of the marketing of OxyContin—which initially targeted the cancer pain market—to assess the role of supply-side factors in the origins of the epidemic. We exploit the differential promotion of OxyContin and its competitors across geographies as a source of exogenous variation in the supply of opioids to quantify its effects on opioid mortality, adult wellbeing, and to assess its intergenerational impacts. We document a strong link between Purdue Pharma's promotional targeting and future increases in the supply of prescription opioids and overdose deaths. The epidemic triggered a significant increase in disability and SNAP claims, a worsening of health at birth, and an increase in non-marital fertility rates.

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I. Introduction

Over the last two decades, mortality from opioid overdoses in the United States has increased at an alarming rate. Since 1999, prescription opioid overdoses have claimed the lives of over 300,000 individuals (CDC, 2021); contributing to the longest sustained decline in life expectancy in the last century, excluding the influenza and Covid pandemics (Dyer, 2018 and Andrasfay and Goldman, 2021). Opioids are highly addictive, with rapid progression to physiological dependence with tolerance and withdrawal, even at prescribed doses and within a short time (Sharma et al., 2016; Hah et al., 2017). In 2012, the national opioid dispensing rate peaked at 81.3 prescriptions per 100 persons (CDC, 2020). Although the dispensing rate has declined since then, by 2020, there were still 43.3 prescriptions per 100. The potential effects of the rise in the supply of prescription opioids can stretch beyond the increase in overdose deaths and include the transition to the use of illegal opioids such as heroin and fentanyl, a decline in one's ability to work, recover from illness, and care for children, among other daily activities (Alpert et al., 2018; Lynch et al., 2018; Meinhofer and Angleró-Díaz, 2019).

Tracing the effects of the opioid crisis and its origin is challenging because the variation in the level of prescription opioids across geographies and over time is not random (Ruhm, 2019). On the one hand, deteriorating socio-economic conditions in certain geographic areas could cause an increase in the demand for opioids and also explain the subsequent decline in outcomes in the same areas, which would lead to negatively biased estimates (Carpenter et al., 2017; Case and Deaton, 2017). On the other hand, the origin of the epidemic coincides with dramatic supply-side changes such as the aggressive marketing of prescription opioids, a shift in physician prescribing attitudes, and the increase in the availability of potent opioids.[1] It has been documented that this increase is positively linked to access to healthcare and the number of physicians per capita (Finkelstein et al., 2018). As a result, areas with higher access to opioids are positively selected along these variables, which could, in turn, attenuate the estimates of the effects of the epidemic.

In this paper, we provide new evidence of the central role that the initial marketing of prescription opioids played in the unfolding of the opioid epidemic. We also document its consequences on the wellbeing of adults and its intergenerational effects. We exploit detailed features of the initial marketing of prescription opioids, which we obtained from unsealed court records from state litigation against Purdue Pharma, the manufacturer of OxyContin, a prescription opioid at the center of the opioid epidemic.[2] We document that OxyContin was initially promoted to the cancer pain market with the plan to quickly expand to the much larger non-cancer pain market. This targeting implied that non-cancer physicians and patients in high-cancer areas were first exposed to OxyContin promotion and gained access to potent prescription opioids to treat moderate and chronic pain. Furthermore, Purdue Pharma's later strategy to target top prescribers—those in the highest deciles of the opioid dispensing distribution—created a path dependency from where the promotion started to where it expanded. Drawing on these insights, we exploit the geographic variation in cancer mortality in the mid-nineties—as a proxy for the cancer pain market served by Purdue Pharma—to assess the role of supply-side factors in the unfolding of the opioid epidemic. We use this variation as an instrument for the supply of prescription opioids and estimate its effect on a broad range of outcomes.

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[1] See for example: Fernandez and Zejcirovic (2018); Alpert et al. (2022); Eichmeyer and Zhang (2020); Schnell and Currie (2018); Finkelstein et al. (2018) and Miloucheva (2021); among others.

[2] These court documents are from case 07-CI-01303 Commonwealth of Kentucky v. Purdue Pharma, and case CJ-2017-816 State of Oklahoma v. Purdue Pharma et al.

We collect data from multiple sources and construct a panel of commuting zones covering the United States from 1989 to 2018.[3] We use data from the Drug Enforcement Agency (DEA) on the distribution of controlled substances to measure the level of prescription opioid at the commuting zone level. We measure adult wellbeing using data on mortality from opioids and other causes from the National Vital Statistics System, and data on beneficiaries of social safety net programs—Supplemental Nutrition Assistance Program (SNAP), Supplemental Security Income (SSI)—and Social Security Disability Insurance (SSDI) program. To capture the intergenerational effects of the epidemic, we exploit linked data on births and maternal outcomes.

We start by showing the link between Purdue's marketing targets and the unfolding of the growth in prescription opioids. Specifically, we estimate a strong and robust relationship between higher cancer mortality in the mid-nineties and the future growth of prescription opioids after the launch of OxyContin. This relationship is mostly driven by prescribed oxycodone, the active ingredient in OxyContin.[4] Commuting zones with the highest cancer incidence—the 95th percentile relative to the 5th percentile—at the time of the launch of OxyContin received 1.96 more doses of opioids per capita, which accounts for 64% of the average growth in prescription opioids from 1999 to 2018.

Turning to the effects of the epidemic we find three key results. In terms of opioid-related mortality, increasing the supply of opioids from the 25th-to-the-75th percentile caused an 89% increase in prescription opioids deaths and a 39% increase in deaths from all opioids. This corresponds to approximately 200,000 deaths. These deaths are concentrated in young and middle-aged adults, with no effects on those 55 and older. We do not find effects of the rise in opioid supply on non-opioid deaths of despair—such as, suicide and alcohol related deaths—or other causes of death.[5] Second, the opioid epidemic had large effects on communities. Claims for social safety net programs increased: A change from the 25th to the 75th percentile of prescriptions caused a 57% increase in the share of SNAP recipients and a 47% increase in the share of the population receiving SSI. We also find a 76% increase in the share of the population receiving SSDI. Third, we document large intergenerational effects. We estimate a 10% increase in fertility rates, which is driven entirely by increases in non-marital births, and is concentrated among women aged 25-29. We find a decline in pregnancy duration of 0.24 weeks, a reduction in birth weight of 0.7%, and a worsening of APGAR scores by 0.9%.[6] We estimate that there is no effect on infant mortality, but we find an increase in the APGAR score of infants who died in the first year, meaning that healthier infants died. Taken together, these results point to a general decline in health at birth.

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[3] Commuting zones are geographic areas defined to capture local economic markets. They encompass all metropolitan and non-metropolitan areas in the US. While less granular than counties, commuting zones are much more granular than states (Tolbert and Sizer, 1996).

[4] See Figure 1. Oxycodone is a semi-synthetic opioid that is 50% more potent than morphine and prescribed for the management of acute pain.

[5] Our measure of deaths of despair follows Case and Deaton (2017)'s definition but excludes drug overdose deaths, these are counted in the prescription opioids and all opioid death categories. More details on these definitions are provided in Section III.

Our identification strategy requires that in the absence of OxyContin's marketing, areas with higher cancer mortality would exhibit the same *trends* as areas with lower cancer mortality in terms of our outcome variables (Goldsmith-Pinkham et al., 2020). To test this, we use an event-study approach and investigate the presence of pre-trends. We do not find any evidence of a relationship between mid-nineties cancer mortality and the growth of any of our outcomes variables before the launch of OxyContin. In contrast, reduced-form event-study graphs show that soon after the introduction of OxyContin, our instrument starts to predict higher opioid mortality, SNAP and disability claims, and fertility. In addition, we document that areas with higher cancer mortality are not on a differential trend with respect to socio-economic variables such as education, income, or other health variables. For example, we find that high- and low-cancer mortality commuting zones were on the same trend regarding suicide mortality and the share of employment in manufacturing and mining industries. These results suggest that the evolution in socio-economic conditions is not different in high and low cancer mortality places. That is not to say that the variation in cancer mortality across space is randomly distributed. In fact, we find strong demographic predictors of cancer, such as the share of the population over 65 and the share non-Hispanic population. What we require and provide evidence in favor of is that high and low cancer areas are on the same trends along our health and economic outcomes.

Further, we propose two placebo exercises. First, we show that mid-1990s mortality rates from other causes, such as cerebrovascular disease mortality, are not predictive of the future prescription opioids distribution. In a second placebo exercise, we relate cancer mortality in 1989-1990—the first year of our data—to the evolution of outcomes of interest before the launch of OxyContin. That is, we test if there is a relationship between lagged cancer mortality and the growth of our outcomes outside the analysis period, and find no evidence of such link. Both of these exercises suggest that the connection between cancer mortality and prescription opioid distribution is not driven by other underlying health trends, but by the link created by Purdue Pharma through the marketing of OxyContin. Finally, we show that our results are not driven by the differential exposure to: Chinese import competition, the 2001 economic recession or unemployment at the time of the introduction of OxyContin.

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[6] The APGAR score is a measure of the physical condition of a newborn infant. It is obtained by adding points (2, 1, or 0) for heart rate, respiratory effort, muscle tone, response to stimulation, and skin coloration; a score of 10 represents the best possible condition.

This paper makes four contributions. First, we provide new evidence linking the launch of OxyContin to the origin and evolution of the opioid epidemic. This adds to the literature documenting the importance of supply-side factors in the evolution of the opioid epidemic. Eichmeyer and Zhang (2020) and Schnell and Currie (2018) document the role of physicians, Powell et al. (2020) highlight the importance of access to healthcare, and Fernandez and Zejcirovic (2018) and Miloucheva (2021) underscore the importance of pharmaceutical promotions. This paper is closest to Alpert et al. (2022), who use state-level variation in the regulations regarding the prescription of Schedule II drugs.[7] They show that five states that had a more cumbersome process for prescribing opioids at the time of OxyContin's launch, were not as targeted by Purdue Pharma in their initial marketing plans.[8] Subsequently, those five states reported lower levels of prescription opioids and overdose deaths. We extend and improve their work in multiple dimensions. Exploiting commuting-zone level variation in the initial marketing of OxyContin, we can account for important counfounders at the state and year level.[9] We also expand the work of Alpert et al. (2022) by investigating the effects of the epidemic on important social outcomes beyond mortality.[10] Mortality from opioids is only one of the many social costs associated with drug use. In 2019, an estimated 10.1 million people in the US aged 12 or older misused opioids (SAMHSA, 2020). These numbers are an order of magnitude larger than the number of deaths.

Second, this paper introduces a novel instrument to identify the causal effect of the opioid epidemic. Previous literature often relies on the staggered introduction of state-level PDMPs—and other policy changes—and its effect on the level of prescription opioids, to then indirectly assess the impact of the opioid epidemic on a broad set of outcomes.[11] The nature of such research designs do not allow researchers to control for state-year fixed effects. Our instrument improves on this literature exploiting commuting-zone quasi-exogenous variation on the level of prescription opioids, which leverage to estimate *direct* effects of the opioid epidemic.

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[7] The DEA defines Schedule II drugs as drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous.

[8] Our reading of Purdue and other pharma and academic documents suggests that the industry's perception of what constitutes a "triplicate" program could differ from the designation used by Alpert et al. (2022). Appendix C examines this evidence and extends the anaylsis in Alpert et al. (2022).

[9] During this period there is relevant state-level variation in response to the opioid epidemic, such as, the implementation of Prescription Drug Monitoring Programs (PDMP), the regulation of "pill mill" clinics, and the availability of naloxone. The term "pill mill" is typically used to describe a doctor, clinic, or pharmacy that prescribes or dispenses controlled prescription drugs inappropriately (Malbran, 2007). Naloxone is a drug that can reverse an opioid overdose if administered quickly. The level of naloxone access varies by state and over time. Between 2001 and 2017, every US state has passed a law that facilitates widespread distribution and use of naloxone (Doleac and Mukherjee, 2019).

[10] We exploit commuting-zone level variation which improves power. Griffin et al. (2020) document that empirical strategies exploiting state-level variation to estimate effects on opioid mortality have very low statistical power to detect a significant policy effect. They assess the relative performance of multiple statistical methods commonly used in evaluation studies of state-level opioid policies using a simulation study based on observed state-level opioid-related outcomes. Their main result indicates that many commonly used methods have very low statistical power to detect a significant policy effect ($< 10\%$) when the policy effect size is small yet sizable (e.g., 5% reduction in opioid mortality).

Third, this paper is the first to document the direct effects of the increase in access to prescription opioids on the demand for disability benefits and on one of the largest anti-poverty programs in the United States, SNAP, which has not been studied before. Our work is related to Savych et al. (2019) who find evidence that an increase in long-term opioid prescribing leads to a considerably longer duration of temporary disability, and to Park and Powell (2021) who document that the rise in access and consumption of illicit opioids—such as heroin and fentanyl—increase disability applications by 7%.

Finally, this paper also contributes to the literature that studies the intergenerational impacts of the opioid epidemic. The epidemic has primarily affected individuals in early adulthood through mid-life, with potential costs beyond the generation directly impacted. Heil et al. (2011) and Caudillo and Villarreal (2021) document a positive correlation between opioid use and unintended pregnancies; and between opioid overdose deaths and non-marital births. We provide the first causal estimates of the effects of the opioid epidemic on fertility and the first direct effects on birth outcomes.

II. Background: The Marketing of OxyContin and the Opioid Epidemic

In 1996, Purdue Pharma introduced OxyContin to the market. When patented, OxyContin was described as a controlled-release oxycodone compound that substantially reduces the time and resources needed to titrate patients who require pain relief on opioid analgesics (Oshlack et al., 1996). Two key technological innovations are responsible for its success. First, its long-acting formula provided 12 hours of continuous pain relief, an improvement over the standard practice of pain relief every 6-8 hours. Second, it is a single-agent narcotic, so there is no ceiling on the amount of oxycodone per tablet.[12] Both of these factors significantly increased patients' access to potent doses of opioids and augmented the risk of dependency and use disorder. For example, Percocet was the most common oxycodone product on the market before 1996 and was mostly sold in the form of 2.5 mg of oxycodone per tablet. In contrast, the most common forms of OxyContin were 20 mg and 40 mg tablets of oxycodone, while 80 mg and 160 mg tablets were also available. Furthermore, OxyContin users rapidly learned that crushing or dissolving the pill causes the oxycodone to be delivered all at once—instead of the slow release over 12 hours—which causes strong euphoric effects.

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[11] There is no consensus on what constitutes an operational or mandatory PDMP; definitions change across the literature, making it difficult to leverage this variation to estimate the effects of the opioids epidemic. See Meara et al. (2016), Buchmueller and Carey (2018), Evans et al. (2020), Ziedan and Kaestner (2020), and Gihleb et al. (2022).

[12] Other oxycodone products on the market were a combination of oxycodone and ibuprofen or acetaminophen, and the toxicity of the former sets a limit on the amount of active ingredients in the formula.

Prior to the introduction of OxyContin, pain management focused on cancer and end-of-life pain treatment. Patients who suffered from debilitating chronic pain but who do not have a terminal illness were excluded from long-term therapy with opioids, based on care providers' fears of the risk of addiction (Melzack, 1990). In this context, MS Contin, a drug also produced by Purdue Pharma, was the gold standard for cancer pain treatment. OxyContin's development was in response to the generic competition Purdue Pharma expected to face when MS Contin's patent protection expired in 1996. In their words: *"Because a bioequivalent AB rated generic control-release morphine sulfate is expected to be available sometime during the later part of 1996, one of the primary objectives is to switch patients who would have been started on MS Contin onto OxyContin as quickly as possible"* (OxyContin Launch Plan, September 1995).

OxyContin was intended to take over MS Contin's market and gain ground in the much larger non-cancer pain treatment market, in which opioids were almost absent. Nonetheless, establishing the use of OxyContin for moderate and chronic pain was not an easy task; it was clear to Purdue that they were going to face pushback when expanding to the non-cancer market. Specifically, based on physicians' focus groups in 1995, Purdue concluded that *"there is not the same level of enthusiasm toward this drug for use in non-cancer pain as we identified in cancer pain"* (Purdue Pharma, 1995). The two main barriers Purdue Pharma faced were (i) the stigma related to the use of opioids for non-terminal or non-cancer pain and (ii) the administrative barriers physicians and pharmacies had to overcome to prescribe and sell Schedule II drugs.

To overcome these obstacles, Purdue deployed a comprehensive marketing strategy based on three main pillars. First, to effectively change physician prescribing behaviors, Purdue Pharma implemented an aggressive marketing plan that pushed the message of an untreated pain epidemic that affected millions of Americans on a daily basis. Pain was introduced as the fifth vital sign, with the goal of encouraging the standardized evaluation and treatment of pain symptoms (Jones et al., 2018). This messaging also included misleading statements—for instance, that opioid addiction rates were lower than 1% and that oxycodone was weaker than morphine when it is 50% more potent.[13]

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[13] *"We are well aware of the view held by many physicians that oxycodone is weaker than morphine. We all know that this is the result of their association of oxycodone with less serious pain syndromes. This association arises from their extensive experience with and use of oxycodone combinations to treat pain arising from a diverse set of causes, some serious, but most less serious. This 'personality' of oxycodone is an integral part of the 'personality' of OxyContin."* Exhibit 11 from Richard Sackler's—chairman and

Second, OxyContin was promoted directly to physicians by the largest and highest-paid sales force in the industry.[14] The continuous promotion of OxyContin through advertisements, gifts, and promoted medical literature was delivered through repeated visits and calls to physicians. These promotional efforts quickly translated into a growing number of prescription from OxyContin (Figure A1). At the same time, the marketing team carefully tracked physician prescription habits to concentrate on the highest prescribers; OxyContin's annual budget plans state that they will focus on physicians in the top 3 deciles of opioid prescription distribution (OxyContin Launch Plan, September 1995; OxyContin Budget Plan, 1996).[15]

Third, Purdue focused its initial marketing efforts on the physicians and pharmacies who faced less stigma around opioids and who knew how to navigate the paperwork related to the distribution of Schedule II drugs: Those in the cancer pain market. *"OxyContin Tablets will be targeted at the cancer pain Market."* (OxyContin Team Meeting, April 1994). *"OxyContin primary market positioning will be for cancer pain."* (OxyContin Team Meeting, March 1995). *"At the time of launch, OxyContin will be marketed for cancer pain."* (OxyContin Launch Plan, September 1995). This, however, was only intended as their entering path to the larger non-cancer pain market. Purdue explicitly stated that: *"The use of OxyContin in cancer patients, initiated by their oncologists and then referred back to FPs/GPs/IMs, will result in a comfort that will enable the expansion of use in chronic non-malignant pain patients also seen by the family practice specialists"* (OxyContin Launch Plan, September 1995). That is, Purdue exploited its previously established network of cancer patients and their physicians to introduce its newest product to the broader pain market. This strategy also solved additional logistical problems related to the sales of Schedule II drugs, such as OxyContin. At the time of launch, only about half of the pharmacies in the country had the paperwork required to sell Schedule II drugs, and because *"pharmacists are generally reluctant to stock Class II opioids"*, Purdue decided that their *"initial targets will be the 25,000 stores who stock MS Contin"*, where there was no additional paperwork or training required for pharmacies to stock OxyContin.

Purdue's marketing strategy succeeded in making the use of opioids the standard practice in the treatment of moderate and chronic pain for a wide range of non-terminal conditions, expanding the use of opioids to the non-cancer pain market. By 2003, nearly half of all physicians prescribing OxyContin were primary care physicians (Van Zee, 2009). This strategy also opened the door for other pharmaceutical companies to promote their prescription opioids beyond the cancer market following Purdue's leadership. These com-

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president of Purdue Pharma—deposition, August 28, 2015.

[14] The average sales representative's annual salary of $55,000, was complemented by annual bonuses that averaged $71,500, with a range of $15,000 to nearly $240,000 (Van Zee, 2009).

[15] From 1996 to 2000, Purdue increased its total physician call list from approximately 33,400 to 44,500 to approximately 70,500 to 94,000 physicians; United States General Accounting Office (2003).

panies—Janssen, Endo, Cephalon-Teva, Actavis, Insys, and Mallinckrodt—who are also part of dozens of lawsuits for their role in the opioid epidemic, closely shadowed OxyContin's marketing intending to grow by reducing OxyContin's market share: *"Success means increasing Duragesic share at the expense of OxyContin"* (Sales Force Memorandum, 2001, Exhibit S0510, State of Oklahoma v. Purdue Pharma et al.).[16]

Finally, Purdue's later strategy to promote only to top opioid prescribing physicians, those in the highest three decile of the distribution (Figure A2), meant that areas with high initial promotion as a result of the cancer market focus, also observed higher future promotion when Purdue's plan shifted to top prescribers.[17] This created a path dependency that made initial targets always relevant as the distribution of opioids expanded.

For our purposes, Purdue's marketing strategy means that areas with a higher incidence of cancer at the time of the launch of OxyContin would receive a disproportionate amount of marketing and prescriptions for OxyContin and other opioids. In practice this created a spillover in high cancer communities from cancer patients to non-cancer patients. Thus, the ideal instrument is a measure of the cancer market Purdue Pharma was serving with MS Contin prior to the introduction of OxyContin. Hypothetically, there are multiple ways to proxy this market. One is to use mid-nineties MS Contin prescription rates as this was Purdue's gateway to the non-cancer pain market. However, for the period of analysis these data are not available at the county or commuting zone level.[18] Another approach would be to exploit a direct measure of Purdue Pharma's marketing efforts—e.g., payments to physicians, areas served by sales representatives, and the number of visits of these representatives—unfortunately, these data are not available to the public.[19] We proxy the market served by Purdue Pharma using cancer mortality between 1994 and 1996. This variable is available at the county level, and is accurately and consistently measured throughout the period. Additionally, it has a close connection to the rates of cancer patients who are using opioid pain-killers to manage cancer pain (e.g., MS Contin), especially in the later stages of cancer treatment.[20]

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[16] Duragesic is a fentanyl patch manufactured by Janssen.

[17] This strategy is also followed by other pharmaceutical companies. For example, Janssen referes to *high decile prescribers* as their *highmost important customers* in a Sales Force Memorandum for Duragesic in 2001.

[18] From reading court litigation's documents we know that at that time, Purdue had access to extremely granular prescription drugs data through a firm called IMS (later called Xponent and today called IQVIA). We have contacted IQVIA to inquire about these data and they stated they do not keep any records of historical data. Additionally, State Drug Utilization Data (SDUD) reports the number of prescriptions paid by Medicaid agencies at the state level, which does not allow us to exploit within-state variation.

[19] Court litigation's documents refer to lists of sales representatives and visits to physicians but we could not access these files; only extracts of these lists are available in the courts' documents. Open Payments Data collected by the Centers for Medicare & Medicaid Services (CMS) are available starting in 2014, eight years after the introduction of OxyContin and four years after the introduction of the abuse-deterrent OxyContin.

[20] An additional measure of cancer incidence is the rate of cancer patients in the population. Unfortunately, incidence measures reported by the CDC and the Surveillance, Epidemiology, and End Results

III. Data and Summary Statistics

A. Prescription Opioids

We digitize historical records from the Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA). These reports contain the distribution records of all Schedule II substances by active ingredient (e.g., oxycodone, hydrocodone, and morphine) at the 3-digit ZIP code level—the smallest geographic unit available—from 1997 to 2018.[21] We construct a geographic crosswalk from 3-digit ZIP codes to commuting zones using *Geocorr* (a geographic correspondence engine) powered by the Missouri Census Data Center. Our main independent variable is grams of prescription opioids per capita at the commuting-zone level; this corresponds to the sum of oxycodone, codeine, morphine, fentanyl, hydrocodone, hydromorphone, and meperidine in morphine-equivalent mg. The group of drugs included in the ARCOS changes over time—e.g., to account for changes in the classification of an ingredient. Nonetheless, we focus on a set of prescription opioids that can be tracked consistently over the period of analysis. We report all ARCOS measures in morphine-equivalent doses, equal to 60 morphine-equivalent mg.

The first panel of Table 1 presents summary statistics of shipments of all prescription opioids and the three main controlled substances: oxycodone, hydrocodone, and morphine. Oxycodone represents around half of all prescription opioids shipments, and the average commuting zone receives 3.15 doses per capita in a given year. This number masks substantial geographical variation. While some commuting zones received no doses, others report as much as 51.31 oxycodone doses per capita in a given year, Map 1 shows this variation. Figure A3 shows the rapid growth of prescription opioids over time and the dominant role of oxycodone in such growth.

B. Cancer Mortality

To proxy the cancer market served by Purdue Pharma at the time of OxyContin's launch we construct the average cancer mortality rate between 1994 and 1996 at the commuting zone level using a restricted-access version of the Detailed Multiple Cause of Death (MCOD) files.[22] These files record every death in the US along with the county of resi-

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(SEER) program are aggregated at the state level and are more likely to be affected by variation in diagnosis rates, especially for early-stage cancers. In contrast, cancer mortality is available at the county level. Importantly, the two measures are highly correlated: the correlation coefficient is 0.88. An alternative plausible instrument is the number of oncologists per capita. However, this measure is far too concentrated in the largest commuting zones.

[21] ARCOS system data are available online from 2000 to the first half of 2020. We retrieved and digitized the reports up to 2018, the last year of our sample. For periods before 2000, we used the WayBack Machine application and to access reports for 1997 to 1999.

[22] We also consider age-adjusted cancer mortality and test if our results are sensitive to any of the years used as our baseline cancer mortality measure. We find very similar and strong first-stage estimates

dence, the underlying cause of death, and up to 20 additional causes and thus represent a census of deaths in the US. The 1989-1998 data use ICD-9 codes to categorize the cause of death, and the 1999-2018 data use ICD-10 codes.[23] Map 2 shows large variation in average cancer mortality in 1994 and 1996.

C. Outcome measures and control variables

Opioid mortality. We construct two main measures of opioid-related deaths: prescription opioids and all opioid deaths. The prescription opioids category captures deaths whose underlying cause is substances usually found in prescription painkillers such as hydrocodone, methadone, morphine, and oxycodone, among others.[24] We also consider a broader measure of opioid-related deaths, in which we include deaths from heroin and synthetic opioids; e.g., fentanyl.[25] Map 3 shows this geographical variation.[26] Prescription opioid deaths vary from no deaths to as many as 106 per 100,000 residents in the most affected commuting zones.

Deaths of despair. We also study how the marketing of prescription opioids affected deaths of despair. Case and Deaton (2015) define deaths of despair as deaths by drug and alcohol poisonings, suicide, and chronic liver diseases and cirrhosis. Our measure of deaths of despair does not include drug poisonings as these are counted in prescription and any opioids deaths. That is, our measure is limited to deaths from suicide, chronic liver disease, cirrhosis, and poisonings that are attributable to alcohol—these deaths amount to, on average, 79% of the deaths studied by Case and Deaton (2017).[27]

Demand for social insurance and welfare programs. We construct a measure of SNAP benefit recipiency rates at the commuting-zone level, using data from the Food and Nutrition Service of the Department of Agriculture. In particular, we use data on county-level participation in the month of January for all years spanning 1989-2018, focusing on beneficiaries of Food Stamps (FSP) and Electronic Benefit Transfers (EBT) in the context of the program. We then aggregate the county-level counts to compute the share

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across these alternative measures.

[23] We construct cancer deaths as those from malignant neoplasms (codes 140-208 in ICD-9 data and C00-C97 in ICD-10 data) and in situ neoplasms, benign neoplasms and neoplasms of uncertain or unknown behavior (codes 210-239 in ICD-9 data and D00-D48 in ICD-10 data).

[24] We use identification codes T40.2 and T40.3 to specify prescription-opioid-related overdoses in the ICD-10 data and codes 965.00, 965.02, 965.09, E850.1, and E850.2 in the ICD-9 data.

[25] We use identification codes T40.0-T40.4, X42, X62, and Y12 to count deaths from any opioid in the ICD10-data and codes 965.00, 965.01, 965.02, 965.09, E850.0, E850.1, and E850.2 in the ICD-9 data.

[26] The CDC reports that the transition from the ICD-9 to ICD-10 resulted in a small increase in poison-related deaths of 2% (Warner et al., 2011). Appendix Figure A4 shows the time series for the US for these two measures.

[27] We use identification codes K70, K73-74 to count deaths from alcoholic liver diseases and cirrhosis in the ICD10-data and codes 571.0 – 571.4 and 57109 in the ICD-9 data. We count deaths from suicide using codes X60-84 and Y87.0 in the ICD10-data and codes E950-E959 in the ICD-9 data. Deaths from alcohol poising are counted using codes X45 and Y15 in the ICD10-data and codes E850-E858, E860, and E980.1 in the ICD-9 data.

of beneficiaries in the population at the commuting-zone level. When information at the local level is not available, we impute the state-level share of SNAP recipients.[28] We include two measures of disability benefits recipiency, constructed as the share of the population 18 to 65 that receives Supplemental Security Income (SSI) and who is blind or disabled, and the share of the population 18 to 65 that receives Social Security Disability Insurance (SSDI). Information on the total number of SSI recipients in each county is based on SSI Annual Statistical Reports and Old Age, Survivors and Disability Insurance (OASDI) reports prepared by the National Social Security Administration, which we aggregate at the commuting-zone level.[29]

Maternal and birth outcomes. Data on birth outcomes come from the Linked Birth and Infant Death Data of the National Vitals Statistic System (NVSS). The microdata for each year between 1995 and 2018 include the deaths of all infants born in that calendar year for which the death certificate can be linked to a birth certificate and all births occurring in a given calendar year.[30] We construct infant mortality as the ratio of infant deaths to live births in a given calendar year. The Linked Birth and Infant Death Data also include data on the infant's condition at birth, such as weight and length of gestation. The main measures of infant health we compute from the birth files are the commuting-zone-level (i) average birth weight for all live births, (ii) share of low-birth-weight newborns, (iii) share of preterm births, (iv) APGAR score of all births, (v) APGAR score of deceased infants, and (vi) median pregnancy duration. Finally, we use the birth files to compute the average fertility rate at the commuting-zone level, defined as the ratio of the number of single pregnancies to the female population aged 15 to 44 years old.[31,32]

Demographic controls: population data. Data on population counts comes from the Survey of Epidemiology and End Results (SEER) which reports population at the county level and by age, race, sex, and Hispanic origin. We use these data construct the denominators for adult mortality rates computations, e.g., opioid mortality and aggregate mortality. Denominators for infant mortality rate comes from the "Denominator File" provided by the NVSS.

In sum, we build a data set at the commuting-zone level, covering the period from 1989 to 2018 for our outcome variables and the instrument. We choose commuting-zones as our unit of observation since it is the geographic space that captures ones economic life—which usually spans beyond county borders—and the access to the local market for prescription opioids.[33] ARCOS data are available since 1997, so analyses using this measure are restricted to a later period.[34] We restrict our sample to areas with more than 25,000 residents. This represents 99.8% of all opioid deaths and 99.3% of the total population. Our final dataset is a balanced panel of 590 commuting zones and consists of 17,110 observations.

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[28] Table A14 shows the result for the sample of commuting zones that do not require state-level imputation. Our results are not sensitive to this sample restriction.

[29] We observe the number of beneficiaries at a given point in time but do not observe the number of beneficiaries entering or exiting the programs. Thus, we cannot speak to the question of whether a change in the stock is due to people entering more quickly or receiving benefits for a longer time.

[30] At least 98% of deaths are linked to their corresponding birth certificate. This figure varies by year; e.g., in 2018, 99.3% of all infant deaths were successfully linked, while in 1998, 98.4% of death records were linked.

[31] We follow the CDC's definition to compute the aggregate or general fertility rate. In additional results, we also present fertility rates for other age breakdowns.

[32] Data for the period 1989-1994 come from the Natality Birth Files. These files provide demographic and health data for all births occurring during the calendar year that we use to construct infant mortality rates, birth weight, fertility rate, and APGAR scores for the analysis we perform in Section IV.B.

IV. Empirical Strategy

The level of prescription opioids in a given place and time is an equilibrium object determined by supply and demand factors. Supply factors, such as the density of the healthcare network, and demand factors, such as the incidence of pain in the population, affect the level of prescription opioids and may also affect the evolution of our outcome variables. Table 2 shows that the distribution of opioids is not random across space, but rather is related to the demographic composition of the commuting zone and its economic performance. A greater share of the white population and higher median income at the commuting-zone level have a positive correlation with prescription opioids per capita; the share of the Hispanic population, the employment rate, and the demand for social insurance have a negative correlation with the opioid supply.[35] This is in line with Finkelstein et al. (2018), who estimate that areas with more physicians per capita, higher levels of income and education, lower Medicare spending per capita, and higher scores on a healthcare quality index have higher opioid abuse rates.

To identify the effect of prescription opioids on opioid-related mortality and our outcomes of interest we use an instrumental variable strategy that exploits geographical variation in the promotional efforts for OxyContin and other prescription opioids as an exogenous source of variation in the opioid supply. We estimate the causal effects of the supply of prescription opioids via the following equations, which are run over our sample of commuting zones for the period 1997-2018:

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[33] We will miss prescription opioid use from those who are willing to cross commuting-zone lines to obtain opioids prescriptions, nonetheless the literature suggests that this is a rare behavior (Buchmueller and Carey, 2018).

[34] We use the crosswalks developed by Autor and Dorn (2013) to go from county-level to commuting-zone-level aggregates. Some commuting zones cross state borders. When this happens, the commuting zone is assigned to the state where the higher share of the zone's population is located. This criterion helps to preserve the strong within-cluster and weak between-cluster commuting ties.

[35] We also find a small negative correlation between the share of employment in the manufacturing industry and opioid prescription rates.

First Stage:

$$\Delta\ Presc.\ Opioids_{ct} = \alpha_0 + \phi\ CancerMR_{ct_0} + \alpha\ \Delta\ X_{ct} + \gamma_{st} + \upsilon_{ct}\ . \tag{1}$$

Second Stage:

$$\Delta\ y_{ct} = \tau_0 + \beta\ \Delta\widehat{Presc.\ Opioids}_{ct} + \tau\ \Delta\ X_{ct} + \lambda_{st} + \varepsilon_{ct}\ , \tag{2}$$

where c indexes commuting zones, t indexes years, s indexes states, and t_0 is defined as the average of the pre-OxyContin period. The operator Δ works as follows: For any random variable W_{ct}, ΔW_{ct} equals the difference $W_{ct} - W_{ct_0}$; we refer to this operation as the long-change of variable W_{ct}. Regarding Equation (1), *Presc. Opioids*$_{ct}$ corresponds to doses of opioids per capita shipped to commuting zone c in year t and $CancerMR_{ct_0}$ is the cancer mortality rate in commuting zone c in 1994-1996 (t_0). In Equation (2), y_{ct} refers to one of our outcomes of interest, e.g., a measure of opioid-related mortality. Both equations include a vector $\Delta\ X_{ct}$ that represents the long-changes in the time-varying control variables. The control variables included are contemporaneous cancer mortality, share of the population over 66, share of the population 18-65, share of the population under 1 year, shares of the white and black populations, share of females, and share of Hispanic population.

We add state times year fixed effects represented by the term γ_{st} (and λ_{st} in the second-stage equation). These fixed effects control for the variation in outcomes over time that is common to all commuting zones within state s, and purge the variation in the supply of prescription opioids that results from a change in state-level policies—such as the implementation of a PDMP, access to naloxone, and regulation of "pill mills". The variables υ_{ct} and ε_{ct} are idiosyncratic error terms. We cluster standard errors at the commuting-zone level, which is the level of exogenous variation.

We have defined our main specification using a long-changes form—i.e., by computing the change relative to a baseline year for each variable in the estimation. This approach has the advantages that it allows us to control for unobservable characteristics at the commuting-zone level. Since our exogenous variation is at the commuting-zone level, we cannot include commuting-zone fixed effects in the regression. However, by expressing our variable in changes, we can partially absorb some of the variation that is specific to the commuting zone.

The parameter of interest β captures the causal effect of an increase in one dose of opioids per capita relative to the baseline year on the change in opioid mortality rate (and other outcomes of interest). That is, for a unit increase in the supply of prescription opioids relative to the period 1994-1996, the mortality rate from prescription opioids (and any other *outcome*) changes in β units relative to the pre-OxyContin's launch period. For the IV estimator of β to be consistent, the cancer mortality rate in the baseline period must be (i) strongly correlated with the opioid supply—i.e., the coefficient ϕ must be statistically different from zero, and (ii) uncorrelated with the error term in the second-stage equation (Equation 2). Evidence supporting our strategy was first presented in Section II, in which we discussed Purdue Pharma's marketing strategy and its rationale for focusing on the cancer market as the place to start and expand from. Next, we provide empirical evidence to support this strategy and assess threats to the validity of the instrument.

A. Does cancer mortality in the mid-1990s predict growth in the supply of prescription opioids?

We start by providing graphical evidence in Figure 1. We divide commuting zones into quartiles according to their level of cancer mortality before the launch of OxyContin and trace the evolution of all prescription opioids, oxycodone, hydrocodone, and morphine in these communities. Panel (a) of Figure 1 shows the evolution of the aggregate of prescription opioids per capita in commuting zones in the bottom and top quartiles of cancer mortality in 1994-1996, as well as the evolution of oxycodone—the active ingredient of OxyContin, which accounts for the largest share of this growth.[36] It is clear from the graph that communities with high rates of cancer experienced a much larger influx of prescribed oxycodone (solid orange line) than low-cancer communities (dashed orange line), even though the two groups started the period with a comparable prevalence of oxycodone. Specifically, between 1997 and 2010, areas in the highest quartile of cancer incidence saw an increase in oxycodone gm per capita of 2,900%, and areas in the lowest quartile experienced a growth that was one-third of that, even though the incidence of cancer varied equally across the two groups, as shown in Figure A5.

Table 3 shows the results of the first-stage regression defined in Equation 1. Column 1 is a bivariate regression of prescription opioids per capita on cancer mortality at t_0. Columns to the right add time-varying controls and different specifications of fixed effects. Our preferred specification is the one in column 5, in which we control for state-times-year fixed effects and our covariates. For all specifications, there is a positive and strong relationship between cancer rates in the mid-1990s and the change in opioids per capita. A one-unit (one-standard-deviation) increase in 1994-1996 cancer mortality increases the change in prescription opioids per capita relative to 1997 by 1.1 (0.13 standard deviation). To put this figure in context, a change from a commuting zone in the 5th percentile of the cancer distribution to the 95th percentile increases opioids per capita by 64% relative to the base period. We can see the strength of this relationship graphically in panel (b) of Figure 1 where we plot the first stage coefficients by year. We find that starting in

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[36] In Appendix Figure A6 we present the analogous analysis, but we split the data based on 8 octiles of cancer mortality and observe the same pattern.

1998, the second year in our data, and until 2018, the last year in our data, there is a positive and statistically significant relationship between cancer rates and prescription opioids per capita.

The literature on weak instruments has developed a variety of tests and confidence sets that remain valid whether or not the instruments are weak, in the sense that their probability of incorrectly rejecting the null hypothesis and covering the true parameter value, respectively, remains well controlled. We implement these procedures and present weak-instrument-robust inference. We follow Andrews et al. (2019) recommendations and present the effective first-stage F statistic proposed by Olea and Pflueger (2013) to assess the instrument's strength. In the rest of this paper, we refer to this as the *effective F-stat*. The value of the F-statistic testing the null hypothesis that the instrument is equal to zero in the first stage is always greater than 10, suggesting that we can reject the null hypothesis. Nonetheless, Lee et al. (2020) suggest that this standard practice of relying on the first-stage F exceeding some threshold (e.g., 10) delivers tests of incorrect size. Thus, to assess the statistical significance of our estimates, we (i) compute the "tF 0.05 standard error" proposed by Lee et al. (2020), which inflates the usual standard errors to take into account the strength of the first stage, and (ii) present *p-values* based on Anderson-Rubin Test (Anderson et al., 1949).[37]

B. Exogeneity and exclusion restriction: Is cancer mortality in the mid-1990s directly related to our outcome variables?

Variation in cancer mortality across locations is not random; rather, it depends on demographic, environmental and socioeconomic variables. In Table A3 we find that cancer mortality is: strongly related to share of the population over 65, negatively associated with the share of Hispanic population and positively associated with mortality from other causes of death. There is not, however, a correlation with our outcome variables: opioid mortality, shares in SNAP and disability, infant mortality rate, or fertility. Nonetheless, the validity of our identification strategy does not require that cancer be randomly distributed across areas, but rather that in the absence of OxyContin marketing, areas with higher cancer mortality in the pre-OxyContin period (t_0) exhibit the same *trend* as areas with lower cancer mortality in t_0 in terms of our outcome variables (Goldsmith-Pinkham et al., 2020).

We provide evidence to support this assumption in three ways. First, we estimate reduced-form type regressions where we interact our instrument with year dummy variables to test for the presence of pre-trends, i.e., we estimate a dynamic version of the reduced form relationship between the outcome variables and our instrument. For each outcome variable we consider the following specification, which is run over a balanced sample of commuting zones for the years 1989 to 2018:

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[37] Based on Lee et al. (2020), we use a correction factor of $\frac{2.75}{1.96} = 1.4031$ to compute the "tF 0.05 standard error." To facilitate its interpretation, we present the *t-statistic* computed with the corrected standard errors. This *t-statistic* should be compared with a critical value of 1.96 to assess the null hypothesis.

$$\Delta\ y_{ct} = \alpha_0 + \sum_{\tau=1989}^{2018} \phi_\tau\ CancerMR_{ct_0} \mathbf{1}(Year = \tau) + \alpha\ \Delta\ X_{ct} + \gamma_{st} + \upsilon_{ct}\ , \tag{3}$$

where Δ is the long change operator, y_{ct} is the outcome of interest, and X_{ct} is a vector of time-varying control variables defined previously. $CancerMR_{ct_0}$ is the cancer mortality rate in commuting zone c at time t_0 and it is interacted with a full set of year fixed effects index by τ. In this specification, the coefficients for the pre-OxyContin period; i.e., ϕ_{1989}, ϕ_{1990}, to ϕ_{1995}, test whether the outcome of interest y_{ct} in high and low cancer mortality areas followed similar trends before OxyContin was introduced to the market in 1996. Figures 2, 3, and 4 show the results of this estimation on main outcomes of interest.[38] We find that areas with higher cancer mortality in the mid-nineties were not on a differential trend along: opioid-related mortality, despair mortality, infant mortality, birth weight, fertility, or share of population using SNAP.[39] There is no evidence of pre-trends, i.e., the estimated coefficients for the pre-OxyContin period are jointly statistically indistinguishable from zero. After the introduction of OxyContin in 1996, strong patterns appear, and mid-nineties cancer mortality starts to predict opioid-related mortality, demand for SNAP, increased fertility, and worsening birth outcomes.

Furthermore, we show that the excess opioid mortality we estimate is entirely driven by young adults, and opioid mortality for adults over 55 years old does not increase (see Panel (a) of Figure 7). This supports the argument that our results are not driven by underlying health conditions, since the population over 55 is the closest to the population that drives the variation in our instrument, and that instead, what we observe is a spillover from the cancer population to the younger and healthier population, through the introduction of OxyContin in those markets. We also report event study estimates for suicide mortality and overall 75+ mortality —excluding cancer, Figure 5. We find that there is no evidence of any pre-trends from suicide or overall mortality prior to the introduction of OxyContin, and we also document that there no effects after either, suggesting there is no evidence of a systemic relationship between lagged cancer mortality and despair or overall health trends.

Second, we provide evidence that higher cancer mortality places were not on a differential trend along economic outcomes. To do so, we perform an out-of-sample dynamic reduced-form analysis in our pre-period. That is, we run Equation 3 over a sample of commuting zones for the years 1989 to 1995 and estimate if lagged cancer mortality—average cancer mortality rate in 1989 and 1990, the first years in our data—predicts our outcome variables. We present the results of this analysis in Figure 6 and Figure A13. These results demonstrate that before the introduction of OxyContin there is no relationship between our outcome measures and lagged cancer mortality—the estimated coefficients are statistically indistinguishable from zero. In Appendix Figure A14, we test for a relationship between the share of employment in the manufacturing and mining industry and cancer mortality before the launch of OxyContin and find no evidence of a differential trends in these variables.

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[38] Appendix Figures A8, A11, and A12 complement this analysis.

[39] Data on SSDI and SSI are not available at the county level before 1996 so we can not conduct this exercise for such outcomes.

Finally, for variables such as income per capita, educational attainment, or our outcome variables SSI and SSDI rates, for which we do not have yearly data for 1989-1995, we test whether lagged cancer mortality in 1989 and 1990, predicts changes in these variables, using a cross-sectional reduced form analysis. Table 4 presents the results of this exercise. In column 1, we find no evidence of a relationship between cancer incidence and relevant economic indicators, and similarly in column 2, which replicates this analysis for our outcome variables, including SSI and SSDI, we do not find any relationship. Taken together these results suggest that in the absence of OxyContin marketing, areas with higher cancer mortality exhibit the same *trends* as areas with lower cancer mortality in terms of our outcome variables and additional socio-economic measures.

V. Results

A. Effects on Opioid-related Mortality

We start by inspecting the raw data; in panel (a) of Figure 2 we split commuting zones based on the cancer mortality distribution and document that early in the 2000s, a wedge starts to appear between high- and low-cancer-incidence groups, and by the end of the sample opioid mortality in high-cancer areas is 75% higher.[40] Second, following the reduced-form approach from Equation 3, we estimate that after the launch of OxyContin a strong relationship emerges between mid-nineties cancer mortality and opioid-related mortality as shown in Panel (b) of Figure 2.[41]

Next we take Equations 1 and 2 to the data. Commuting zones with the highest cancer incidence at the time of OxyContin's launch received 64% more opioids per capita than their counterparts—i.e., the 95th percentile relative to the 5th percentile. Using this increase as an exogenous change, we estimate that an additional dose of prescription opioids per capita caused an increase in prescription opioid mortality of 0.0068 points and in all opioid mortality of 0.0065 points. The estimates presented in columns 3 and 6 of Table 5 are statistically significant using t-ratio inference, Anderson-Rubin weak instrument robust inference, and the recent tF procedure suggested by Lee et al. (2020). Our results imply that when doses per capita increase from the 25th to the 75th percentile—i.e., a 5.02 dose increase—mortality from prescription opioids increases by 88.6% and all opioid mortality increases by 39.3%.[42]

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[40] In Appendix Figure A7 we present the analogous analysis, but we split the data based on 8 octiles of cancer mortality and observe the same pattern.

[41] In Appendix Figure A8 we replicate this analysis for any opioid mortality and document similar trends.

The ordinary least squares (OLS) estimates (columns 1 and 4 of Table 5) differ considerably from the IV estimates. We find a positive correlation between opioid supply and opioid mortality rate, but the difference in magnitude between the OLS and the IV estimates suggests that the former suffers from attenuation bias. Put another way, by looking at the correlation between opioid supply and opioid deaths, we would underestimate the role of the supply of prescription opioids in explaining the rise in mortality. The negative bias in the OLS estimates is consistent with commuting zones that receive a disproportionate amount of marketing being positively selected on observable characteristics: Areas initially targeted by OxyContin campaigns had better access to healthcare and a larger number of physicians per capita, which served as OxyContin initial network. These results are consistent with Finkelstein et al. (2018), who document that higher opioid abuse rates are correlated with more physicians per capita, higher levels of income and education, lower Medicare spending per capita, and higher scores on a healthcare quality index.

Heterogeneous effects. The excess opioid-related mortality induced by the marketing of OxyContin is by and large coming from young and middle-aged adults and is driven mainly by white adults at the begging of the epidemic. In Figure 7, we present the interactive-reduced-form analysis for three age groups (panel a) and for men and women (panel b). The analysis by age shows (i) no evidence of pretends on opioid mortality for any of these groups, and (ii) opioid mortality increases that are concentrated among individuals aged less than 55 years old. For those 55 and older we see no effects. This pattern also alleviates concerns that our results could be driven by underlying health trends that correlate with mid-nineties cancer mortality. Additionally, we find the epidemic affected men and women similarly. We also study the effects by race, we find that estimates for whites are positive and statistically significant starting soon after the launch of OxyContin. For non-whites it takes around a decade for estimates to be positive and statistically significant (Appendix Figure A10).

The opioid crisis can be viewed as having occurred in three waves (Maclean et al., 2020). Panel A of Table A4 reproduces the estimates of the first stage for different starting and ending years, and Panel B replicates the main instrumental variables regressions. We find a strong first-stage relationship between mid-nineties cancer mortality and the supply of prescription opioids in all the stages of the crisis. In terms of the effects, our results suggest that the increase in the supply of prescription opioids had a stronger impact on opioid-related mortality in the first wave of the epidemic. However, differences across periods are not statistically significant.

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[42] The standard deviation of the distribution of prescription opioids per capita between 1997-2018 is 4.34, thus a change from the 25th to the 75th percentile in such distribution represents 1.15 of a standard deviation.

B. Adult Wellbeing and Intergenerational effects

In this section, we study whether the access to potent opioids has deteriorated the well-being of adults by looking at the demand for social insurance and welfare programs and assess its intergenerational effects.

Other mortality measures. We ask whether the dramatic increase in opioid supply affected all-cause mortality, excluding cancer deaths. These results are presented in Table 6. We find no relationship between overall mortality and the increase in prescription opioids. To put this result into context, note that at their peak in 2017, opioid-related deaths accounted for 1.8% of all deaths. The introduction of very effective pain medication could have improved the wellbeing of individuals with high incidence of pain and low risks of addiction. To asses if there is any indication of such improvements we estimate our reduced-form exercise on mortality rate for those 75 and older, but find no evidence of any reduction or increase in mortality (Appendix Figure 5).

Case and Deaton (2017) document a dramatic decline in life expectancy for white non-Hispanic Americans, which is mostly driven by deaths from despair such as drug overdoses, suicides, and alcohol-related liver mortality, and point to a possible connection to the opioid epidemic. We explore this connection studying the effects of opioid supply on *non-opioid-related* deaths of despair. In Appendix Figure A11 we show that there is only a weak link between the increase in the supply of opioids and deaths of despair during the last wave of the opioid epidemic that is driven by alcohol-related deaths. We estimate a positive but small increase in deaths from alcoholic liver diseases and cirrhosis significant only at the 10% level and no effect on suicides, see Table 6. The category alcoholic liver diseases includes causes of deaths such as hepatitis and related conditions, that may be directly affected by opioid use (Ruhm, 2021), so it is possible this small effect is directly driven by opioid use. Furthermore, the fact that we do not find an effect on suicides (Figure A11), suggests that first, there are no pre-trends between our instrument and this measure of despair, and second, that the marketing of OxyContin did not trigger further despair. Similarly, we do not find evidence of changes in smoking rates (Figure A15).

Demand for social insurance and welfare programs. Addiction to and misuse of prescription opioids could reduce work capacity and put people at risk of permanently reducing their labor supply; in this context, disability insurance applications are a useful proxy for socioeconomic conditions and longer-term labor force attachment. We document a tight link between the opioid epidemic and an increase in disability beneficiaries. These results are presented in Table 7. We find positive and significant effects for measures of both disability programs. A change from the 25th to the 75th percentile in the growth of opioids per capita caused a 47% increase in the share of the population receiving SSI and a 76% increase in the share receiving SSDI.[43] We do not have data for SSI or SSDI claims in the pre-period, but we can estimate our reduced-form event-study after the introduction of OxyContin. Figure A9 shows the strong positive pattern between mid-nineties cancer mortality and disability claims.

SNAP is designed to act as a safety net for low-income families. In our context, applications to SNAP are a useful proxy for deteriorating economic conditions. We find a positive effect on the share of SNAP beneficiaries: Our estimates suggest that a change from the 25th to the 75th percentile in the growth of oxycodone per capita caused a 57% increase in the share of the population enrolled in SNAP. This effect is comparable to an increase of 3.78 percentage points in the unemployment rate (Ganong and Liebman, 2018).[44] These results point to a substantial worsening of economic conditions. The effects we observe on SSDI and SNAP are particularly strong during the third wave of the epidemic, when the incidence of illicit drug use, such as of heroin and fentanyl, increased (Table A5). Figure 3 shows the dynamic evolution of these effects.

Maternal and birth outcomes. One in five pregnant women filled a prescription for opioids from 2000 to 2007 (Desai et al., 2014); and between 2008 and 2012, 39% of women of reproductive age covered by Medicaid obtained a prescription for opioids. These figures, joint with the staggering increase in the incidence of neonatal abstinence syndrome (NAS) (Patrick et al., 2015) raise concerns about the risks and consequences of opioid abuse in this population.[45] To the best of our knowledge, we are the first to document a causal rise in fertility as a result of the opioid epidemic. Specifically, a 25th-to-75th percentile increase in opioids increases fertility by 10% (Table 8). This result is entirely explained by non-marital births as we can see in column 1 of Appendix Table A6. By age, we find that most of the increase in fertility is coming from women 25 to 29 years old, which compensates a decline in fertility for those over 35 years old. Terplan et al. (2015) document that the higher rates of unwanted pregnancies in the population of women who take opioids is mostly driven by the lack of adherence to contraception.

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[43] SSDI uses 1996 data as the baseline year, and SSI uses 1998 as the baseline year.

[44] The receipt of benefits from multiple programs is not uncommon. SNAP administrative data from 2011 indicate that 20% of SNAP households received SSI benefits and 22% received Social Security benefits (see, for example, Strayer et al., 2012). We claim that our estimated effect on SNAP applications cannot be entirely driven by dual applicants. Under the assumption that 20% of SNAP recipients are also SSI recipients, the lower bound for the effect on SNAP recipiency rate is 15.6% (0.20 × 78). Our estimated effect is well above this figure, suggesting that the average effect on SNAP applications is also driven by low-income workers.

[45] Neonatal abstinence syndrome is a result of the sudden discontinuation of fetal exposure to medicine or drugs that were used or abused by the mother during pregnancy.

Regarding birth outcomes, we find evidence that a 25th-to-75th-percentile increase in the supply of prescription opioids decreases birth weight by 0.7%, deteriorates APGAR scores by 1% relative to its mean value, and reduces median pregnancy duration by 0.63% which translates to a reduction in the median length of pregnancy of 0.24 weeks. We also estimate increases in the incidence of preterm births and the share of low-weight births, but these are not statistically significant. We find an increase in the APGAR score of infants who died in the first year, which means that healthier infants died. However, in aggregate terms we do not find any increase in the infant mortality rate.

Our estimated declines in birth weight are not small in magnitude. For a reference, Almond et al. (2011) estimate an increase in birth weight of 0.5% as a result of the roll-out of food stamps among participants, i.e., a treatment on the treated estimates.[46] Hoynes et al. (2015) find a 0.3% increase in birth weight from the expansion of the Earned Income Tax Credit (EITC). This is particularly relevant in light of evidence on the importance of birth weight and health at birth for future health, schooling, and earnings (Behrman and Rosenzweig, 2004).

In summary, our results suggest that the opioid epidemic lead to important increases in fertility, driven by young and unmarried mothers. While not affecting directly the infant mortality rate, the epidemic worsened birth outcomes through reductions in pregnancy duration and infant health at birth. In 24 states and the District of Columbia, the use of any illegal substance during pregnancy constitutes child abuse, and can lead to foster care placement. Nonetheless, Eichmeyer and Kent (2021) document that treatment for opioid use disorder increases in the year after childbirth, and that the timing of this increase is consistent with pregnancy triggering treatment for a pre-existing disorder. Using, state-level data, Buckles et al. (2020) document that greater exposure to the crisis increases the likelihood that a child's mother or father is absent from the household and it increases the likelihood that he or she lives in a household headed by a grandparent. Unfortunately, after multiple efforts we were not able to access foster care records with county or commuting zone identifiers.[47] Future work is needed to quantify the effect of the opioid crisis on foster care placements, and to assess the future outcomes for these children.

C. Complier Analysis

Our instrumental variable estimates identify the causal effects of the increased supply of opioids for commuting zones where marketing was more aggressive because of higher cancer mortality in the mid-nineties. Variation in underlying characteristics across commuting zones could have made such opioids' marketing more or less successful. In Table 9 we characterize compliers based on observable characteristics before OxyContin's launch.

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[46] Estimates are higher for black participants: between 0.4% and 1.4%.

[47] The Adoption and Foster Care Analysis and Reporting System (AFCARS) provides case level data, but county identifiers are only available for counties with more than a 1,000 cases.

First, we assess the strength of the first stage in different sub-samples. Column 1 shows that the positive and strong relationship between cancer rates in the mid-1990s and the change in opioids per capita is present in all the considered sub-samples. Nonetheless, there are important differences on the strength of this relationship. The first-stage is stronger in commuting zones with higher poverty rates, employment in mining, and cocaine and alcohol mortality rates, however, these difference are not statistically significant. Next, we follow Abadie (2003), to recover the fraction of compliers for different characteristics. We find that commuting zones with higher poverty rates, lower educational attainment, and a higher share of mining employment are more likely to be compliers. In terms of health outcomes, areas with a higher number of primary care physicians (PCP) per capita are overrepresented among the compliers, as is the case for places with higher smoking rates and higher cocaine and alcohol mortality rates.

VI. Robustness Checks

In this section, we explore alternative explanations for our findings and test the robustness of our results. We start by presenting alternative specifications of the first stage and then test the robustness of the main results.

A. First Stage

A potential concern with our choice of instrument is that mid-nineties cancer mortality may be capturing demographic variation along the age distribution. Our baseline regression already controls for the change in the share of the population over 65, but our instrument is expressed in levels, so some of this variation may still be important. We directly test this by including the share of population over 65, the size of the population over 65, and total population as additional control variables. Table A8 shows the results of this exercise. We find that the first stage regression is as strong as in our baseline regression.

Additionally, we test the robustness of the first stage to alternative choices of instruments. Column 1 of Table A9, replicates the first stage with age-adjusted cancer mortality, we find a very similar and strong first-stage estimates. We also test whether the relationship between future opioid distribution and mid nineties cancer mortality is sensitive to any of the years used as our baseline cancer mortality measure. Columns two to four show there is a strong first-stage for 1994, 1995 and 1996 cancer mortality. In column five we estimate a population weighted regression and find similar results. As an additional robustness check, in panel b we construct a measure of cancer mortality that exclude deaths from lung cancer, this measure is less likely to be driven by behavioral and environmental factors that could correlate with our outcome variables. As with other alternative instruments, in column one, we find a strong first stage coefficient. In columns two to four we use mid-nineties cancer mortality for those over 55, 65 and 75 respectively, and find a positive and statistically significant first stage in all cases. Finally, we inspect the dynamic relation between mid-nineties cancer mortality and opioid supply. Panel (a) of Figure A16 presents the dynamic first-stage using cancer mortality in 1994 as the instrument and the remaining panels in this Figure show the dynamic reduced-form for the main outcomes of interest. The pattern of the estimated coefficients is equivalent to the one we obtain using the cancer 1994-1996 as instrument. Additionally, we do not find evidence of pre-trends in the relation between opioid mortality—and the main outcomes of interest—and mid-nineties cancer mortality in this alternative specification.

Our instrumental variable approach is similar in spirit to a shift-share instrument. In this research design, the shares measure differential exposure to common shocks and identification is based on its exogeneity (Goldsmith-Pinkham et al., 2020). In our application, the shares are cancer rates in the mid-1990s, which capture exposure to the marketing of prescription opioids, and the shift is the national growth of Purdue Pharma's marketing or the growth in the supply of prescription opioids. Our preferred specification uses as an instrument cancer mortality before the launch of OxyContin, which highlights the fact that our only source of exogenous variation corresponds to the shares. In Appendix Table A7, we show results using the shift-share instrument. To construct this instrument, we use the national growth rate of prescription opioids as the shift component. The results are quantitatively indistinguishable from our preferred specification. As Goldsmith-Pinkham et al. (2020) point out, using a Bartik instrument is "equivalent" to exploiting the shares as an instrument. This is because the temporal variation induced by the growth of prescription opioids is mostly absorbed by the time dimension of our state times year fixed effects.

Finally, we test whether the positive relationship in our first stage is driven by a state or a group of states. Figure A17 presents the estimate of the first stage coefficient restricting the sample to (i) all non-triplicate states, (ii) only triplicate states, and (iii) to the exclusion of all states, one at the time. We find that the relationship between mid-nineties cancer mortality and the supply of opioids is present in both triplicate and non-triplicate states, and is robust to the exclusion of any state.

B. Placebo checks

Are other mid-1990s mortality rates predictive of future prescription opioids per capita distribution? Our identification strategy connects mid-1990s cancer mortality to future growth in the supply of prescription opioids through the targeted marketing of Purdue Pharma. This implies that we can test the validity of our design by estimating first-stage regressions for placebo instruments—i.e., mid-1990s mortality from causes unrelated to cancer. Finding a good placebo instrument is challenging, given that the causes that underlie the incidence of cancer and other conditions, such as heart disease are not independent (Chiang, 1991 and Honoré and Lleras-Muney, 2006). As a result, there is substantial overlap across underlying causes and the correlation across measures is very high. With this caveat, in Table A10 we show placebo instrument regressions for three mortality rates that are less likely to be affected by the previous concern: Cerebrovascular disease (CVD), transit accidents, and homicide.[48] We find that none of these measures predict future distribution of opioids (Columns 1 to 3) or change the predicted power of our instrument (Columns 4 to 6).

C. Alternative Definitions: Opioid Supply and Opioid Mortality

Many pharmaceutical companies—Janssen, Endo, Cephalon-Teva, Actavis, Insys, and Mallinckrodt—promoted their prescription opioids beyond the cancer market following Purdue's leadership. Nonetheless, Purdue Pharma was the pioneer of the use of opioids in the non-cancer pain market. So, as an additional check, we use data only on Oxycodone—the active ingredient in OxyContin—as an alternative measure of opioid supply. We find a positive relationship between cancer mortality rates and this measure of opioid supply. In Table A11, columns (2) and (3) we estimate that an additional dose of oxycodone per capita caused an increase in prescription opioid mortality of 91% and in all opioid mortality of 40%.

Drug overdose deaths can be hard to categorize, specially when using data that spans more than one version of the ICD codes. We construct an additional outcome measure for opioid mortality and present the results using this measure in Table A12. This measure has the advantage that comparisons across years are less affected by changes in the ICD classification, but this comes at the cost of including a broader set of drugs as the cause of deaths.[49] Exploiting this measure, we arrive at similar conclusions: An additional dose of opioids per capita caused an increase in the drug-induced mortality rate of 0.0112 points. An increase from the 25th to the 75th percentile of prescription opioids per capita increases drug-induced mortality by 47%.

D. Alternative Sample Restrictions and Specifications

In our main specification, we restrict our sample to areas with more than 25,000 residents, which represents 99.8% of all opioid deaths and 99.3% of the total population. In Table

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[48] A good candidate for this placebo check is mortality from external causes of deaths. External causes are defined as intentional and unintentional injury and poisoning (including drug overdose). From this category, we construct measures of mortality that do not include any of our outcome measures: accidental poisoning and suicide.

[49] Drug-induced deaths category includes deaths from poisoning and medical conditions caused by the use of legal or illegal drugs, as well as deaths from poisoning due to medically prescribed and other drugs.

A13 we reproduce our analysis using alternative restrictions on the size of commuting zones. We arrive at analogous conclusions to the main analysis; there is a strong and positive relation between mid-nineties cancer mortality and supply of prescription opioids which translates to (i) increases in opioid-related mortality, and (ii) deteriorating economic conditions and health outcomes.

Finally, SNAP benefit recipiency rates at the commuting-zone level required imputations for some commuting zones with no available data at the local level. Table A14 shows the result for the sample of commuting zones that do not require state-level imputation. Our results are not sensitive to this sample restriction. Finally, in Table A15 we expand the set of controls in our regression to include either the unemployment rate or the employment rate and we find our results are quantitatively indistinguishable.

E. Trade shocks & the 2001 Economic Recession

During our period of study, the US experienced significant economic changes that affected communities differentially. In October, 2000, the US Congress passed a bill granting permanent normal trade relations (PNTR) with China. This trade liberalization communities, as a function of the importance of the manufacturing industries for local employment, in industries subjected to import competition from China. Researchers have estimated the impact of this trade shock on a host of outcomes. Regions more exposed to Chinese import competition experienced relatively large declines in employment and a greater uptake of social welfare programs (Autor and Dorn, 2013). Additionally, areas more exposed to Chinese import competition exhibit relative increases in fatal drug overdoses (Pierce and Schott, 2020).

In light of this evidence, we ask whether our results are confounded or mediated by this trade policy. To answer this, we follow the trade literature to construct two alternative measures of exposure to PNTR and then estimate our first-stage and reduced-form models controling for these exposure measures (Pierce and Schott, 2020 and Autor and Dorn, 2013). Table A16 columns two to four reproduce the first stage when we control for exposure to Chinese import competition. We find the results are unaffected by the inclusion of these variables. Figure A18 replicates our main results adding the china shock measures to our event-study specification. Here as well we find our estimates do not change with this exercise. This is the result of a very low correlation between our instrument and the exposure to Chinese import competition. Similarly, the timing of some of our results overlaps with the 2001 economic recession. To asses whether the recession is mediating some of our effects, we construct a measure of exposure to the recession as the change in the unemployment rate from 2001 to 2000 at the commuting zone. Similar to the china shock, we find that our instrument and this exposure measure have a very low correlation level (ρ=0.03), and our first stage estimate are completely unaffected (column 1 in Table A16). More broadly, in the last three columns of Table A16 we add controls for the unemployment rate in years 1994 to 1996, respectively, and find that our estimates do not change.

VII. Policy Implications and Conclusions

This paper studies the origins of the opioid epidemic and its effect on a broad range of outcomes. We exploit geographical variation in the initial promotion of OxyContin that targeted the cancer patients market. We document that this initial targeting had long-term effects on the supply of prescription opioids, overdose deaths involving opioids, along with a deterioration in adult wellbeing measured by the demand for SSDI, SSI, and SNAP. This effects will continue to unfold as a result of the increase in non-marital fertility and the worsening of birth outcomes. In this paper, we sought to provide a complete picture of the effects of the opioid epidemic. However, data access limitations have prevented us from speaking to some important topics, such as the effects on children's living arrangements and environments, foster care referrals, and the demand for and use of healthcare. We hope that future research will shed light on these subjects. In terms of policy recommendations we want to highlight how complex and far-reaching the effects of the opioids epidemic are, and how this calls for a coordinated response from multiple policy angles. Monitoring, limiting and restricting access to prescription opioids, which has been the main policy response, is important, but it falls short to the needs of the affected population. Increasing access to rehabilitation treatments and programs aimed at reincorporating parents and workers to their lives should be at the center of this response.

Finally, our results have direct policy implications regarding the desirability of promotional efforts of addictive drugs by pharmaceutical companies that target physicians, pharmacies, and patients. We document the devastating consequences of aggressive and deceitful marketing. Although marketing expanded over the 25 years since the introduction of OxyContin, regulatory oversight remains relatively limited.[50] Some regulatory initiatives constitute small steps in the right direction, such as the Sunshine Act of 2010 that required the reporting of payments from the pharmaceutical industry to physicians, with a recent expansion that includes payments to physician assistants, nurse practitioners, nurses, pharmacists, and dietitians. Furthermore, a growing segment of the medical community has spoken out against the pharmaceutical industry's effort to influence doctors, and a number of teaching hospitals have enacted policies that restrict or ban visits from pharmaceutical representatives. However, most of these initiatives are concerned with the rising costs of prescription drugs, and not with the risks of abuse and addiction.

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[50] Currently, prescription drug marketing practices in the US include direct-to-consumer and professional branded advertising, detailing visits, free drug samples, and direct physician and hospital payments (e.g., speaker fees, food, travel accommodations).

More can be done to restrict the pharmaceutical promotion that carries this risk.

References

Abadie, Alberto. 2003. “Semiparametric Instrumental Variable Estimation of Treatment Response Models.” *Journal of Econometrics*, 113(2): 231–263.

Ailes, Elizabeth C., April L. Dawson, Jennifer N. Lind, Suzanne M. Gilboa, Meghan T. Frey, Cheryl S. Broussard, and Margaret A. Honein. 2015. “Opioid Prescription Claims Among Women of Reproductive Age - United States, 2008-2012.” *MMWR. Morbidity and Mortality Weekly Report*, 64(2): 37.

Aliprantis, Dionissi, Kyle Fee, and Mark Schweitzer. 2019. “Opioids and the Labor Market.” FRB of Cleveland Working Paper No. 18-07R2.

Almond, Douglas, Hilary W. Hoynes, and Diane Whitmore Schanzenbach. 2011. “Inside the War on Poverty: The Impact of Food Stamps on Birth Outcomes.” *The Review of Economics and Statistics*, 93(2): 387–403.

Alpert, Abby, David Powell, and Rosalie Liccardo Pacula. 2018. “Supply-Side Drug Policy in the Presence of Substitutes: Evidence From the Introduction of Abuse-Deterrent Opioids.” *American Economic Journal: Economic Policy*, 10(4): 1–35.

Alpert, Abby E., Sarah E. Dykstra, and Mireille Jacobson. 2020. “How Do Prescription Drug Monitoring Programs Reduce Opioid Prescribing? The Role of Hassle Costs versus Information.” NBER Working Paper No. 27584.

Alpert, Abby, William N Evans, Ethan M J Lieber, and David Powell. 2022. “Origins of the Opioid Crisis and its Enduring Impacts.” *The Quarterly Journal of Economics*. qjab043.

Anderson, Theodore W, Herman Rubin, et al. 1949. “Estimation of The Parameters of a Single Equation in a Complete System of Stochastic Equations.” *Annals of Mathematical statistics*, 20(1): 46–63.

Andrasfay, Theresa, and Noreen Goldman. 2021. “Reductions in 2020 US life expectancy due to COVID-19 and the disproportionate impact on the Black and Latino populations.” *Proceedings of the National Academy of Sciences*, 118(5): e2014746118.

Andrews, Isaiah, James H Stock, and Liyang Sun. 2019. “Weak Instruments in Instrumental Variables Regression: Theory and Practice.” *Annual Review of Economics*, 11: 727–753.

APA. 2017. “Opioid Use Disorder.”

Autor, David. H., and David Dorn. 2013. “The Growth of Low-Skill Service Jobs and the Polarization of the US Labor Market.” *American Economic Review*, 103(5): 1553–97.

Beheshti, D. 2019. “The Impact of Opioids on the Labor Market: Evidence From Drug Rescheduling.” Technical report, Working Paper.

Behrman, Jere R, and Mark R Rosenzweig. 2004. “Returns to Birthweight.” *Review of Economics and Statistics*, 86(2): 586–601.

Buchmueller, Thomas C, and Colleen Carey. 2018. “The Effect of Prescription Drug Monitoring Programs on Opioid Utilization in Medicare.” *American Economic Journal: Economic Policy*, 10(1): 77–112.

Buckles, Kasey, William N. Evans, and Ethan M.J. Lieber. 2020. “The Drug Crisis and the Living Arrangements of Children.” NBER Working Paper No. 27633.

Carpenter, Christopher S., Chandler B. McClellan, and Daniel I. Rees. 2017. “Economic Conditions, Illicit Drug Use, and Substance Use Disorders in the United States.” *Journal of Health Economics*, 52: 63–73.

Case, Anne, and Angus Deaton. 2015. “Rising Morbidity and Mortality in Midlife Among White Non-Hispanic Americans in the 21st Century.” *Proceedings of the National Academy of Sciences*, 112(49): 15078–15083.

Case, Anne, and Angus Deaton. 2017. “Mortality and Morbidity in the 21st Century.” *Brookings Papers on Economic Activity*, 2017: 397.

Caudillo, Mónica L, and Andrés Villarreal. 2021. “The Opioid Epidemic and Nonmarital Childbearing in the United States, 2000-2016.” *Demography*, 58(1): 345–378.

CDC. 2020. “U.S. Opioid Dispensing Rate Maps.”

CDC. 2021. “Prescription Opioid Epidemic: Know the Facts.”

CDC, Prescription Drug Overdose Team. 2013. “Guide to ICD-9-cm and ICD-10 Codes Related to Poisoning and Pain.” *National Center for Injury Prevention and Control.*

Chiang, Chin Long. 1991. “Competing risks in mortality analysis.” *Annual review of public health*, 12(1): 281–307.

Currie, Janet, and Hannes Schwandt. 2020. “The Opioid Epidemic Was Not Caused by Economic Distress But by Factors That Could Be More Rapidly Addressed.” NBER Working Paper No. 27544.

Dave, Dhaval, Monica Deza, and Brady Horn. 2020. "Prescription Drug Monitoring Programs, Opioid Abuse, and Crime." NBER Working Paper No. 24975.

David, H, David Dorn, and Gordon H Hanson. 2013. "The China Syndrome: Local Labor Market Effects of Import Competition in the United States." *American Economic Review*, 103(6): 2121–68.

DEA Office of Diversion Control. 1997-2018. "ARCOS Drug Retail Summary Reports." U.S. Department of Justice, Drug Enforcement Administration, Office of Diversion Control. https://www.deadiversion.usdoj.gov/arcos/.

DeCicca, Philip, Donald S Kenkel, and Michael F Lovenheim. 2022. "The Economics of Tobacco Regulation: A Comprehensive Review." *Journal of Economic Literature. Forthcoming.*

Deiana, Claudio, and Ludovica Giua. 2018. "The US Opidemic: Prescription Opioids, Labour Market Conditions and Crime." CSEF Working Paper No. 525.

Desai, Rishi J., Sonia Hernandez-Diaz, Brian T. Bateman, and Krista F. Huybrechts. 2014. "Increase in Prescription Opioid Use During Pregnancy Among Medicaid-Enrolled Women." *Obstetrics and Gynecology*, 123(5): 997.

Doleac, Jennifer L, and Anita Mukherjee. 2019. "The moral hazard of lifesaving innovations: naloxone access, opioid abuse, and crime." *Opioid Abuse, and Crime (March 31, 2019).*

Dowell, Deborah, Tamara M. Haegerich, and Roger Chou. 2016. "CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016." *JAMA*, 315(15): 1624–1645.

Dyer, Owen. 2018. "US Life Expectancy Falls for Third Year in a Row." *BMJ: British Medical Journal (Online)*, 363.

Eichmeyer, Sarah, and Christina Kent. 2021. "Parenthood in Poverty." Working Paper.

Eichmeyer, Sarah, and Jonathan Zhang. 2020. "Can a Single Opioid Prescription Make a Difference? Evidence From Physician Prescribing Variation in Emergency Departments." Working Paper.

Evans, Mary F, Matthew Harris, and Lawrence Kessler. 2020. "The hazards of unwinding the prescription opioid epidemic: implications for child abuse and neglect." *Claremont McKenna College Robert Day School of Economics and Finance Research Paper*, , (3582060).

Evans, William N., Ethan M.J. Lieber, and Patrick Power. 2019. "How the Reformulation of OxyContin Ignited the Heroin Epidemic." *Review of Economics and Statistics*, 101(1): 1–15.

Fernandez, Fernando, and Dijana Zejcirovic. 2018. "The Role of Pharmaceutical Promotion to Physicians in the Opioid Epidemic."

Finkelstein, Amy, Matthew Gentzkow, and Heidi Williams. 2018. "What Drives Prescription Opioid Abuse? Evidence From Migration." *Stanford Institute for Economic Policy Research Working Paper*, 18–028.

Fishman, Scott M, Jennifer S Papazian, Susana Gonzalez, Paul S Riches, and Aaron Gilson. 2004. "Regulating opioid prescribing through prescription monitoring programs: balancing drug diversion and treatment of pain." *Pain Medicine*, 5(3): 309–324.

Ganong, Peter, and Jeffrey B Liebman. 2018. "The Decline, Rebound, and Further Rise in SNAP Enrollment: Disentangling Business Cycle Fluctuations and Policy Changes." *American Economic Journal: Economic Policy*, 10(4): 153–76.

Gihleb, Rania, Osea Giuntella, and Ning Zhang. 2022. "The Effect of Mandatory-Access Prescription Drug Monitoring Programs on Foster Care Admissions." *Journal of Human Resources*, 57(1): 217–240.

Goldsmith-Pinkham, Paul, Isaac Sorkin, and Henry Swift. 2020. "Bartik Instruments: What, When, Why, and How." *American Economic Review*, 110(8): 2586–2624.

Griffin, Beth Ann, Megan S. Schuler, Elizabeth A. Stuart, Stephen Patrick, Elizabeth McNeer, Rosanna Smart, David Powell, Bradley Stein, Terry Schell, and Rosalie Liccardo Pacula. 2020. "Variation in Performance of Commonly Used Statistical Methods for Estimating Effectiveness of State-Level Opioid Policies on Opioid-Related Mortality." NBER Working Paper No. 27029.

Hah, Jennifer M., Brian T. Bateman, John Ratliff, Catherine Curtin, and Eric Sun. 2017. "Chronic Opioid Use After surgery: Implications for Perioperative Management in the Face of the Opioid Epidemic." *Anesthesia and Analgesia*, 125(5): 1733.

Harris, Matthew C., Lawrence M. Kessler, Matthew N. Murray, and Beth Glenn. 2020. "Prescription Opioids and Labor Market Pains: The Effect of Schedule II Opioids on Labor Force Participation and Unemployment." *Journal of Human Resources*, 55(4): 1319–1364.

Heil, Sarah H, Hendree E Jones, Amelia Arria, Karol Kaltenbach, Mara Coyle, Gabriele Fischer, Susan Stine, Peter Selby, and Peter R Martin.

2011. “Unintended pregnancy in opioid-abusing women.” *Journal of substance abuse treatment*, 40(2): 199–202.

Honoré, Bo E, and Adriana Lleras-Muney. 2006. “Bounds in Competing Risks models and The War on Cancer.” *Econometrica*, 74(6): 1675–1698.

Hoynes, Hilary, Doug Miller, and David Simon. 2015. “Income, the Earned Income Tax Credit, and Infant Health.” *American Economic Journal: Economic Policy*, 7(1): 172–211.

Jones, Mark R., Omar Viswanath, Jacquelin Peck, Alan D. Kaye, Jatinder S. Gill, and Thomas T. Simopoulos. 2018. “A Brief History of the Opioid Epidemic and Strategies for Pain Medicine.” *Pain and Therapy*, 7(1): 13–21.

Joranson, David E, Grant M Carrow, Karen M Ryan, Linda Schaefer, Aaron M Gilson, Patricia Good, John Eadie, Susan Peine, and June L Dahl. 2002. “Pain management and prescription monitoring.” *Journal of pain and symptom management*, 23(3): 231–238.

Kaplan, Jacob. 2020. “Jacob Kaplan’s Concatenated Files: Uniform Crime Reporting Program Data: Offenses Known and Clearances by Arrest, 1960-2019.” Ann Arbor, MI: Inter-university Consortium for Political and Social Research. https://doi.org/10.3886/E100707V16.

Keefe, Patrick Radden. 2017. “The Family That Built an Empire of Pain: The Sackler Dynasty’s Ruthless Marketing of Painkillers Has Generated Billions of Dollars - And Millions of Addicts.” *The New Yorker.*

Krueger, Alan B. 2017. “Where Have All the Workers Gone? An Inquiry into the Decline of the U.S. Labor Force Participation Rate.” *Brookings Papers on Economic Activity*, 2017(2): 1.

Lee, David L., Justin McCrary, Marcelo J. Moreira, and Jack Porter. 2020. “Valid t-ratio Inference for IV.” *arXiv preprint arXiv:2010.05058.*

Lynch, Sean, Laura Sherman, Susan M. Snyder, and Margaret Mattson. 2018. “Trends in Infants Reported to Child Welfare with Neonatal Abstinence Syndrome (NAS).” *Children and Youth Services Review*, 86: 135–141.

Maclean, Catherine, Justine Mallatt, Christopher J. Ruhm, and Kosali Ilayperuma Simon. 2020. “Review of Economic Studies on the Opioid Crisis.” NBER Working Paper No. 28067.

Macy, Beth. 2018. *Dopesick: Dealers, Doctors, and The Drug Company that Addicted America.* Little, Brown.

Malbran, Pia. 2007. "What's a Pill Mill?" *CBS News, May*, 31.

Mallatt, Justine. 2018. "The Effect of Prescription Drug Monitoring Programs on Opioid Prescriptions and Heroin Crime Rates." *Available at SSRN 3050692.*

Meara, Ellen, Jill R Horwitz, Wilson Powell, Lynn McClelland, Weiping Zhou, A James O'malley, and Nancy E Morden. 2016. "State legal restrictions and prescription-opioid use among disabled adults." *New England Journal of Medicine*, 375(1): 44–53.

Meier, Barry. 2018. *Pain Killer: An Empire of Deceit and the Origin of America's Opioid Epidemic.* Random House.

Meinhofer, Angélica, and Yohanis Anglerό-Díaz. 2019. "Trends in Foster Care Entry Among Children Removed From Their Homes Because of Parental Drug Use, 2000 to 2017." *JAMA Pediatrics*, 173(9): 881–883.

Melzack, Ronald. 1990. "The tragedy of Needless Pain." *Scientific American*, 262(2): 27–33.

Miloucheva, Boriana. 2021. "Pharmaceutical Promotion, Physician Response, and Opioid Abuse: Identifying the Role of Physicians in the Opioid Crisis." Working Paper.

Missouri Census Data Center. n.d.. "Geocorr: Geographic Correspondence Engine." https://mcdc.missouri.edu/applications/geocorr.html.

National Center for Health Statistics. 1989-1994. "Natality Birth Data - Restricted Access Database." U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. .

National Center for Health Statistics. 1991-2018*b*. "Multiple Cause of Death - Restricted Access Database." U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

National Center for Health Statistics. 1995-2018*a*. "Linked Birth and Infant Death Records on CDC WONDER Online Database." U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

NSDUH. 2017. U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. Retrieved from https://datafiles.samhsa.gov/.

Office, United States. General Accounting. 2003. *Prescription Drugs OxyContin Abuse and Diversion and Efforts to Address The Problem: Report to Congressional Requesters.* DIANE Publishing.

Olea, José Luis Montiel, and Carolin Pflueger. 2013. "A Robust Test for Weak Instruments." *Journal of Business & Economic Statistics*, 31(3): 358–369.

Oshlack, Benjamin, Mark Chasin, John J Minogue, and Robert Kaiko. 1996. "Controlled Release Oxycodone Compositions."

OxyContin Budget Plan. 1996. Purdue Pharma.

OxyContin Budget Plan. 1997. Purdue Pharma.

OxyContin Budget Plan. 1998. Purdue Pharma.

OxyContin Budget Plan. 1999. Purdue Pharma.

OxyContin Budget Plan. 2000. Purdue Pharma.

OxyContin Budget Plan. 2001. Purdue Pharma.

OxyContin Budget Plan. 2002. Purdue Pharma.

OxyContin Launch Plan. September 1995. Purdue Pharma.

OxyContin Team Meeting. April 1994. Purdue Pharma.

OxyContin Team Meeting. March 1995. Purdue Pharma.

Park, Sujeong, and David Powell. 2021. "Is the Rise in Illicit Opioids Affecting Labor Supply and Disability Claiming Rates?" *Journal of Health Economics*, 76: 102430.

Patrick, Stephen W, Matthew M Davis, CU Lehmann, and William O Cooper. 2015. "Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012." *Journal of Perinatology*, 35(8): 650–655.

Pierce, Justin R, and Peter K Schott. 2020. "Trade Liberalization and Mortality: Evidence from US Counties." *American Economic Review: Insights*, 2(1): 47–64.

Powell, David, Rosalie Liccardo Pacula, and Erin Taylor. 2020. "How Increasing Medical Access to Opioids Contributes to the Opioid Epidemic: Evidence From Medicare Part D." *Journal of Health Economics*, 71: 102286.

Purdue Pharma. 1995. "Purdue Frederick Company Focus Groups Research and Findings: OxyContin for Non-Cancer Pain Management."

Ruhm, Christopher J. 2019. "Drivers of the Fatal Drug Epidemic." *Journal of Health Economics*, 64: 25–42.

Ruhm, Christopher J. 2021. "Living and Dying in America: An Essay on Deaths of Despair and the Future of Capitalism."

Sales Force Memorandum. 2001. Purdue Pharma.

SAMHSA. 2020. "Key Substance Use and Mental Health Indicators in the United States: Results from the 2019 National Survey on Drug Use and Health."

Savych, Bogdan, David Neumark, and Randall Lea. 2019. "Do Opioids Help Injured Workers Recover and Get Back to Work? The Impact of Opioid Prescriptions on Duration of Temporary Disability." *Industrial Relations: A Journal of Economy and Society*, 58(4): 549–590.

Schnell, Molly, and Janet Currie. 2018. "Addressing the opioid epidemic: is there a role for physician education?" *American journal of health economics*, 4(3): 383–410.

Schwartz, Lisa M., and Steven Woloshin. 2019. "Medical Marketing in the United States, 1997-2016." *JAMA*, 321(1): 80–96.

Sharma, Bikash, Ann Bruner, Gabriela Barnett, and Marc Fishman. 2016. "Opioid Use Disorders." *Child and Adolescent Psychiatric Clinics*, 25(3): 473–487.

Strayer, Mark, Joshua Leftin, Esa Eslami, et al. 2012. "Characteristics of Supplemental Nutrition Assistance Program Households: Fiscal Year 2011 (Executive Summary)." Mathematica Policy Research.

Szalavitz, Maia, and Khary K. Rigg. 2017. "The Curious (Dis)Connection Between the Opioid Epidemic and Crime." *Substance Use & Misuse*, 52(14): 1927–1931.

Terplan, Mishka, Dennis J Hand, Melissa Hutchinson, Elizabeth Salisbury-Afshar, and Sarah H Heil. 2015. "Contraceptive Use and Method Choice Among Women with Opioid and Other Substance Use Disorders: A Systematic Review." *Preventive medicine*, 80: 23–31.

Tolbert, Charles M, and Molly Sizer. 1996. "US Commuting Zones and Labor Market Areas: A 1990 Update."

U.S. Bureau of Labor Statistics. 1990-2018. "Local Area Unemployment Statistics." https://www.bls.gov/lau/.

U.S. Department of Agriculture. 1989-2018. "SNAP Data Tables: Bi-Annual State Project Area/County Level Participation and Issuance Data." Food and Nutrition Service. https://www.fns.usda.gov/pd/supplemental-nutrition-assistance-program-snap.

U.S. Social Security Administration. 1996-2018. “OASDI Beneficiaries by State and County.” Office of Retirement and Disability Policy, Office of Research, Evaluation, and Statistics.

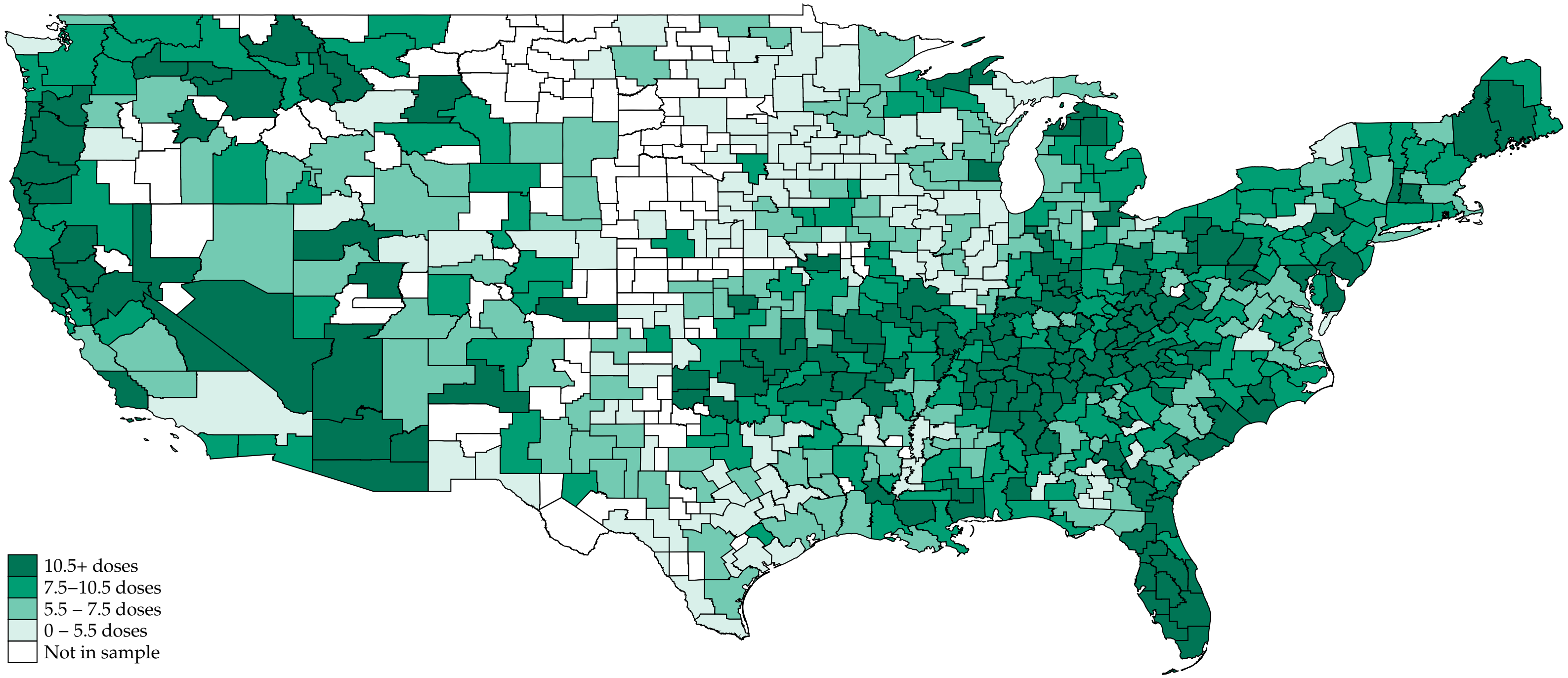
Van Zee, Art. 2009. “The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy.” *American Journal of Public Health*, 99(2): 221–227.

Warner, Margaret, Li Hui Chen, Diane M. Makuc, Robert N. Anderson, and Arialdi M. Miniño. 2011. “Drug Poisoning Deaths in the United States, 1980-2008.” *NCHS Data Brief*, 81(81): 1–8.

Ziedan, Engy, and Robert Kaestner. 2020. “Effect of Prescription Opioids and Prescription Opioid Control Policies on Infant Health.” NBER Working Paper No. 26749.

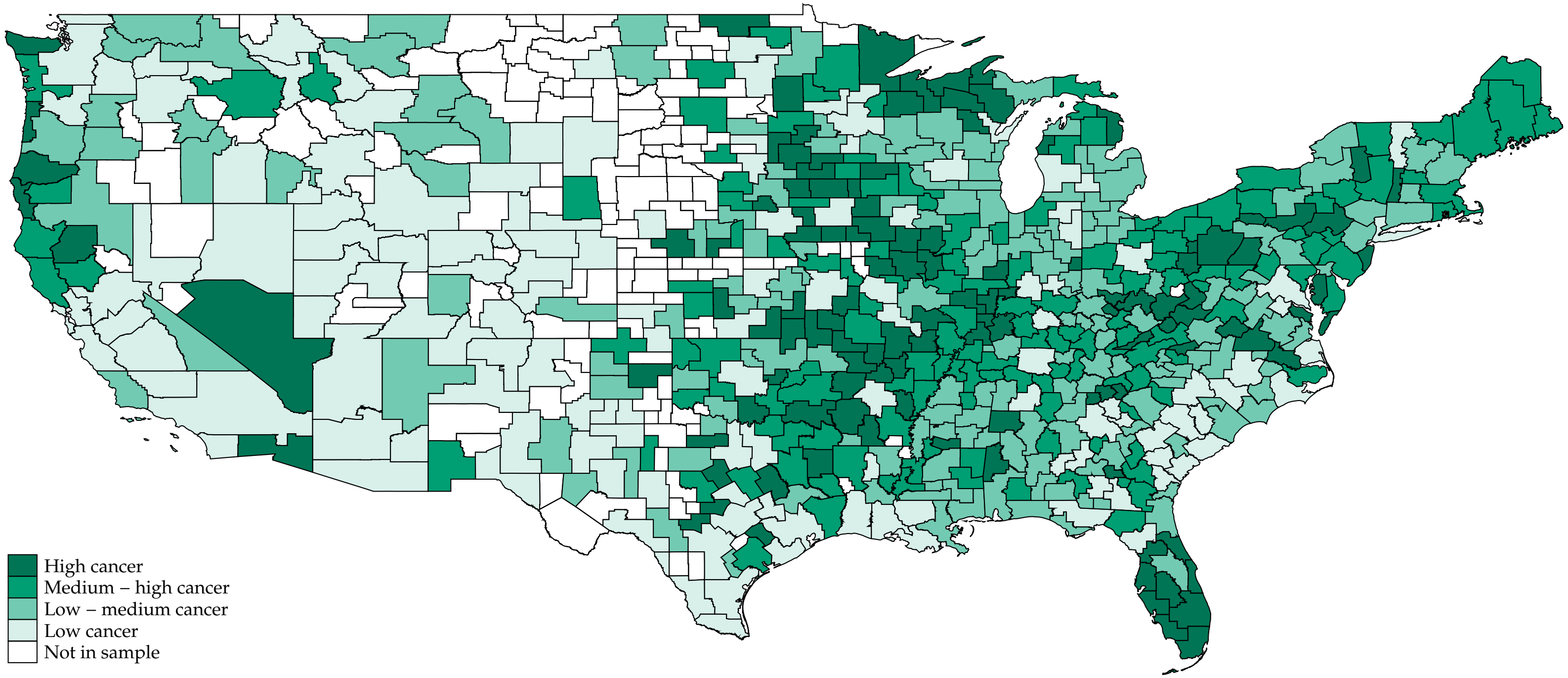
VIII. Maps and Figures

Map 1: Prescription Opioids Distribution at the Peak of the Epidemic (2010).



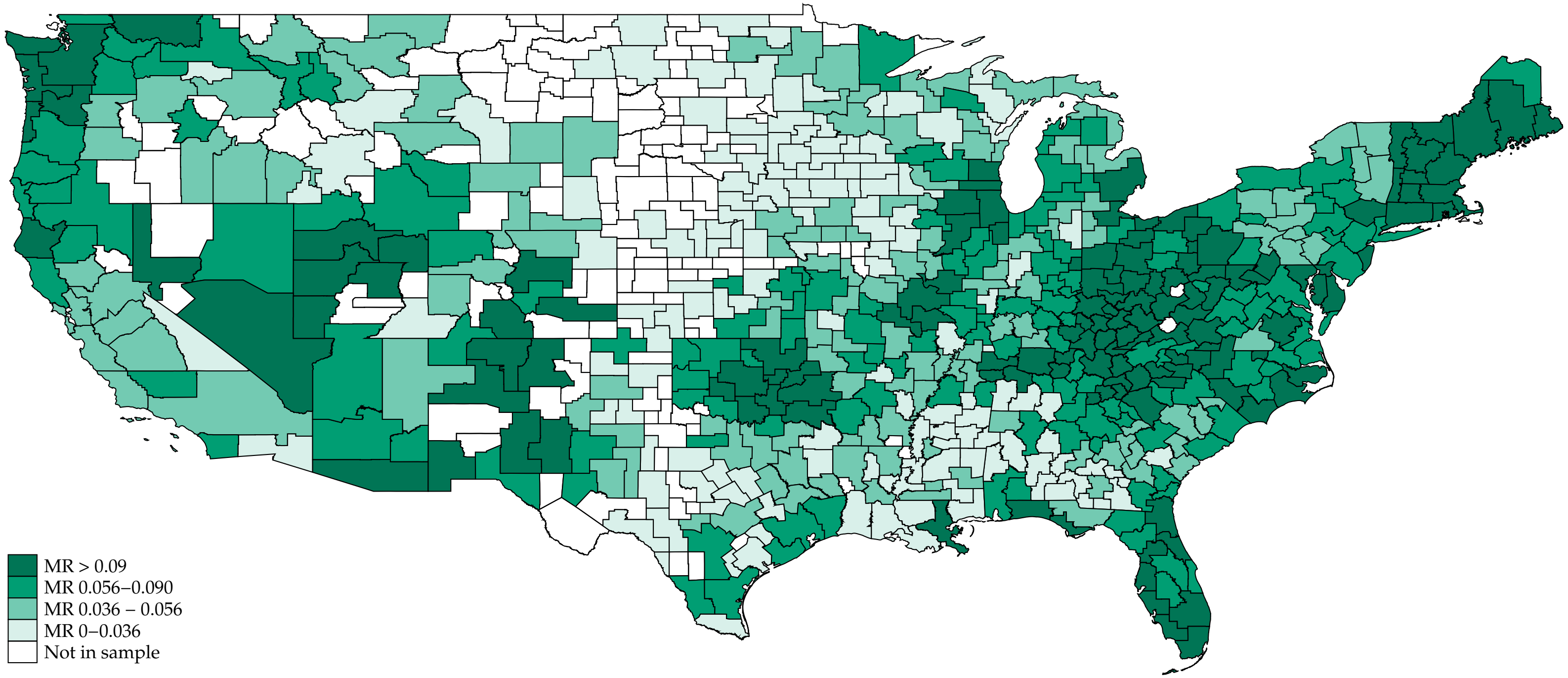
Notes: This map shows the distribution of prescription opioids at the commuting zone level in 2010, the year when the distribution of prescription opioids peaked as shown in Figure 1. Lighter shades indicate commuting zones with a lower prescription-opioid supply and darker shades indicate commuting zones with a higher prescription-opioid supply. Each group corresponds to one quartile of the prescription opioids distribution; i.e., each color accumulates 25% of the mass of this distribution. Commuting zones included in our sample represent 99.8% of all opioid deaths and 99.3% of the total population. This figure is referenced in Section III.A.

Map 2: Distribution of Cancer Mortality Rates Before the OxyContin's Launch.


High cancer
Medium – high cancer
Low – medium cancer
Low cancer
Not in sample

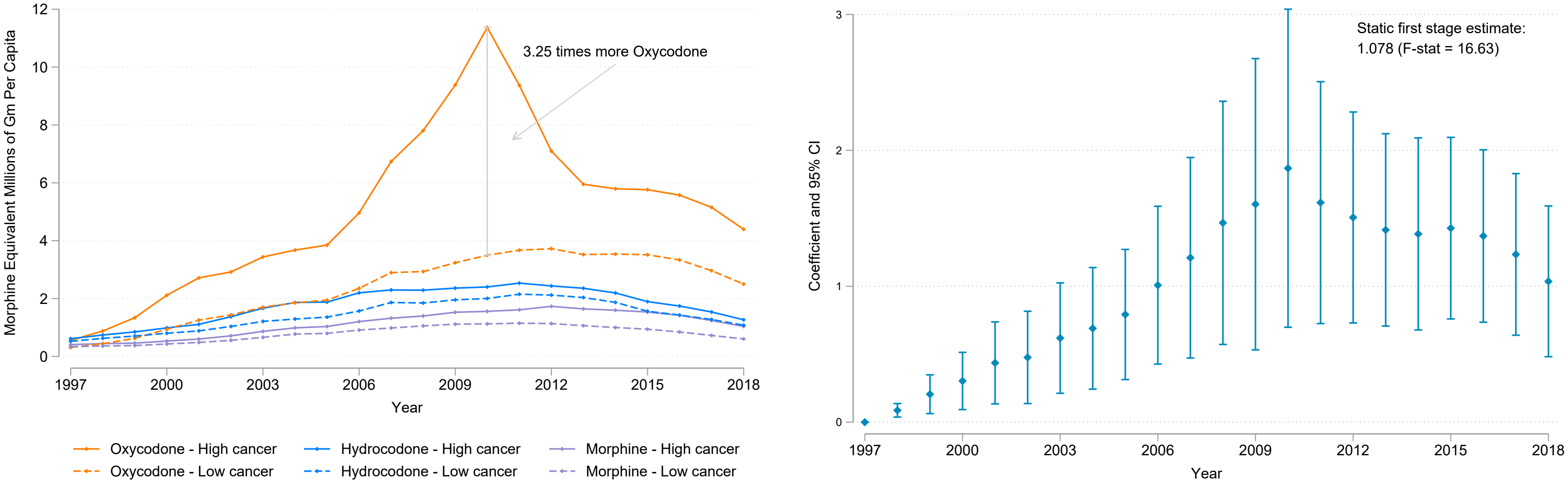
Notes: This map shows the cancer mortality rate at the commuting-zone level for the year 1994 - 1996, before OxyContin was introduced to the market. Lighter shades indicate commuting zones with lower cancer prevalence, while darker shades indicate commuting zones with higher cancer prevalence. Each group corresponds to one quartile of the cancer mortality distribution; i.e., each color accumulates 25% of the mass of this distribution. Commuting zones included in our sample represent 99.8% of all opioid deaths and 99.3% of the total population. This figure is referenced in Section III.B.

Map 3: Prescriptions Opioid Mortality Rate 1999 - 2018



Notes: This map shows the distribution of prescription opioid mortality at the commuting zone level for the period 1999 - 2018. Lighter shades indicate commuting zones with lower opioid mortality, while darker shades indicate commuting zones with higher opioid mortality. Each group corresponds to one quartile of the opioid mortality distribution; i.e., each color accumulates 25% of the mass of this distribution. Commuting zones included in our sample represent 99.8% of all opioid deaths and 99.3% of the total population. This figure is referenced in Section III.C.

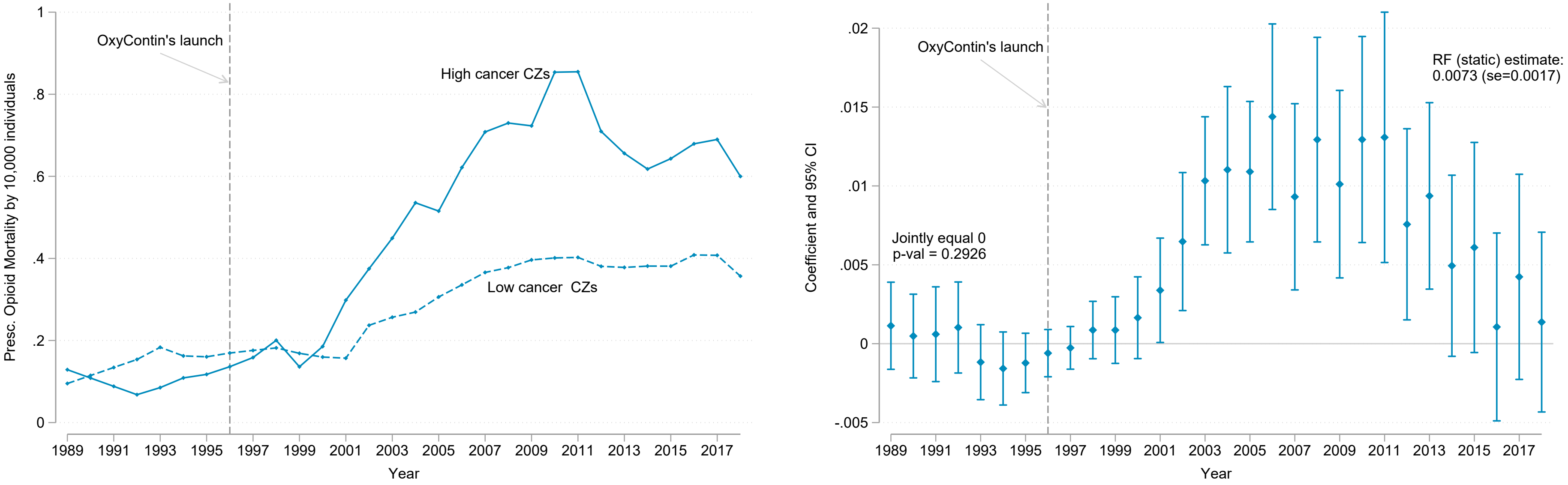
Figure 1: Prescription Opioids Distribution by Cancer Prevalence


(a) Trends in High versus Low Cancer Mortality CZs

(b) Dynamic First Stage

Notes: Panel (a) shows the evolution oxycodone, hydrocodone, and morphine in commuting zones in the bottom (dashed lines) and top (solid lines) quartiles of cancer mortality before the launch of OxyContin. Oxycodone is OxyContin's active ingredient. Between 1997 and 2010, areas in the highest quartile of cancer incidence saw an increase in oxycodone grams per capita of 2,900%, while areas in the lowest quartile experienced a growth that was one-third that. All prescription opioids and oxycodone are measured in morphine-equivalent doses. Panel (b) shows estimates of the coefficients of the dynamic first stage. We regress our measure of prescription opioids distribution on a set of year-dummy variables interacted with the instrument—cancer mortality in 1994-1996—and present estimates of these coefficients. This figure is referenced in Section I., Section IV.A., and in Section VI.

Figure 2: Effects of Purdue Pharma's Mid-nineties Cancer-market Targeting on Prescription Opioid Mortality

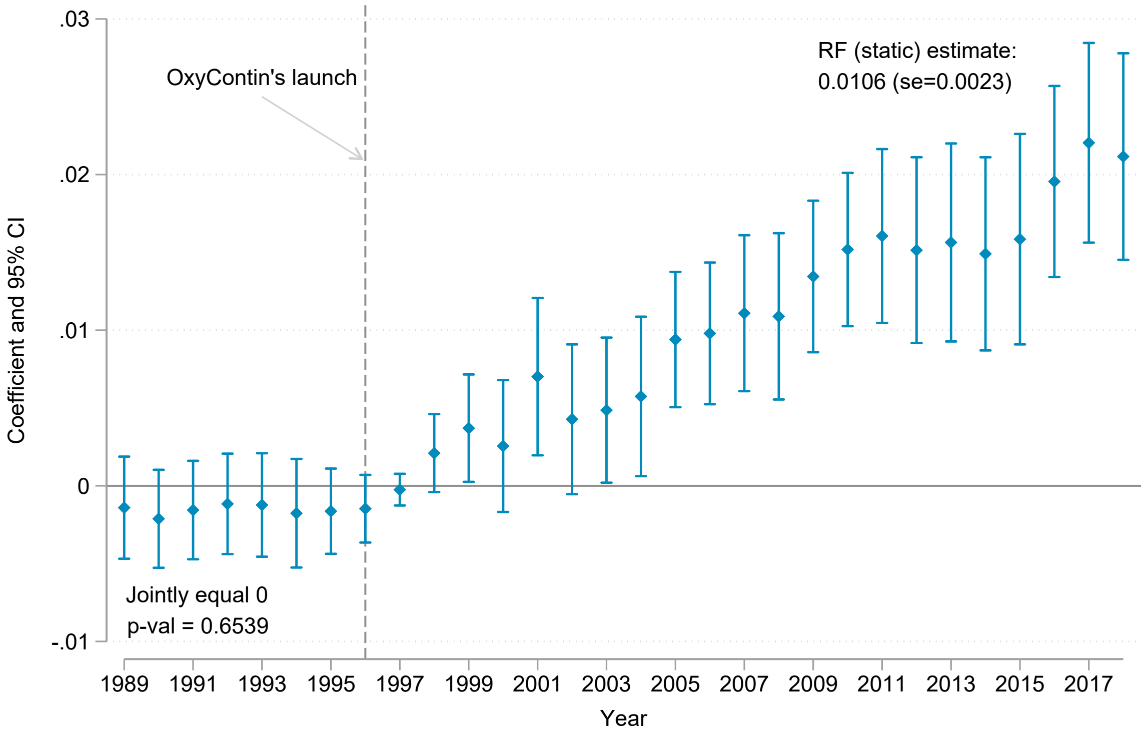


(a) High versus Low Cancer Mortality CZs

(b) Reduced Form - Event Study Approach

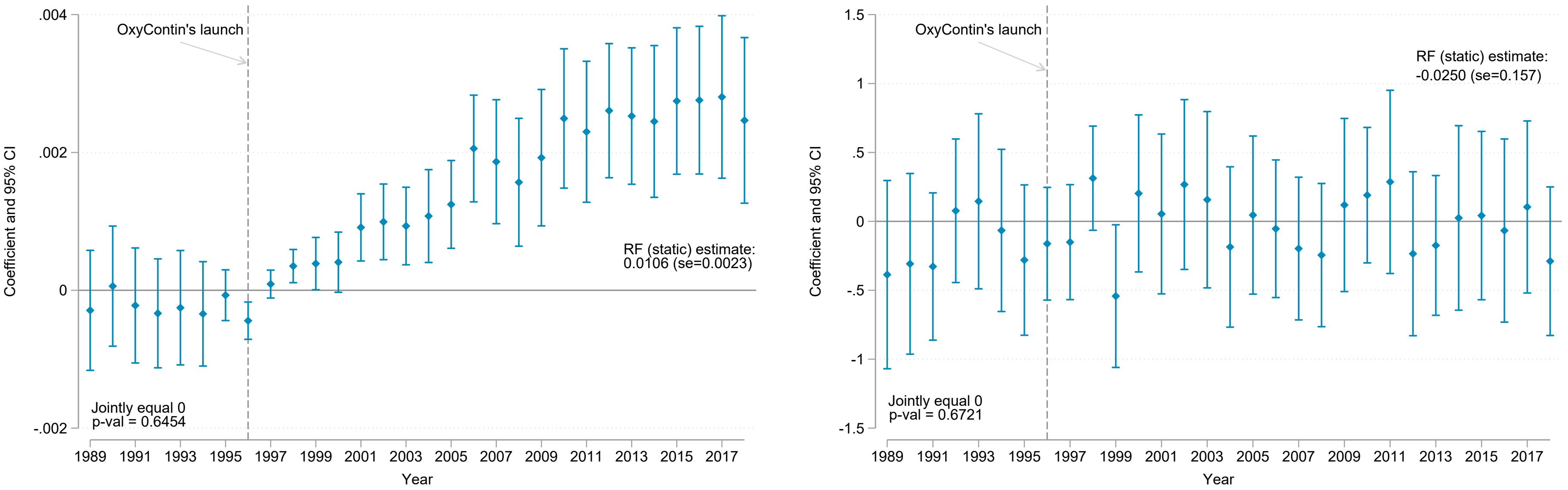
Notes: This figure shows the effects of the increase in prescription opioid supply in prescription opioid mortality. Panel (a) shows the raw data, early in the 2000s, a wedge starts to appear between high- and low-cancer-incidence groups, and by 2018 prescription opioid mortality in high-cancer areas is 75% higher. Panel (b) shows the dynamic reduced-form estimation. We regress prescription opioid mortality on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. These coefficients corresponds to the estimate of ϕ_t in Equation 3. We use this specification to test for the presence of pre-trends in the relation between opioid mortality and mid-nineties cancer mortality; we do not reject the null hypothesis that the estimated coefficients before 1996 are jointly equal to zero, the p value of this test equals 0.2926. This figure is referenced in Section IV.B., and in Section V.A.

Figure 3: Effects of Purdue Pharma's Mid-nineties Cancer-market Targeting on Demand for Social Assistance



Notes: This figure shows the effects of the increase in prescription opioid supply on SNAP claims per capita. We present the results of a dynamic reduced-form estimation were we regress SNAP claims per capita on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. These coefficients corresponds to the estimate of ϕ_t in Equation 3. We use this specification to test for the presence of pre-trends in the relation between SNAP claims and mid-nineties cancer mortality; we do not reject the null hypothesis that the estimated coefficients before 1996 are jointly equal to zero, the p value of this test equals 0.6539. This figure is referenced in Section IV.B., and in Section V.B.

Figure 4: Effects of Purdue Pharma's Mid-nineties Cancer-market Targeting on Fertility Rates and Birth Outcomes

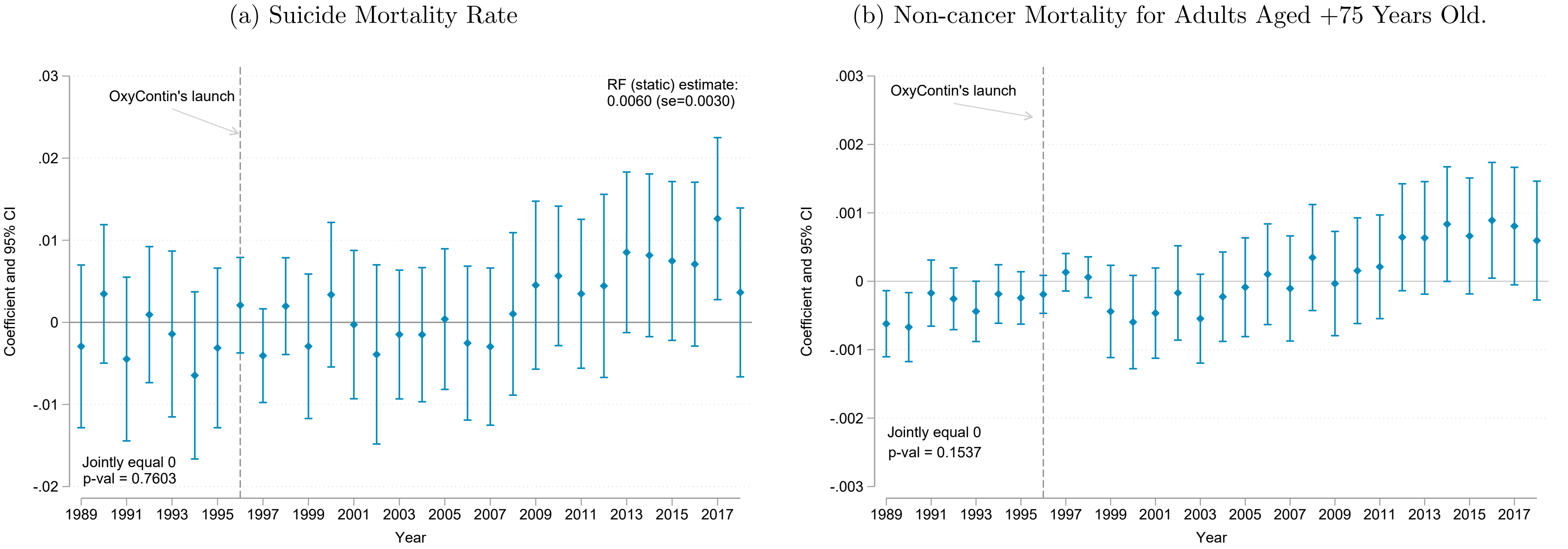


(a) Fertility Rate of Unmarried Women

(b) Infant Mortality Rate

Notes: This figure shows the effects of the increase in prescription opioid supply in the fertility rate of unmarried women (panel a) and in infant mortality rate (panel b). We present the results of a dynamic reduced-form estimation were we regress these outcomes on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. These coefficients corresponds to the estimate of ϕ_t in Equation 3. We use this specification to test for the presence of pre-trends in the relation between birth and maternal outcomes and mid-nineties cancer mortality; we do not reject the null hypothesis that the estimated coefficients before 1996 are jointly equal to zero, the p value of these tests are presented in the figures. This figure is referenced in Section IV.B., and in Section V.B.

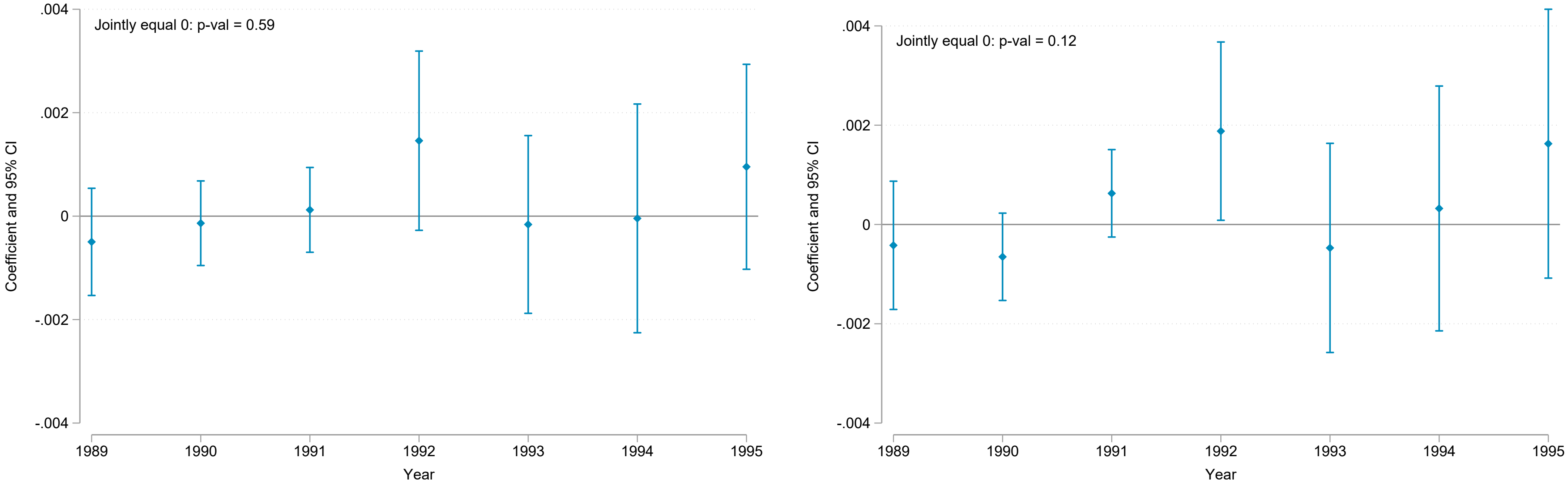
Figure 5: Trends on Despair and Overall Health


(a) Suicide Mortality Rate

(b) Non-cancer Mortality for Adults Aged +75 Years Old.

Notes: This figure shows the dynamic reduced-form relationship between suicide mortality rate (panel a) and mortality of 75-years-old and older adults (panel b) and our instrument. That is, the figure presents the results of a dynamic reduced-form estimation were we regress these outcomes on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. We use this specification to test for the presence a relationship between our outcomes and mid-nineties cancer mortality before the introduction of OxyContin. We do not reject the null hypothesis that the estimated coefficients are jointly equal to zero, the p value of these tests are presented in the figures. This figure is referenced in Section IV.B.

Figure 6: Robustness Check: Dynamic Reduced Form for Out-of-sample Opioid-Mortality

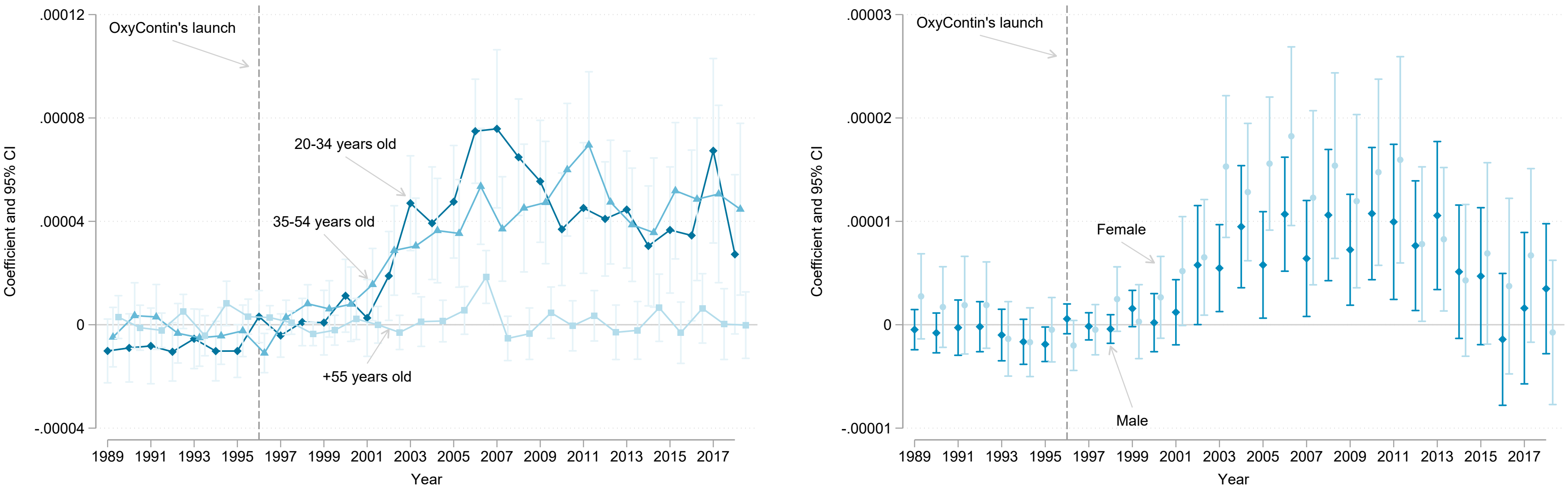


(a) Prescription Opioids Mortality

(b) All Opioid Mortality

Notes: This figure shows the dynamic reduced-form relationship between outcomes of interest and our instrument in a out-of-sample period. That is, we replicate our dynamic reduced-form analysis in the pre-OxyContin period. We regress each outcome on a set of year-dummy variables interacted with the out-of-sample instrument—cancer mortality in 1989 - 1990. We use this specification to test for the presence a relationship between our outcomes and mid-nineties cancer mortality before the introduction of OxyContin. We do not reject the null hypothesis that the estimated coefficients are jointly equal to zero, the *p* value of these tests are presented in the figures. This figure is referenced in Section IV.B.

Figure 7: Effects of Purdue Pharma's Mid-nineties Cancer-market Targeting on Opioid Mortality by Age and Gender



(a) Age groups

(b) Gender

Notes: This figure shows the effects of the increase in prescription opioid supply in opioid related mortality by age group (panel a) and by gender (panel b). We present the results of a dynamic reduced-form estimation were we regress these outcomes on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. These coefficients corresponds to the estimate of ϕ_t in Equation 3. We use this specification to test for the presence of pre-trends in the relation between opioid mortality and mid-nineties cancer mortality; we do not reject the null hypothesis that the estimated coefficients before 1996 are jointly equal to zero, the p values of these tests are: 0.4946 (20-34 years old); 0.7302 (35-54 years old); 0.1934 (+55 years old) for the estimates presented in panel (a), and 0.3823 (female) and 0.3103 (male) for the estimates presented in panel (b). This figure is referenced in Section V.A.

IX. Tables

Table 1: Summary Statistics for 1999-2018

	Mean (1)	Median (2)	SD (3)	Min (4)	Max (5)	Obs. (6)
Opioid Prescriptions: Doses per capita						
All Prescription Opioids	6.42	5.48	4.32	0.00	57.65	11,800
Oxycodone	3.15	2.52	2.60	0.00	51.31	11,800
Hydrocodone	1.93	1.55	1.50	0.00	16.66	11,800
Morphine	0.94	0.77	0.69	0.00	10.67	11,800
Cancer Mortality per 1,000						
Cancer mortality rate 1994-1996	2.53	2.53	0.58	0.12	6.24	590
Cancer mortality rate	2.48	2.49	0.55	0.59	4.75	11,800
Opioid-related Mortality per 1,000						
Prescription opioids	0.04	0.03	0.05	0.00	1.06	11,800
Any opioids	0.07	0.05	0.07	0.00	1.22	11,800
Other Mortality Measures per 1,000						
All-cause mortality (+20 years old)	9.87	9.93	2.06	2.79	20.92	11,800
Deaths of despair	0.27	0.25	0.10	0.00	1.17	11,800
Alcoholic liver diseases and cirrhosis	0.12	0.11	0.06	0.00	0.63	11,800
Suicide	0.15	0.14	0.06	0.00	0.48	11,800
Demand for Social Services						
Share SSI	0.04	0.03	0.02	0.00	0.30	11,800
Share SSDI	0.05	0.04	0.02	0.01	0.16	11,800
Share SNAP	0.12	0.11	0.07	0.00	1.20	11,800
Infant and Maternal Outcomes						
Infant MR (per 1,000 births)	6.86	6.54	2.87	0.00	30.61	11,800
Birth weight	3,274.25	3,276.53	79.47	2,930.28	3,569.76	11,800
Share low birth weight	0.08	0.08	0.02	0.02	0.20	11,800
Share preterm	0.12	0.12	0.03	0.05	0.62	11,800
APGAR score - all infants	8.82	8.84	0.19	5.00	10.00	11,800
APGAR score - dead infants	5.62	6.00	2.28	0.00	10.00	11,460
Median gestation	38.95	39.00	0.24	35.00	40.00	11,800
Fertility rate	0.08	0.08	0.01	0.04	0.19	11,800
Fertility rate 25-29	0.13	0.12	0.02	0.05	0.27	11,800
Fertility rate - unmarried women	0.03	0.03	0.01	0.00	0.09	11,800

Notes: This table presents summary statistics for our main outcomes, measures of the prescription opioid supply, and cancer mortality incidence for the period 1999 - 2018. We leverage data from multiple sources. Prescription drugs distribution data come from the DEA. Data on opioid, cancer, birth, and maternal outcomes come from the NVSS. We use data from the Food and Nutrition Service of the Department of Agriculture and the SSA to construct demand for the Supplemental Nutrition Assistance Program (SNAP), Supplemental Security Income (SSI), and Social Security Disability Insurance (SSDI). This table is referenced in Section III.

Table 2: Determinants of the Opioid Distribution in 2000

Dependent variable: Prescription opioids per capita	(1)		(2)
Demographics (in shares)		*Crime (in rates)*	
White	3.526***	Overall	-0.0000622
	[0.961]		[0.0000752]
Hispanic	-3.323***	Violent	0.00160***
	[0.807]		[0.000614]
Female	6.709	*Economic characteristics*	
	[9.973]	Ln income	2.517***
Aged 18-65	21.67***		[0.922]
	[4.348]	Share below poverty line	0.0521
Aged +66	6.211		[0.0625]
	[7.665]	Share employed in manufacturing	-0.0374***
Infants	-100.8*		[0.0105]
	[56.42]	Share with some college education	0.00938
Labor market			[0.0135]
Employment rate	-16.18***	*Health outcomes*	
	[6.031]	Cancer mortality rate	-0.164
Labor Force Participation	-1.805		[0.330]
	[2.493]	Infant mortality rate	-0.0117
Safety net and social insurance			[0.0199]
SSDI	48.45***	Birth weight	0.000336
	[9.821]		[0.00127]
SSI	5.740	Share preterm births	2.330
	[8.944]		[4.796]
SNAP	-1.914	Gestation	-0.200
	[3.848]		[0.396]
		Fertility rate	52.51***
			[14.07]
Mean dependent variable			2.8567
Year			2000
Observations			590

Notes: This table presents estimated coefficients from a cross-section regression of oxycodone distribution per capita on demographic characteristics, labor market outcomes, measures of social assistance demand, crime outcomes, economic characteristics, and health outcomes at the commuting-zone level. Data on economic characteristics come from county-level tabulations of Decennial Census Data. The variable *share with some college* measures the share of the population older than 25 years old who have some education at the college level or higher. Standard errors are robust to heteroskedasticity. *$p<0.10$, **$p<0.05$, *** $p<0.01$. This table is referenced in Section IV.

Table 3: First-stage Results

Dependent variable: Prescription opioids per capita	(1)	(2)	(3)	(4)	(5)
Cancer MR 94-96	0.960***	1.091***	1.061***	1.132***	1.078***
se	[0.210]	[0.222]	[0.231]	[0.258]	[0.264]
t-stat	4.571	4.914	4.593	4.388	4.083
Effective F-stat	20.894	24.147	21.096	19.254	16.630
Effect size	56.92	64.69	62.91	67.12	63.92
Controls	No	No	No	Yes	Yes
FE	No	State Year	State × Year	State Year	State × Year
Observations	11,800	11,800	11,800	11,800	11,800
Clusters	590	590	590	590	590
Adj. R^2	0.019	0.524	0.559	0.533	0.564

Notes: This table presents estimates of the first-stage equation. The dependent variable is the long change in prescription opioids per capita and it is constructed using a baseline the year 1997—the first year ARCOS data are available. Control variables are contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years, share of Black, White, and Hispanic population, and share of female population. Effect size is computed as the predicted changes in doses of prescription opioids per capita from an increase in cancer mortality that would change a commuting zone in the 5th percentile of the cancer distribution to the 95th percentile. $t-stat$ corresponds to the $t-statistic$ for the null hypothesis that the coefficient on cancer mortality rate is equal to zero. *Effective F-stat* corresponds to the the effective first-stage F statistic proposed by Olea and Pflueger (2013). Standard errors are clustered at the CZ level. * p<0.10, ** p<0.05, *** p<0.01. This table is referenced in Section IV.A.

Table 4: Cancer Mortality Rate: Out-of-sample Analysis

	Cancer MR 89-90 (1)		Cancer MR 89-90 (2)
Dependent variables:		*Dependent variables:*	
Income per capita	19.42	Prescription Opioids MR	-0.000795
	[62.24]		[0.000580]
Share with some college	0.0063	Any Opioids MR	-0.00101
	[0.00386]		[0.000671]
Share with high school or less	0.00257	Share SNAP	-0.000529
	[0.00420]		[0.000840]
Share working in manufacturing	0.0063	Share SSDI	-0.000523
	[0.00386]		[0.000890]
Labor Force Participation	-0.00153*	Share SSI	0.000151
	[0.000821]		[0.000345]
Employment rate	-0.000781	Infant Mortality Rate	-0.0989
	[0.000489]		[0.154]
Total crime rate	44.5	Fertility rate	-0.641
	[28.63]		[0.490]

Notes: Each coefficient corresponds to a separate regression where the dependent variable is measured as the change with respect to 1989-1990. For prescription opioids, any opioids, labor market variables, SNAP, and infant mortality rate, we run a panel regression; for the other variables, where yearly data are not available, we run one cross-sectional regression. MR stands for mortality rate. All regressions include as control variables: cancer mortality rate, share of population under 1 year, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. In panel-level regressions, standard errors are clustered at the commuting-zone level; in cross-sectional regressions, standard errors are robust to heteroskedasticity. * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is referenced in Section IV.B.

Table 5: Direct Effects on Opioid Mortality

Dependent var:	Prescription opioids MR			Any Opioid MR		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.00374***		0.00679***	0.00419***		0.00646***
	[0.00117]		[0.00200]	[0.00139]		[0.00231]
tF 0.05 se			(0.00281)			(0.00324)
t-stat using tF 0.05 se			2.3876			1.9747
AR p-value			0.0000			0.0019
Cancer MR 94-96		0.00732***			0.00697***	
		[0.00167]			[0.00229]	
Effect size (%)	49.47		88.63	25.73		39.30
Model	OLS	RF	IV	OLS	RF	IV
Observations	11,800	11,800	11,800	11,800	11,800	11,800
Clusters	590	590	590	590	590	590
Adj R^2	0.4304	0.3908		0.5368	0.5144	
Effective F-stat			16.63			16.63
Cragg-Donald Wald F-stat			358.58			358.58

Notes: Control variables are contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. All regressions include state times year fixed effects. MR stands for mortality rate. Effect size indicates the percent change in the dependent variable relative to its mean when doses of prescription opioids per capita increase from the 25th to the 75th percentile. Standard errors in square brackets are clustered at the CZ level. Using these standard errors, we report * $p<0.10$, ** $p<0.05$, *** $p<0.01$. tF 0.05 se, t-stat using tF0.05 se, and the *AR p-value* correspond to weak-instrument-robust inference procedures. This table is referenced in Section V.A.

Table 6: Effects of the Opioid Epidemic on Other Mortality Measures

Dependent var:	All cause mortality			Deaths of Despair		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.0213		0.0286	-0.000442		-0.00494
	[0.0136]		[0.0469]	[0.000732]		[0.00621]
tF 0.05 se			(0.0658)			(0.0087)
t-stat using tF 0.05 se			0.4346			-0.459
AR p-value			0.5319			0.4311
Cancer MR 94-96		0.0309			-0.00533	
		[0.0515]			[0.00699]	
Effect size (%)	3.68		4.94	-0.74		-7.39
Model	OLS	RF	IV	OLS	RF	IV

Dependent var:	Alcoholic Liver Diseases and Cirrhosis			Suicide		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.000765**		0.00552*	-0.0000460		-0.00582
	[0.000353]		[0.00292]	[0.000430]		[0.00378]
tF 0.05 se			(0.0041)			(0.0053)
t-stat using tF 0.05 se			1.3473			-1.0974
AR p-value			0.0351			0.1065
Cancer MR 94-96		0.00596**			-0.00628	
		[0.00302]			[0.00402]	
Effect size (%)	3.23		23.34	-0.16		-19.80
Model	OLS	RF	IV	OLS	RF	IV

Notes: The all-cause mortality measure excludes deaths from cancer. Deaths of despair refers to deaths from suicide, chronic liver disease, cirrhosis, and poisonings that are attributable to alcohol. Each regression is run over a sample of 11,800 observations with 590 clusters (commuting zones). Control variables are contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. All regressions include state times year fixed effects. Effect size: indicates the percent change in the respective dependent variable relative to its mean when doses of prescription opioids per capita increase from the 25th to the 75th percentile. Standard errors in square brackets are clustered at the CZ level; using these standard errors, we report * $p<0.10$, ** $p<0.05$, *** $p<0.01$. tF 0.05 se, *t*-stat using tF0.05 se, and the *AR p-value* correspond to weak-instrument-robust inference procedures. This table is referenced in Section V.B.

Table 7: Effects of the Opioid Epidemic on Demand for Social Services

Dependent var:	SSDI			SSI		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.000444***		0.00574***	0.00000709		0.00311**
	[0.0000985]		[0.00132]	[0.000147]		[0.00144]
tF 0.05 se			(0.0018)			(0.0020)
t-stat using tF 0.05 se			3.1250			1.5833
AR p-value			0.0000			0.0114
Cancer MR 94-96		0.00619***			0.00335**	
		[0.000385]			[0.00137]	
Effect size (%)	5.36		76.39	0.11		46.88
Model	OLS	RF	IV	OLS	RF	IV

Dependent var:	SNAP		
	(1)	(2)	(3)
Prescription opioids pc	0.000144		0.00982***
	[0.000285]		[0.00299]
tF 0.05 se			(0.0041)
t-stat using tF 0.05 se			2.4134
AR p-value			0.0000
Cancer MR 94-96		0.0106***	
		[0.00227]	
Effect size (%)	0.58		56.70
Model	OLS	RF	IV

Notes: Each regression is run over a sample of 11,800 observations with 590 clusters (commuting zones). Control variables are contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. All regressions include state times year fixed effects. Effect size: indicates the percent change in the respective dependent variable relative to its mean when doses of prescription opioids per capita increase from the 25th to the 75th percentile. Standard errors in square brackets are clustered at the CZ level; using these standard errors, we report * $p<0.10$, ** $p<0.05$, *** $p<0.01$. tF 0.05 se, *t*-stat using tF0.05 se, and the *AR p-value* correspond to weak-instrument-robust inference procedures. This table is referenced in Section V.B.

Table 8: Effects of the Opioid Epidemic on Infant and Maternal Outcomes

Dependent var:	Infant Mortality Rate			Birth Weight		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.0511**		-0.0232	-0.552*		-4.490**
	[0.0242]		[0.140]	[0.331]		[2.143]
tF 0.05 se			(0.19643)			(3.00676)
t-stat using tF 0.05 se			-0.1181			-1.4933
AR p-value			0.8678			0.0163
Cancer MR 94-96		-0.0250			-4.843**	
		[0.157]			[2.127]	
Effect size (%)	4.06		-1.84	-0.08		-0.69
Model	OLS	RF	IV	OLS	RF	IV

Dependent var:	Share low birth weight			Preterm births		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.000169*		0.000905	0.000270*		0.00141
	[0.000102]		[0.000640]	[0.000150]		[0.000937]
tF 0.05 se			(0.00090)			(0.00131)
t-stat using tF 0.05 se			1.0023			1.0649
AR p-value			0.1272			0.1126
Cancer MR 94-96		0.000976			0.00152	
		[0.000665]			[0.00100]	
Effect size (%)	0.62		5.55	0.84		5.90
Model	OLS	RF	IV	OLS	RF	IV

Dependent var:	APGAR Score - All Infants			APGAR Score - infant casualties		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	-0.000501		-0.0169*	0.0155		0.282*
	[0.00188]		[0.00994]	[0.0179]		[0.153]
tF 0.05 se			(0.01395)			(0.21467)
t-stat using tF 0.05 se			-1.2118			1.3137
AR p-value			0.0674			0.0383
Cancer MR 94-96		-0.0189*			0.319*	
		[0.0107]			[0.164]	
Effect size (%)	-0.03		-0.96	1.38		25.17
Model	OLS	RF	IV	OLS	RF	IV

Dependent var:	Fertility rate			Gestation		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.0000665		0.00153***	-0.000164		-0.0489***
	[0.0000621]		[0.000566]	[0.00304]		[0.0186]
tF 0.05 se			(0.00079)			(0.02610)
t-stat using tF 0.05 se			1.9266			-1.8738
AR p-value			0.001			0.0011
Cancer MR 94-96		0.00165***			-0.0527***	
		[0.000482]			[0.0171]	
Effect size (%)	0.43		9.85	0.00		-0.63
Model	OLS	RF	IV	OLS	RF	IV

Notes: Each regression is run over a sample of 11,800 observations with 590 clusters (commuting zones). Control variables are contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. All regressions include state times year fixed effects. Effect size: indicates the percent change in the respective dependent variable relative to its mean when doses of prescription opioids per capita increase from the 25th to the 75th percentile. Standard errors in square brackets are clustered at the CZ level; using these standard errors, we report * $p<0.10$, ** $p<0.05$, *** $p<0.01$. tF 0.05 se, *t*-stat using tF0.05 se, and the *AR p-value* correspond to weak-instrument-robust inference procedures. This table is referenced in Section V.B.

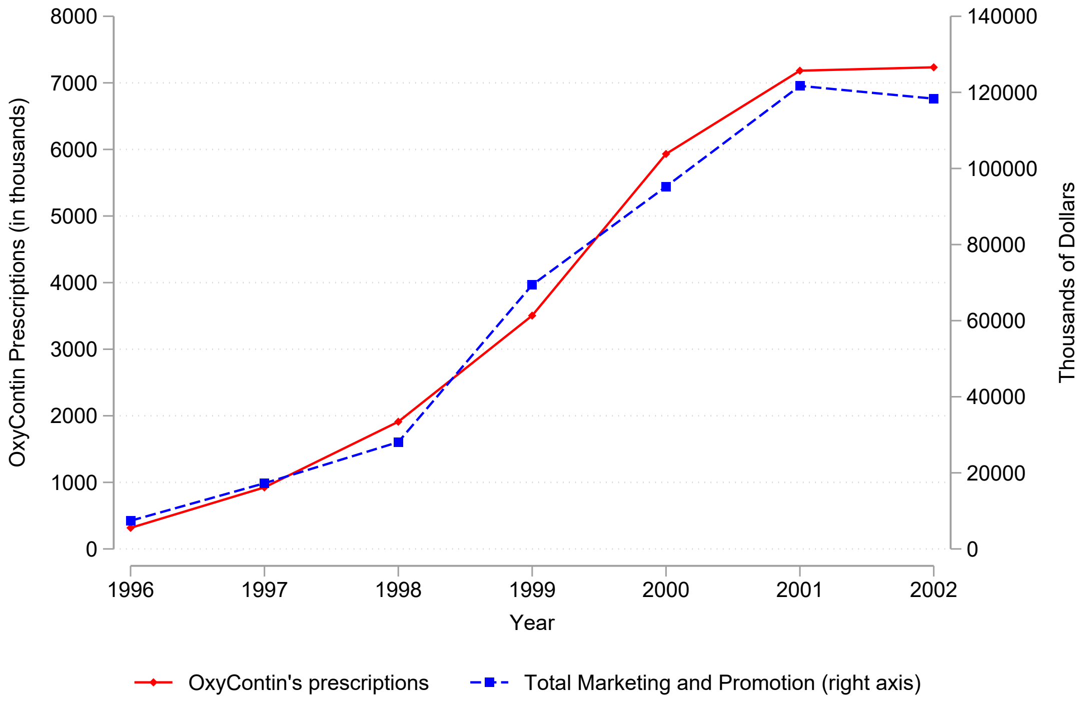
Table 9: Complier Analysis

Commuting zone characteristic	First Stage (1)	$P[X=x]$ (2)	$P[X=x \mid \text{Complier}]$ (3)	$\frac{P[X=x \mid \text{Complier}]}{P[X=x]}$ (4)
High sh. of pop below poverty line	1.382*** [0.499]	0.52	0.991 [0.178]	1.923
Low sh. of pop below poverty line	0.629*** [0.236]	0.48	0.00863 [0.178]	0.018
High sh. of pop w/ less than HS degree	1.125*** [0.419]	0.51	0.964 [0.210]	1.883
Low sh. of pop w/ less than HS degree	0.855*** [0.322]	0.49	0.0365 [0.210]	0.075
High sh. of employment in mining	1.232*** [0.356]	0.50	0.931 [0.235]	1.856
Low sh. of employment in mining	0.820* [0.471]	0.50	0.0694 [0.235]	0.139
High sh. of PCP per capita	1.180** [0.518]	0.50	1.427 [0.224]	2.854
Low sh. of PCP per capita	1.103*** [0.218]	0.50	-0.427 [0.224]	-0.854
High sh. of smoking	1.012*** [0.365]	0.54	0.645 [0.213]	1.197
Low sh. of smoking	0.825*** [0.298]	0.46	0.355 [0.213]	0.770
High cocaine and alcohol MR	1.273*** [0.440]	0.50	1.12 [0.188]	2.240
Low cocaine and alcohol MR	0.656** [0.275]	0.50	-0.12 [0.188]	-0.240

Notes: Column 1 corresponds to the first stage regression for each specific group. Column 2 is the frequency of the group in the estimation sample. Column 3 corresponds to the estimation of the characteristic in the complier sample, following Abadie (2003) this is a 2SLS regression where the dependent variable corresponds to the endogenous variable multiplied by the indicator of the group. Column 4 divides column 3 by column 2 and corresponds to the complier relative likelihood. For each of the commuting zone characteristics, we consider a commuting zone to be in the low (high) group if the value of such characteristic is below (above) the median value. Poverty, share of the population with less than a high school (HS) degree, and employment in the mining sector are measured in 1994. Primary care physicians (PCP) per capita, smoking, and cocaine and alcohol mortality rates are measured in 1996. This table is referenced in Section V.C.

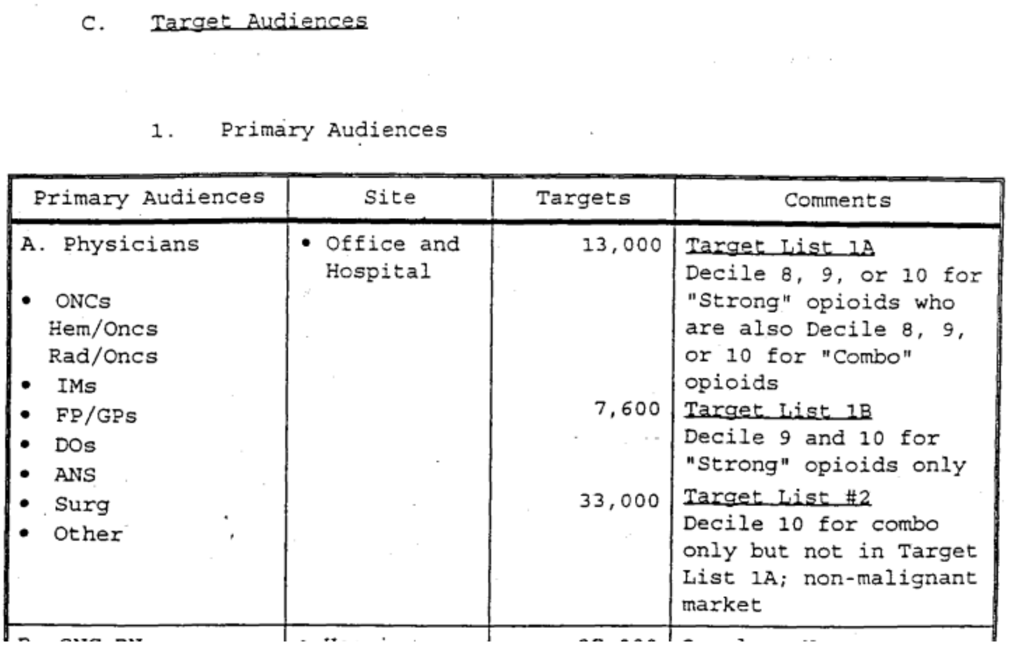
A Additional Figures

Figure A1: OxyContin Marketing Budget and Total Prescription Sales



Notes: Author's constructions based on OxyContin Budget Plans 1998-2002 and United States. General Accounting Office (GAO). Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem: Report to Congressional Requesters. 2003. This figure is referenced in Section II.

Figure A2: Purdue Pharma Budget Plan 1997: Target Audiences



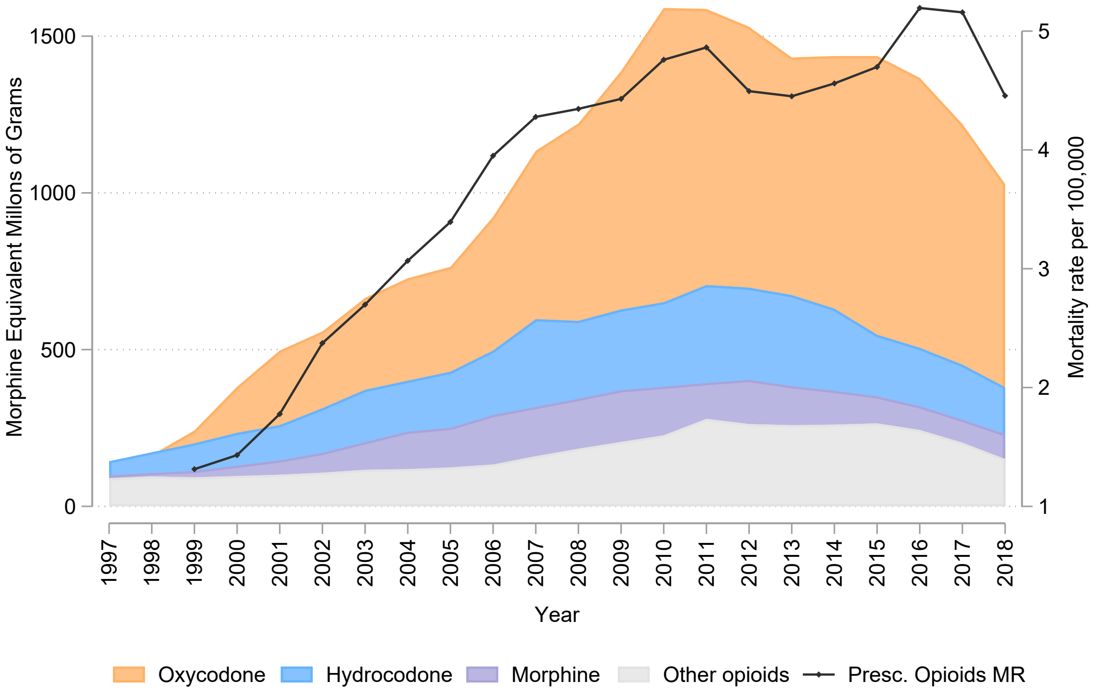
C. Target Audiences

1. Primary Audiences

Primary Audiences	Site	Targets	Comments
A. Physicians • ONCs Hem/Oncs Rad/Oncs • IMs • FP/GPs • DOs • ANS • Surg • Other	• Office and Hospital	13,000 7,600 33,000	Target List 1A Decile 8, 9, or 10 for "Strong" opioids who are also Decile 8, 9, or 10 for "Combo" opioids Target List 1B Decile 9 and 10 for "Strong" opioids only Target List #2 Decile 10 for combo only but not in Target List 1A; non-malignant market

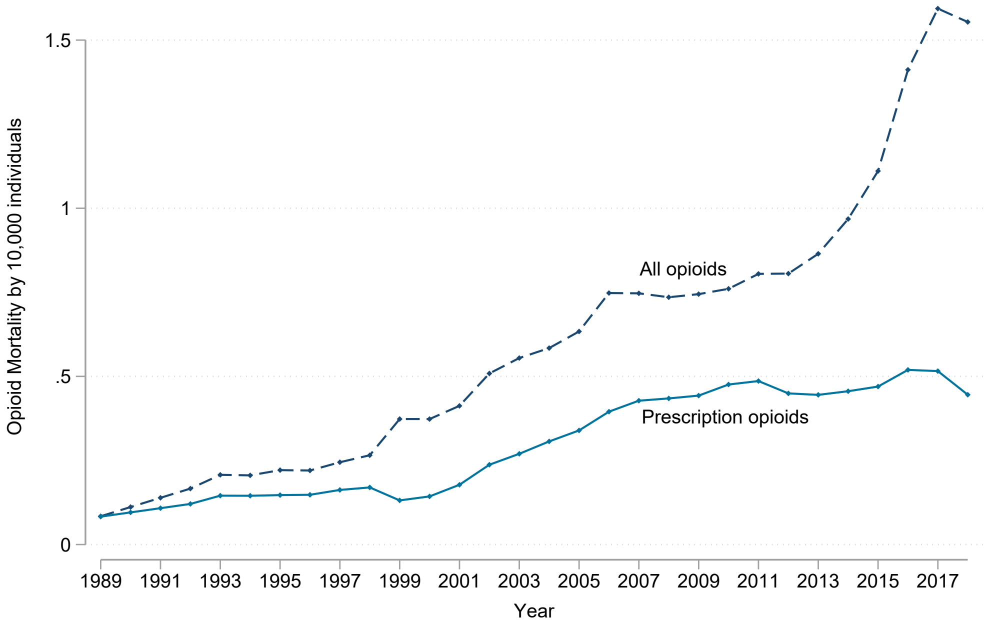
Notes: This figure is an extract of Purdue Pharma marketing plan. It shows that Purdue marketing targeted top opioid prescribers. Purdue Pharma Budget Plan 1997, p.25. This figure is referenced in Section II.

Figure A3: Evolution of Prescription Opioid Distribution



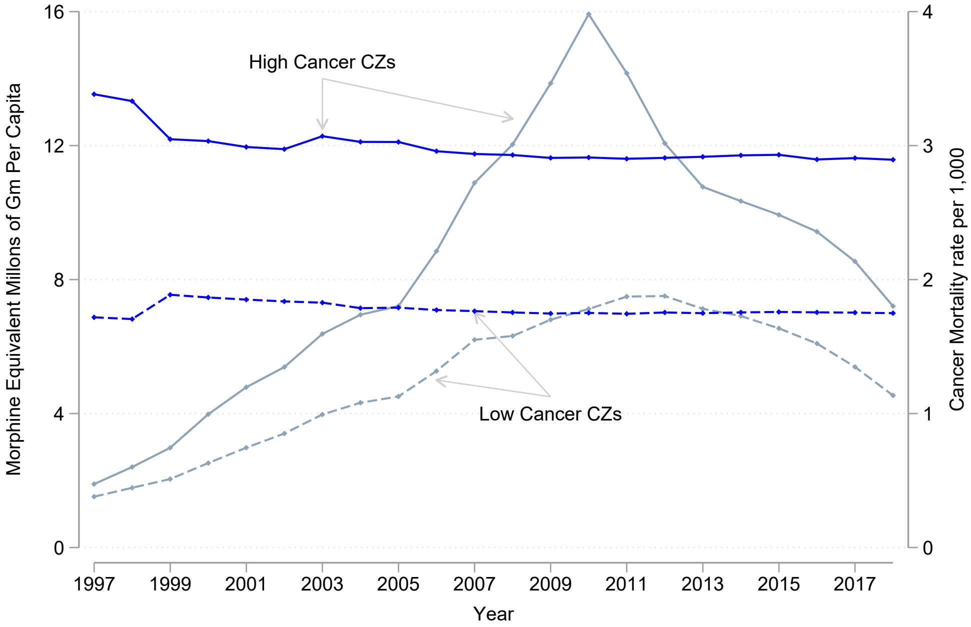
Notes: This figure shows the evolution of shipments of all prescription opioids and the three main components: oxycodone, hydrocodone and morphine. Oxycodone is the active ingredient of OxyContin. Shipments of prescription opioids are expressed in morphine-equivalent doses. Data on opioids distribution come from the ARCOS. The mortality rate (MR) from prescription opioids is constructed using data from the National Vital Statistic System and plotted in the right-hand-side axis. Details on the construction of this measure are found in C. This figure is referenced in Section III.A.

Figure A4: Evolution of Prescription Opioid and All Opioid Mortality Rates



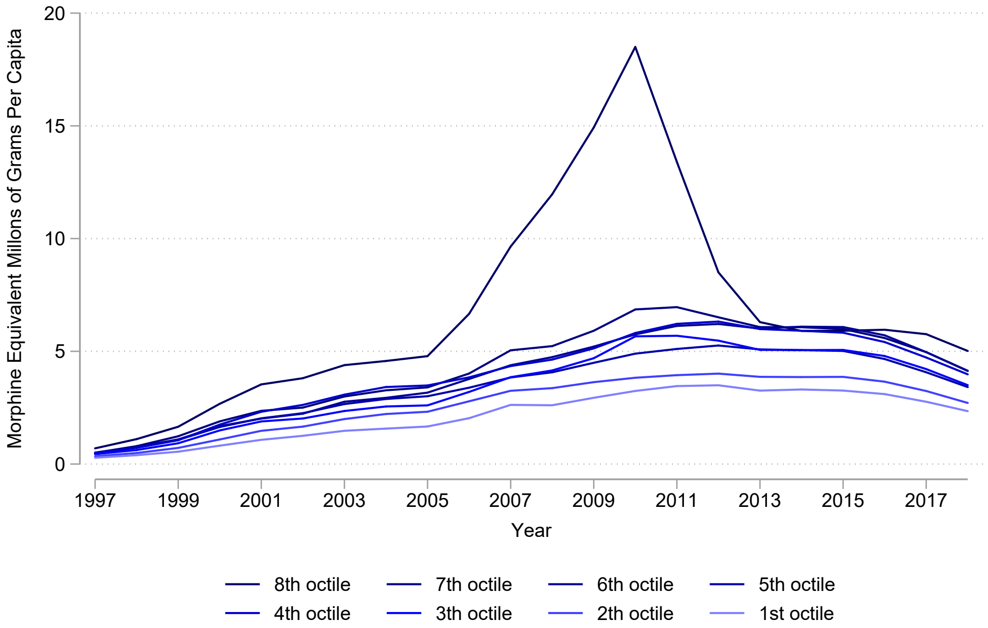
Notes: This figure shows the evolution of prescription opioid and all opioid mortality rates from 1989 to 2018. The 1989-1998 data use ICD-9 codes to categorize the cause of death, and the 1999-2018 data use ICD-10 codes. The time series show that the transition from ICD-9 to ICD-10 classifications resulted in a small increase in poison-related deaths; this is consistent with what the CDC reports (Warner et al., 2011). This figure is referenced in Section III.C.

Figure A5: Evolution of Cancer Mortality and Prescription Opioid Supply



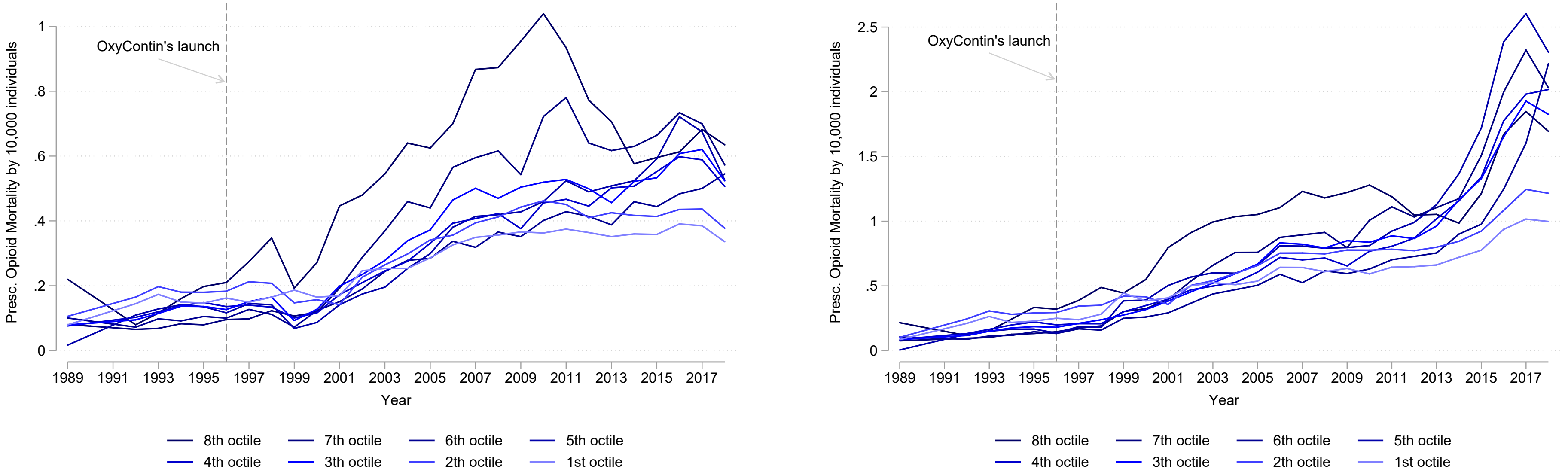
Notes: This figure shows the evolution of prescription opioids (light blue lines in the left-hand axis) and cancer mortality rates (dark-blue lines in the right-hand axis) over time for commuting zones in the top and bottom quartiles of the cancer mortality distribution. Areas in the top quartile of the cancer distribution experienced an influx of opioids that was up to 3 times larger than the one experience by areas in the bottom quartile. Changes in cancer mortality does not explain this discrepancy; trends in carcer mortality rates in these groups of commuting zones suggest that mortality was quite stable in the period. Prescription opioids is measured in morphine-equivalent mg. This figure is referenced in Section IV.A.

Figure A6: Evolution of Oxycodone by Octiles of the 1994-1996 Cancer Prevalence



Notes: This figure shows the evolution of oxycodone in eight groups of commuting zones. Each group is composed of those commuting zones in the *n-th* octile of the cancer mortality rate distribution before the launch of OxyContin. Darker colors indicate groups with higher cancer prevalence (e.g., the 8th octile corresponds to the series that peaked in 2010 at 19 morphine-equivalent millions of gm per capita). Lighter colors indicate groups with lower cancer prevalence. This figure is referenced in Section IV.A.

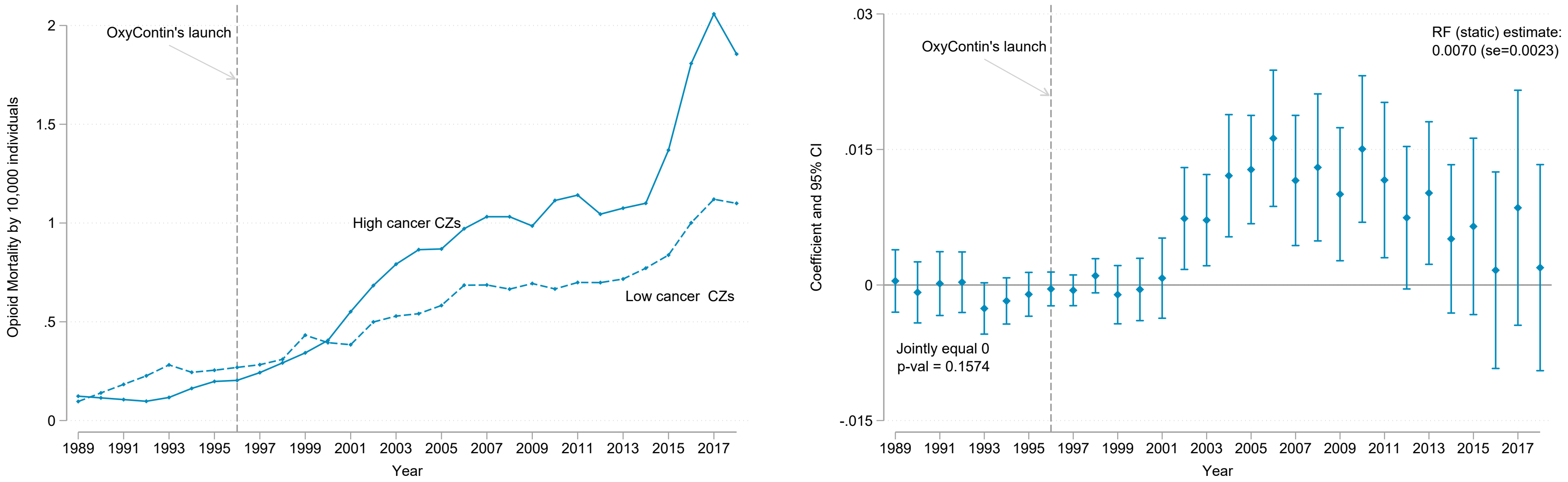
Figure A7: Opioid Mortality Rate by Octiles of the 1994-1996 Cancer Prevalence


(a) Prescription Opioids

(b) All Opioids

Notes: This figure shows the evolution of prescription opioid (panel a) and all opioids (panel b) mortality in eight groups of commuting zones. Each group is composed of those commuting zones in the *n-th* octile of the cancer mortality rate distribution before the launch of OxyContin. Darker colors indicate groups with higher cancer prevalence. Lighter colors indicate groups with lower cancer prevalence. This figure is referenced in Section V.A.

Figure A8: Effects of Purdue Pharma's Mid-nineties Cancer-market Targeting on All-Opioid Mortality

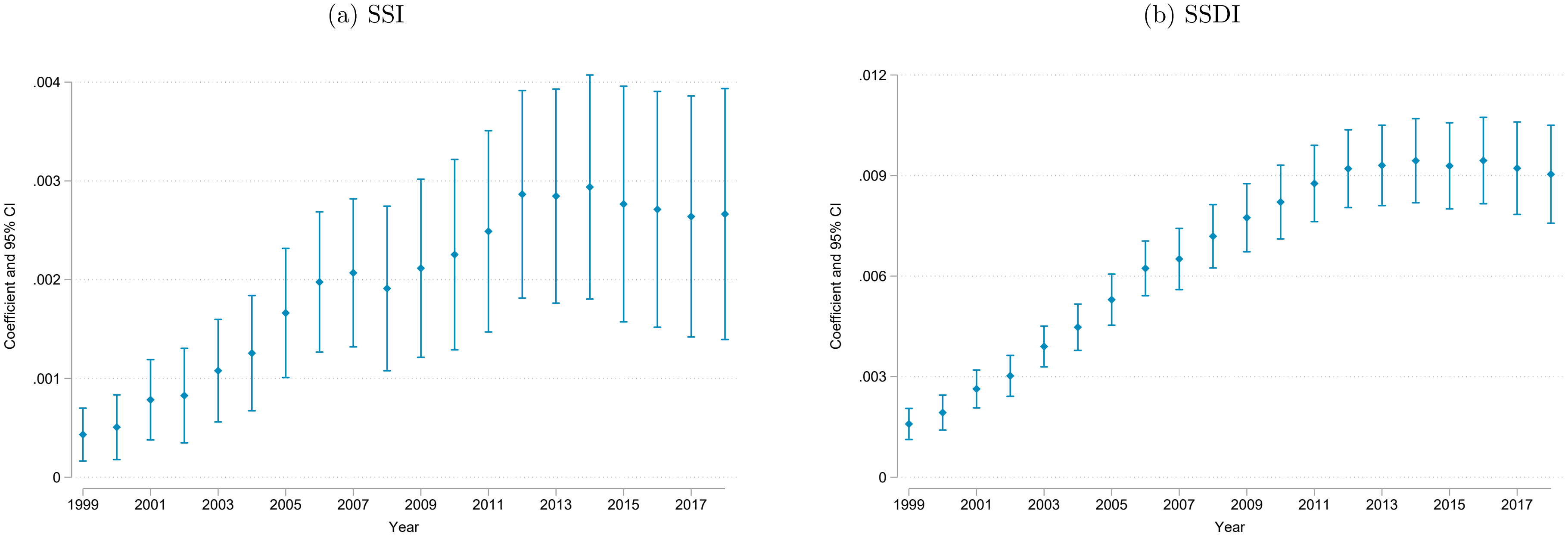


(a) High vs Low Cancer Mortality CZs

(b) Reduced Form - Event Study Approach

Notes: This figure shows the effects of the increase in prescription opioid supply in all-opioid mortality. Panel (a) shows the raw data, early in the 2000s, a wedge starts to appear between high- and low-cancer-incidence groups. Panel (b) shows the dynamic reduced-form estimation. We regress all-opioid mortality on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. These coefficients corresponds to the estimate of ϕ_t in Equation 3. We use this specification to test for the presence of pre-trends in the relation between opioid mortality and mid-nineties cancer mortality; we do not reject the null hypothesis that the estimated coefficients before 1996 are jointly equal to zero, the p value of this test equals 0.1574. This figure is referenced in Section IV.B., in Section V.A., and in Section V.B.

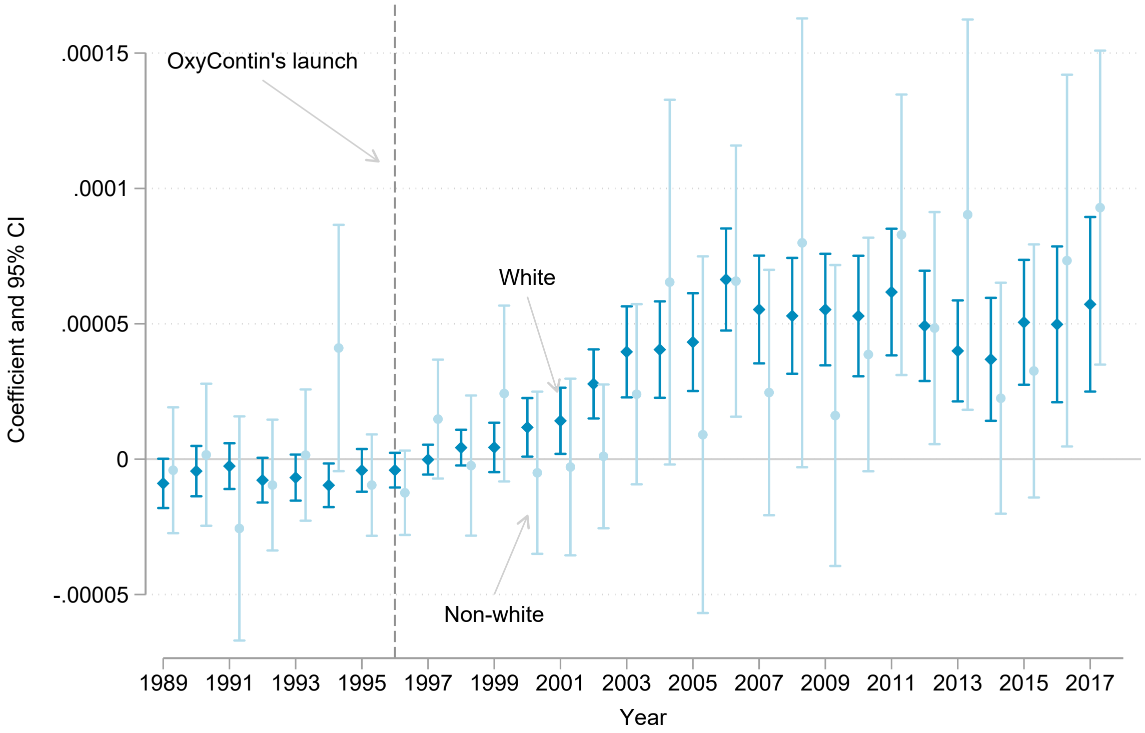
Figure A9: Effects of Purdue Pharma's Mid-nineties Cancer-market Targeting on Disability Claims


(a) SSI

(b) SSDI

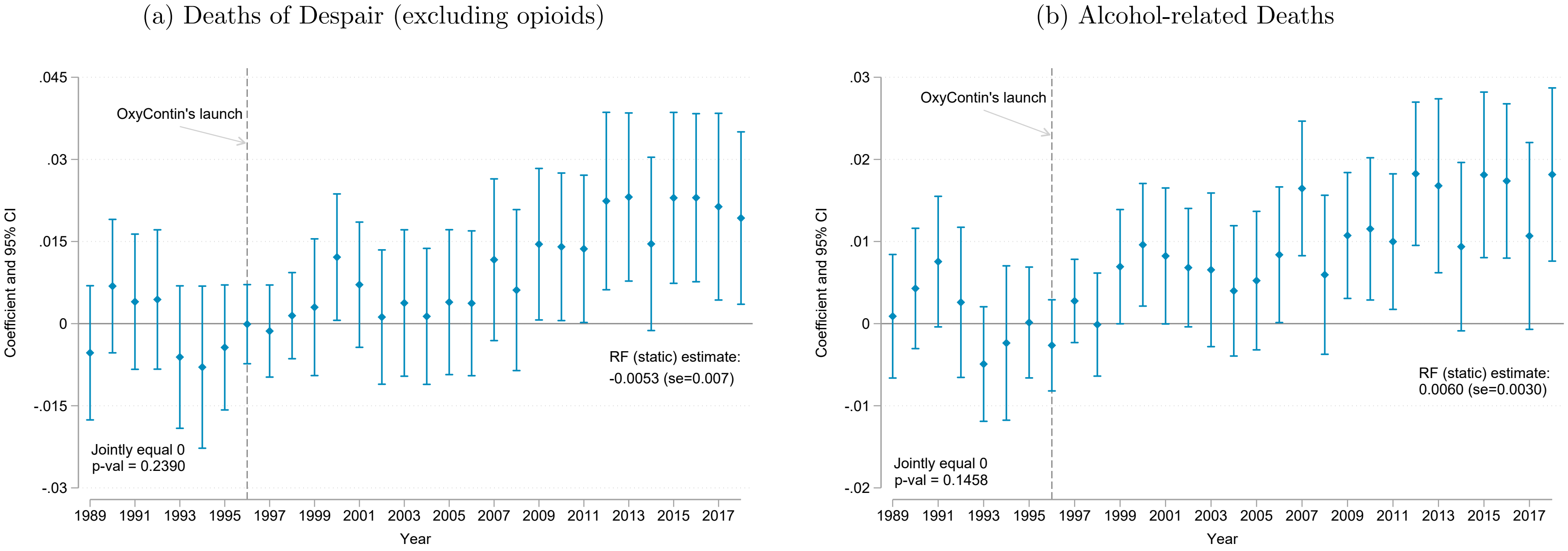
Notes: We present the results of a dynamic reduced-form estimation were we regress these outcomes on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. These coefficients corresponds to the estimate of ϕ_t in Equation 3. This figure is referenced in Section V.B.

Figure A10: Effects of Purdue Pharma's Mid-nineties Cancer-market Targeting on Opioid Mortality by Race



Notes: This figure shows the effects of the increase in prescription opioid supply in opioid related mortality by race. We present the results of a dynamic reduced-form estimation were we regress these outcomes on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. These coefficients corresponds to the estimate of ϕ_t in Equation 3. We use this specification to test for the presence of pre-trends in the relation between opioid mortality and mid-nineties cancer mortality; we do not reject the null hypothesis that the estimated coefficients before 1996 are jointly equal to zero, the p values of these tests are: 0.2551 (white) and 0.3021 (non-white). This figure is referenced in Section V.A.

Figure A11: Effects of Purdue Pharma's Mid-nineties Cancer-market Targeting on Deaths of Despair

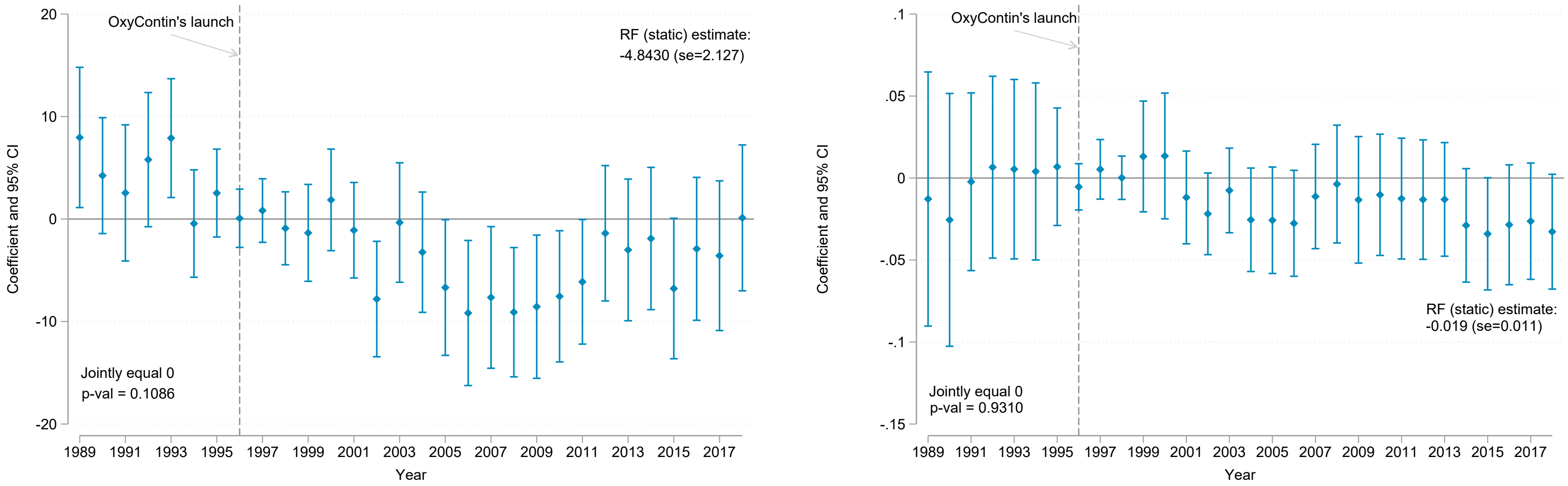


(a) Deaths of Despair (excluding opioids)

(b) Alcohol-related Deaths

Notes: This figure shows the effects of the increase in prescription opioids supply in various measures of deaths of despair; excluding deaths which cause is opioid poisoning. We present the results of a dynamic reduced-form estimation were we regress these outcomes on a set of year-dummy variables interacted with our instrument. We test for the presence of pre-trends in the relation between deaths of despair and mid-nineties cancer mortality and do not reject the null hypothesis that the estimated coefficients before 1996 are jointly equal to zero. This figure is referenced in Section IV.B., in Section V.A., and in Section V.B.

Figure A12: Effects of Purdue Pharma's Mid-nineties Cancer-market Targeting on Birth Outcomes



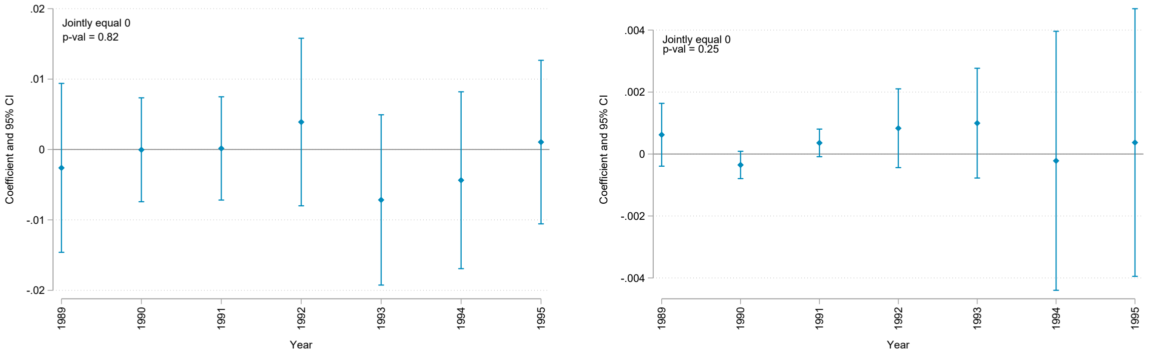
(a) Birth Weight

(b) APGAR Score

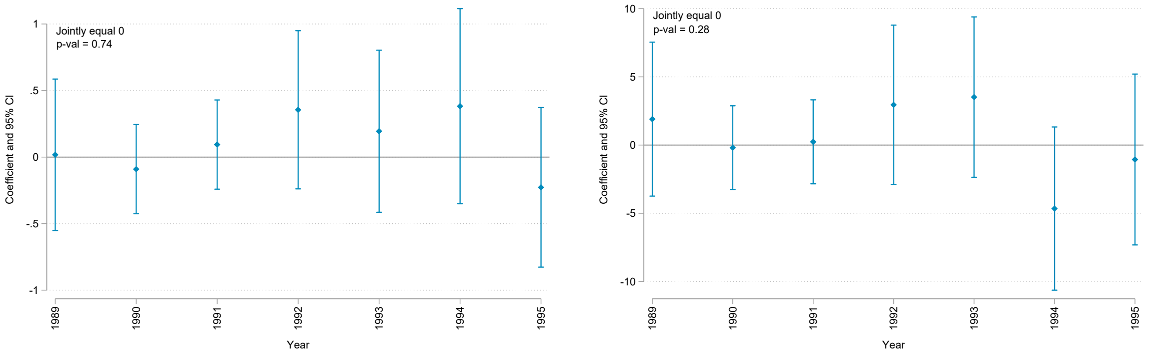
Notes: This figure shows the effects of the increase in prescription opioids supply in birth weight (panel a) and in APGAR score (panel b). The APGAR score is a measure of the physical condition of a newborn infant. It varies from 0 to 10, a score of 10 represents the best possible condition. We present the results of a dynamic reduced-form estimation were we regress these outcomes on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. These coefficients corresponds to the estimate of ϕ_t in Equation 3. We use this specification to test for the presence of pre-trends in the relation between infant outcomes and mid-nineties cancer mortality; we do not reject the null hypothesis that the estimated coefficients before 1996 are jointly equal to zero, the p value of these tests are presented in the figures. This figure is referenced in Section IV.B., in Section V.A., and in Section V.B.

Figure A13: Dynamic Reduced Form Estimates - Out-of-sample Analysis

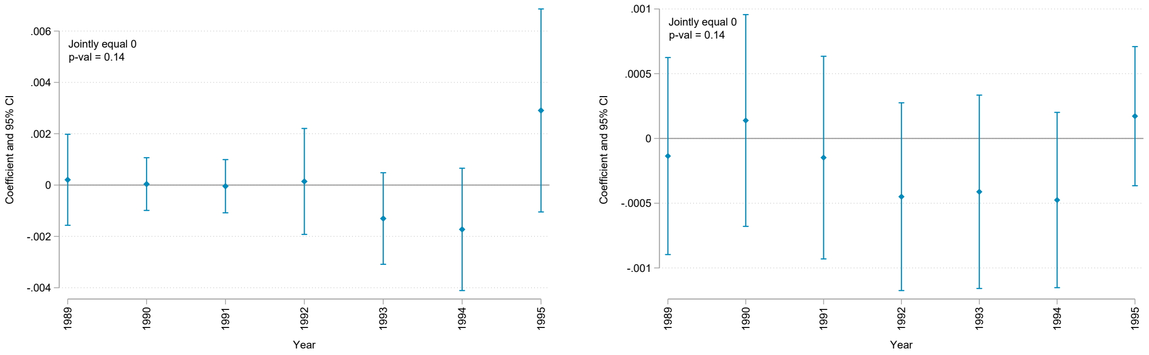
(a) Deaths of Despair (b) SNAP



(c) Infant Mortality Rate (d) Birth Weight

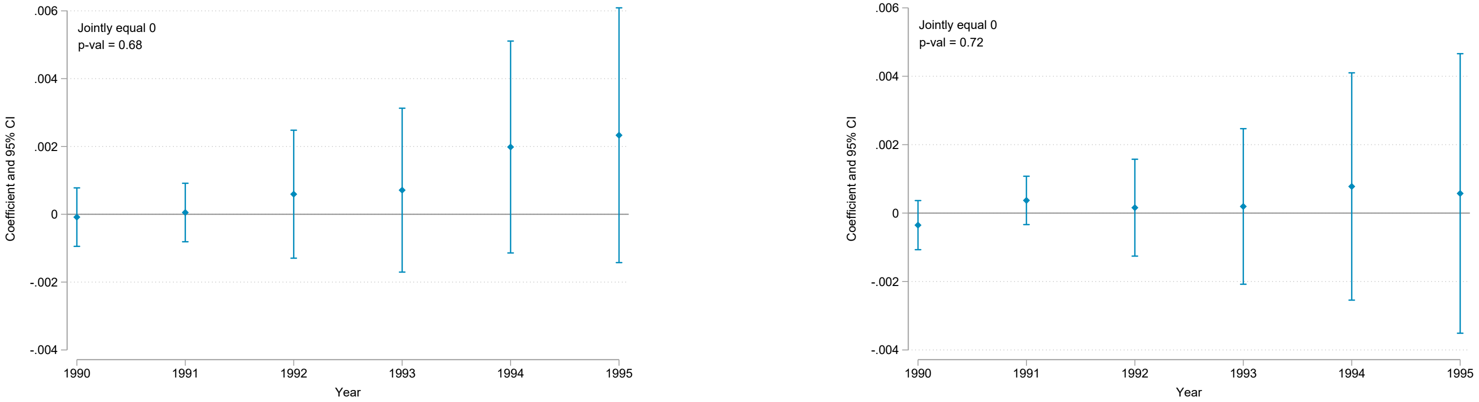


(e) Fertility Rate - 25 to 29 years old (f) Fertility Rate - unmarried woman



Notes: This figure shows the dynamic reduced-form relationship between outcomes of interest and our instrument in an out-of-sample period. That is, we replicate our dynamic reduced-form analysis in the pre-OxyContin period. We regress each outcome on a set of year-dummy variables interacted with the out-of-sample instrument—cancer mortality in 1989 - 1990. We use this specification to test for the presence a relationship between our outcomes and mid-nineties cancer mortality before the introduction of OxyContin. We do not reject the null hypothesis that the estimated coefficients are jointly equal to zero, the *p* value of these tests are presented in the figures. This figure is referenced in Section IV.B.

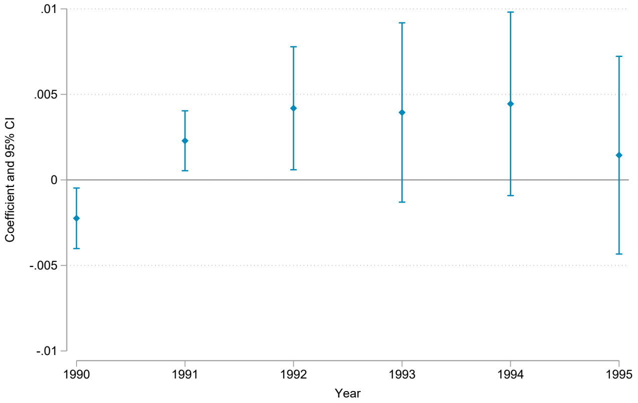
Figure A14: Dynamic Reduced Form Estimates - Out-of-sample Analysis: Labor Market Outcomes



(a) Manufacturing

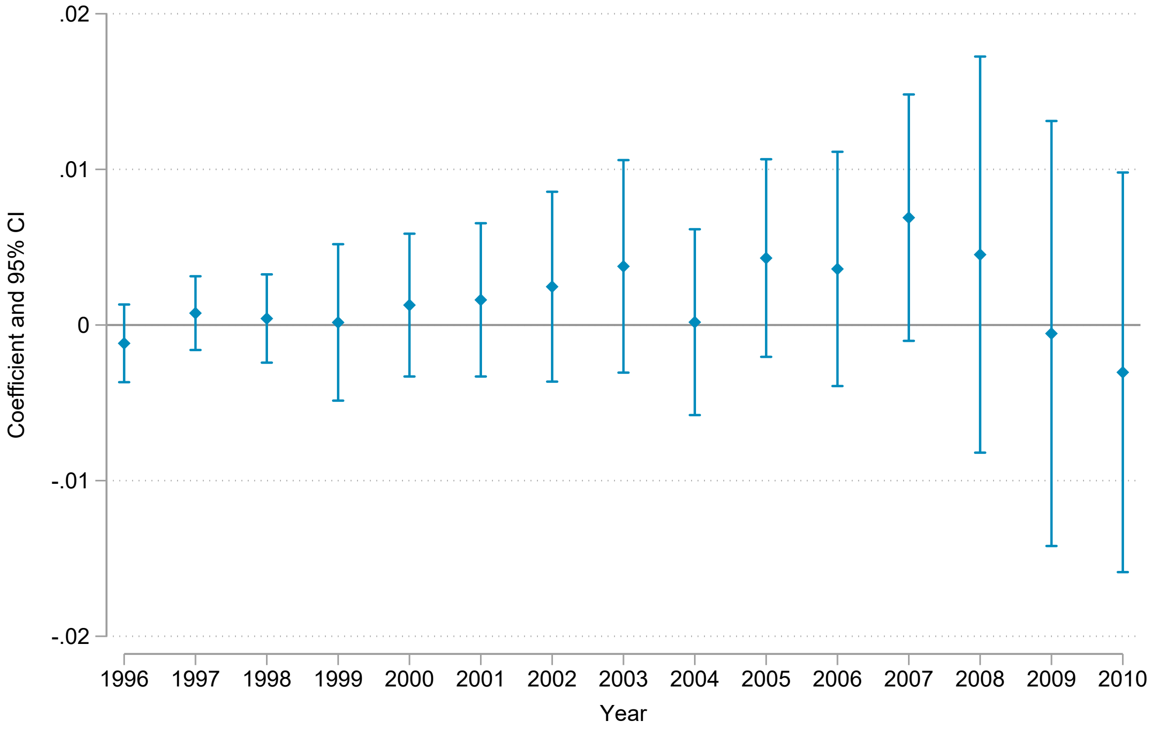
(b) Mining

(c) Labor Force Participation



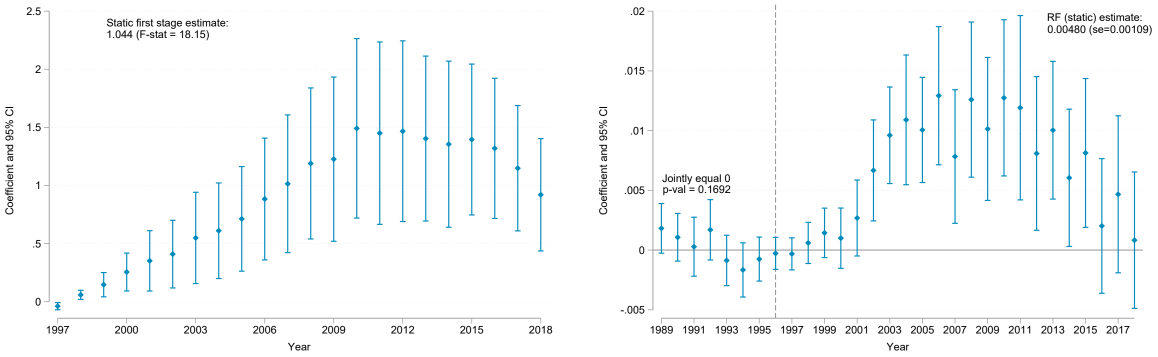
Notes: This figure shows the dynamic reduced-form relationship between the share of employment in the manufacturing and mining industries and labor force participation and our instrument in an out-of-sample period. The first year of available data is 1990. We use this specification to test for the presence a relationship between our outcomes and mid-nineties cancer mortality before the introduction of OxyContin. We do not reject the null hypothesis that the estimated coefficients are jointly equal to zero, the p value of these tests are presented in the figures. This figure is referenced in Section IV.B.

Figure A15: Effects of Purdue Pharma's Mid-nineties Cancer-market Targeting on Share of Smokers



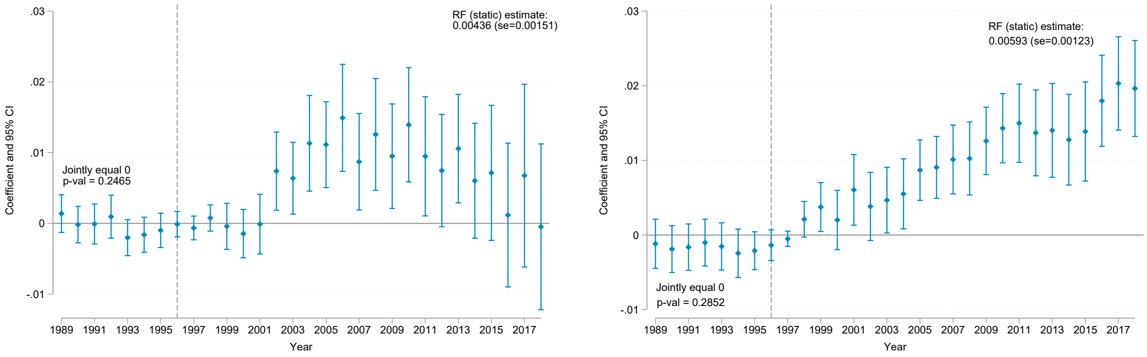
Notes: This figure shows the effects of the increase in prescription opioids supply in the share of smokers. We present the results of a dynamic reduced-form estimation were we regress the outcome on a set of year-dummy variables interacted with our instrument. We construct the share of smokers using data from the Behavioral Risk Factor Surveillance System (BRFSS). We perform the analysis up to 2010 since starting in 2011, BRFSS changed its data collection, structure, and weighting methodology. In 2011 there is an increase in the proportion of people being surveyed on cell phones and it also coincides with a rise in the percentage of respondents with unknown smoking status as documented by DeCicca et al. (2022). This figure is referenced in Section V.B.

Figure A16: Dynamic First Stage and Reduced Form Estimates - Alternative specification



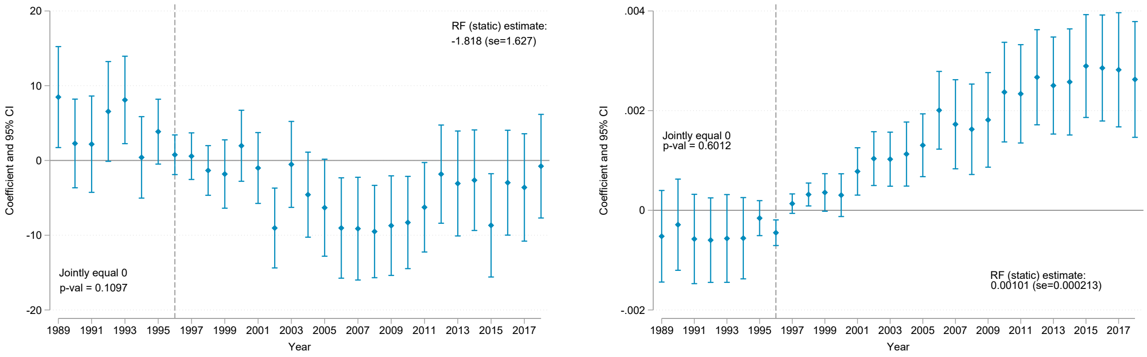
(a) First Stage

(b) Prescription Opioid Mortality



(c) Any Opioid Mortality

(d) SNAP



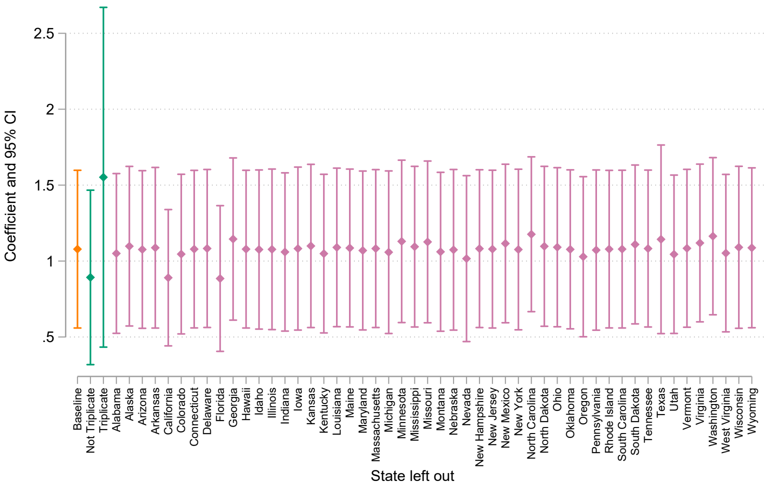
(e) Birth Weight

(f) Fertility Rate of Unmarried woman

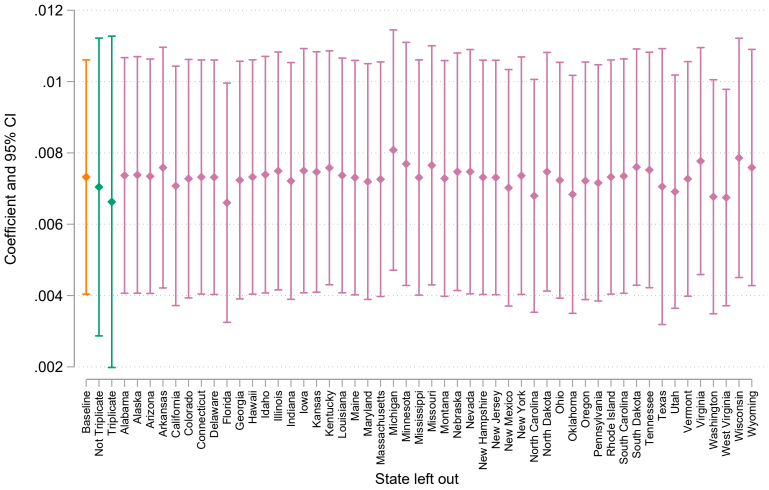
Notes: This figure shows the dynamic first stage (panel a) and reduced-form (panels b to f) relations between outcomes of interest and an alternative instrument: cancer mortality rate in 1994. That is, we regress the outcomes of interest on a set of year-dummy variables interacted with cancer mortality in 1994. This figure provides a robustness check for our preferred specification which uses cancer mortality in 1994-1996 as an instrument. We do not find evidence for the presence of pre-trends in the relation between opioid mortality—and other outcomes of interest—and mid-nineties cancer mortality in this alternative specification. We test if the estimated coefficients before 1996 are jointly equal to zero and do not reject the null hypotheses, the *p* values are reported in each panel. This figure is referenced in Section VI.A.

Figure A17: Robustness check: Leave-ones-out estimates

(a) First-stage coefficient estimates



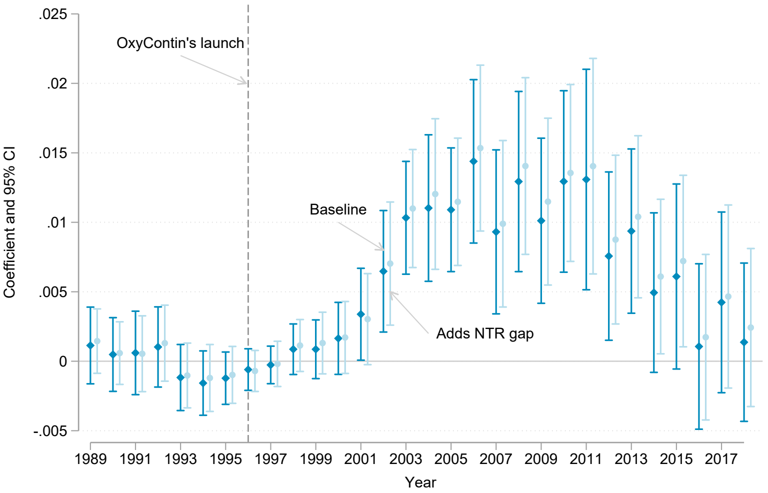
(b) Prescription opioids: Reduced-form coefficient estimates



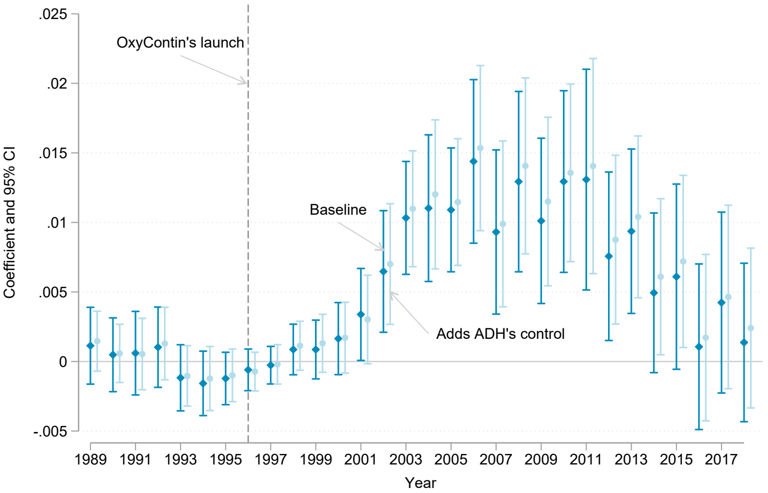
Notes: Panel (a) of this figure reports the estimated coefficient ϕ of the first stage equation (Equation 1) and the corresponding 95% confidence interval. Panel (b) of this figure reports the estimated reduced-form coefficient. The first coefficient and confidence interval of each graph replicate the main result result—see column 5 of Table 3 and column 2 of Table 5. Each of the subsequent coefficients are computed by excluding all commuting zones in the state or group of states indicated on the horizontal axis. Triplicate states are: California, Idaho, Illinois, New York, and Texas. Not triplicate group excludes all these 5 states. This figure is referenced in Section VI.A.

Figure A18: Robustness check: Control for exposure to permanent normal trade relations to China ("China shock")

(a) NTR gap (Pierce and Schott, 2020)



(b) Change in Chinese import exposure (ADH, 2013)



Notes: This figure presents the baseline dynamic reduced-form estimates and the dynamic reduced-form estimates when we control for exposure to permanent normal trade relations (PNTR) to China—termed the China shock in the trade literature. In October, 2000, the US Congress passed a bill granting permanent normal trade relations to China, a trade liberalization that granted China imports access to normal trade relations (NTR) tariff rates. This trade liberalization differentially exposed US regions to increased import competition from China via their industry structure. We test whether results on opioid mortality are driven by this differential exposure. First, we follow Pierce and Schott (2020) and construct a measure of exposure to trade liberalization as the difference between the non-NTR rates to which tariffs could have risen prior to PNTR and the NTR rates that were locked in by the change in policy. A higher NTR gap indicates a larger trade liberalization after the passage of PNTR. Panel (a) shows estimates of the reduced-form when we control for the commuting-zone-level NTR gap. Second, we measure exposure to trade liberalization following David et al. (2013): in this case, we control for the change in Chinese import exposure per worker in a commuting zone. These results are presented in Panel (b). This figure is referenced in Section VI.E.

B Additional Tables

Table A1: Additional Summary Statistics: Opioid Prescriptions, doses per capita

	Mean	**Median**	**SD**	**Min**	**Max**	**Observations**
1997						
All opioids	1.49	1.40	0.67	0.04	7.64	590
Oxycodone	0.35	0.32	0.21	0.01	1.76	590
Hydrocodone	0.55	0.49	0.34	0.01	2.73	590
Morphine	0.31	0.29	0.17	0.01	1.89	590
2007						
All opioids	7.03	6.24	4.01	0.22	36.24	590
Oxycodone	3.26	2.76	2.33	0.08	26.86	590
Hydrocodone	2.33	1.87	1.72	0.04	14.30	590
Morphine	1.04	0.89	0.68	0.04	8.58	590
2017						
All opioids	6.97	6.30	3.50	0.19	27.47	590
Oxycodone	3.75	3.42	2.25	0.11	15.34	590
Hydrocodone	1.86	1.63	1.17	0.04	10.57	590
Morphine	0.92	0.82	0.50	0.03	5.27	590

Notes: This table presents summary statistics for our measure of the prescription opioids supply and the distribution of oxycodone, hydrocodone, and morphine for the years 1997, 2007, and 2017. Data come from the ARCOS and are expressed in morphine-equivalent mg. This table is referenced in Section III.A.

Table A2: Summary statistics: Pre-period and sample period.

	1989 - 1995		1999 - 2018	
	Mean (1)	SD (2)	Mean (3)	SD (4)
Cancer Mortality per 1,000				
Cancer mortality rate 1994-1996	2.53	0.58	2.53	0.58
Cancer mortality rate	2.53	0.59	2.48	0.55
Opioid-related Mortality per 1,000				
Prescription opioids	0.01	0.01	0.04	0.05
Any opioids	0.01	0.02	0.07	0.07
Other Mortality Measures per 1,000				
All-cause mortality (+20 years old)	9.81	2.07	9.87	2.06
Deaths of despair	0.24	0.08	0.27	0.10
Deaths of despair - alcohol only	0.09	0.04	0.12	0.06
Deaths of despair - suicide only	0.13	0.05	0.15	0.06
Demand for Social Services				
Share SNAP	0.10	0.06	0.12	0.07
Infant and Maternal Outcomes				
Infant MR (per 1,000 births)	8.87	3.22	6.86	2.87
Birth weight	3416.31	80.77	3274.25	79.47
Share low birth weight	0.07	0.02	0.08	0.02
Share preterm	0.11	0.02	0.12	0.03
APGAR score - all infants	8.24	2.65	8.82	0.19
APGAR score - dead infants	6.14	2.15	5.62	2.28
Median gestation	39.12	0.32	38.95	0.24
Fertility rate	0.08	0.03	0.08	0.01
Fertility rate 25-29	0.12	0.04	0.13	0.02
Fertility rate - unmarried women	0.02	0.01	0.03	0.01

Notes: This table presents summary statistics for our main outcomes and cancer mortality incidence for the period before the launch of OxyContin (1989-1995) and the period of analysis (1999 - 2018). We leverage data from multiple sources. The last two columns reproduce columns (2) and (4) of Table 1. Data on opioid, cancer, birth, and maternal outcomes come from the NVSS. We use data from the Food and Nutrition Service of the Department of Agriculture and the SSA to construct demand for the Supplemental Nutrition Assistance Program (SNAP), Supplemental Security Income (SSI), and Social Security Disability Insurance (SSDI). This table is referenced in Section III.

Table A3: Determinants of Cancer Mortality Rate 94-96

Dependent variable: Cancer MR 94-96			
	(1)		(2)
Sh. of population over 66	11.13***	Adult MR excluding cancer	0.0439**
	[1.895]		[0.0179]
Sh. of population 18-65	-0.664	Income per capita	-0.00000857
	[1.361]		0.118
Sh. of population under 1	2.156	Share with some college	0.518*
	[9.066]		[0.274]
Share Black	0.127	Share with high school or less	0.124
	[0.241]		[0.191]
Share Hispanic	-1.215***	Share working in manufacturing	-0.199
	[0.303]		[0.133]
Share female	-1.48	Labor Force Participation	0.528
	[1.565]		[0.399]
Prescription Opioids MR	1.093	Employment rate	-1.984*
	[1.078]		[1.118]
Infant Mortality rate	-0.00288	Share SNAP	0.484
	[0.00337]		[0.383]
Fertility rate	0.311	Share SSDI	1.856
	[0.426]		[1.929]
Observations	590	R^2	0.847

Notes: This table presents estimates of the determinants of the 1994-1996 cancer mortality rate at the commuting zone level. This regression includes state fixed effects. Robust to heteroskedasticity standard errors are in brackets. MR stands for Mortality rate. * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is referenced in Section IV.B.

Table A4: Baseline Results with Different Time Periods

Panel A: First Stage				
Dependent variable:	Prescription Opioids pc			
	(1)	(2)	(3)	(4)
Cancer MR 94-96	1.078***	0.916***	1.047***	1.474***
se	[0.264]	[0.258]	[0.277]	[0.330]
t-stat	4.08	3.55	3.78	4.46
Effective F-stat	16.63	12.62	14.25	19.90
Observations	11,800	7,080	8,850	5,310
Adjusted R^2	0.564	0.565	0.582	0.425
Sample	**All**	**1999-2010**	**1999-2013**	**2010-2018**

Panel B: Instrumental Variables				
Dependent variable:	Prescription Opioids Mortality Rate			
	(1)	(2)	(3)	(4)
Presc. Opioids pc	0.00679***	0.00785***	0.00769***	0.00533***
	[0.00200]	[0.00259]	[0.00230]	[0.00169]
Observations	11,800	7,080	8,850	5,310
Sample	**All**	**1999-2010**	**1999-2013**	**2010-2018**
Dependent variable:	Any Opioid Mortality Rate			
	(1)	(2)	(3)	(4)
Presc. Opioids pc	0.00646***	0.00677***	0.00672***	0.00562**
	[0.00231]	[0.00256]	[0.00232]	[0.00237]
Observations	11,800	7,080	8,850	5,310
Sample	**All**	**1999-2010**	**1999-2013**	**2010-2018**

Notes: Panel A presents results for the first-stage regression using alternative periods. Column (1) reproduces the main results for 1999-2018, column (2) presents estimates for the first wave of the opioid epidemic, column (3) presents estimates for the first and second waves pooled together, and column (4) presents estimates for the after-OxyContin reformulation period. Panel B presents results from a regression of the opioid mortality measure on all prescription opioids distribution per capita, instrumenting the latter by the cancer incidence in the commuting zone in 1994-1996; i.e., reproduces the results presented in Table 5 under alternative periods. All regressions include state times year fixed effects and a set of control variables: contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. Standard errors are clustered at the CZ level. * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is referenced in Section V.A.

Table A5: Baseline Results with Different Time Periods. IV Estimates.

	SNAP			SSDI		
	(1)	(2)	(3)	(4)	(5)	(6)
Presc. Opioids pc	0.00455*	0.00487**	0.00680***	0.00584***	0.00605***	0.00718***
	[0.00250]	[0.00219]	[0.00205]	[0.00144]	[0.00141]	[0.00135]
Effective F	15.22	17.06	25.70	15.22	17.06	25.70
Sample	**1999-2010**	**1999-2013**	**2010-2018**	**1999-2010**	**1999-2013**	**2010-2018**

	SSI			IMR		
	(1)	(2)	(3)	(4)	(5)	(6)
Presc. Opioids pc	0.00226*	0.00248*	0.00320*	0.0458	0.0512	0.0846
	[0.00133]	[0.00141]	[0.00174]	[0.185]	[0.160]	[0.113]
Effective F	15.22	17.06	25.70	15.22	17.06	25.70
Sample	**1999-2010**	**1999-2013**	**2010-2018**	**1999-2010**	**1999-2013**	**2010-2018**

	Birth weight			Fertility		
	(1)	(2)	(3)	(4)	(5)	(6)
Presc. Opioids pc	-5.989**	-5.093**	-2.915*	0.00210***	0.00233***	0.00350***
	[2.811]	[2.316]	[1.623]	[0.000696]	[0.000674]	[0.000778]
Effective F	15.22	17.06	25.70	15.22	17.06	25.70
Sample	**1999-2010**	**1999-2013**	**2010-2018**	**1999-2010**	**1999-2013**	**2010-2018**

Notes: This table presents results from a regression of outcome y on prescription opioids distribution per capita, instrumenting the latter by the cancer incidence in the commuting zone in 1994-1996; i.e., reproduces the results presented in Tables 7 and 8 under alternative periods. Columns (1) and (4) present estimates for the first wave of the opioid epidemic, columns (2) and (5) present estimates for the first and second waves pooled together, and columns (3) and (6) present estimates for the after-OxyContin reformulation period. All regressions include state times year fixed effects and a set of control variables: contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. Standard errors are clustered at the CZ level. * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is referenced in Section V.B.

Table A6: Effects on Fertility Rate by Marital Status and Age

Dependent variable: Fertility rate	(1)	(2)	(3)	(4)	(5)	(6)
Pres. Opioids pc	0.00166***	-0.000119	-0.00107	0.00327***	0.0000223	-0.00123**
	[0.000475]	[0.000517]	[0.00111]	[0.00115]	[0.000446]	[0.000497]
Sample	Non-marital births	Marital births	All 20-24	All 25-29	All 30-34	All 35-39
Observations	11,800	11,800	11,800	11,800	11,800	11,800
Clusters	590	590	590	590	590	590

Notes: This table presents results from a regression of measures of fertility rate on prescription opioids distribution per capita, instrumenting the latter by the cancer incidence in the commuting zone in 1994-1996. All regressions include state times year fixed effects and a set of control variables: contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. Standard errors are clustered at the CZ level. * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is referenced in Section V.B.

Table A7: Baseline Results under a Shift-share Instrument

Dependent var:	Presc. Opioids pc	Presc. Opioids MR	Any Opioids MR	SNAP	SSDI
	(1)	(2)	(3)	(4)	(5)
Shift Share	0.00417*** [0.000997]				
Effective F	17.47				
Presc. Opioids pc		0.00644*** [0.00188]	0.00635*** [0.00219]	0.00927*** [0.00277]	0.00553*** [0.00127]
Model	FS	IV	IV	IV	IV

Dependent var:		SSI	Infant Mortality Rate	Fertility rate	Birth weight
		(6)	(7)	(8)	(9)
Presc. Opioids pc		0.00319** [0.00158]	-0.0218 [0.120]	0.00149*** [0.000548]	-4.344** [1.964]
Model		IV	IV	IV	IV

Notes: Column 1 reports the estimated coefficient for the first stage. Columns 2 to 9 present results from IV regressions using the shift-share instrument. Each regression is run over a sample of 11,800 observations with 590 clusters (commuting zones). All regressions include state times year fixed effects and a set of control variables: contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. Standard errors are clustered at the CZ level. * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is referenced in Section VI.A.

Table A8: First Stage Results with Population Size Controls

Dependent variable: Prescription opioids per capita	(1)	(2)	(3)	(4)	(5)
Cancer MR 94-96	1.078***	1.635***	1.072***	1.046***	1.608***
se	[0.264]	[0.483]	[0.276]	[0.266]	[0.490]
t-stat	4.08	3.39	3.88	3.94	3.28
Effective F-stat	16.63	11.49	15.05	15.52	10.76
Share pop +65 yo	No	Yes	No	No	Yes
Total pop +65 yo	No	No	Yes	No	No
Total population	No	No	No	Yes	Yes
Observations	11,800	11,800	11,800	11,800	11,800
Clusters	590	590	590	590	590
Adj. R^2	0.56	0.57	0.56	0.57	0.57

Notes: All specifications include as control variables: contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years, share of Black, White, and Hispanic population, and share of female population. Standard errors are clustered at the commuting-zone level. * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is referenced in Section VI.A.

Table A9: First Stage Robustness Check - Alternative choices of instrument

Panel A.					
Dependent variable:	Prescription Opioids pc				
	(1)	(2)	(3)	(4)	(5)
Cancer MR	0.868***	1.171***	0.930***	0.754***	1.417***
	[0.229]	[0.272]	[0.260]	[0.223]	[0.284]
Mean cancer MR	2.5168	2.5403	2.5477	2.5221	2.2582
Instrument version:	Age adjusted MR 94-96	1994	1995	1996	Weighted
Observations	11,800	11,800	11,800	11,800	11,800
Clusters	590	591	592	593	594
Adj. R^2	0.553	0.565	0.557	0.551	0.553

Panel B.					
Dependent variable:	Prescription Opioids pc				
	(1)	(2)	(3)	(4)	(5)
Cancer MR	1.186***	0.402***	0.210**	0.127**	11.72***
	[0.315]	[0.149]	[0.0988]	[0.0563]	[4.317]
Mean cancer MR	0.6836	9.8072	13.1382	17.5892	0.1342
Instrument version:	Excluding lung cancer	55+	65+	75+	Sh. Pop 66+
Observations	11,800	11,800	11,800	11,800	11,800
Clusters	590	590	590	590	590
Adj. R^2	0.55	0.55	0.56	0.56	0.57

Notes: All regressions include state times year fixed effects and a set of control variables: contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years, share of Black, White, and Hispanic population, and share of female population. Standard errors are clustered at the commuting-zone level. * $p<0.10$, ** $p<0.05$, ***$p<0.01$. This table is referenced in Section VI.A.

Table A10: Placebo Check - Alternative Instruments

Dependent variable: Prescription opioids per capita	(1)	(2)	(3)	(4)	(5)	(6)
CVD MR 94 96	0.372			-2.023**		
	[0.611]			[0.822]		
Accidental MR 94 96		1.067			-1.639	
		[1.411]			[1.406]	
Homicides MR 94 96			0.214			-0.474
			[3.379]			[3.173]
Cancer MR 94 96				1.381***	1.015***	0.923***
				[0.347]	[0.245]	[0.233]
Model	FS	FS	FS	FS	FS	FS
Observations	11,800	11,800	11,800	11,800	11,800	11,800
Clusters	590	590	590	590	590	590
Adjusted R^2	0.55	0.549	0.549	0.565	0.561	0.562

Notes: CVD stands for cerebrovascular diseases. Columns 1-3 report first-stage regression with alternative instrument. Columns 4-6 add our baseline instrument. All regressions include state times year fixed effects and a set of control variables: labor force participation, contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. Standard errors are clustered at the CZ level. * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is referenced in Section VI.B.

Table A11: Alternative Measure of Opioid Supply.

Dependent var:	Oxycodone pc (1)	Presc. opioids MR (2)	All opioids MR (3)
Cancer MR 94-96	0.605***		
	[0.186]		
Oxycodone pc		0.0121***	0.0115***
		[0.00412]	[0.00436]
tF 0.05 se		(0.00578)	(0.00612)
t-stat using tF 0.05 se		2.0932	1.8799
Effect size (%)	38.00	91.50	40.37
Model	FS	IV	IV
Observations	11,800	11,800	11,800
Clusters	590	590	590
Adjusted R^2	0.526		

Notes: All regressions include state times year fixed effects. Control variables are contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. This table reproduces the main analysis using Oxycodone shipments as the measure of opioid supply. Effect size in column (1) is computed as the predicted changes in doses of oxycodone and prescription opioids per capita from an increase in cancer mortality that would change a commuting zone in the 5th percentile of the cancer distribution to the 95th percentile. Effect sizes in columns (2) and (3) indicate the percent change in the dependent variable relative to its mean when doses of prescription opioids per capita increase from the 25th to the 75th percentile. Standard errors in square brackets are clustered at the CZ level; using these standard errors, we report * p<0.10, ** p<0.05, *** p<0.01. tF 0.05 se, and t-stat using tF0.05 se correspond to weak-instrument-robust inference procedures. This table is referenced in Section VI.C.

Table A12: Direct Effects. Alternative Measure of Opioid Mortality

Dependent var:	Drug Induced Mortality Rate		
	(1)	(2)	(3)
Prescription opioids pc	0.00505***		0.0112***
	[0.00152]		[0.00369]
tF 0.05 se			0.00518
t-stat using tF 0.05 se			2.16329
AR p-value			0.00010
Cancer MR 94-96		0.0121***	
		[0.00314]	
Effect size (%)	20.96		46.94
Model	OLS	RF	IV
Observations	11,800	11,800	11,800
Clusters	590	590	590
Adjusted R^2	0.4304	0.3908	
Effective F-stat			16.63
Cragg-Donald Wald F-stat			358.58

Notes: Control variables are contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. Effect size indicates the percent change in the dependent variable relative to its mean when doses of prescription opioids per capita increase from the 25th to the 75th percentile. Standard errors in square brackets are clustered at the CZ level. Using these standard errors, we report * p<0.10, ** p<0.05, *** p<0.01. tF 0.05 se, t-stat using tF0.05 se, and the *AR p-value* correspond to weak-instrument-robust inference procedures. This table is referenced in Section VI.C.

Table A13: Baseline Results under Alternative Sample Restrictions

Dependent var:	Presc. Opioids pc			Prescription Opioids MR		
	(1)	(2)	(3)	(4)	(5)	(6)
Cancer MR 94-96	1.191***	1.055***	1.018***			
	[0.249]	[0.297]	[0.288]			
Presc. Opioids pc				0.00355***	0.00684***	0.00826***
				[0.00134]	[0.00231]	[0.00268]
Sample	**15,000+**	**40,000+**	**55,000+**	**15,000+**	**40,000+**	**55,000+**

	Any Opioids MR			All-cause mortality over 20		
	(1)	(2)	(3)	(4)	(5)	(6)
Presc. Opioids pc	0.00152	0.00697**	0.00885***	0.0137	0.0515	0.102
	[0.00171]	[0.00273]	[0.00329]	[0.0361]	[0.0477]	[0.0668]
Sample	**15,000+**	**40,000+**	**55,000+**	**15,000+**	**40,000+**	**55,000+**

	SSDI			SSI		
	(1)	(2)	(3)	(4)	(5)	(6)
Presc. Opioids pc	0.00504***	0.00586***	0.00652***	0.00204**	0.00339**	0.00438*
	[0.00106]	[0.00155]	[0.00173]	[0.000851]	[0.00169]	[0.00239]
Sample	**15,000+**	**40,000+**	**55,000+**	**15,000+**	**40,000+**	**55,000+**

	SNAP			IMR		
	(1)	(2)	(3)	(4)	(5)	(6)
Presc. Opioids pc	0.00941***	0.00997***	0.00919***	0.175	-0.0297	0.0604
	[0.00248]	[0.00336]	[0.00307]	[0.130]	[0.142]	[0.150]
Sample	**15,000+**	**40,000+**	**55,000+**	**15,000+**	**40,000+**	**55,000+**

	Birth weight			Fertility		
	(1)	(2)	(3)	(4)	(5)	(6)
Presc. Opioids pc	-4.896***	-3.770*	-6.480**	0.00108***	0.00156**	0.00160**
	[1.852]	[2.240]	[2.624]	[0.000404]	[0.000632]	[0.000706]
Sample	**15,000+**	**40,000+**	**55,000+**	**15,000+**	**40,000+**	**55,000+**

Notes: This table presents results for the first-stage regression and IV results using alternative sample definitions. Our preferred specification restricts the sample to commuting zones with population higher than 25,000 residents. When the sample is restricted to population above 15,000, the sample size is 12,820 observations and 641 clusters. Analogously, when restricted to population above 40,000, sample size is 10,880 and 544 cluster, and 9,620 and 481 clusters when restriction is above 55,000. All regressions include state times year fixed effects and a set of control variables: contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. Standard errors are clustered at the CZ level. * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is referenced in Section III.C. and in Section VI.D.

Table A14: Alternative Sample Results for SNAP

Dependent variable:	Share SNAP					
	(1)	(2)	(3)	(4)	(5)	(6)
Presc. Opioids pc	0.000144		0.00982***	0.000213		0.0106***
	[0.51]		[3.28]	[0.74]		[3.23]
Cancer 94 96		0.0106***			0.0116***	
		[4.67]			[5.53]	
Effective F-stat			16.63			13.70
Model	OLS	RF	IV	OLS	RF	IV
Sample	Baseline	Baseline	Baseline	Restricted	Restricted	Restricted
Observations	11,800	11,800	11,800	9,962	9,962	9,962
Clusters	590	590	590	533	533	533

Notes: Columns 1-3 report baseline results and columns 4-6 report results only for commuting zones where county-level data were available. All regressions include state times year fixed effects and a set of control variables: labor force participation, contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. Standard errors are clustered at the CZ level. * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is referenced in Section VI.D.

Table A15: Alternative Specifications

Dependent var:	Presc. Op Mortality	Any Op. Mortality	SSDI	SSI	SNAP	Fertility
Presc. Opioids pc	0.00684***	0.00643***	0.00579***	0.00322**	0.00922***	0.00145***
	[0.00204]	[0.00232]	[0.00136]	[0.00152]	[0.00270]	[0.000529]
Extra covariate	**Empl.**	**Empl.**	**Empl.**	**Empl.**	**Empl.**	**Empl.**
Observations	11,800	11,800	11,800	11,800	11,800	11,800
Clusters	590	590	590	590	590	590

Dependent var:	Presc. Op Mortality	Any Op. Mortality	SSDI	SSI	SNAP	Fertility
Presc. Opioids pc	0.00684***	0.00643***	0.00579***	0.00322**	0.00922***	0.00145***
	[0.00204]	[0.00232]	[0.00136]	[0.00152]	[0.00270]	[0.000529]
Extra covariate	**Unemp.**	**Unemp.**	**Unemp.**	**Unemp.**	**Unemp.**	**Unemp.**
Observations	11,800	11,800	11,800	11,800	11,800	11,800
Clusters	590	590	590	590	590	590

Notes: All regressions include state times year fixed effects and a set of control variables: contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. Standard errors are clustered at the CZ level. * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is referenced in Section VI.D.

Table A16: First Stage with Additional Control Variables: Recession, China Shock & Unemployment

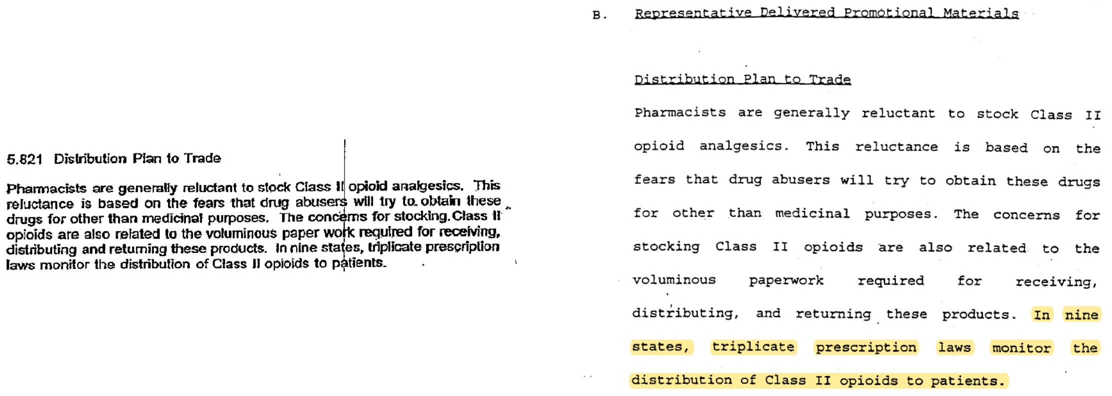
Presc. Opioids pc	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Cancer MR 94 96	1.078***	1.137***	1.101***	1.104***	1.075***	1.074***	1.075***
	[0.266]	[0.272]	[0.268]	[0.268]	[0.264]	[0.264]	[0.263]
Extra control	**Recession**	**NTR Gap**	**ADH 1990**	**ADH 2000**	**Unemp. 94**	**Unemp. 95**	**Unemp. 96**
Observations	11,800	11,800	11,740	11,740	11,800	11,800	11,800
Adjusted R^2	0.57	0.57	0.57	0.57	0.56	0.56	0.56
Clusters	590	590	587	587	590	590	590

Notes: This table estimate the first stage including additional control variables to account for the 2001 Economic Recession and the China Shock. All regressions include state times year fixed effects and a set of control variables Standard errors are clustered at the CZ level. All regressions are run on panel at the CZ level with 11,800 observations and 590 clusters. * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is referenced in Section VI.E.

C Triplicate States and the Promotion of OxyContin

From our review of Purdue Pharma and other pharmaceutical companies' internal documents, we believe that when Purdue referred to "Triplicate States" it meant a group of nine states and not five as stated in Alpert et al. (2022). At least on two separate occasions, Purdue explicitly referred to triplicates as the *"nine states"* (Figure C1), and to our knowledge, never mentioned only five. Academic documents that explain the prescription drug monitoring programs that were in effect at the time, also refer to a group of nine states. These documents are more precise in their language and refer to these programs as multiple-copy prescription programs (Joranson et al., 2002 and Fishman et al., 2004). Similar to today's PDMPs, different states had different versions of the program, but the informal industry name for these programs was "triplicate programs". In an internal email between Mallinckrodt sales specialists, also disclosed as part of the opioid litigation, one sales specialist lists and explains to the other the history of the triplicate programs, and lists the original nine states (see Figure C2). These states are: California, Hawaii, Idaho, Indiana, Michigan, Illinois, New York, Rhode Island, and Texas.[51]

Figure C1: Reference to Nine Triplicate States in OxyContin Launch Plan



5.821 Distribution Plan to Trade

Pharmacists are generally reluctant to stock Class II opioid analgesics. This reluctance is based on the fears that drug abusers will try to obtain these drugs for other than medicinal purposes. The concerns for stocking Class II opioids are also related to the voluminous paper work required for receiving, distributing and returning these products. In nine states, triplicate prescription laws monitor the distribution of Class II opioids to patients.

B. Representative Delivered Promotional Materials

Distribution Plan to Trade

Pharmacists are generally reluctant to stock Class II opioid analgesics. This reluctance is based on the fears that drug abusers will try to obtain these drugs for other than medicinal purposes. The concerns for stocking Class II opioids are also related to the voluminous paperwork required for receiving, distributing, and returning these products. In nine states, triplicate prescription laws monitor the distribution of Class II opioids to patients.

Notes: This figure shows extracts of OxyContin Launch plans. The left panel reproduces a segment of the OxyContin Launch Plan, page 27 September 27th 1995. The right panel is an extract from OxyContin Budget Plan 1996, page 29. This figure is referenced in Section C.

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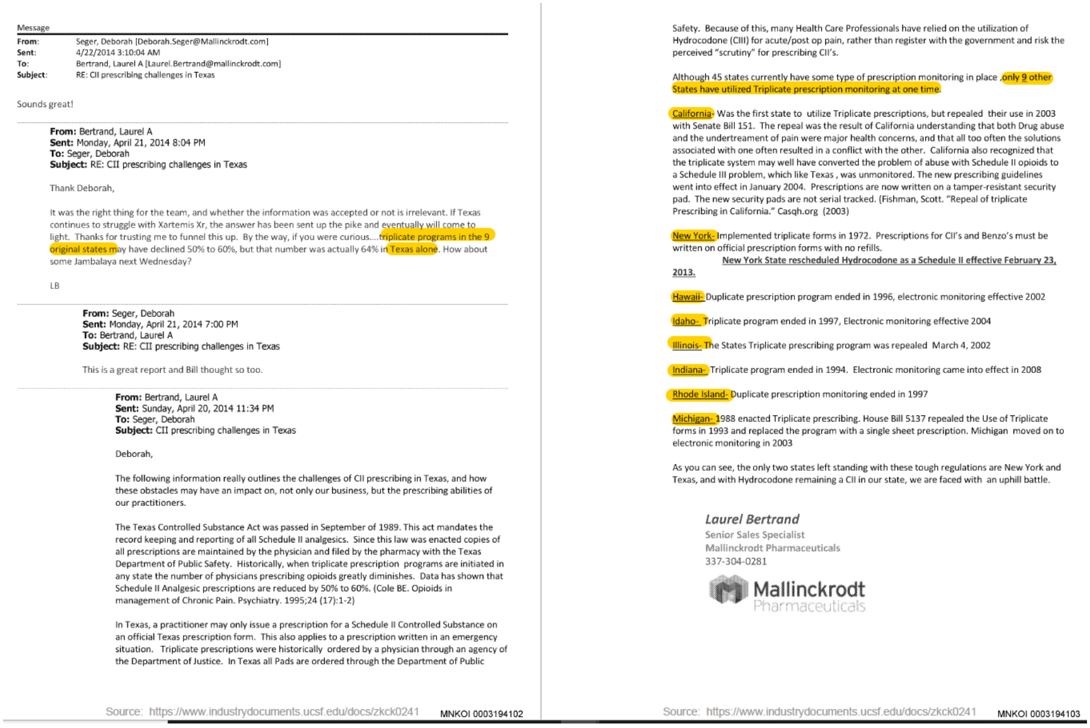
[51] Mallinckrodt is a pharmaceutical company that is also part of the opioid litigation for their role in the opioid epidemic. More precisely, *"Collectively, Purdue, Actavis, Cephalon, Janssen, Endo, Insys, and Mallinckrodt are referred to as "Marketing Defendants"* Case No. 17-md-2804. United States District Court for the Northern District of Ohio Eastern Division.

Figure C2: Reference to Nine Triplicate States in Internal Communications



Message

From: Seger, Deborah [Deborah.Seger@Mallinckrodt.com]
Sent: 4/22/2014 3:10:04 AM
To: Bertrand, Laurel A [Laurel.Bertrand@mallinckrodt.com]
Subject: RE: CII prescribing challenges in Texas

Sounds great!

From: Bertrand, Laurel A
Sent: Monday, April 21, 2014 8:04 PM
To: Seger, Deborah
Subject: RE: CII prescribing challenges in Texas

Thank Deborah,

It was the right thing for the team, and whether the information was accepted or not is irrelevant. If Texas continues to struggle with Xartemis Xr, the answer has been sent up the pike and eventually will come to light. Thanks for trusting me to funnel this up. By the way, if you were curious....triplicate programs in the 9 original states may have declined 50% to 60%, but that number was actually 64% in Texas alone. How about some Jambalaya next Wednesday?

LB

From: Seger, Deborah
Sent: Monday, April 21, 2014 7:00 PM
To: Bertrand, Laurel A
Subject: RE: CII prescribing challenges in Texas

This is a great report and Bill thought so too.

From: Bertrand, Laurel A
Sent: Sunday, April 20, 2014 11:34 PM
To: Seger, Deborah
Subject: CII prescribing challenges in Texas

Deborah,

The following information really outlines the challenges of CII prescribing in Texas, and how these obstacles may have an impact on, not only our business, but the prescribing abilities of our practitioners.

The Texas Controlled Substance Act was passed in September of 1989. This act mandates the record keeping and reporting of all Schedule II analgesics. Since this law was enacted copies of all prescriptions are maintained by the physician and filed by the pharmacy with the Texas Department of Public Safety. Historically, when triplicate prescription programs are initiated in any state the number of physicians prescribing opioids greatly diminishes. Data has shown that Schedule II Analgesic prescriptions are reduced by 50% to 60%. (Cole BE. Opioids in management of Chronic Pain. Psychiatry. 1995;24 (17):1-2)

In Texas, a practitioner may only issue a prescription for a Schedule II Controlled Substance on an official Texas prescription form. This also applies to a prescription written in an emergency situation. Triplicate prescriptions were historically ordered by a physician through an agency of the Department of Justice. In Texas all Pads are ordered through the Department of Public

Source: https://www.industrydocuments.ucsf.edu/docs/zkck0241 MNKOI 0003194102

Safety. Because of this, many Health Care Professionals have relied on the utilization of Hydrocodone (CIII) for acute/post op pain, rather than register with the government and risk the perceived "scrutiny" for prescribing CII's.

Although 45 states currently have some type of prescription monitoring in place ,only 9 other States have utilized Triplicate prescription monitoring at one time.

California- Was the first state to utilize Triplicate prescriptions, but repealed their use in 2003 with Senate Bill 151. The repeal was the result of California understanding that both Drug abuse and the undertreament of pain were major health concerns, and that all too often the solutions associated with one often resulted in a conflict with the other. California also recognized that the triplicate system may well have converted the problem of abuse with Schedule II opioids to a Schedule III problem, which like Texas , was unmonitored. The new prescribing guidelines went into effect in January 2004. Prescriptions are now written on a tamper-resistant security pad. The new security pads are not serial tracked. (Fishman, Scott. "Repeal of triplicate Prescribing in California." Casqh.org (2003)

New York- Implemented triplicate forms in 1972. Prescriptions for CII's and Benzo's must be written on official prescription forms with no refills.
New York State rescheduled Hydrocodone as a Schedule II effective February 23, 2013.

Hawaii- Duplicate prescription program ended in 1996, electronic monitoring effective 2002

Idaho- Triplicate program ended in 1997, Electronic monitoring effective 2004

Illinois- The States Triplicate prescribing program was repealed March 4, 2002

Indiana- Triplicate program ended in 1994. Electronic monitoring came into effect in 2008

Rhode Island- Duplicate prescription monitoring ended in 1997

Michigan- 1988 enacted Triplicate prescribing. House Bill 5137 repealed the Use of Triplicate forms in 1993 and replaced the program with a single sheet prescription. Michigan moved on to electronic monitoring in 2003

As you can see, the only two states left standing with these tough regulations are New York and Texas, and with Hydrocodone remaining a CII in our state, we are faced with an uphill battle.

Laurel Bertrand
Senior Sales Specialist
Mallinckrodt Pharmaceuticals
337-304-0281

Source: https://www.industrydocuments.ucsf.edu/docs/zkck0241 MNKOI 0003194103

Notes: This figure shows extracts of the internal email from the opioid litigation with details on the list of triplicate states. This figure is referenced in Section C.

In light of these alternative definitions of the group of states with triplicate programs we inspect the time trends of overdose mortality in triplicate states and replicate the main results in Alpert et al. (2022).[52] First, in Figure C3 we inspect patterns in the raw data. Panels (a) and (b) show the evolution of overdose mortality in five triplicate states and in nine triplicate states respectively, compared to the evolution in the rest of the country. Using the alternative definition of triplicates provide a less clear evidence that "triplicate states" fare better in terms of overdose mortality.

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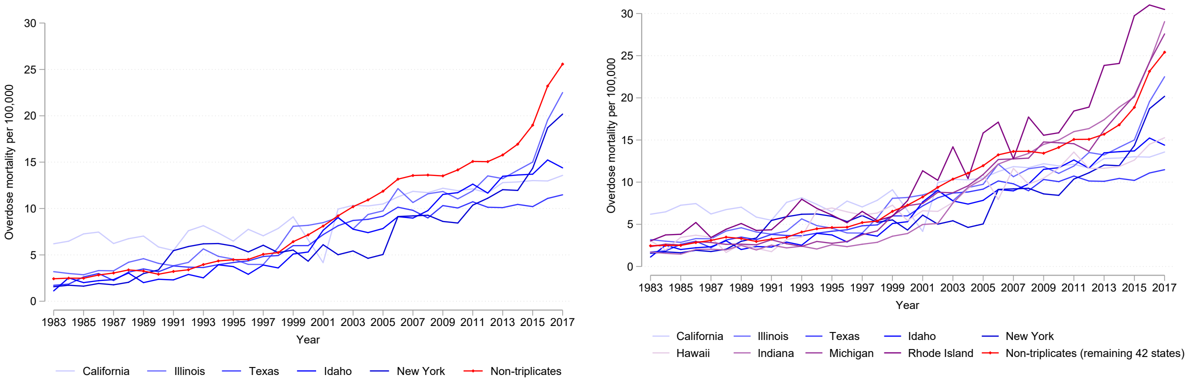
[52] We define overdose deaths as deaths involving underlying cause of death ICD-9 codes E850-E858, E950.0-E950.5, E962.0, or E980.0-E980.5 and ICD-10 codes X40-X44, X60-64, X85, or Y10-Y14.

Figure C3: All Drug Overdose Mortality By Triplicate Status.



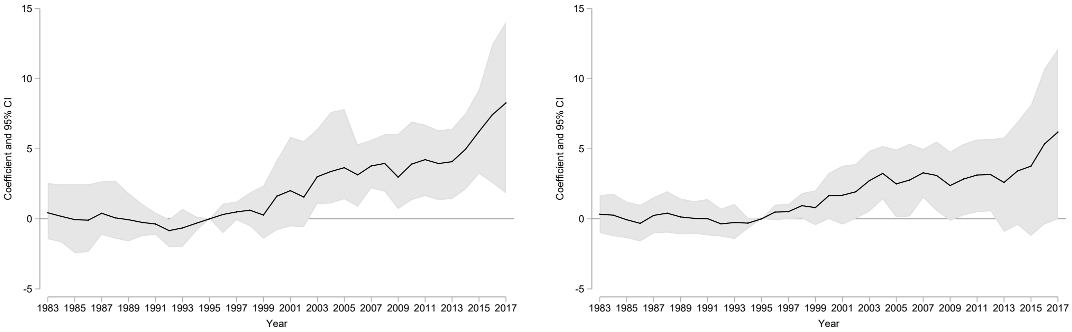
(a) Triplicate definition as in Alpert et al. (2022).

(b) Alternative triplicate definition

Notes: Time series for all drug overdose mortality. Panel (a) defines triplicates as California, Idaho, Illinois, New York, and Texas. Panel (b) adds Hawaii, Indiana, Michigan, and Rhode Island for a total of 9 triplicate states. This figure is referenced in Appendix C.

Event studies models in Figure C4 suggest a similar story. While the main results are mostly robust to this alternative definition, they are attenuated and are often equal to zero statistically, suggesting a smaller effect of the triplicate status on overdose mortality. We estimate the event studies with and without population weights. The unweighted version is more sensitive to the definition of triplicate status, which is natural since even though the sample of "treated" states is increasing by 80%, the treated population is only changing by 21%. Finally, Table C1 replicates the main estimate in Alpert et al. (2022). Consistent with the event study estimates, results are attenuated when using the alternative definition and are more sensitive when regressions are not weighted by population.

Figure C4: All Drug Overdose Mortality By Triplicate Status - Unweighted analysis.

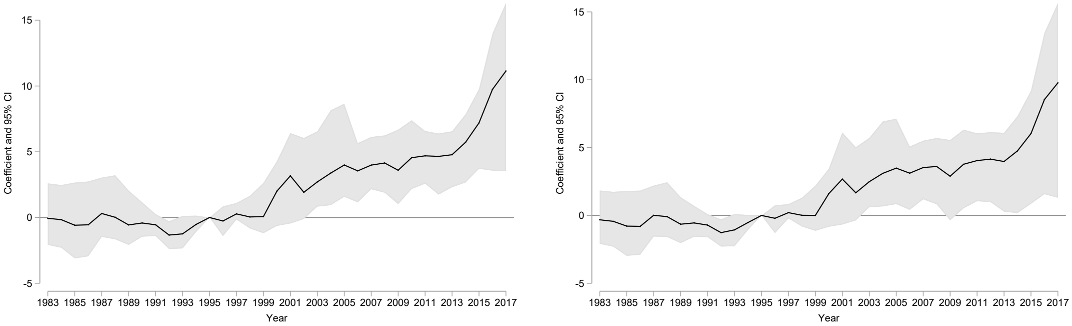


(a) 5 Triplicates unweighted

(b) 9 Triplicates unweighted

(c) 5 Triplicates weighted

(d) 9 Triplicates weighted



Notes: Figures in panels (a) and (c) reproduce Figure 4 in Alpert et al. (2022). Panels (b) and (d) present the analysis using the alternative definition of triplicate states: we add Hawaii, Indiana, Michigan, and Rhode Island for a total of 9 triplicate states. Event study models include state and year fixed effects. 95% confidence intervals are generated using a clustered (at state) wild bootstrap. Estimates are normalized to zero in 1995. This figure is referenced in Appendix C.

Table C1: Replication of Table 1 Alpert et al. (2022)

Triplicate state group (n) Nontriplicate ×	Nine (1)	Five (2)	Nine (3)	Five (4)
1996–2000	0.998***	1.173	0.711	1.229**
SE, CI	[0.356]	[0.390, 2.374]	[0.538]	[0.017, 2.483]
Coeff. change		14.9%		42.1%
2001–2010	2.257**	3.667**	1.998**	3.232**
SE, CI	[0.913]	[1.521, 6.210]	[0.994]	[1.011, 5.318]
Coeff. change		38.5%		38.2%
2011–2017	2.793	6.061**	3.203**	4.714***
SE, CI	[1.891]	[2.812, 9.371]	[1.337]	[1.811, 7.253]
Coeff. change		53.9%		32.1%
Weighted	No	No	Yes	Yes
Covariates	No	No	Yes	Yes
Region-time dummies	No	No	Yes	Yes
Observations	1,377	1,377	1,377	1,377

Notes: Columns (2) and (4) of this table reproduce columns (1) and (4) of Table 1 in Alpert et al. (2022) respectively. Columns (1) and (3) present the analysis using an alternative definition of triplicate status. This table is referenced in Section C.