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

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Abstract

This paper provides new evidence on the origins and effects of the opioid crisis, emphasizing the critical role played by the pharmaceutical industry. Drawing on unsealed records from litigation against Purdue Pharma, we uncover rich geographic quasi-exogenous variation in the marketing of OxyContin, to causally connect supply-side factors to the origin of the opioid crisis. Our results indicate a strong causal link between Purdue Pharma's promotional targeting and future increases in the level of prescription opioids. We then use this variation to quantify the epidemic's effects on the wellbeing of adults and its inter-generational impact. We estimate that the rise in the access to potent prescription opioids is responsible for a dramatic increase in opioid mortality as well as far-reaching declines in the quality of life, measured by the share of the population on SNAP. Further, it triggered inter-generational effects through its impact on fertility and birth outcomes.

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I. Introduction

Over the past two decades, mortality from opioid overdoses in the United States has increased at an alarming rate, claiming the lives of over 700,000 individuals (CDC, 2023*a*; CDC, 2023*b*). These tragic losses coincide with an increase in the level of prescription opioids per capita, which grew 232% from 1997 to 2018 (DEA, 2020). Prescription opioids are highly addictive. Even at medically prescribed doses and within short periods of time, they can lead to physiological dependence, with users experiencing tolerance and withdrawal (Sharma et al., 2016; Hah et al., 2017). The potential effects of the rise in the supply of prescription opioids stretch beyond the increase in overdose deaths and include transitions to the use of illegal opioids such as heroin and fentanyl and declines 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; Buckles et al., 2022).

Understanding how we arrived at this situation and the extent of the consequences of the opioid crisis is challenging given the non-random variation in the use of prescription opioids across geographies and over time (Ruhm, 2019; Currie and Schwandt, 2021). On the one hand, deteriorating socio-economic conditions in certain geographic areas could cause an increase in the demand for opioid painkillers and also explain the subsequent decline in the same areas, which would lead to negatively biased estimates (Carpenter et al., 2017; Case and Deaton, 2017; Hungerman et al., 2022). On the other hand, the origin of the epidemic coincides with dramatic supply-side changes such as aggressive marketing of prescription opioids, a shift in physician prescribing attitudes, and an 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 on these variables, which could, in turn, attenuate the estimates of the effects of the epidemic.

In this paper, we uncovered rich geographic quasi-exogenous variation in the level of prescription opioids to credibly link the pharmaceutical industry to the origin and unfolding of the opioid epidemic. We also use this variation to present causal evidence of the epidemic's tragic consequences for the well-being of adults and its intergenerational effects. Our approach exploits detailed features of the initial marketing of prescription opioids, which we obtained from unsealed court records drawn from litigation against Purdue Pharma, the manufacturer of OxyContin —a prescription opioid at the center of the epidemic.[2] Those records show OxyContin was initially promoted to the cancer pain

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

[2] These court documents are from cases 07-CI-01303 Commonwealth of Kentucky v. Purdue Pharma and case CJ-2017-816 State of Oklahoma v. Purdue Pharma et al.; C.A.No. 1884-cv-01808 Commonwealth of Massachusetts v. Purdue Pharma et al. and Case no. 17-md-2804 (N.D. Ohio).

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. Purdue Pharma's later strategy to disproportionately target top prescribers—those in the highest deciles of the opioid dispensing distribution—meant that those initial targets always received more marketing, even in the expansion phase of OxyContin, when the attention was not on the cancer market. Furthermore, Purdue's successful strategy paved the way for the widespread promotion of opioids beyond the cancer market. Other pharmaceutical companies in the market seized this opportunity and closely emulated Purdue's marketing. 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 and other pharmaceutical companies to assess the role of supply-side factors in the unfolding of the opioid epidemic. We then use this variation as an instrument for the exposure of the opioid epidemic, allowing us to estimate its effects on the well-being of adults and its intergenerational effects.

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 opioids. We measure adult well-being as health and social assistance need, using data on mortality from opioids and other causes from the National Vital Statistics System (NVSS) and data on beneficiaries of public assistance—namely, the Supplemental Nutrition Assistance Program (SNAP), Supplemental Security Income (SSI)—and social security programs—Social Security Disability Insurance (SSDI). 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 when introducing OxyContin and the future growth in prescription opioids. Specifically, we estimate a strong positive relationship between higher cancer mortality in the mid-nineties and the rise in prescription opioids after the launch of OxyContin. Commuting zones with the highest cancer incidence at the time of the launch of OxyContin—those at the 95th percentile—received 1.96 more doses of opioids per capita relative to the 5th percentile, accounting for 64% of the 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, we estimate that at its peak in 2010, an increase in mid-nineties cancer mortality from the 5th percentile to the 95th percentile caused a 55% increase in prescription opioid deaths and a 33% increase in deaths from all opioids. These deaths are

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

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 suicides or other causes of death.[4]

Second, the opioid epidemic had important effects beyond overdose mortality. The number of individuals participating in public assistance and social insurance programs increased. A move from the 5th to the 95th percentile of mid-cancer mortality corresponds to a 32% increase in the share of SNAP recipients and a 35% increase in the share of the population receiving SSDI. We also find an 8% increase in the share of population receiving SSI. Third, we document intergenerational effects. We estimate a 6% increase in fertility rates, driven entirely by increases in non-marital births. We find an increase in the share of infants born with a low birth weight of 5%, and a worsening of APGAR scores by 0.64%.[5] We estimate that there was 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 deterioration in the lives of adults with serious consequences for their children's health.

Our identification strategy requires that in the absence of OxyContin's marketing, outcomes in areas with higher cancer mortality would have exhibited the same *trends* as in areas with lower cancer mortality (Goldsmith-Pinkham et al., 2020). To test this identifying assumption, we use an event-study approach and investigate the possible presence of differential pre-trends. We do not find any evidence of a relationship between mid-nineties cancer mortality and growth in our outcome variables before the launch of OxyContin. In contrast, reduced-form event-study graphs show that for the period soon after the introduction of OxyContin, our instrument predicts higher opioid mortality, a higher share of the population receiving SNAP and higher fertility rates. In addition, we document that areas with higher cancer mortality were not on a differential trend with respect to other socioeconomic variables that affect outcomes, such as education, income, or other health variables.[6] 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 Hispanic population share.[7] What is needed to establish a causal interpretation—and what we provide evidence to substantiate—is that areas with high and low cancer mortality were on the same trends

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

[5]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.

[6]For example, we find that commuting zones with high and low cancer mortality were on the same trend regarding suicide mortality and the share of employment in manufacturing and mining industries.

[7]We control flexibly for the baseline share of Hispanics and the share of individuals over 65 years old by including year-dummies interactions with these two control variables, and estimates of the first stage and reduced form coefficients are robust to their inclusion.

in terms of underlying health and economic outcomes.

Further, we propose two placebo exercises to probe the validity of our strategy. First, we show that mid-1990s mortality rates from other causes, such as cerebrovascular disease mortality, are not predictive of the future prescription opioid distribution. In a second placebo exercise, we relate cancer mortality in 1980-1981 to the evolution of the 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. We find no evidence of such a 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 the pharmaceutical industry's marketing of opioids. Finally, our results are not driven by differential exposure to Chinese import competition, the 2001 economic recession, or unemployment at the time of the introduction of OxyContin.

The contribution of this paper is twofold. First, we provide new evidence that links the origin and unfolding of the opioid epidemic to the marketing strategy of OxyContin and the pharmaceutical industry. While a large literature documents the role of supply-side factors as contributing forces to the epidemic, its *origins* remain understudied.[8] We build on the work of Alpert et al. (2022), who use state-level variation in the regulation regarding the prescription of opioids. They show that five states with early versions of prescription drug monitoring programs (PDMPs), or triplicate prescriptions, received less marketing from Purdue Pharma and reported lower levels of prescription opioids and fewer overdose deaths.[9] In this paper, we exploit richer commuting zone-level variation in the initial marketing strategy of OxyContin to provide new evidence linking its launch to the origin and unfolding of the opioid epidemic.[10]

The proposed variation in marketing strategies allows us to account for important confounders at the state and year level and serves as a rich instrument for future work on the epidemic. During this period, there was widespread variation in state-level responses to curb the opioid epidemic, such as the implementation of Prescription Drug Monitoring Programs (PDMP), the regulation of "pill mill" clinics, and the availability of naloxone.[11]

[8] Eichmeyer and Zhang (2020) and Schnell and Currie (2018): physicians; Powell et al. (2020): access to healthcare; and Fernandez and Zejcirovic (2018) and Miloucheva (2021): pharmaceutical promotions, among others.

[9] These early versions of PDMPs were often referred to as "triplicate" programs. Our reading of Purdue and other pharma industry 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.3 examines this evidence and extends the analysis in Alpert et al. (2022).

[10] Previous literature often relies on changes in the access to prescription opioids induced by the adoption of state-level policies, e.g., PDMPs, to indirectly assess the impact of the opioid epidemic on a broad set of outcomes. See Meara et al. (2016), Buchmueller and Carey (2018), Evans et al. (2020), Ziedan and Kaestner (2020), and Gihleb et al. (2022). There is, however, debate on what constitutes an operational or mandatory PDMP; the definitions vary across the literature, making it difficult to leverage this variation to estimate the effects of the opioid epidemic.

[11] The term "pill mill" is typically used to describe a doctor, clinic, or pharmacy that prescribes or

Additionally, we quantify the gains in power from this empirical strategy and source of variation. Simulation exercises suggest that we can identify effects that are 25% of the size of those based on the empirical strategy proposed by Alpert et al. (2022)[12].

Second, this paper is the first to document the *direct* effects of the epidemic on important health and social insurance and public assistance beyond overdose mortality.[13] 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 U.S. aged 12 or older misused opioids (SAMHSA, 2020). These numbers are orders of magnitude larger than the number of deaths. We document the effects on the demand for disability benefits and on participation in one of the largest antipoverty programs in the United States, SNAP, which has not been studied before. Our work is related to that of Savych et al. (2019), who find evidence that an increase in long-term opioid prescribing behavior leads to a considerably longer duration of temporary disability, and to the work of Park and Powell (2021), who document that the rise in access to and consumption of illicit opioids such as heroin and fentanyl increased disability applications by 7%. Finally, we also document 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 affected. 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 on fertility and the first estimates of the 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; Quinones, 2015).[14] Two key technological innovations are responsible for its success. First, its long-acting formula provided an extended window of pain relief, an improvement over the standard practice of 6-8 hours. Second, it is

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 U.S. state passed a law that facilitates the widespread distribution and use of naloxone (Doleac and Mukherjee, 2019).

[12]See Appendix C.2 for detailed definitions.

[13]There is a large literature that documents the *indirect* effects of the epidemic, by evaluating the effects of policies aimed at curving the epidemic and then looking at the effects on downstream outcomes. This literature includes: Buchmueller and Carey (2018), Evans et al. (2020), Ziedan and Kaestner (2020), and Gihleb et al. (2022); among others.

[14]Oxycodone is a semisynthetic opioid that is 50% more potent than morphine and is prescribed for acute pain management.

a single-agent narcotic, so there is no ceiling on the amount of oxycodone per tablet.[15] 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 induces strong euphoric effects.

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 did not have a terminal illness were excluded from long-term therapy with opioids, based on care providers' fears of the risk of severe 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 fear and 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

[15] 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.

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.[16]

Second, OxyContin was promoted directly to physicians by the largest and highest-paid sales force in the industry.[17] The continuous promotion of OxyContin through advertisements, gifts, and promoted medical literature was delivered through repeated visits and calls to physicians. Furthermore, the marketing team carefully tracked physician prescription habits to optimize and personalize their detailing messages.[18] These promotional efforts quickly translated into a growing number of prescriptions from OxyContin (Figure A1).

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. On repeated occasions, Purdue states clearly that: *"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.

[16] *"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 president of Purdue Pharma—deposition, August 28, 2015.

[17] 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).

[18] From 1996 to 2000, Purdue increased its total physician call list from approximately 33,400 to approximately 70,500 physicians; United States General Accounting Office (2003). See Figure A2 for details on the targeting of top deciles prescribers by Purdue Pharma.

Purdue's marketing strategy succeeded in making the use of highly addictive opioids standard practice in the treatment of moderate and chronic pain for a wide range of conditions. 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 companies—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, Janssen Exhibit S0510, State of Oklahoma v. Purdue Pharma et al.).[19]

Finally, Purdue's later strategy to promote only to top opioid prescribing physicians, those in the highest three deciles 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 the broader pain market.[20] This created a path dependency that made initial targets always relevant even when the distribution of opioids expanded.

For our identification purposes, Purdue's marketing strategy means that areas with a higher incidence of cancer at the time of the launch of OxyContin received 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, through their common physicians. In this context, 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. Alternatively, we could leverage the State Drug Utilization Data (SDUD), which reports the number of prescriptions paid by Medicaid agencies at the state level. This dataset does not allow us to exploit within-state variation. However, it is useful to document that, at the state level, there is a strong relationship between MS Contin prescription rates and mid-nineties cancer mortality prior to the launch of OxyContin (see Figure A3).[21]

[19]Duragesic is a fentanyl patch manufactured by Janssen, the pharmaceutical company of Johnson& Johnson.

[20]Other pharmaceutical companies follow this strategy. For example, Janssen referred to *high decile prescribers* as their *highmost important customers* in a Sales Force Memorandum for Duragesic in 2001.

[21]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 historical data records. A plausible alternative instrument is the number of oncologists per capita. This measure, however, is far too concentrated in the largest commuting zones.

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 painkillers to manage cancer pain (e.g., MS Contin), especially in the later stages of cancer treatment.[22] This instrument allows for the identification of the role of the pharmaceutical industry in the origin of the crisis and to estimate the causal effect of the opioid epidemic on important community outcomes.

III. Data

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.[23] 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 opioid shipments, and the average commuting zone receives 3.15 per capita per 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 A4 shows the rapid growth of prescription opioids over time and the dominant

[22] 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 (SEER) program are aggregated at the state level. Importantly, the two measures are highly correlated: the correlation coefficient is 0.88.

[23] ARCOS system data are available online from 2000 to the first half of 2022. 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 to access reports from 1997 to 1999. These data are available here.

role of oxycodone in such growth. Additional summary statistics on opioids shipment over time are presented in Table A1.

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.[24] These files record every death in the US along with the county of residence, 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.[25] 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 following definitions in CDC (2013*a*), Ruhm (2018), and Alpert et al. (2022). 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.[26] We also consider a broader measure of opioid-related deaths, in which we include deaths from heroin and synthetic opioids, e.g., fentanyl.[27] Map 3 shows this geographical variation; mortality rates vary from no deaths to as many as 106 per 100,000 residents in the most affected commuting zones.[28]

Deaths of despair. We also study how the opioid epidemic affected other 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 separately in our analysis. That is, our measure is limited to

[24] 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 across these alternative measures, see Section VI.A.

[25] 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).

[26] We follow the prescription opioids definition of CDC (2013*a*) and use identification codes X40–X44, X60–64, X85, or Y10–Y14 with contributing causes 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. We exclude deaths with contributing cause T40.4 from this definition since these deaths include synthetic opioid involvement, e.g., fentanyl (Ruhm, 2018).

[27] We use identification codes X40–X44, X60–64, X85, or Y10–Y14 with contributing causes T40.0-T40.4, 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.

[28] 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).

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).[29]

Demand for social insurance and welfare programs.[30] 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 of beneficiaries in the population at the commuting-zone level.[31] We include two measures of disability benefits recipiency, constructed as the share of the population 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.[32]

Birth outcomes and fertility. 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.[33] 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) share of low-birth-weight newborns, (ii) APGAR score of all births, (iii) APGAR score of deceased infants, and (iv) median pregnancy duration. Finally, we use

[29]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.

[30]Our choice of outcomes is driven by our priors on first-order effects on communities' well-being and by the availability of granular geographic data. Labor market outcomes and foster care placement rates are outcomes we hypothesized are relevant; however, data availability prevents us to study these topics.

[31]When information at the local level is not available, we impute the state-level share of SNAP recipients. Table A10 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.

[32]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.

[33]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.

the birth files to compute the average fertility rate at the commuting-zone level, defined as the ratio of single pregnancies to female population aged 15 to 44 years old.[34,35]

Demographic controls. 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 to construct the denominators for adult mortality rate measures, e.g., opioid and aggregate mortality. Denominators for infant mortality rate come 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 one's economic life—which often spans beyond county borders—and the access to the local market for prescription opioids.[36,37] ARCOS data are available from 1997, so analyses using this measure are restricted to a later period.[38] 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.

IV. Empirical Strategy

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 A3 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.[39] This is in line with Finkelstein et al. (2018), who estimate that areas with more physicians per

[34]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.

[35]Data for the period 1989-1994 come from the Natality Birth Files. These files provide demographic and health data for all births during the calendar year. We use these data to construct infant mortality rates, birth weight, fertility rate, and APGAR scores, though these data do not allow us to construct pregnancy duration.

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

[37]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.

[38]Table A2 presents summary statistics for the pre-Oxycontin launch period.

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

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 the opioid epidemic, we exploit rich geographical variation in the promotional efforts of prescription opioids as an exogenous source of variation in the exposure to the opioid epidemic. We start by running the following specification—the first stage relationship between prescription opioids and mid-nineties cancer mortality—over our sample of commuting zones for the period 1997-2018:

First Stage:

$$\Delta \ Presc. \ Opioids_{ct} = \alpha_1 + \phi \ CancerMR_{ct_0} + \alpha \ \Delta \ X_{ct} + \gamma_{st} + \upsilon_{ct} \ , \tag{1}$$

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}. $Presc. \ Opioids_{ct}$ 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). 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}. 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". These policy changes were quite common, for example, between 2007 and 2013, 17 states implemented some version of a PDMP (Buchmueller and Carey, 2018). Between 2001 and 2017, every US state passed a law that facilitates the widespread distribution and use of naloxone (Doleac and Mukherjee, 2019). 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. We cluster standard errors at the commuting-zone level.

We examine how changes in the supply of prescription opioids relate to the initial cancer mortality rate—our measure of the market initially targeted by pharmaceutical companies. Thus, ϕ captures the growth in the supply of prescription opioids per capita for an additional point increase in cancer mortality. For this estimation to be valid, cancer mortality at baseline should be (i) strongly correlated with the opioid supply, and (ii) uncorrelated with unobservable variables related to our outcomes. Evidence supporting

our strategy was first presented in Section II., in which we discussed Purdue Pharma's and competitors marketing strategies and the 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 its validity.

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

We start by providing graphical evidence in panel (a) of 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. 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 2 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. Across 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).[40] To put this figure in context, a change from a commuting zone in the 5th percentile of the cancer distribution to the 95th percentile explains 64% of the increase in opioids relative to the base period.

We show the strength of this relationship graphically in panel (b) of Figure 1 where we plot the first stage coefficients by year following this specification:

[40] We follow Andrews et al. (2019) recommendations and present the effective first-stage F statistic proposed by Montiel Olea and Pflueger (2013) to assess the strength of the first stage. In the rest of this paper, we refer to this as the *effective F-stat*.

First Stage - Event study:

$$\Delta \ Presc. \ Opioids_{ct} = \alpha_1 + \sum_{\tau=1998}^{2018} \phi_\tau \ CancerMR_{ct_0} \mathbf{1}(Year = \tau) + \alpha \Delta X_{ct} + \gamma_{st} + \upsilon_{ct} \ , \quad (2)$$

where ϕ_τ captures the relationship between cancer mortality and prescription opioids by year. We find that starting in 1998, the second year of the opioids data, and until 2018, the last year in our data, there is a positive and statistically significant relationship between cancer mortality rates and prescription opioids per capita. However, due to the limited data availability on the illicit opioid market, our first stage analysis underestimates the impact of the initial marketing of opioids on the overall level of both legal and illegal opioid use. Previous research has established a strong causal link between prescription opioid use and illegal opioid use (Alpert et al., 2018; Evans et al., 2019).

Our hypothesis is that the connection between pre-OxyContin cancer rates and future opioid inflows is generated by the marketing efforts from Purdue and other pharmaceutical companies. Unfortunately, most of the data that could test this hypothesis is still confidential. We perform two exercises that provide evidence in this direction, one using public data and the second, using new unsealed records we digitized. First, we examine pharmaceutical marketing in 2013–2018 using the CMS Open Payments database. These data report visits and payments from pharmaceutical manufacturers to physicians related to promoting specific drugs, including payments for meals, travel, and gifts. Panels A and B of Figure 2 show that, even 17 years after the introduction of OxyContin, the share of visits and the share of payments to promote opioids relative to all other drugs was higher in high-cancer commuting zones. Commuting zones at the top quartile of the cancer distribution in the mid-nineties, relative to commuting zones in the bottom quartile, received on average 22% more opioids-related visits, and the share of payments was 83% higher. We interpret this as a measure of persistent effect of the initial targeting of cancer areas by pharmaceutical companies.

Second, records from May 2007 to December 2018 on all sales representatives' visits to promote OxyContin in Massachusetts have been released, as part of recent litigation (Figure A6). We digitized these data for 2007 to 2011 and created aggregate measures at the county level of the number of visits per 1,000, and the number of targets–either physicians or pharmacists, per 1,000. Panels C and D of Figure 2 show scatter plots of these variables on the y-axis and mid-nineties cancer mortality on the x-axis. Both of these measures show a positive relationship between cancer mortality at the time of launch and persistent future marketing in those areas. This persistence of the initial targeting is consistent with the marketing strategy discussed in the internal documents and supports our identification strategy.

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

Variation in mid-1990s cancer mortality across locations is not random; rather, it depends on demographic, environmental, and socioeconomic variables. In Table A4 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 cross-sectional 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 four ways. First, we estimate reduced-form type regressions where we interact our instrument with year dummy variables to directly test for the presence of pre-trends, i.e., we estimate an event-study version of the reduced form relationship between the outcome variables and our measure of exposure to the epidemic. For each outcome variable we consider the following specification, which is run over a balanced panel of commuting zones for the years 1989 to 2018:

Reduced Form - Event Study:

$$\Delta\, y_{ct} = \alpha_1 + \sum_{\tau=1989}^{2018} \phi_\tau\, CancerMR_{ct_0} \mathbf{1}(Year = \tau) + \alpha\, \Delta\, X_{ct} + \gamma_{st} + \upsilon_{ct}\ , \qquad (3)$$

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 higher and lower cancer mortality areas followed similar trends before OxyContin was introduced to the market in 1996. This research design allows us to control for state-specific trends and state-level policy changes which were common during this period that directly affected the supply of opioids—e.g., the implementation of PDMP, the regulation of "pill mill" clinics, and the availability of naloxone—and also the evolution of our outcome variables—e.g., welfare reform and child support policies.

Figures 3, 4, 5, and 6 show the results of this estimation on our main outcomes of interest.[41] We find that areas with higher cancer mortality in the mid-nineties were not

[41] Figures 8 and A7 complement this analysis.

on a differential trend along: opioid-related mortality, despair mortality, infant mortality, birth weight, fertility, or share of population using SNAP.[42] 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, and fertility.

Second, there is no evidence of a systemic relationship between lagged cancer mortality and past or future overall health trends and despair. We show that young adults entirely drive the estimated excess opioid mortality, and for adults over 55 years old opioid mortality does not increase (see Figure 7). This supports the argument that our results are not driven by underlying health conditions since the population over 55 would be 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 opioids in those markets. We also report event study estimates for suicide mortality and overall 75+ mortality —excluding cancer (see Figure 8). We find no evidence of pre-trends for suicide and overall mortality prior to or after the introduction of OxyContin. Finally, in Figure A8 we document that high cancer places were not on a differential trend along health behaviors such as smoking.

Third, we perform an out-of-sample dynamic reduced-form analysis to test if lagged cancer mortality predicts future opioid mortality before the introduction of OxyContin. That is, we run Equation 3 over a sample of commuting zones for the years 1982 to 1995 and estimate if the average cancer mortality rate in 1980 and 1981 predicts prescription and all opioids mortality in the next twelve years. We present the results of this analysis in Figure 9. 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 and there is no evidence of a pattern. In Appendix Figures A10 and A11, we perform a similar exercise for deaths of despair, SNAP, infant mortality rate, fertility rate, and the share of employment in the manufacturing and mining industry.[43] We find no evidence of a differential trends in these variables.

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 A5 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 presents this analysis for

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

[43]We perform this exercise for the period 1989-1995 due to data availability constraints.

our outcome variables, including SSI and SSDI, we do not find any relationship.

Taken together these results suggest that in the absence of OxyContin's 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 3 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.[44] 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 3.[45] At its peak in 2010, an increase from the 5th to the 95th percentile of mid-nineties cancer mortality increased prescription opioids deaths by 55% relative to its mean.

In Appendix D we estimate instrumental variables regressions, which allow us to scale our reduced-form results by the increase in prescription opioids. The instrumental variable estimates presented in column 3 of Table D1 implies that when doses per capita increase by one standard deviation, mortality from prescription opioids increases by 73% relative to the mean.[46]

Heterogeneous effects. The excess opioid-related mortality induced by the marketing of prescription opioids is by and large coming from young and middle-aged adults and at the begging of the epidemic, is driven mainly by white adults. In Figure 7, we present the interactive-reduced-form analysis for three age groups and in Figure A12 we split the data by race and gender. The analysis by age shows (i) no evidence of pre-trends on opioid mortality for any of these groups, and (ii) opioid mortality increases that are concentrated among individuals aged less than 55 years old. Furthermore, different from the trends in prescription opioids mortality, for the case of any opioid mortality—which adds deaths from heroin and fentanyl—the effects are persistent even in the last years of our sample, for those under 55. Additionally, we find the epidemic affected men and women similarly. When splitting the data by race, we find that estimates for whites are positive and statistically significant starting soon after the launch of OxyContin.

[44] In Appendix Figure A9 we present the analogous analysis, but we split the data based on 8 octiles of cancer mortality and observe the same pattern.

[45] In Appendix Figure 4 we replicate this analysis for any opioid mortality and document similar patterns.

[46] A change 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%.

For non-whites it takes around a decade for estimates to be positive and statistically significant.

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 overall mortality, the demand for social insurance, and welfare programs. We then turn to the intergenerational effects of the epidemic.

Non-opioid mortality measures. We ask whether the dramatic increase in opioid supply affected all-cause mortality, excluding cancer deaths. These results are presented in Figure A13. 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 effective pain medication could have improved the quality of life of individuals with high incidence of pain and low risks of addiction, and those potential improvements could translate into health indicators. To asses if there is any indication of such improvements we estimate our reduced-form exercise on mortality for those 75 and older, but find no evidence of any effects in mortality (Figure 8 Panel b).

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 the exposure to the opioid epidemic on *non-opioid-related* deaths of despair. In Figure 8 we show that there is only a weak link between the opioid epidemic and deaths of despair. We do not find any effect on suicides and only a small increase in alcohol-related deaths during the last stages of the opioid epidemic, see Table D2. 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.

Beneficiaries of social insurance and welfare programs. Addiction to and misuse of prescription opioids could deteriorate one's health, reduce productive capacity, and put one at risk of permanently reducing ones attachment to the economy. We document a tight link between the opioid epidemic and an increase in SNAP and disability-programs beneficiaries. Figures 5 and A14 show the dynamic evolution of these effects. These results point to a substantial worsening of economic conditions. These effects are particularly strong during the third wave of the epidemic, when the incidence of illicit drug use, such as of heroin and fentanyl, increased.

Our estimates suggest that, at its peak in 2017, a change from the 5th to the 95th percentile in mid-nineties cancer mortality distribution caused a 32% increase in the

share of the population enrolled in SNAP. This effect is comparable to an increase of 2 percentage points in the unemployment rate (Ganong and Liebman, 2018). Similarly, a change from the 5th to the 95th percentile in mid-nineties cancer mortality caused a 8% increase in the share of the population receiving SSI and a 35% increase in the share receiving SSDI relative to its means.

Fertility and birth outcomes. An important feature of the crisis is that it has primarily impacted a population in early adulthood through mid-life with potential intergenerational costs. 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 (Patrick et al., 2015), raise concerns about the risks and consequences of opioid misuse in this population.[47] 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. Additionally, opioid use early in pregnancy, often before women know they are pregnant, can increase the risk for some birth defects and other poor pregnancy outcomes, such as preterm birth or low birth weight (Ailes et al., 2015).

We find substantial increases in non-marital fertility rates as a result of exposure to the opioid epidemic. Panel a of Figure 6 shows the continue increase in fertility. At its peak in 2017, an increase from the 5th to the 95th percentile of mid-nineties cancer mortality increases non-marital fertility by 15%.[48] Figure A15 shows that marital fertility did not change change as result of the opioid epidemic. This is in line with cross-sectional estimates of the higher risk of unintended pregnancies for women with opioid use disorder (Stone et al., 2020), and with work that documents access barriers to contraceptives for women with substance use disorders (Rinehart et al., 2021).

Regarding birth outcomes, we do not find any increase in infant mortality rate (Figure 6), but we do find suggestive evidence of declines in health at birth measured as the share of low-weight births and a decline in APGAR scores (Figure A7). A 5th-to-95th-percentile increase in mid-nineties cancer mortality increases the share of newborns with low birth weight by 5% relative to its mean. We document a deterioration in APGAR scores by around 1% relative to its mean value and an increase in the APGAR score of infants who died in the first year, which means that healthier infants died. Additionally, we find declines in pregnancy duration. This is particularly relevant in light of evidence on the importance of health at birth for future health, schooling, and earnings (Behrman and Rosenzweig, 2004).

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

[48] We compute non-marital fertility as the ratio between births to unmarried mothers and the female population aged 15 to 44 years old. We do this, as data on the population of unmarried females does not exist at the year–commuting-zone level.

In summary, our results suggest that the opioid epidemic lead to important increases in fertility, driven by unmarried mothers. While not affecting directly the infant mortality rate, the epidemic worsened birth outcomes through reductions in 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. (2022) 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.[49] 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.

VI. Robustness Checks

In this section, we explore alternative explanations for our findings and test the robustness of our results.

A. First Stage and Reduced Form Specification Checks

Additional demographic controls. A potential concern with using mid-nineties cancer mortality as a proxy for the exposure to the opioid epidemic is that it 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. However, our instrument is expressed in levels, so some of this variation may still be important. We directly test this by including the share of the population over 65, the size of the population over 65, and total population as additional control variables. Table A6 shows the results of this exercise. We find that the first stage regression is as strong as in our baseline regression. Figure A16 shows estimates of the dynamic first stage and reduced form regressions when we add a set of year-dummy variables interacted with the share of the Hispanic population and the share of the population over 65 years old measured in 1994-1996. This specification flexibly controls for the evolution of the share of the Hispanic and over 65-year-old population, which are the main predictors of cancer mortality in 1996. Estimates of the first stage and reduced form coefficients are similar across specifications, and the main conclusions remain unchanged.

[49] 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.

Alternative measures of our instrument. Additionally, we test the robustness of the first stage to alternative choices of instruments. Column 1 of Table 3, replicates the first stage with age-adjusted cancer mortality, and Panel (a) of Figure A17 presents the corresponding dynamic first stage estimates. We find similar and strong first-stage estimates when using age-adjusted mid-nineties cancer mortality. We also test whether the estimated first stage is sensitive to the choice of a specific year in our baseline period. Columns two to four in Table 3 show there is a strong first-stage for 1994, 1995, and 1996 cancer mortality, and Panel (a) of Figure A18 presents the dynamic first-stage using cancer mortality in 1994 as the instrument. Next, in column five and Panel (b) of Figure A17, we add population weights and find similar results. As an additional robustness check, in Panel b of Table 3, we construct a measure of cancer mortality that excludes 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.

We also examine how these alternative versions of our instrument impact the estimates of the reduced form coefficients. Panels (c) and (d) of Figure A17 present estimates of the effects on prescription opioid mortality using age-adjusted cancer mortality and weighting our baseline specification, respectively. Figure A18 uses cancer mortality in 1994 as the instrument and shows the dynamic reduced form for prescription opioids mortality. In summary, this battery of tests shows the robustness of the reduce-form effects and the lack of pre-trends or anticipatory effects.

Alternative measures of prescription opioids. Even though Purdue Pharma was the pioneer in the use of opioids in the non-cancer pain market with OxyContin, many pharmaceutical companies—Janssen, Endo, Cephalon-Teva, Actavis, Insys, and Mallinckrodt—promoted their prescription opioids beyond the cancer market following Purdue's leadership. To assess whether the positive relationship that we observe between the total level of prescription opioids and mid-nineties cancer mortality is present across different opioids' categories, in Panel C of Table 3, we split opioids between oxycodone—which captures the supply of Oxycontin—and the rest of opioids. We find there is a strong positive first stage for both categories.

Mechanical Effects. A potential threat to our hypothesis is that commuting zones with higher cancer mortality would see a larger uptake of opioids from innovations in the pain medication market, even in the absence of marketing efforts. Several facts suggest this is not the mechanism at play. First, cancer patients had access to equally potent opioids before the launch of OxyContin, as this was standard pain management practice. For these patients, the introduction of OxyContin represented a switch from MS Contin—the gold standard to treat cancer pain—to OxyContin. Second, our results suggest there is

no evidence of misuse of opioids in the population most affected by cancer, as we find no increases in deaths from prescriptions and non-prescription opioids for those over 55 years of age (Figure 7).

Additional sample restrictions. We test whether the positive relationship in our first stage is driven by a state or a group of states. Figure A19 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 positive 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 given state. Furthermore, the first stage is stronger in the five triplicate states defined in Alpert et al. (2022), which would be consistent with a story in which pharmaceutical companies need to be more strategic in promoting opioids in places where they face additional barriers.[50]

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 4 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.[51] 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 Mortality and Opioid Supply

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 Figure A20 and Table A7. This measure has the advantage that comparisons across years are less affected by changes

[50] The first stage coefficient is 1.542 in the five triplicate states defined in Alpert et al. (2022), and 0.917 in the other states. This difference is not statistically different and the p-value of such test is 0.203.

[51] 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.

in the ICD classification, but this comes at the cost of including a broader set of drugs as the cause of deaths.[52] Exploiting this measure, we arrive at the same conclusions. As an additional check, we use data only on Oxycodone as an alternative measure of opioid supply. We find a positive relationship between cancer mortality rates and this measure of opioid supply. In Table A8, columns (2) and (3) we estimate that an additional dose of oxycodone per capita caused an increase in prescription opioid mortality and in all opioid mortality.

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 A9 we reproduce our instrumental variable 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. SNAP benefit recipiency rates at the commuting-zone level required imputations for some commuting zones with no available data at the local level. Table A10 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 A11 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 impact on communities is a function of the importance of the manufacturing industries for local employment, especially 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 larger 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

[52] 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.

alternative measures of exposure to PNTR and then estimate our first-stage and reduced-form models controlling for these exposure measures (Pierce and Schott, 2020 and Autor and Dorn, 2013). Table A12 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 A21 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.

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 A12). More broadly, in the last three columns of Table A12 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 and effects of the opioid epidemic, one of the most tragic episodes in recent history. To do so, we uncover novel 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, a deterioration in adult wellbeing measured by the demand for disability, and SNAP and has inter-generational effects through its impacts on fertility and birth-outcomes. The breadth and timing of these effects show the far-reaching ripples of the epidemic. Although, according to the CDC, opioid prescriptions reached their peak in 2012, its effects persist. Mortality from prescription opioids rose for another five years to reach its maximum in 2017, and deaths involving any opioids were at an all-time high in 2021. Furthermore, the individual and community-level *paths* from opioid misuse to addiction, to poverty and disability, to changes in family formation and mortality are complex, and beyond the scope of this paper. In this paper, we sought to provide a comprehensive picture of the effects of the opioid epidemic. However, data access limitations have prevented us from speaking about important topics, such as the effects on children's well-being, foster care referrals, and healthcare use. 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 opioid 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 essential, but it falls short for the needs of the affected population. Increasing access to rehabilitation treatments and programs aimed at reincorporating parents and workers into their lives should be 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 of addictive drugs. Although marketing has expanded over the 25 years since the introduction of OxyContin, regulatory oversight remains relatively limited.[53] Some regulatory initiatives constitute small steps in the right direction, however, most of these initiatives are concerned with the rising costs of prescription drugs and not with the risks of abuse and addiction. More can be done to restrict the pharmaceutical promotion that carries this risk.

[53]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).

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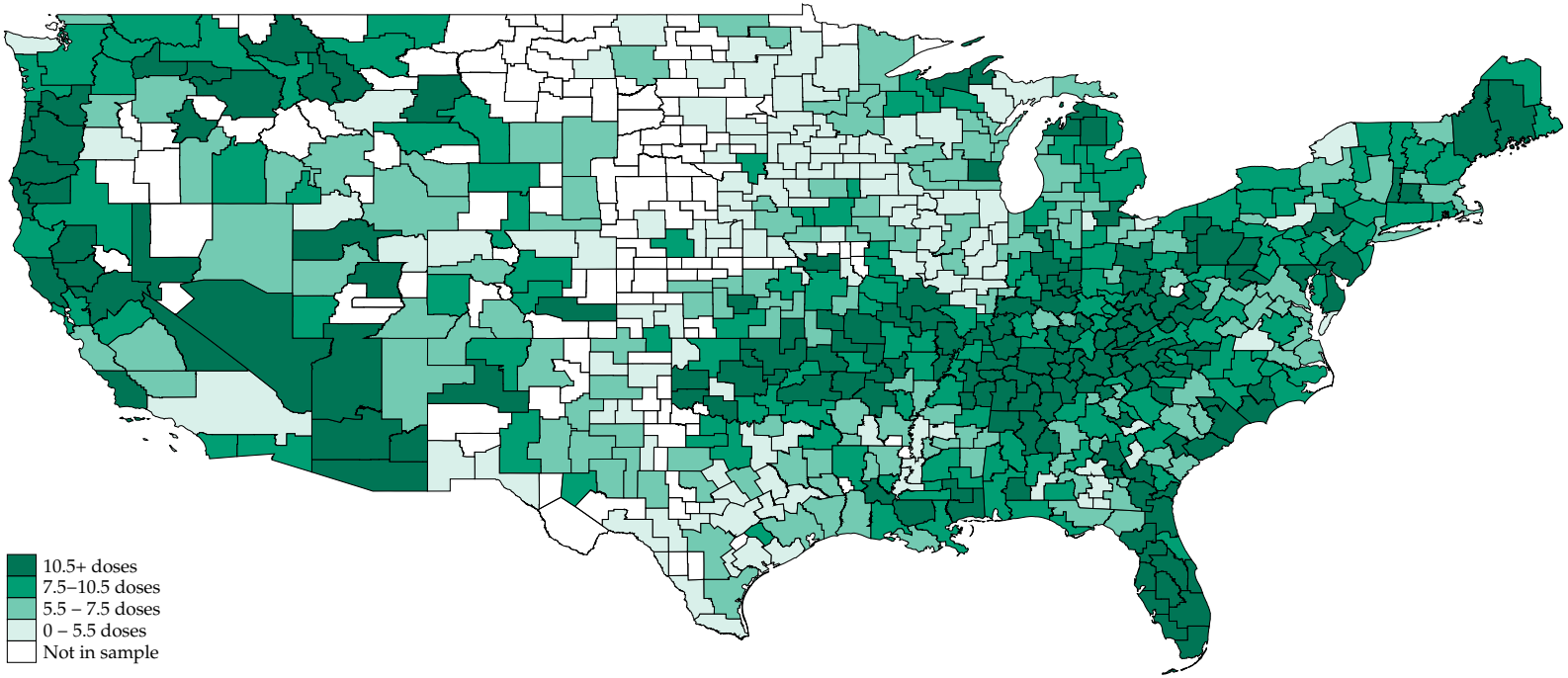
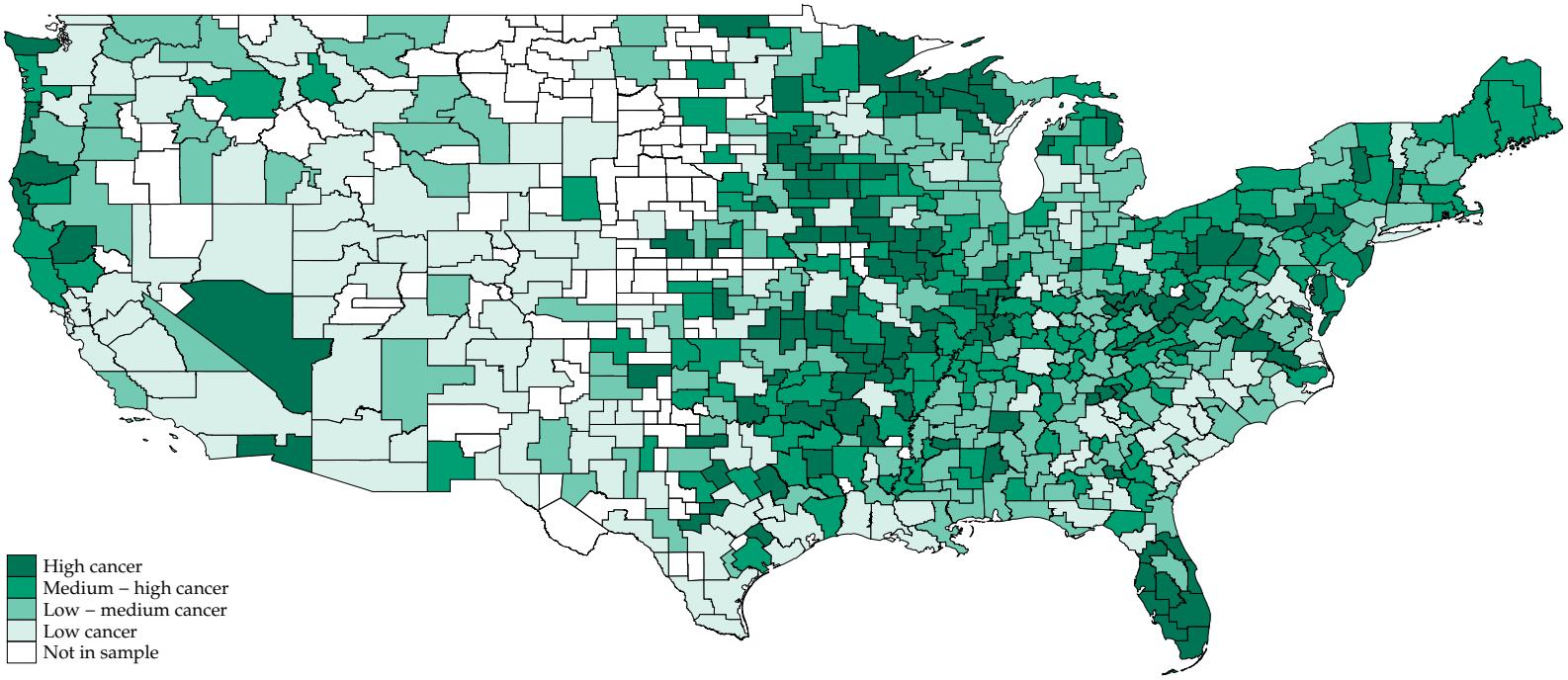
VIII. Maps and Figures

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



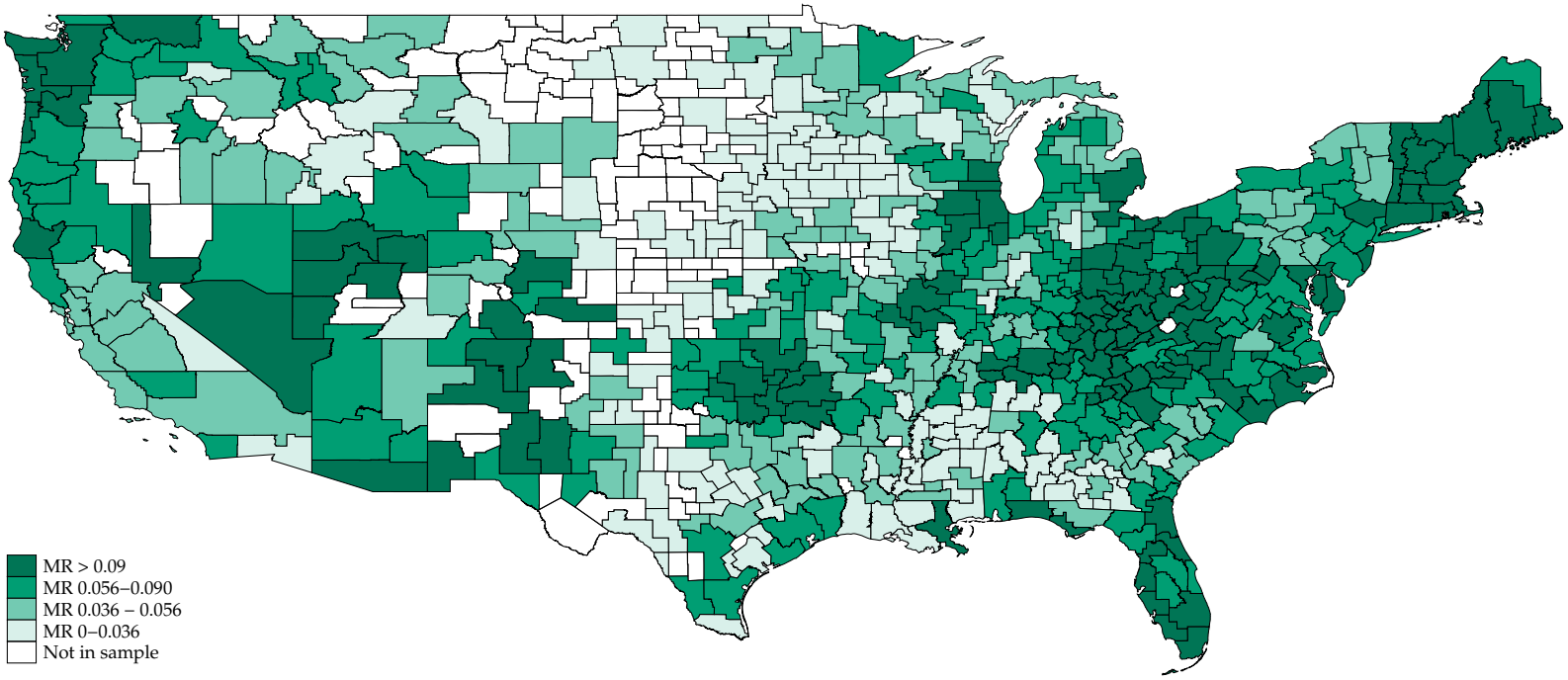
Notes: This map shows the distribution of prescription opioids at the commuting zone level in 2010, the year when the distribution of prescription opioids peaked as shown in Figure 1. Lighter shades indicate commuting zones with a lower prescription-opioid supply and darker shades indicate commuting 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.



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.

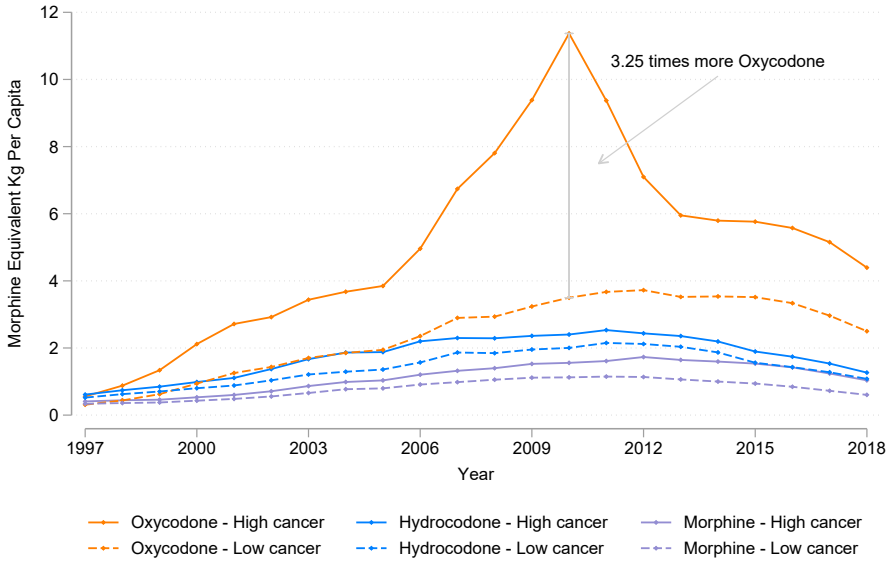
Map 3: Prescriptions Opioid Mortality Rate 1999 - 2018



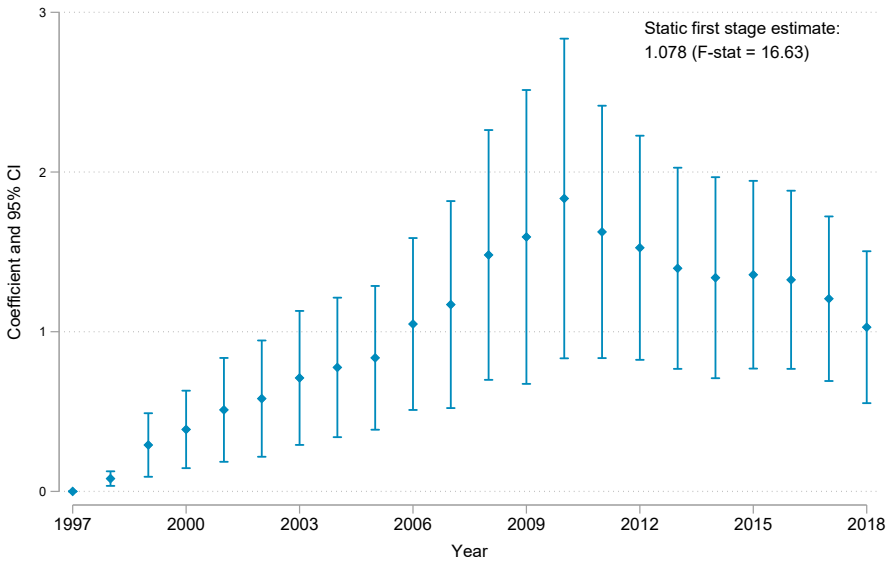
Notes: This map shows the distribution of prescription opioid mortality at the commuting zone level for the period 1999 - 2018. Lighter shades indicate commuting zones with lower opioid mortality, while darker shades indicate commuting zones with higher opioid mortality. Each group corresponds to one 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 Mid-nineties Cancer Prevalence

(a) Trends in High versus Low Cancer Mortality CZs

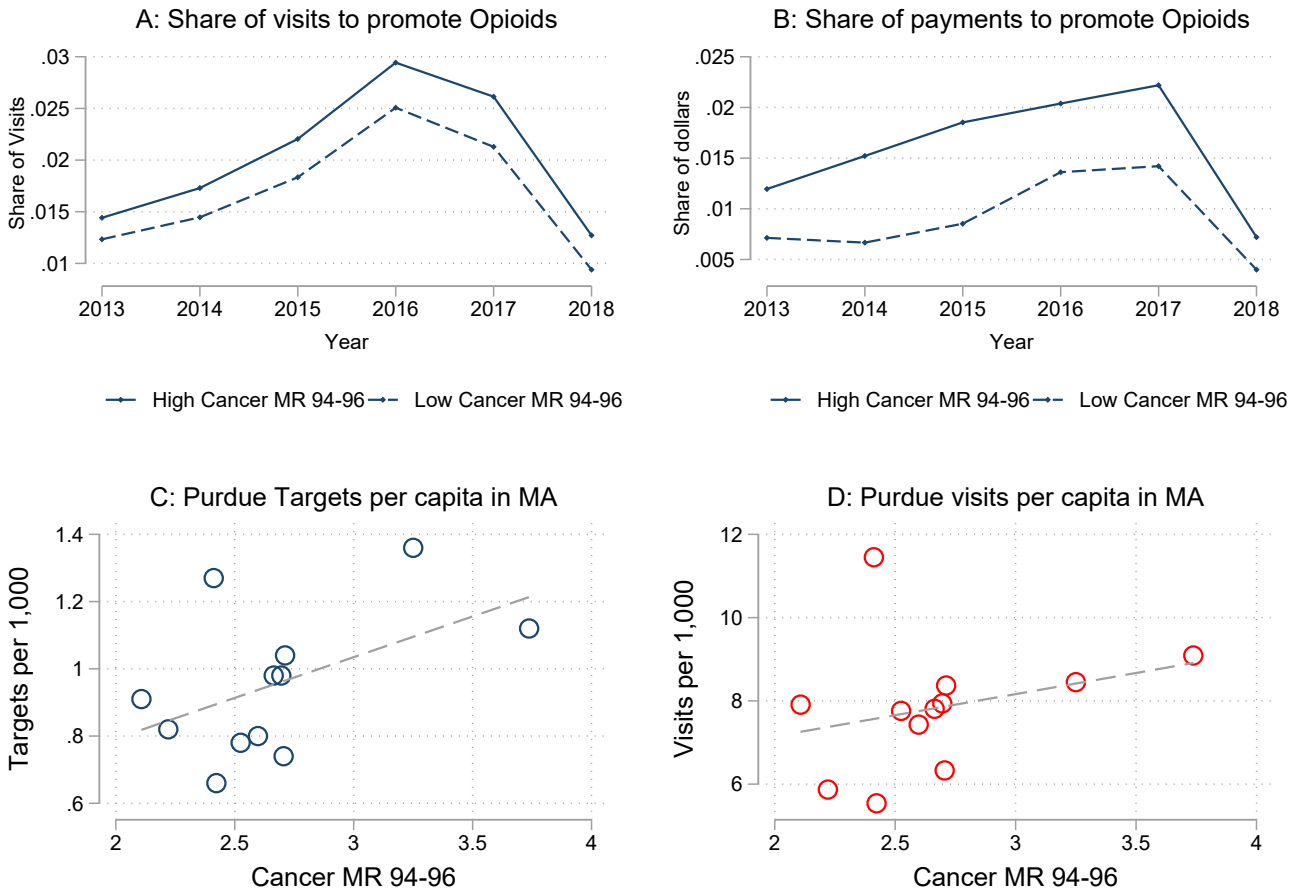


(b) Dynamic First Stage



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 IV.A. and in Section VI.

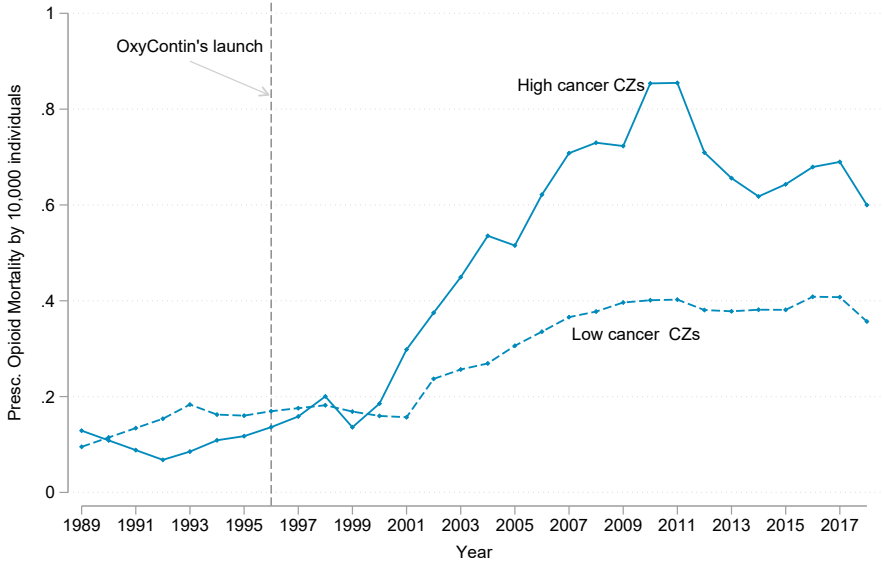
Figure 2: Opioids Marketing and Mid-nineties Cancer Mortality



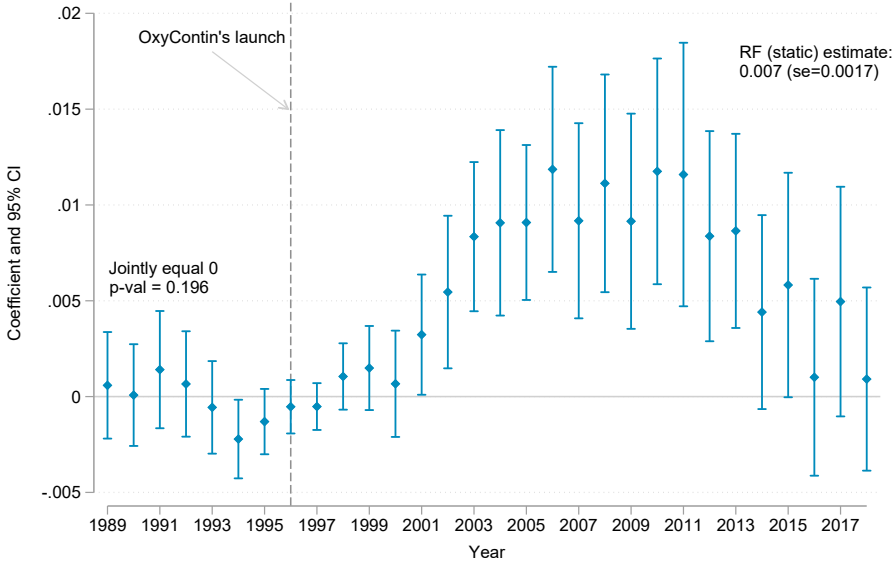
Notes: Panels A and B use data from the CMS Open Payments. High cancer corresponds to the top quartile of cancer incidence in 1994-1996, and low cancer to the bottom quartile. Panels C and D use digitized data from "Exhibit 1 - Sales Visits By Purdue In Massachusetts. Commonwealth of Massachusetts v. Purdue Pharma c.a. No. 1884-cv-01808"(Figure A6) to construct county-level averages. This figure is referenced in Section IV.A.

Figure 3: Effects of Mid-nineties Cancer-market Targeting on Prescription Opioid Mortality

(a) High versus Low Cancer Mortality CZs



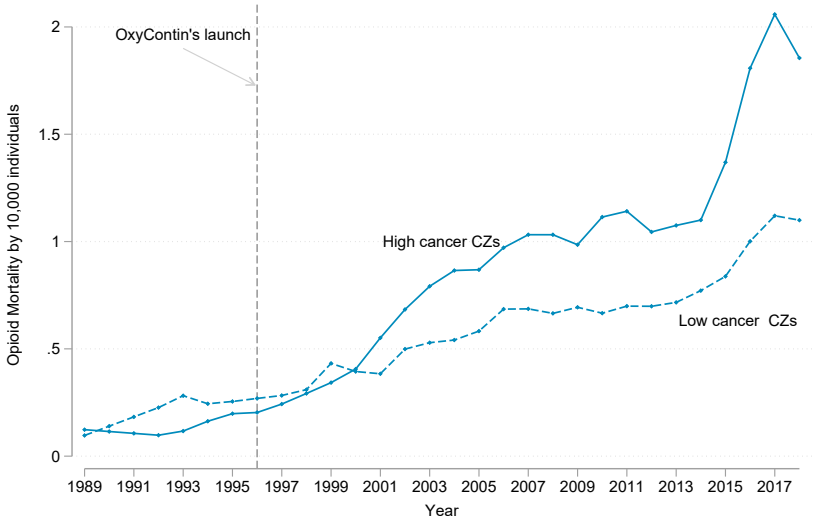
(b) Reduced Form - Event Study Approach



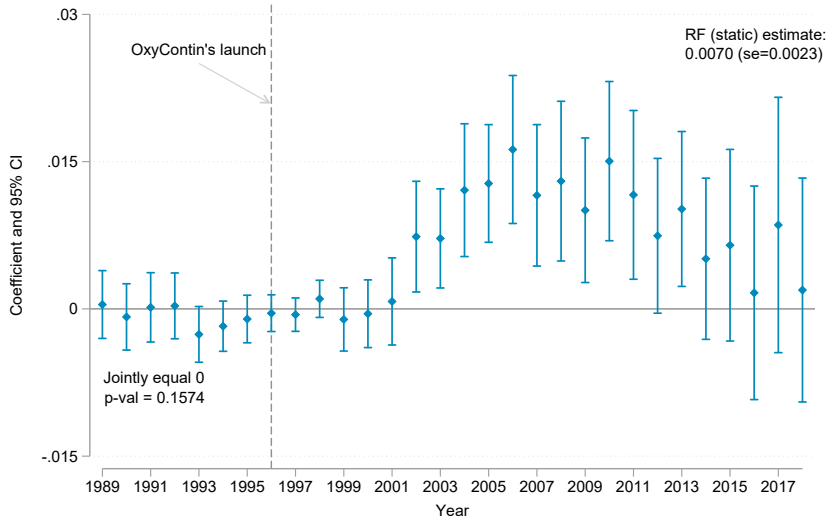
Notes: This figure shows the effects of the increase in prescription opioid supply in prescription opioid mortality. Panel (a) shows the raw data, early in the 2000s, a wedge starts to appear between high- and low-cancer-incidence groups, and by 2018 prescription opioid mortality in high-cancer areas 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 4: Effects of Mid-nineties Cancer-market Targeting on All-Opioid Opioid Mortality

(a) High versus Low Cancer Mortality CZs

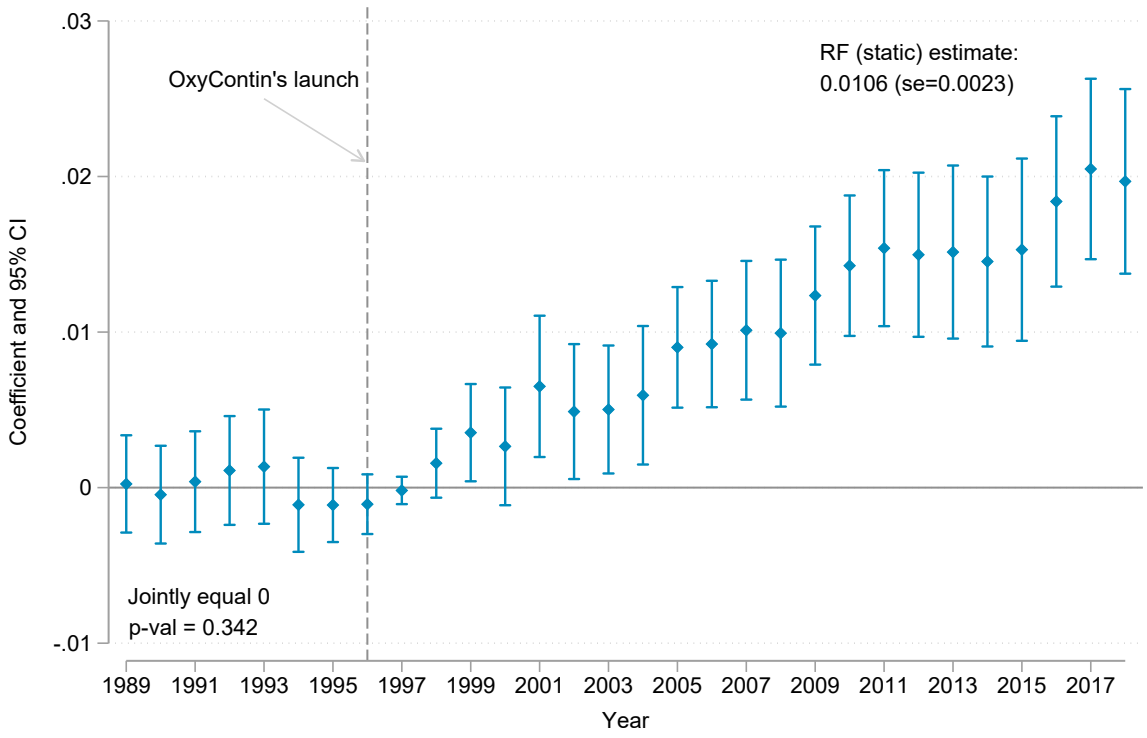


(b) Reduced Form - Event Study Approach



Notes: This figure shows the effects of the increase in prescription opioid supply in 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.

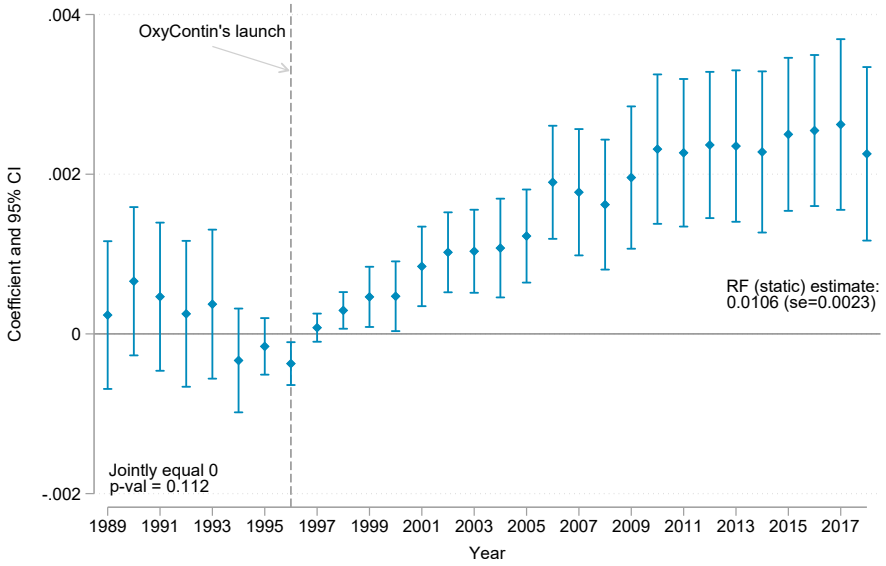
Figure 5: Effects of Mid-nineties Cancer-market Targeting on the Sh. of SNAP Recipients



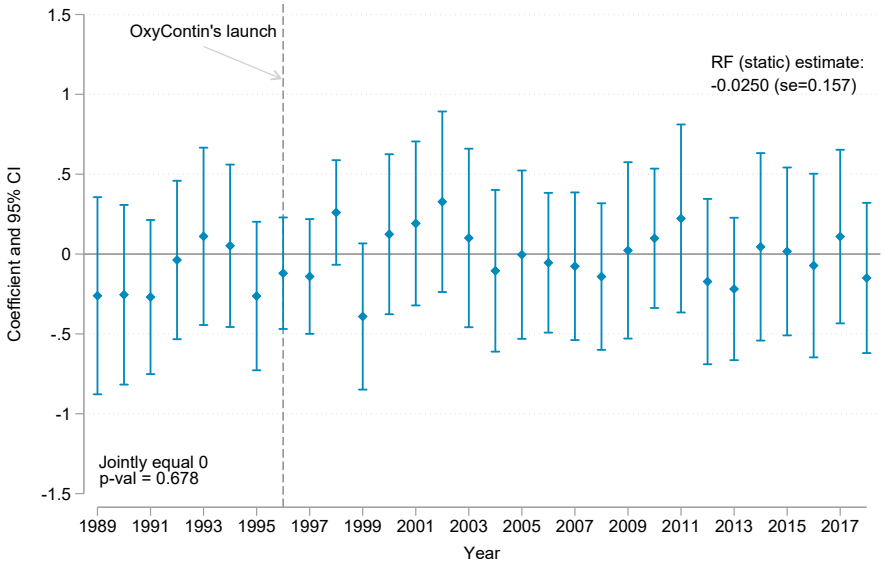
Notes: This figure shows the effects of the increase in prescription opioid supply on SNAP recipients per capita. We present the results of a dynamic reduced-form estimation were we regress SNAP claims per capita on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. 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 6: Effects of Mid-nineties Cancer-market Targeting on Fertility Rates and Birth Outcomes

(a) Non-marital Fertility Rate



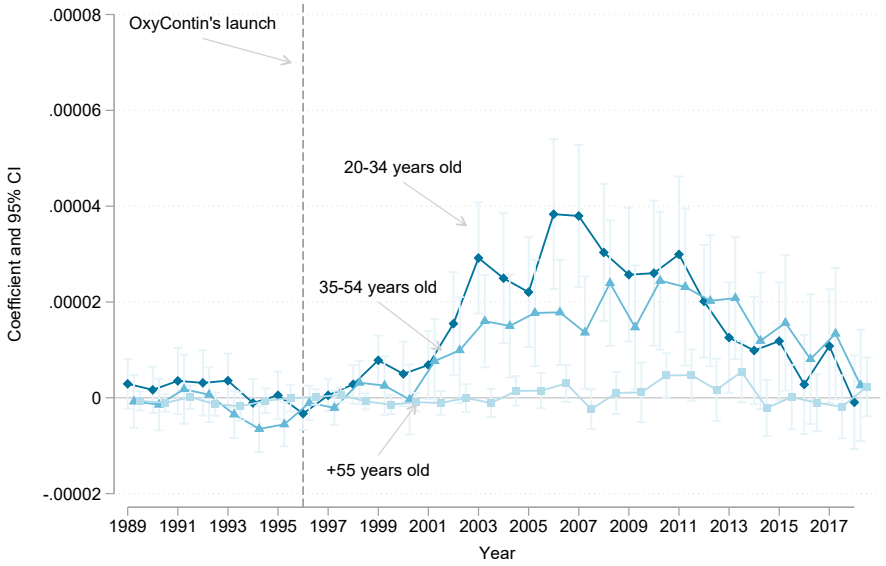
(b) Infant Mortality Rate



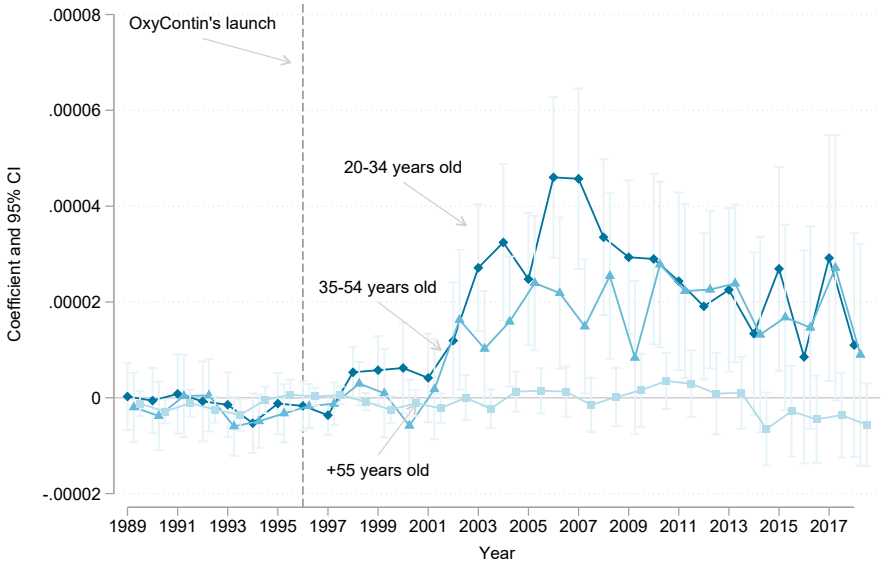
Notes: This figure shows the effects of the increase in prescription opioid supply in the fertility rate of unmarried women (panel a) and in infant mortality rate (panel b). We present the results of a dynamic reduced-form estimation were we regress these outcomes on a set of year-dummy variables interacted 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 fertility 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 7: Effects of Mid-nineties Cancer-market Targeting on Opioid Mortality by Age

(a) Prescription Opioids



(b) Any Opioids

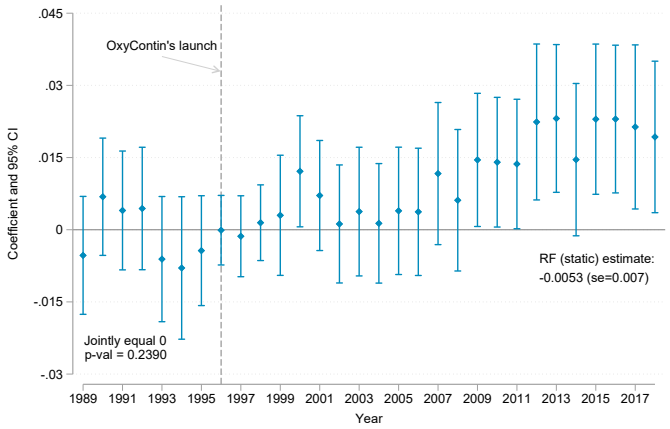


Notes: This figure shows the effects of the increase in prescription opioid supply in opioid related mortality by age group. We present the results of a dynamic reduced-form estimation were we regress these outcomes on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. These coefficients corresponds to the estimate of ϕ_t in Equation 3. This figure is referenced in Section IV.B., and in Section V.A.

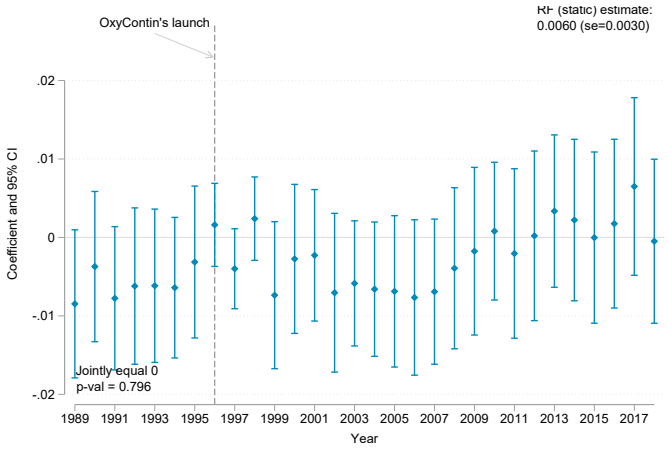
Figure 8: Trends on Overall Health and Despair Mortality

(a) Non-cancer Mortality. Adults +75 Years Old.

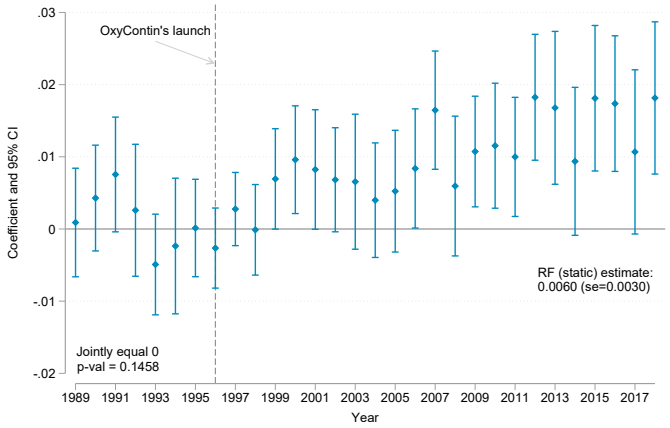
(b) Deaths of Despair (excluding opioids)



(c) Suicide Mortality Rate



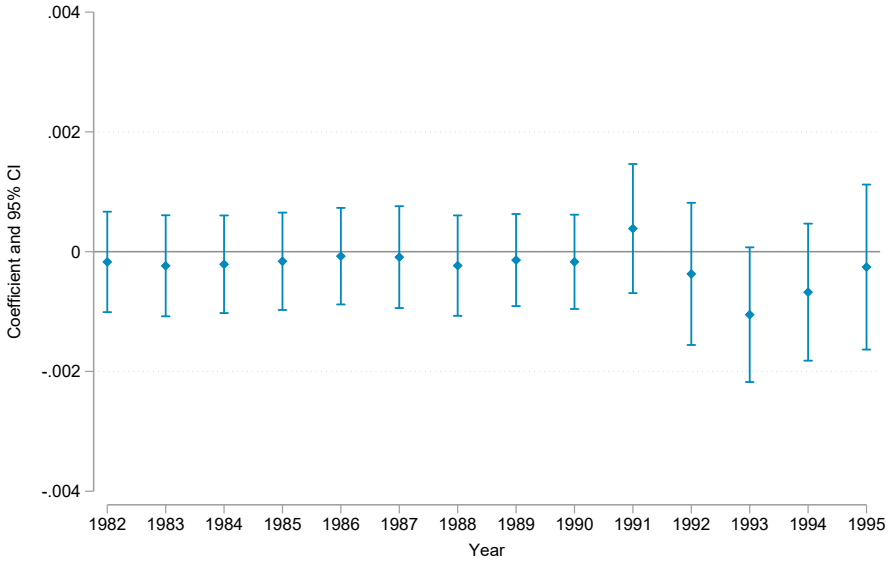
(d) Alcohol-related Deaths



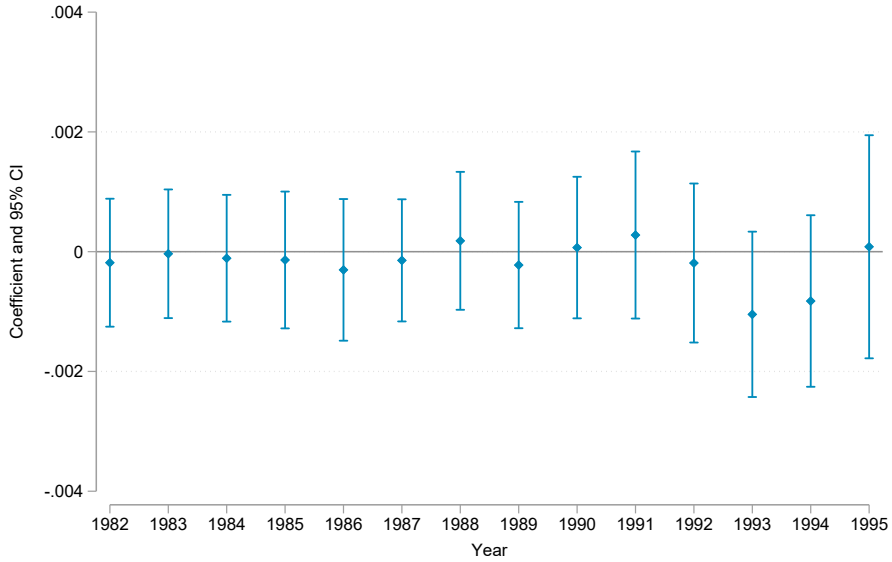
Notes: This figure shows the dynamic reduced-form relationship between mortality of 75-years-old and older adults (panel a) and despair mortality measures (panels b to d) and our instrument. We regress these outcomes on a set of year-dummy variables interacted with cancer mortality in 1994-1996. We test for the presence a relationship between our outcomes and mid-nineties cancer mortality before the introduction of OxyContin and 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 Sections IV.B. and V.B.

Figure 9: Robustness Check: Dynamic Reduced Form for Out-of-sample Opioid-Mortality

(a) Drug Induced 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. This figure is referenced in Section IV.B.

IX. Tables

Table 1: Summary Statistics for 1999-2018

	Mean	Median	SD	Min	Max	Obs.
	(1)	(2)	(3)	(4)	(5)	(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 Fertility 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 fertility 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: 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 in long changes 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 explained 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, relative to change in our period. $t-stat$ 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 Montiel 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 3: First Stage Robustness Check

Panel A. Alternative choices of instruments					
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	590	590	590	590
Adj. R^2	0.553	0.565	0.557	0.551	0.553

Panel B. Alternative choices of instruments					
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

Panel C. Alternative measures of prescription opioids supply			
Dependent variable:	Oxycodone pc	Non-oxycodone prescription opioids	
	(1)	(2)	
Cancer MR	0.605***	0.473***	
	[0.186]	[0.107]	
Mean cancer MR	2.5312	2.5312	
Instrument version:	Baseline	Baseline	
Observations	11,800	11,800	
Clusters	590	590	
Adj. R^2	0.526	0.594	

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.

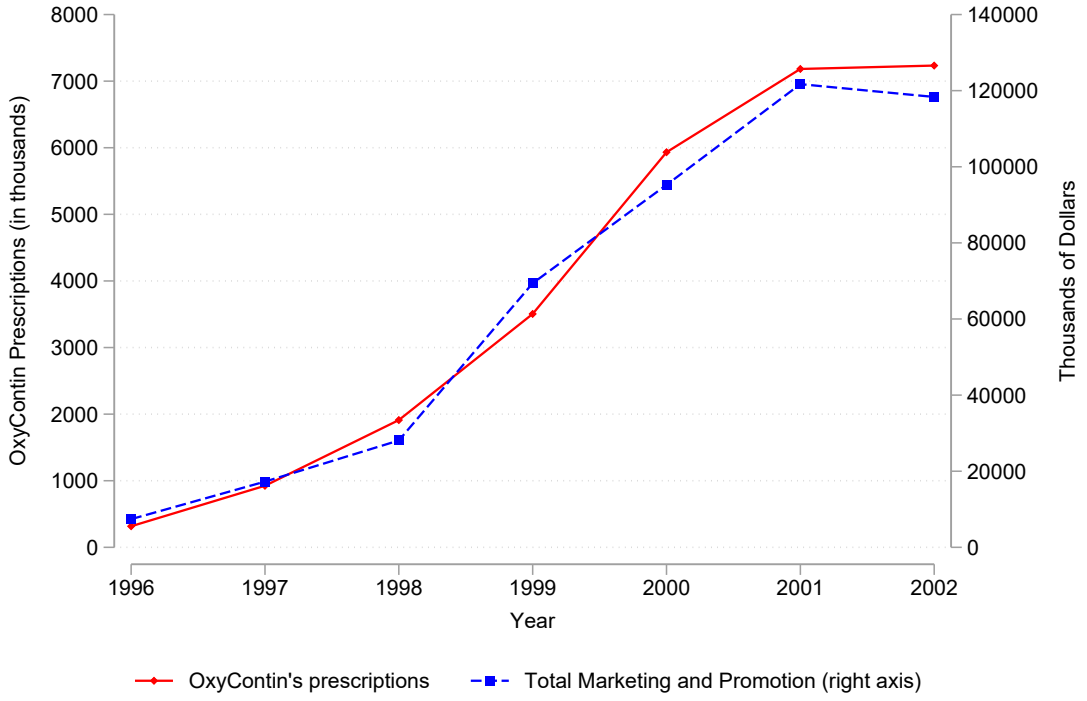
Table 4: Placebo Check - Alternative Measures of Mortality

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 measures of exposure to the opioid epidemic. 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.

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

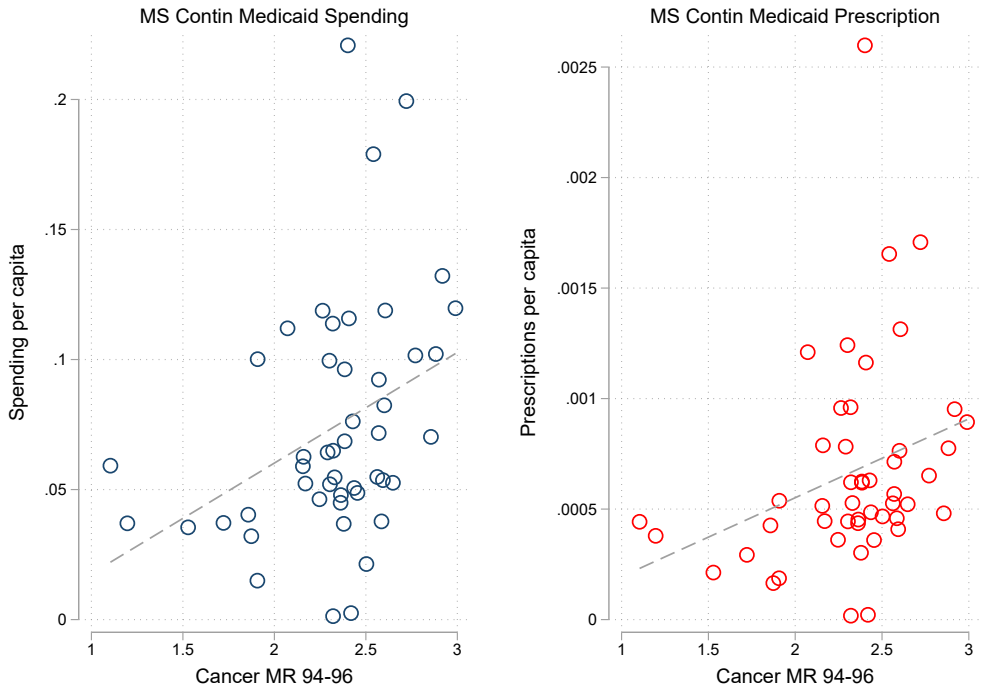
C. Target Audiences

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

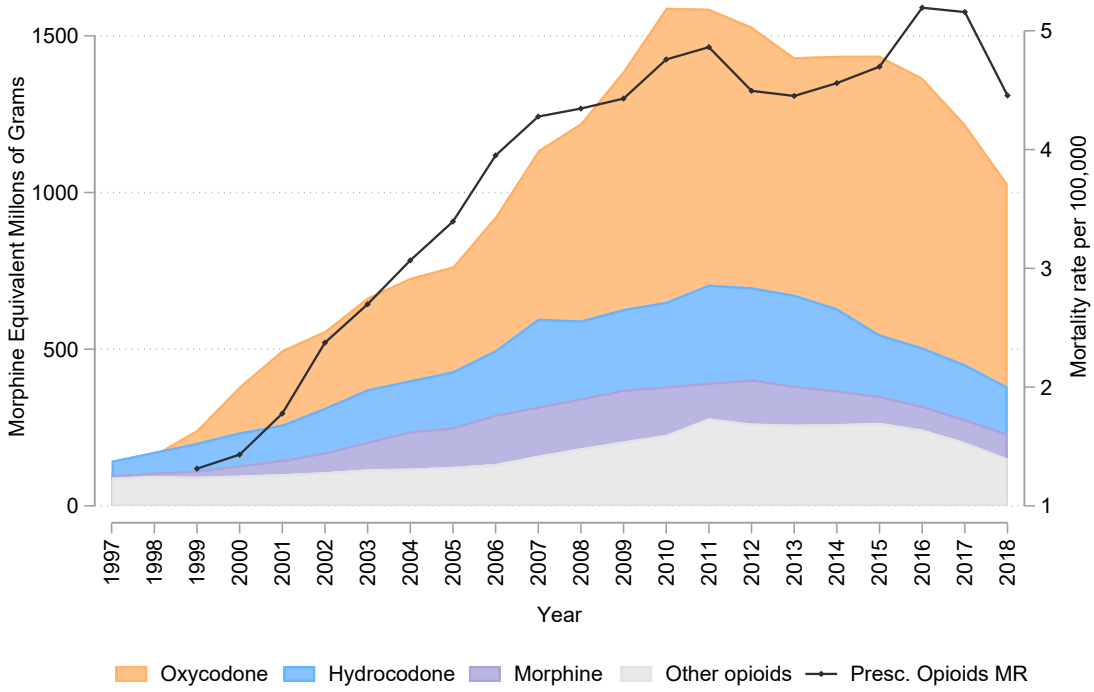
Notes: This figure is an extract of Purdue Pharma marketing plan. It shows that Purdue marketing targeted top opioid prescribers. Purdue Pharma Budget Plan 1997, p.25. This figure is referenced in Section II.

Figure A3: Mid-nineties Cancer Mortality Rate and 1994 MS Contin prescriptions



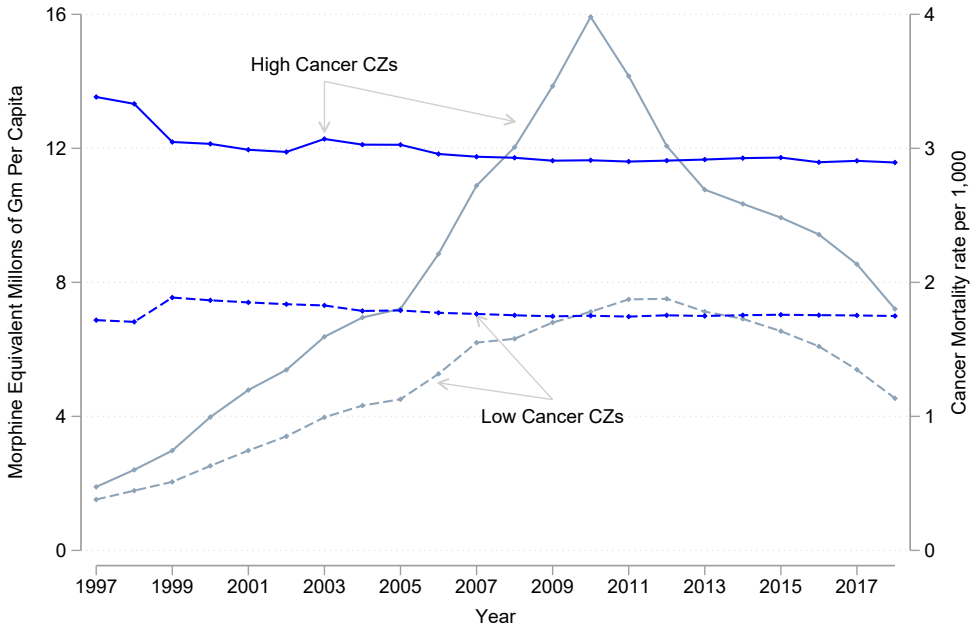
Notes: This figure shows the relationship between MS Contin prescription rates prior to the launch of OxyContin and mid-nineties cancer mortality. Source: CMS- Medicaid State Drug Utilization. This figure is referenced in Section II.

Figure A4: 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 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: Extract Exhibit 1 - Sales Visits By Purdue In Massachusetts

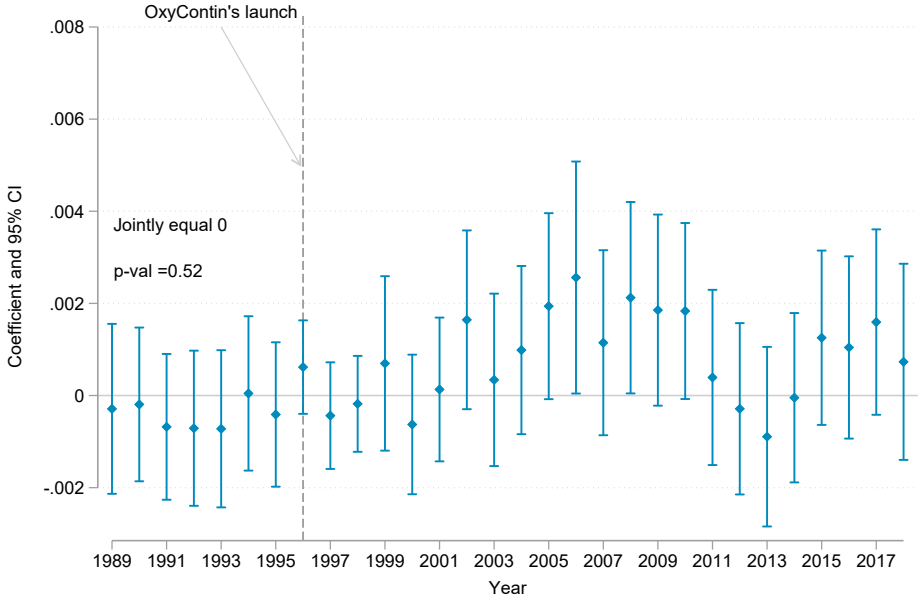
Commonwealth of Massachusetts v. Purdue Pharma et al.
Exhibit 1 - Sales Visits By Purdue In Massachusetts

Date	Purdue Sales Rep	Target	Address	City
5/16/2007	Raczkowski, Paula J	Belezos, Elias	164 South Street Harrington Hospital Medical Arts Bld	Southbridge
5/16/2007	Raczkowski, Paula J	Jeznach, Gary	118 Main St Rte 131	Sturbridge
5/16/2007	Raczkowski, Paula J	Welch, Heidi	118 Main Street	Sturbridge
5/16/2007	Raczkowski, Paula J	Keaney, Stephanie	100 South Street Medical Arts Bldg Suite#201	Southbridge
5/16/2007	Raczkowski, Paula J	Kereshi, Stjepan	100 South St Harrington Hospital	Southbridge
5/16/2007	Raczkowski, Paula J	Litani, Vladas	100 South St Harrington Mem Hos	Southbridge
5/16/2007	Raczkowski, Paula J	CVS Pharmacy Southbridge	380 Main St	Southbridge
5/16/2007	Mulcahy, Maurice	Boyd, Kenneth	23 Whites Path	South Yarmouth
5/16/2007	Mulcahy, Maurice	Hartley, Marie	23 Whites Path	South Yarmouth
5/16/2007	Mulcahy, Maurice	Terrill, Donna	269 Chatham Rd	Harwich
5/16/2007	Mulcahy, Maurice	Fair, Dianne	269 Chatham Rd	Harwich
5/16/2007	Mulcahy, Maurice	CVS Patriot Square-So. Dennis	Paqtriot Square/Route 134	S Dennis
5/16/2007	Mulcahy, Maurice	CVS Rt 28 S.Yarm.	976 Route 28 Yarmouth Shopping Plaza	S Yarmouth
5/16/2007	Arias, Alexander	Huang, Wynne	1 Roosevelt	Peabody
5/16/2007	Arias, Alexander	CVS - Main St [Woburn]	415 Main St	Woburn
5/16/2007	Ritter, Andrew	Kehlman, Glenn	637 Washington St	Brookline

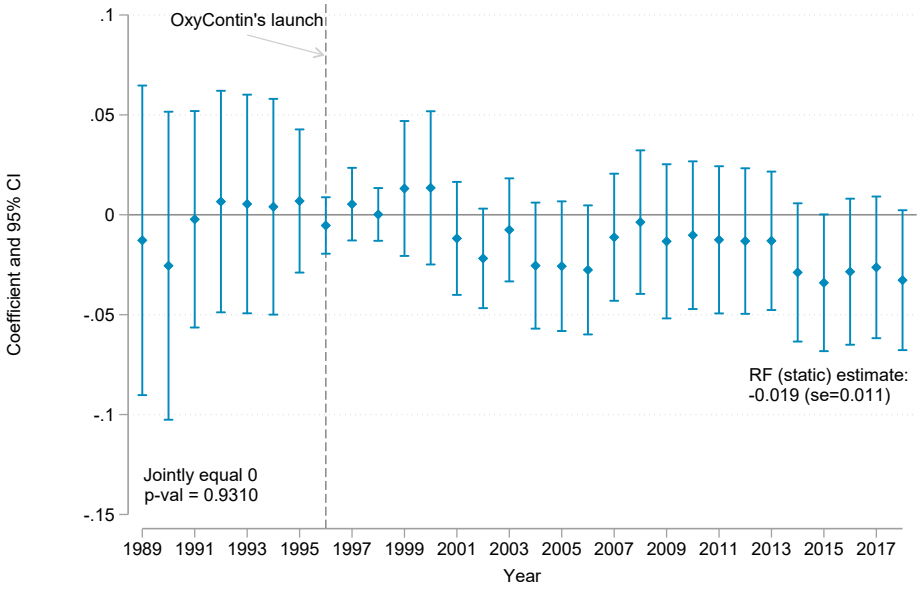
Notes: Extract of Exhibit 1 - Sales Visits By Purdue In Massachusetts. COMMONWEALTH OF MASSACHUSETTS v.PURDUE PHARMA C.A. No. 1884-cv-01808. This figure is referenced in Section IV.A.

Figure A7: Effects of Mid-nineties Cancer-market Targeting on Birth Outcomes

(a) Share infants born with low weight ($< 2,500$kg)

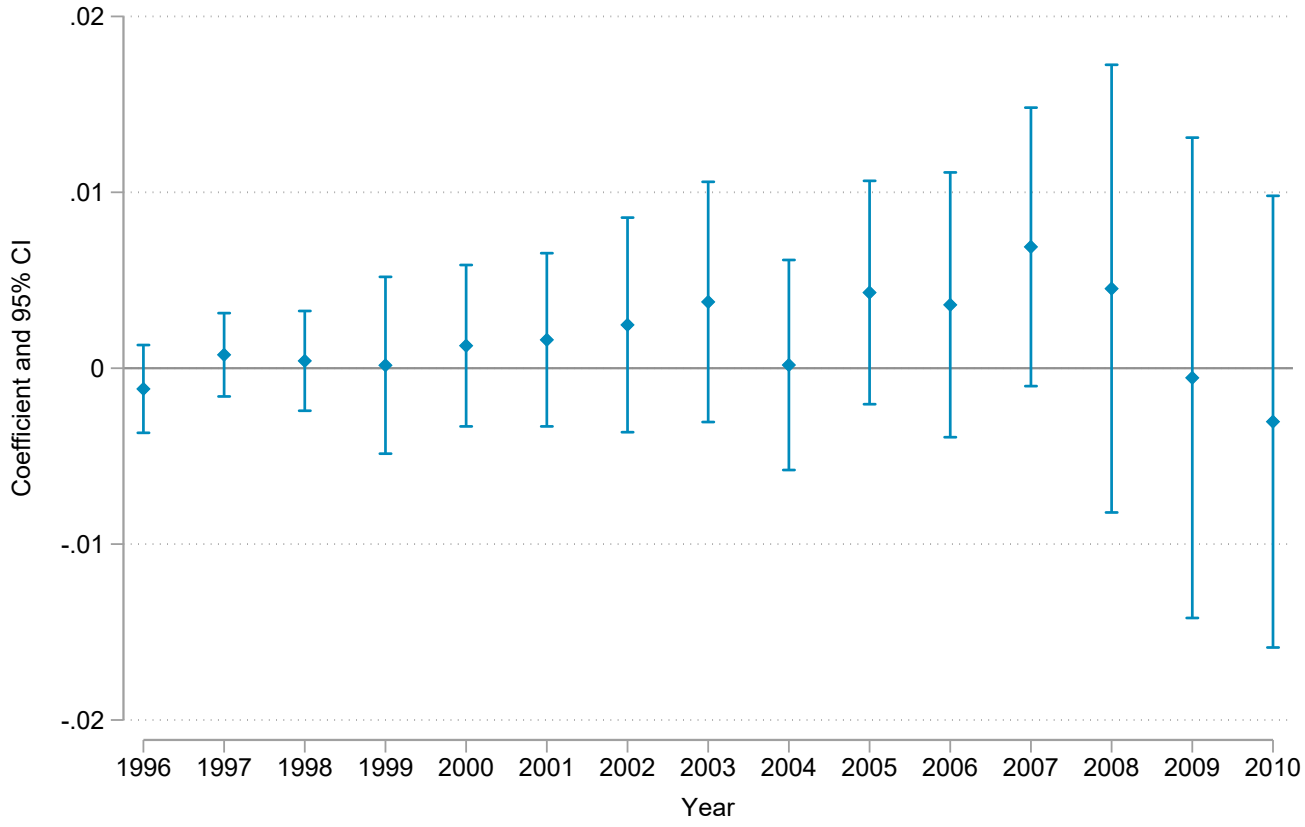


(b) APGAR Score



Notes: This figure shows the effects of the increase in prescription opioids supply in the share of infants with low 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 (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 values are presented in the figures. This figure is referenced in Section IV.B., in Section V.A., and in Section V.B.

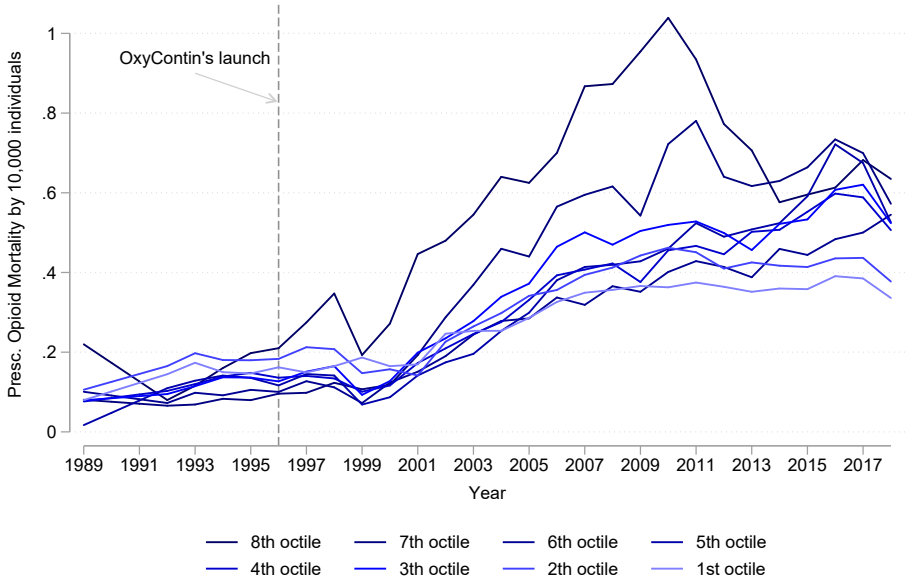
Figure A8: Effects of Mid-nineties Cancer-market Targeting on Share of Smokers



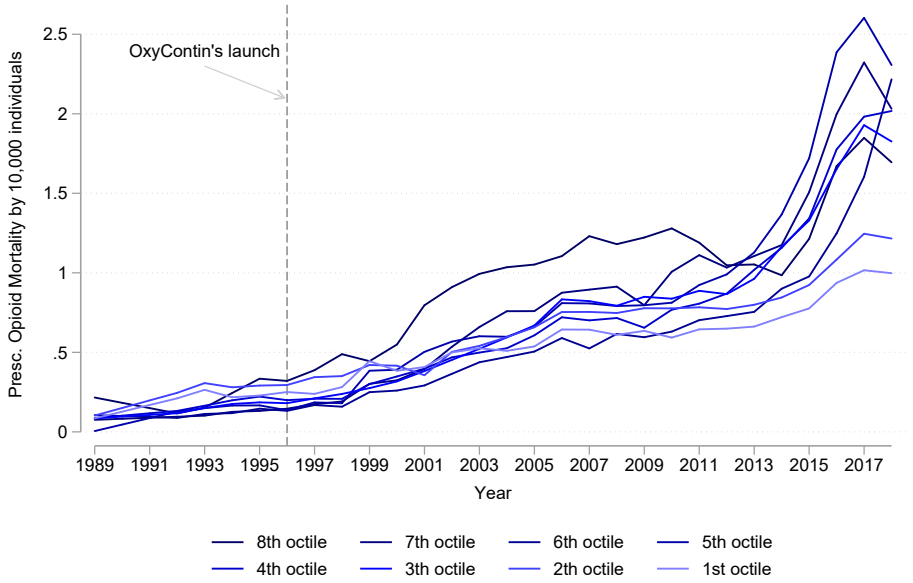
Notes: This figure shows the effects of the increase in prescription opioids supply in the share of smokers. We present the results of a dynamic reduced-form estimation were we regress the outcome on a set of year-dummy variables interacted with our instrument. We construct the share of smokers using 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 IV.B. and Section V.B.

Figure A9: Opioid Mortality Rate by Octiles of the 1994-1996 Cancer Prevalence

(a) Prescription Opioids



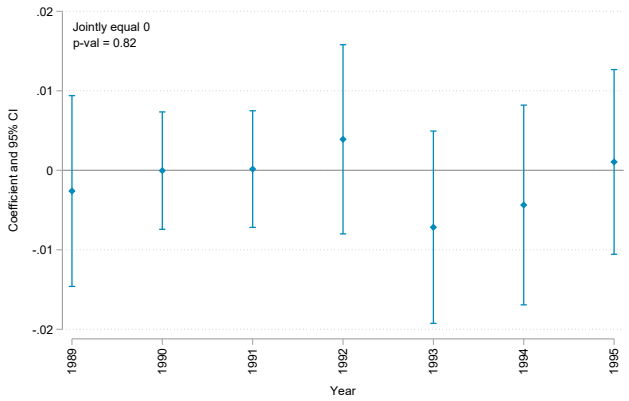
(b) All Opioids



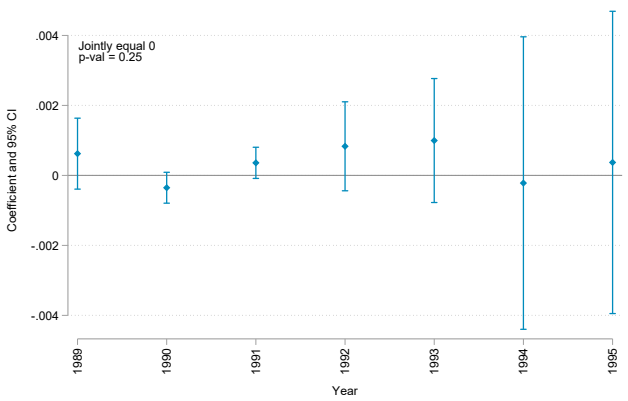
Notes: This figure shows the evolution of prescription opioid (panel a) and all opioids (panel b) mortality in eight groups of commuting zones. Each group is composed of those commuting zones in the *n-th* octile of the cancer mortality rate distribution before the launch of OxyContin. Darker colors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

Figure A10: Dynamic Reduced Form Estimates - Out-of-sample Analysis

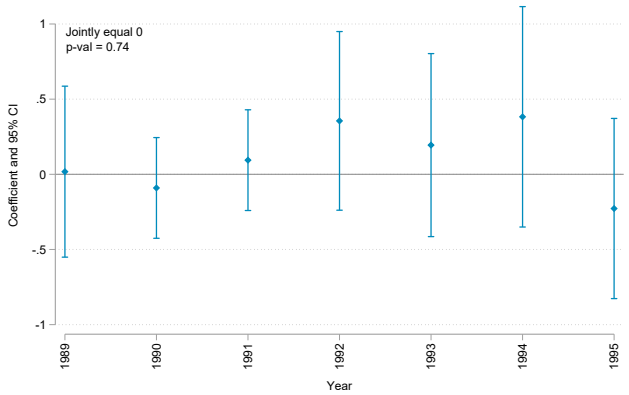
(a) Deaths of Despair



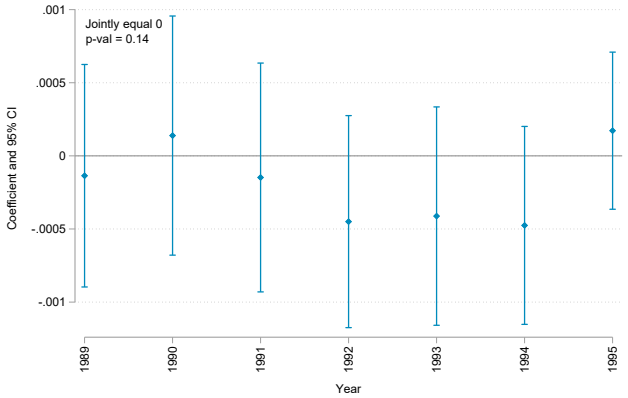
(b) SNAP



(c) Infant Mortality Rate



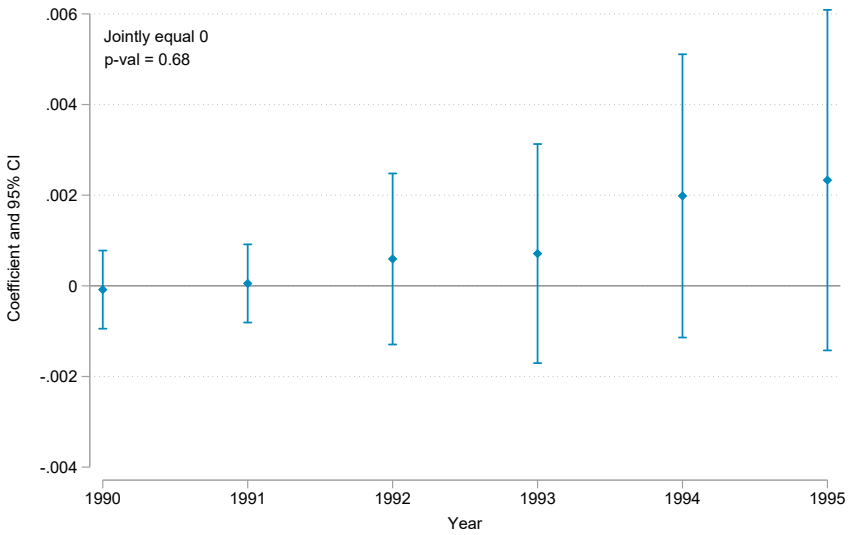
(d) Fertility Rate - unmarried woman



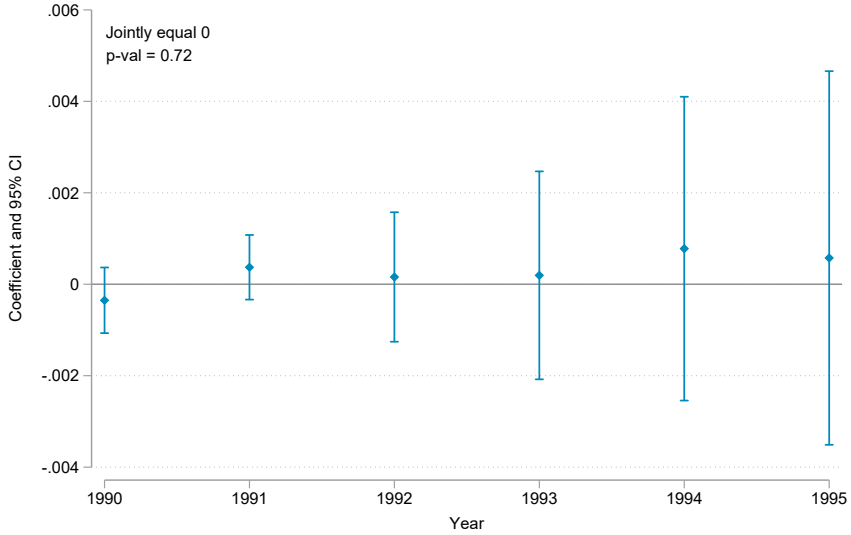
Notes: This figure shows the dynamic reduced-form relationship between outcomes of interest and our instrument in an out-of-sample period. That is, we replicate our dynamic reduced-form analysis in the pre-OxyContin period. We regress each outcome on a set of year-dummy variables interacted with the 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 A11: Dynamic Reduced Form Estimates - Out-of-sample Analysis: Labor Market Outcomes

(a) Manufacturing

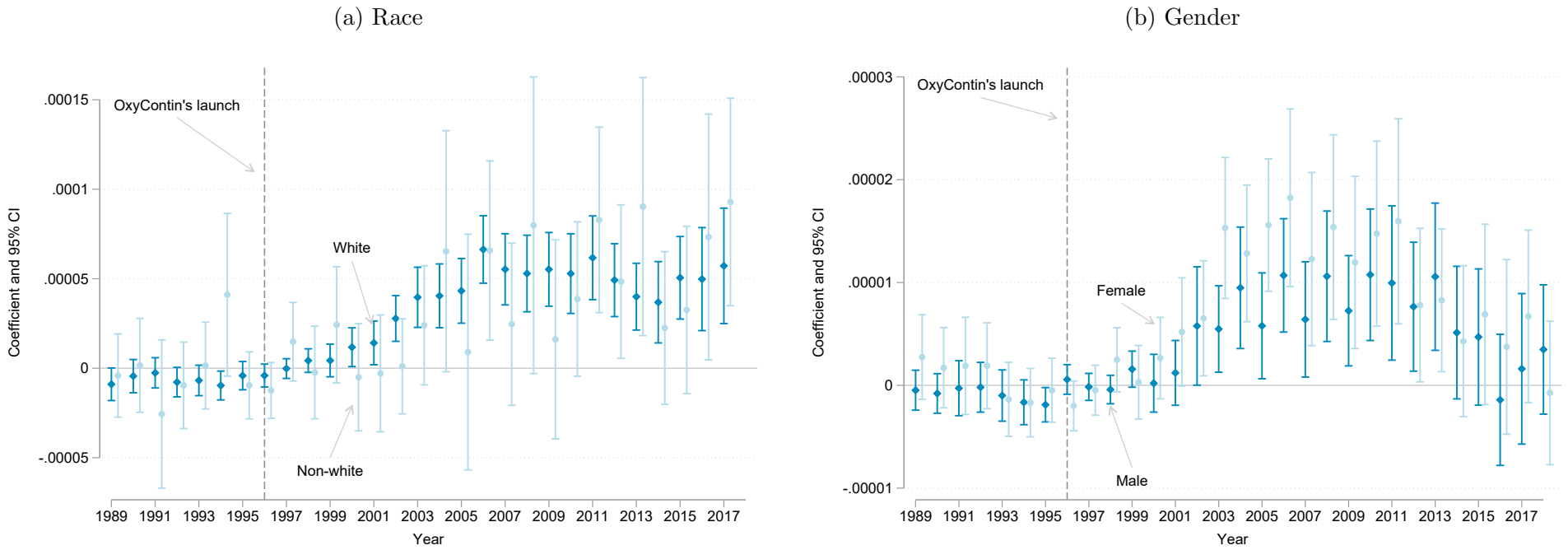


(b) Mining



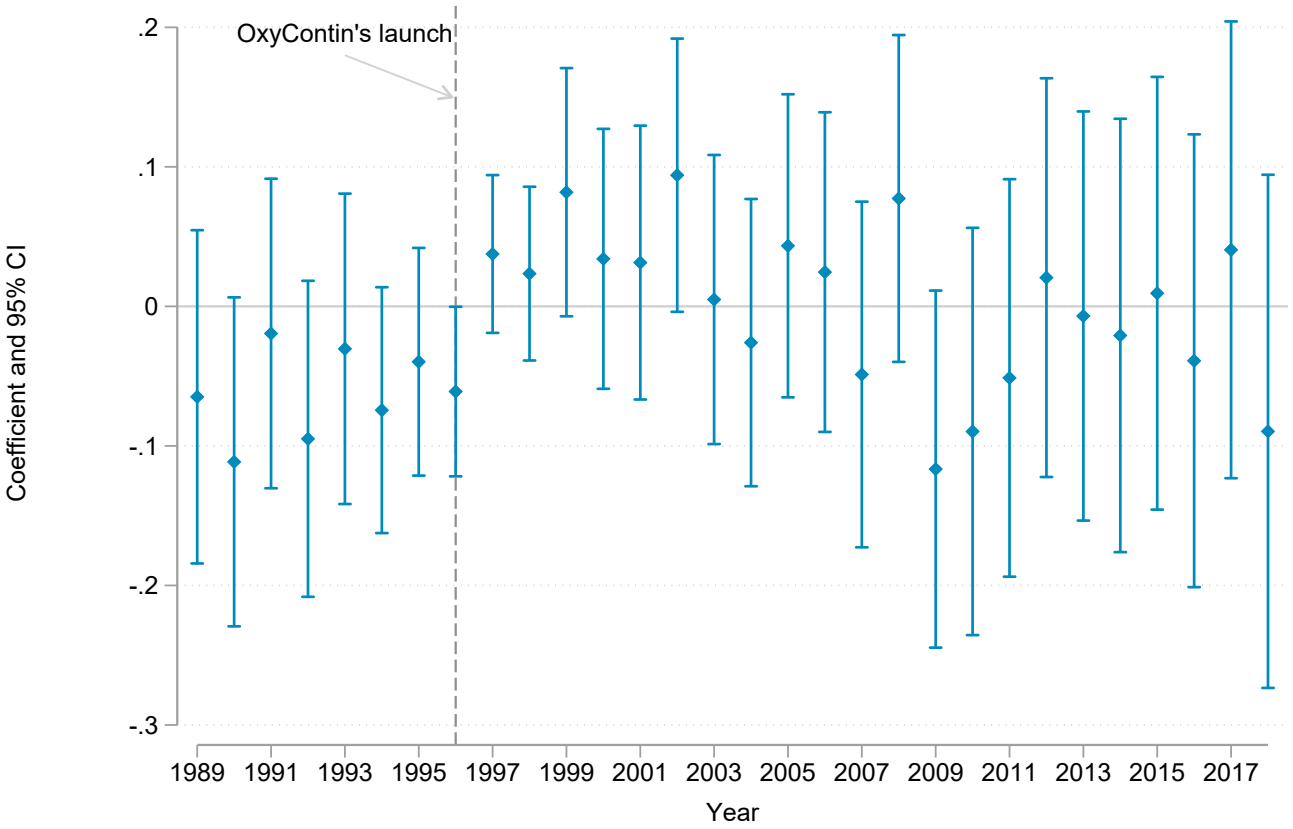
Notes: This figure shows the dynamic reduced-form relationship between the share of employment in the manufacturing and mining industries and our instrument in an out-of-sample period. The first year of available data is 1990. We use this specification to test for the presence a relationship between 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 A12: Effects of Mid-nineties Cancer-market Targeting on Opioid Mortality by Race and Gender



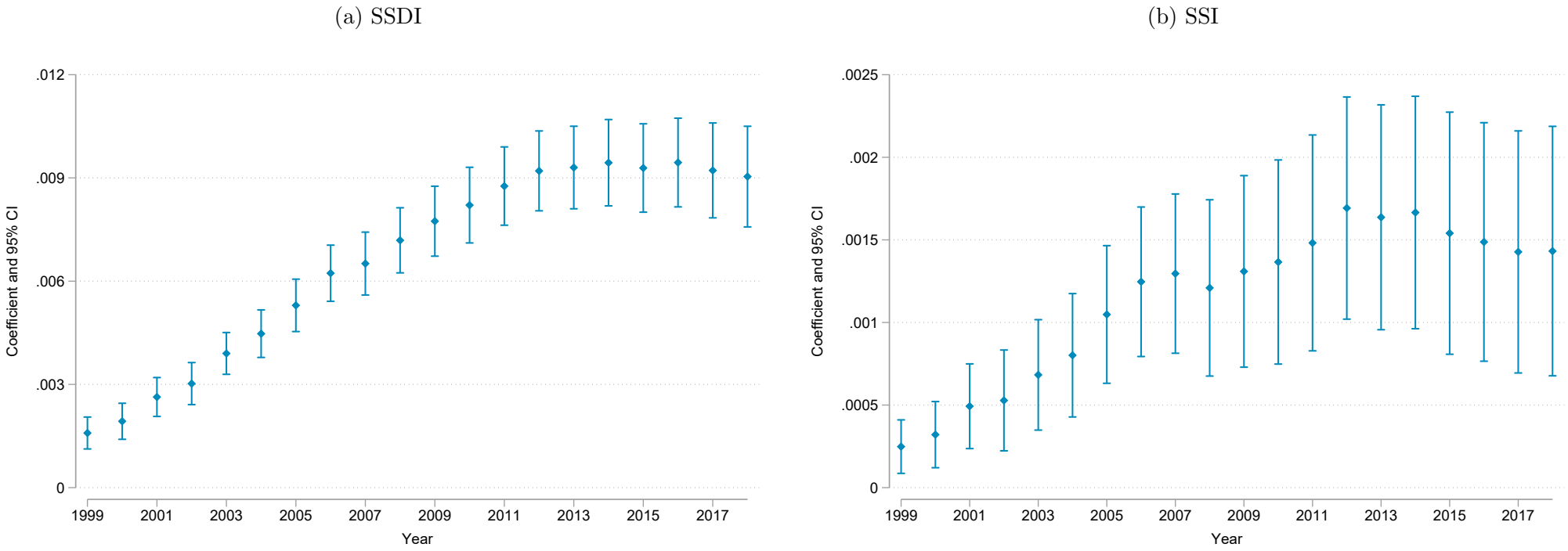
Notes: This figure shows the effects of the increase in prescription opioid supply in opioid related mortality by race group (panel a) and by gender (panel b). We present the results of a dynamic reduced-form estimation were we regress these outcomes on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. These coefficients corresponds to the estimate of ϕ_t in Equation 3. This figure is referenced in Section V.A.

Figure A13: Effects of Mid-nineties Cancer-market Targeting on Non-cancer Mortality



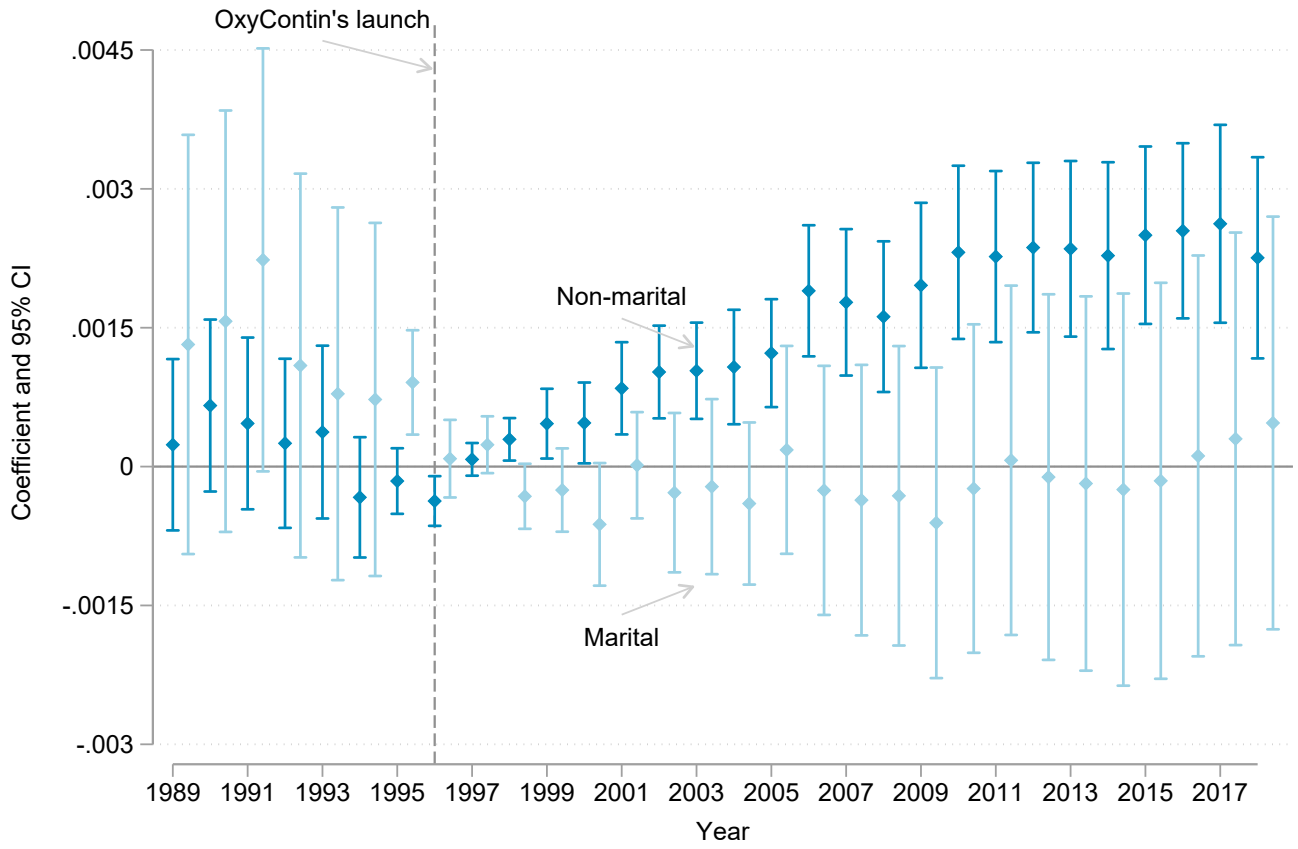
Notes: This figure shows the effects of the increase in prescription opioid supply in non-cancer mortality for adults aged 20 years and older. We present the results of a dynamic reduced-form estimation were we regress these outcomes on a set of year-dummy variables interacted with our instrument—cancer 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 A14: Effects of Mid-nineties Cancer-market Targeting on Disability Claims



Notes: This figure shows the effects of the increase in prescription opioid supply in the share of population enrolled in SSDI (panel a) and SSI (panel b) programs. 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 A15: Effects of Mid-nineties Cancer-market Targeting on Marital and Non-marital Fertility

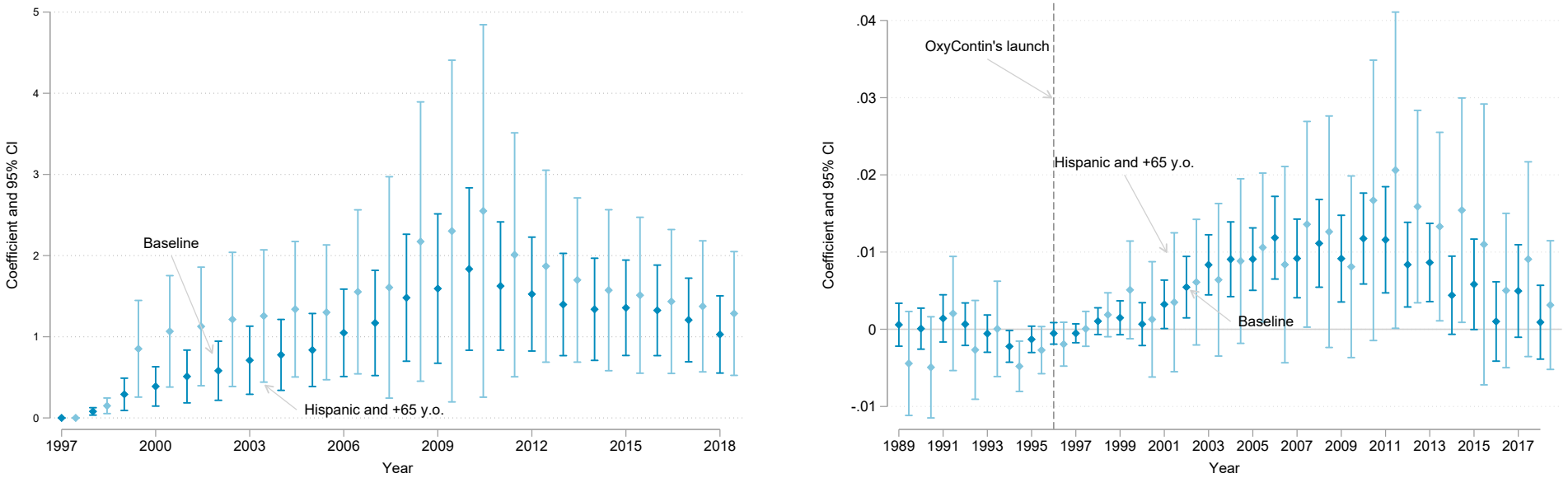


Notes: This figure shows the effects of the increase in prescription opioid supply in marital and non-marital fertility. We present the results of a dynamic reduced-form estimation were we regress these outcomes on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996.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

Figure A16: Flexible Controls for the Share of Hispanic and +65 Years Old Population

(a) First Stage

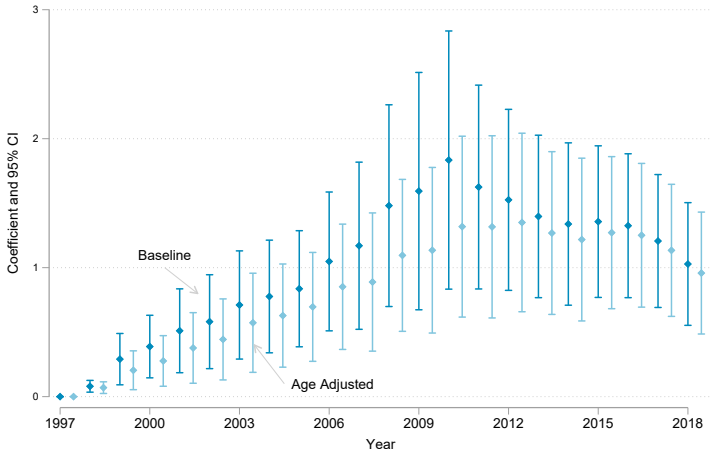
(b) Prescription Opioid Mortality



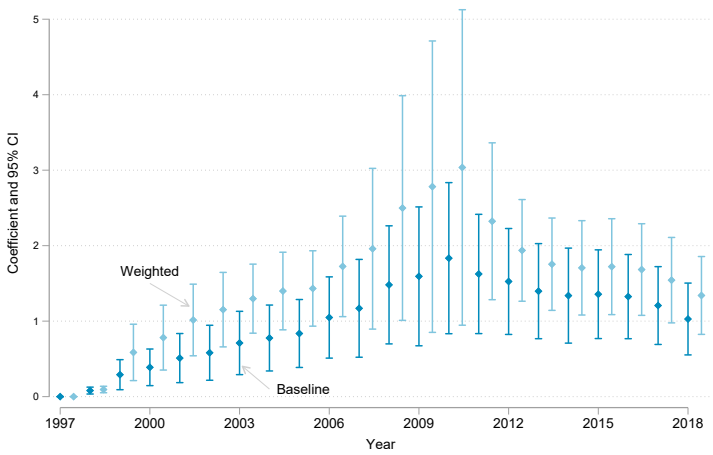
Notes: This figure shows estimates of the coefficients of the dynamic first stage and the effect of the increase in prescription opioid supply using our baseline specification and adding controls for the share of Hispanic population and the share of population over 65 years old measured in 1994-1996 and interacted with a set of year-dummy variables. That is, adding flexible controls to capture the evolution of variables that predict cancer mortality in 1996. This figure is referenced in Section VI.A.

Figure A17: Alternative Instruments: Dynamic First Stage and Effects of Mid-nineties Cancer-market Targeting

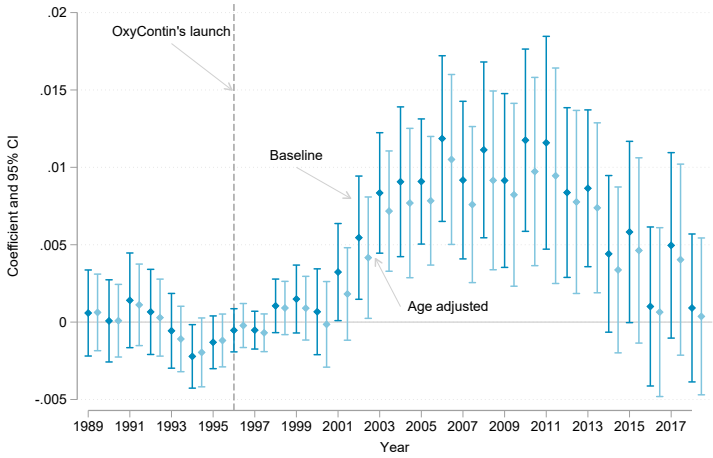
(a) First Stage - Age Adjusted



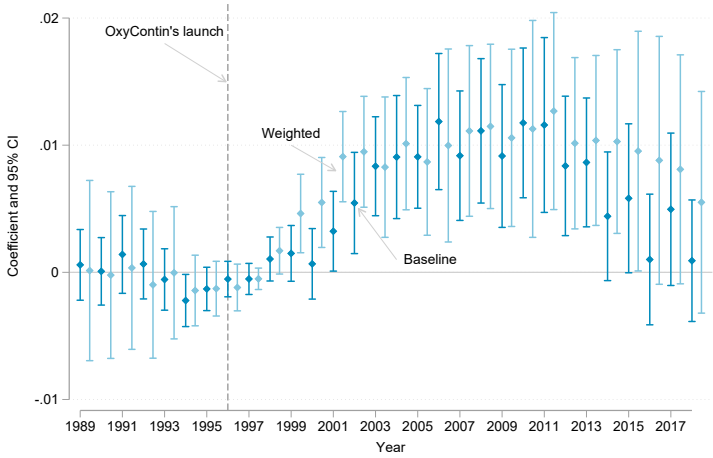
(b) First Stage - Weighted



(c) Prescription Opioid Mortality - Age Adjusted



(d) Prescription Opioid Mortality - Weighted

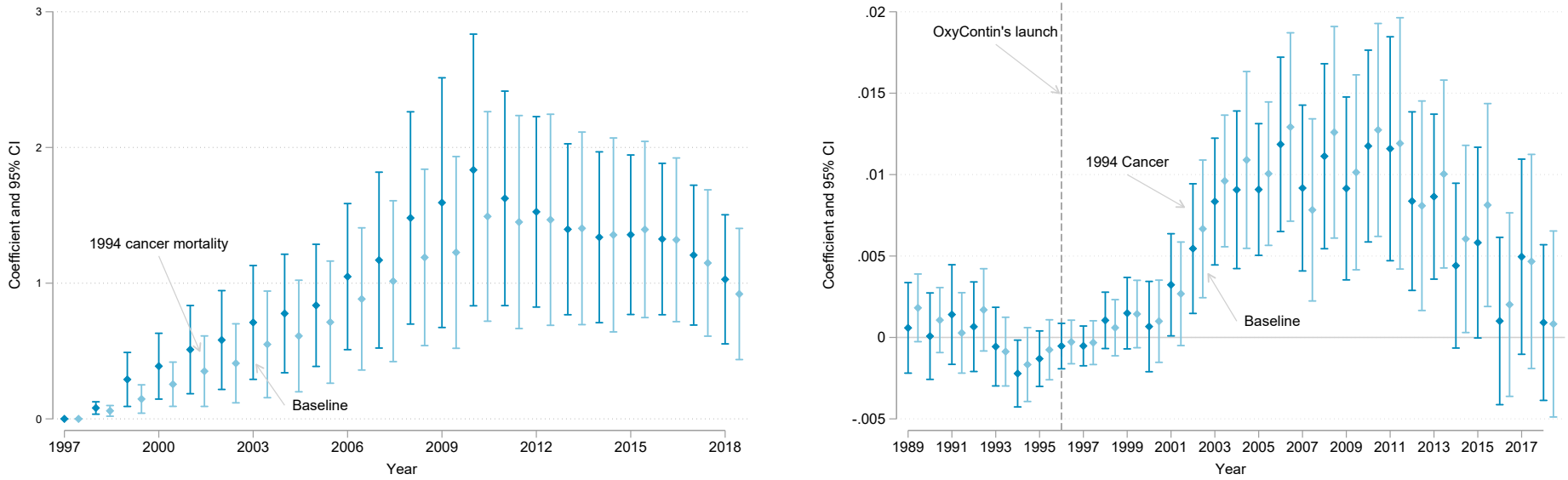


Notes: This figure shows the effects of the increase in prescription opioid supply in prescription opioid mortality, it shows the baseline specification and reproduces this analysis using population weights in the estimation of the event study coefficients. This figure is referenced in Section VI.A.

Figure A18: Alternative Instrument: Cancer Mortality 1994.

(a) First Stage

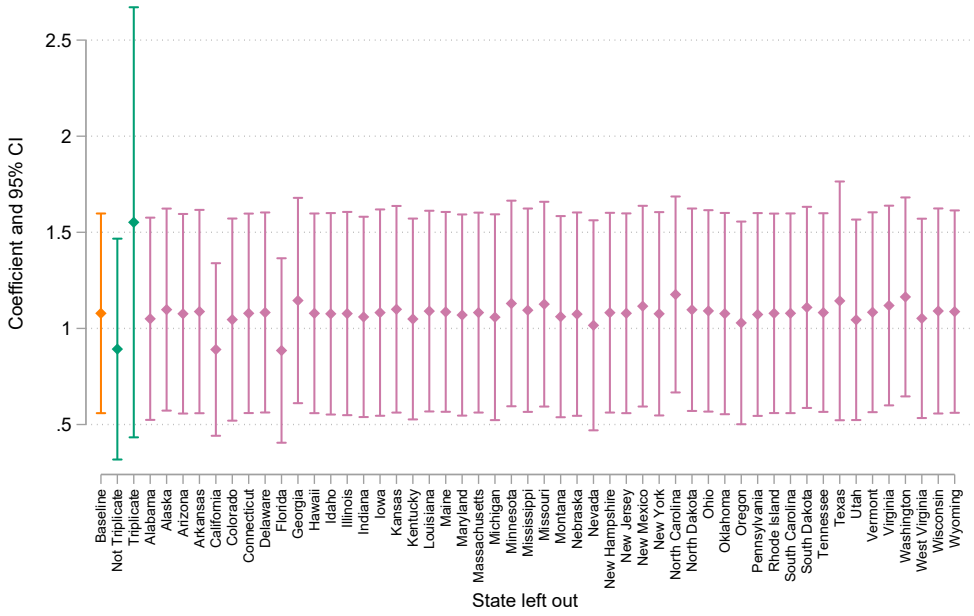
(b) Prescription Opioid Mortality



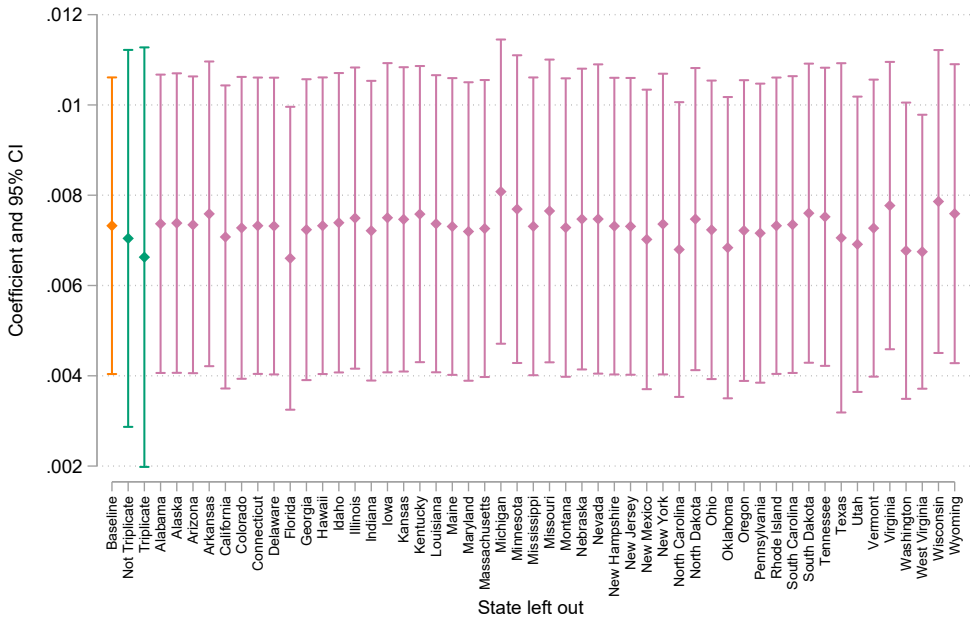
Notes: This figure shows the dynamic first stage (panel a) and reduced-form (panels b to f) relations between outcomes of interest and an alternative instrument: cancer mortality rate in 1994. This figure provides a robustness check for our preferred specification which uses cancer mortality in 1994-1996 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 A19: Robustness check: Leave-ones-out estimates

(a) First-stage coefficient estimates

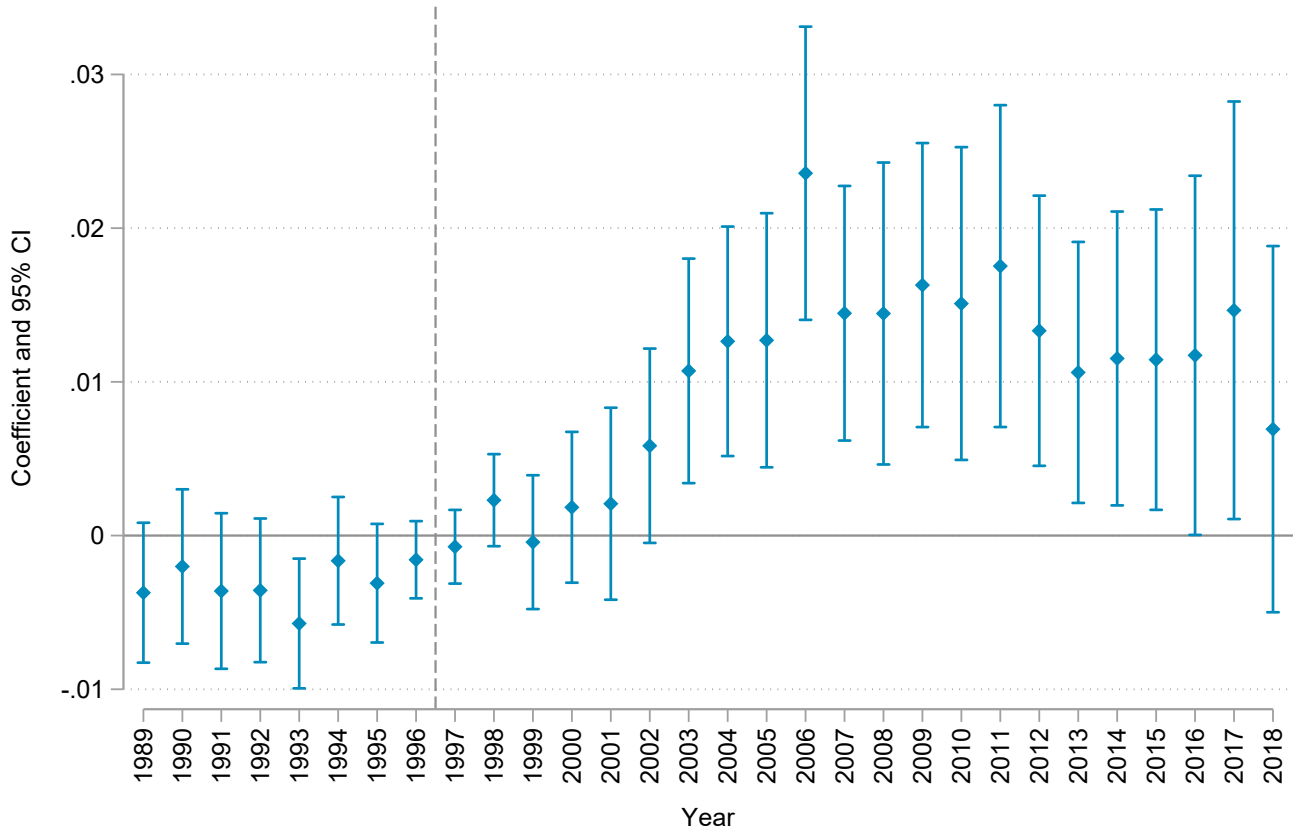


(b) Prescription opioids: Reduced-form coefficient estimates



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 2 and column 2 of Table D1. Each of the subsequent coefficients are computed by excluding all commuting zones in the state or group of states indicated on the horizontal axis (thus, the x-axis label). 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.

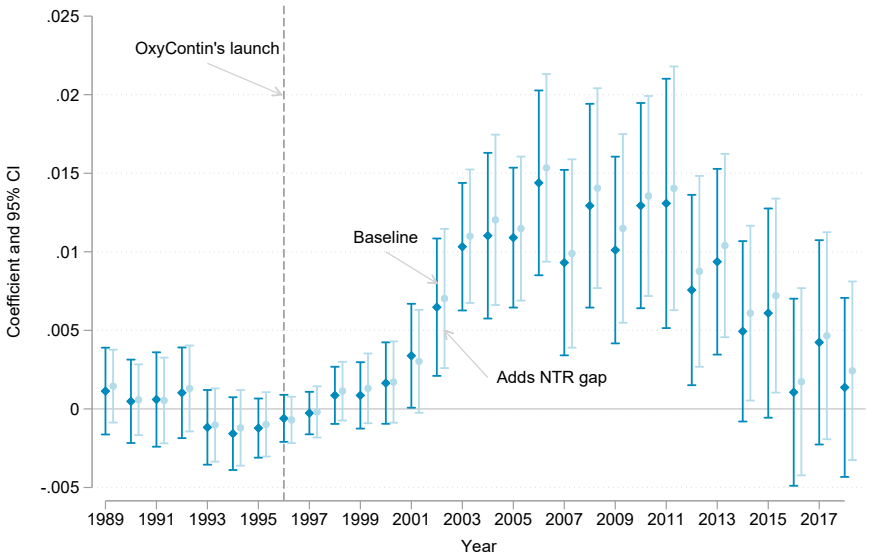
Figure A20: Alternative Measure of Opioid-related Deaths



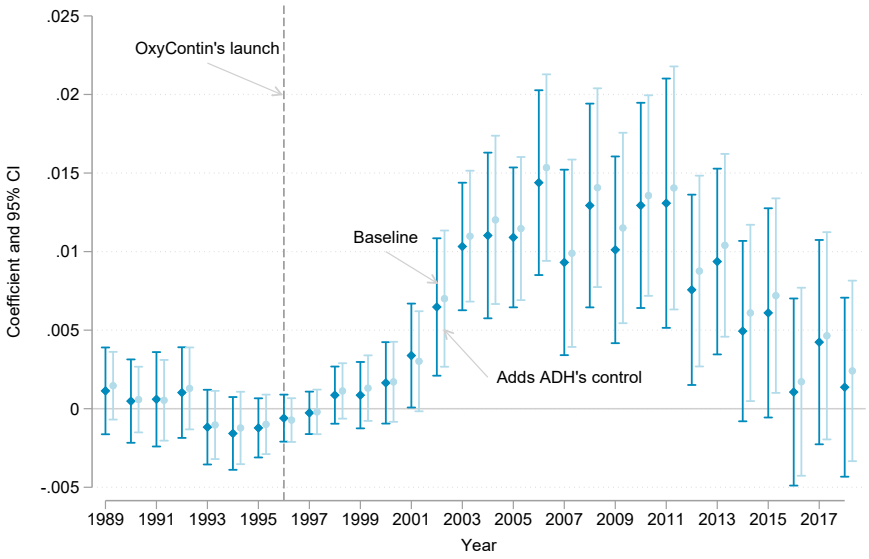
Notes: This figure shows the dynamic reduced-form estimation. We regress drug induced opioid mortality on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. These coefficients corresponds to the estimate of ϕ_t in Equation 3This figure is referenced in Section VI.C.

Figure A21: Robustness check: Control for exposure to the "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	SD	Mean	SD
	(1)	(2)	(3)	(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 Fertility 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 fertility 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 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 A4: 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 A5: 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 in long changes: 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 A6: 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 A7: 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 A8: 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 A9: 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 A10: 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 A11: 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 A12: 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 Alternative Sources of Variation in the Marketing of OxyContin

In this appendix, we compare the approach presented in this paper to the work of Alpert et al. (2022). We pay special attention to the ways in which we improve on their work, with focus on the differences in specifications, the statistical power of the two approaches, and we highlight concerns around the source of variation.

Both papers exploit geographic exposure to the initial marketing of OxyContin. Alpert et al. (2022) use a state-level binary variation, whereas we exploit continuous commuting-zone variation.[54] Alpert et al. (2022) show that five states with early versions of prescription drug monitoring programs, or triplicate prescriptions, received less marketing from Purdue Pharma. These early versions of PDMPs were often referred to as "triplicate" programs. We exploit a different dimension of the initial marketing strategy of OxyContin: the fact that prescription opioids were initially promoted to the cancer pain market, with the plan to expand from there to the much larger non-cancer pain market. This produces variation in the marketing of opioids that tracks the cancer pain market and that we measure as commuting-zone level cancer mortality between 1994 and 1996.

C.1 Specification

Exploiting different dimensions of the initial marketing strategy of OxyContin translates into different empirical strategies. The event study specification proposed in each paper is given by:

$$\text{AELP:}\;\; y_{st} = \sum_{\tau=1983}^{2017} \beta_\tau \times \mathbf{1}(\text{ Nontriplicate }\,)_s \times \mathbf{1}(\text{t} = \tau) + \tilde{\alpha}_s + \tilde{\gamma}_t + \zeta X_{st} + \varepsilon_{st}\ ,$$

$$\text{AB:}\;\; \Delta\, y_{sct} = \sum_{\tau=1989}^{2018} \phi_\tau \times \text{CancerMR}_{sct_0} \times \mathbf{1}(Year = \tau) + \gamma_{st} + \alpha\ \Delta\ X_{ct} + \upsilon_{ct}\ .$$

where s indexes state, t indexes time, c indexes commuting zone, t_0 defines the pre-OxiContin period (1994-1996), and τ indexes event time. AELP reproduces Equation (1) in Alpert et al. (2022), augmented to include the baseline controls (X_{st}) considered by the authors: the fraction of the population that is white non-Hispanic, Black non-Hispanic, Hispanic, the fraction ages 25–44, 45–64, 65+, the fraction with a college degree, and log population. This specification includes state (α_s) and year (γ_s) fixed effects. The indicator variable $\mathbf{1}(\text{Nontriplicate})_s$ is based on the initial triplicate status of the state in 1996.

[54] Using state-level data implies 50 potential units of analysis: 49 continental US states and the District of Columbia. Using commuting-zone level data implies 740 potential units of analysis.

AB reproduces Equation 3 of this paper and its terms have been defined before. Different from Alpert et al. (2022), this specification allows the inclusion of state times year fixed effects (γ_{st}) to account for important confounders at the state and year level. During the period of analysis there was 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. These policy changes were quite common, for example, between 2007 and 2013, 17 states implemented some version of a PDMP (Buchmueller and Carey, 2018). Between 2001 and 2017, every US state passed a law that facilitates the widespread distribution and use of naloxone (Doleac and Mukherjee, 2019). These changes are likely related to both the levels of opioid in the population and downstream outcomes of the epidemic, biasing regression estimates.

C.2 Statistical precision

We study how the two strategies compare in their statistical power to measure the impacts of the opioid epidemic on the outcomes of interest. To assess the statistical power of each model, we compute the *minimum detectable effect* and compare its distribution. We define this statistic as follows:

$$\text{Minimum detectable effect } = t_{critical} \times \frac{se_{\min}}{\text{SD}_y} \ , \tag{C.1}$$

where $t_{critical}$ corresponds to the xth percentile of the $t-$distribution and SD_y is the standard deviation of the outcome variable, e.g., opioid-related mortality or change in the share of the population on the SNAP. In the previous expression, $se_{\min}$ is given by:

$$se_{\min} = \min\{se_\tau\} = \min\{se_{\tau_0}, se_{\tau_1}, se_{\tau_2}, \ldots, se_{\tau_T}\} \ ,$$

where se_τ corresponds to the standard error of the $\hat{\beta}_\tau$ and $\hat{\phi}_\tau$ coefficients respectively, e.g., $se_\tau = se(\hat{\beta}_\tau)$. Thus, the minimum detectable effect of the vector of parameters $\boldsymbol{\beta}_\tau$ is the smallest effect size on the outcome variable y for which the researcher can reject the null hypothesis that the β_τ with the smallest variance equals zero. Analogously, the minimum detectable effect of the vector of parameters $\boldsymbol{\phi}_\tau$ requires the computation of $se_\tau = se(\hat{\phi}_\tau)$.

We construct the distribution of this statistic for each model $\{AELP, AB\}$. To do so, we perform S simulations of each model, and for each iteration s, we compute the minimum detectable effect as defined in Equation C.1. In doing this exercise, we need to take a stand on the data-generating process for the outcome variable of interest (y and Δy, respectively). We consider alternative distributions of the outcome variable and parameter values. Table C1 summarizes the results of this exercise and Figure C1

presents selected distributions. We run 500 simulations for each proposed distribution of the outcome variable and work with a $t_{critical} = 1.96$. For example, the series labeled Beta(1,3) in Panel (a) corresponds to the distribution of the *minimum detectable effect* of the vector of parameters $\boldsymbol{\beta}_{\tau}$ when the outcome y follows a Beta (1,3) distribution. The Log-normal(8.85,7.15) closely captures the distribution of opioid-related mortality as defined by Alpert et al. (2022). Similarly, the Log-normal(0.02, 0.04) closely captures the distribution of the change in prescription opioid mortality as defined in this paper. Our results in Figure C1 and Table C1 show that across distributions, the variation and specification presented in this paper has substantially higher statistical power. Specifically, at the median, we can identify effects that are 25% of the size that the model proposed by Alpert et al. (2022).

C.3 Definition of triplicate status

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). We base this statement on the fact that at least on two separate occasions, Purdue explicitly referred to triplicates as the *"nine states"* (Figure C2), and to our knowledge, *never* mentioned only five. A footnote in Alpert et al. (2022) comments on *one* of these references to the nine states and deemed it an incorrect reference by Purdue. 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 (Figure C3). These are California, Hawaii, Idaho, Indiana, Michigan, Illinois, New York, Rhode Island, and Texas.[55]

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).[56] First, in Figure C4 we inspect patterns in the raw data. Panels (a) and (b) show the evolution of overdose mortality in five triplicate states and nine triplicate states, respectively, compared to the evolution in the rest of the

[55]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.

[56]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.

country. Using the alternative definition of triplicates provides less clear evidence that "triplicate states" fare better regarding overdose mortality.

Event studies models in Figure C5 suggest a similar story. While the main results are not overturned, 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 C2 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.

Finally, we test whether our instrument has predictive power in the group of triplicates states as defined by Alpert et al. (2022). We find that the positive relationship between mid-nineties cancer mortality and the supply of opioids is present in both triplicate and non-triplicate states (Figure A19). In fact, the first stage is stronger in the five triplicate states. This result is consistent with a story in which pharmaceutical companies need to be more strategic in promoting opioids in places where they face additional barriers and do not avoid the largest markets in the country (For example, California, Texas, New York, and Illinois).[57] Anecdotal evidence is consistent with this fact: All five "triplicate" states filed lawsuits against Purdue Pharma and other pharmaceutical companies for their direct responsibility in the unfolding of the opioid epidemic.[58] We corroborate this, in the reduced form estimates, our results are indistinguishable, both qualitatively and statistically, in the five states triplicate states and the rest of the states, as panel b of Figure A19 shows.[59]

[57]The first stage coefficient is 1.542 in the five triplicate states defined in Alpert et al. (2022), and 0.917 in the other states. This difference is not statistically different, and the p-value of such test is 0.203.

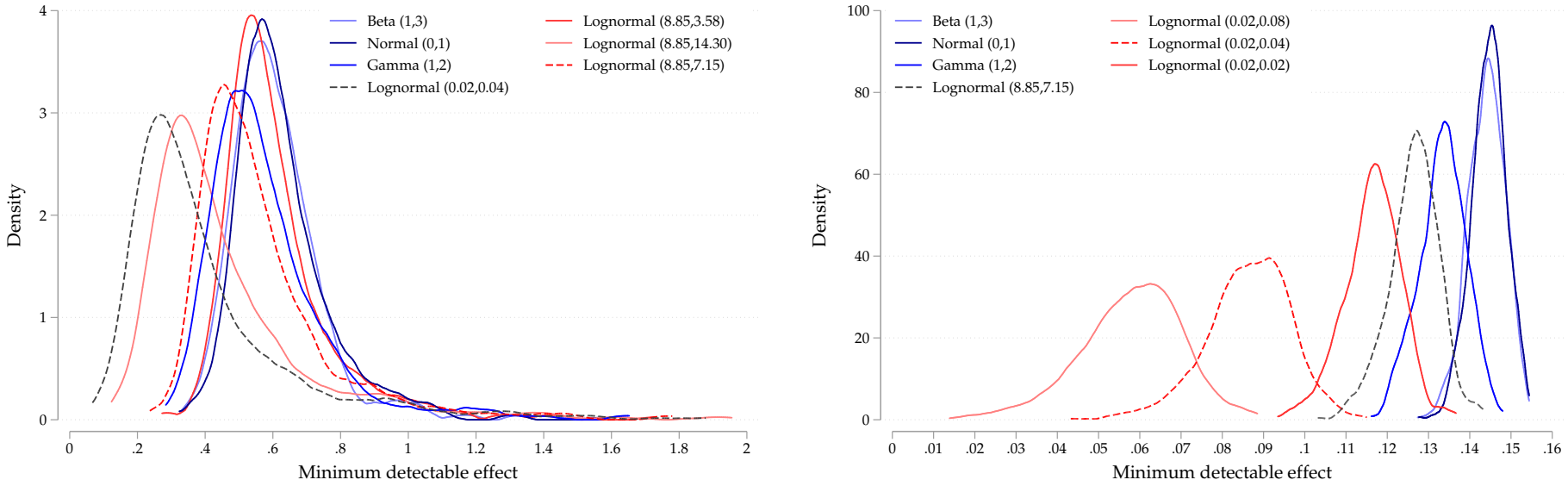
[58]For example, "New York State is in the throes of an opioid epidemic that has ravaged the lives of its residents and drained its public coffers for more than two decades. This statewide catastrophe happened because the Defendants in this case deliberately betrayed those duties through a persistent course of fraudulent and illegal misconduct, in order to profiteer from the plague they knew would be unleashed"—the People of New York, -against-Purdue Pharma et al.; March 28, 2019.

[59]The reduced form coefficient is 0.0072 in the five triplicate states defined in Alpert et al. (2022), and 0.0073 in the other states. This difference is not statistically different, and the p-value of such test is 0.97.

Figure C1: Distribution of the Minimum Detectable Effect: Alternative Specifications

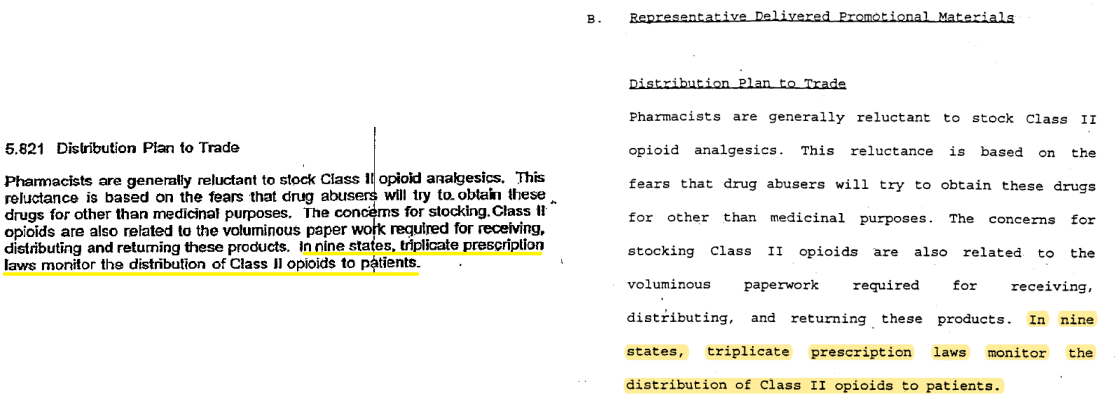
(a) State-level Variation: Triplicate programs

(b) Commuting-zone level variation: Cancer market



Notes: Panel (a) shows the distribution of the minimum detectable effect for the AELP model under alternative distributions of the outcome variable. For example, the series labeled Beta(1,3) corresponds to the distribution of the *minimum detectable effect* of the vector of parameters $\boldsymbol{\beta}_\tau$ when the outcome y follows a Beta(1,3) distribution. The Log-normal(8.85,7.15) closely captures the distribution of opioid-related mortality as defined by Alpert et al. (2022). The additional Log-normal distributions have the same mean but change the variance. Similarly, panel (b) shows the distribution of the minimum detectable effect of the vector of parameters $\boldsymbol{\phi}_\tau$, i.e., it corresponds to this paper's model under alternative distributions of the outcome variable. The Log-normal(0.02, 0.04) closely captures the distribution of the change in prescription opioid mortality as defined in this paper. This figure is referenced in Section C.2

Figure C2: 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.

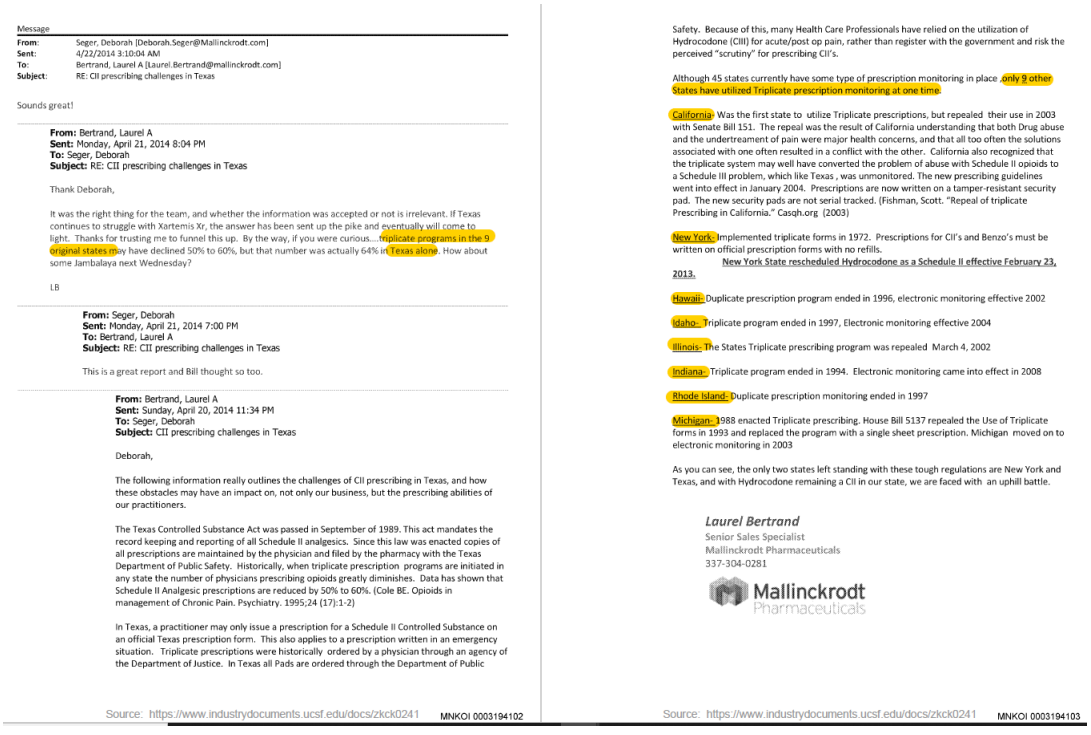
B. Representative Delivered Promotional Materials

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 Appendix C.3.

Figure C3: 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." Casgh.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

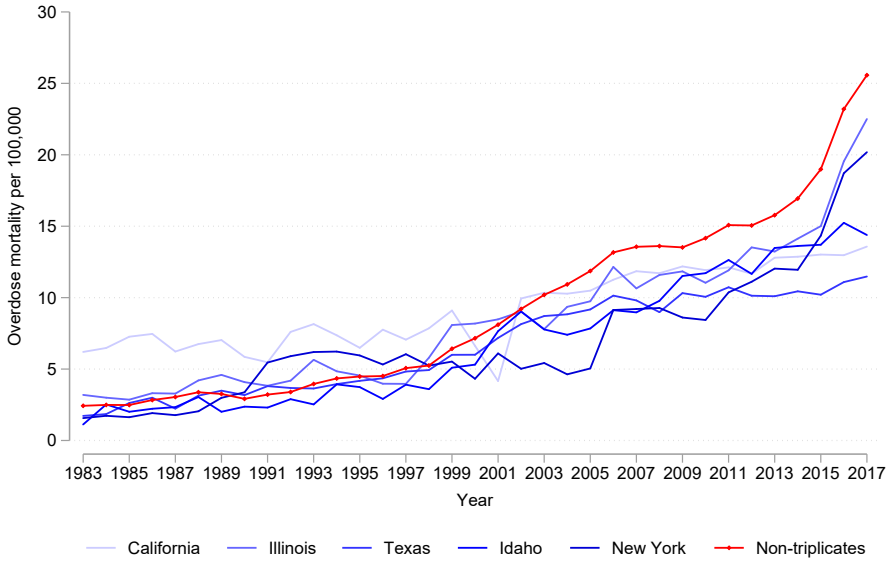
Mallinckrodt Pharmaceuticals

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

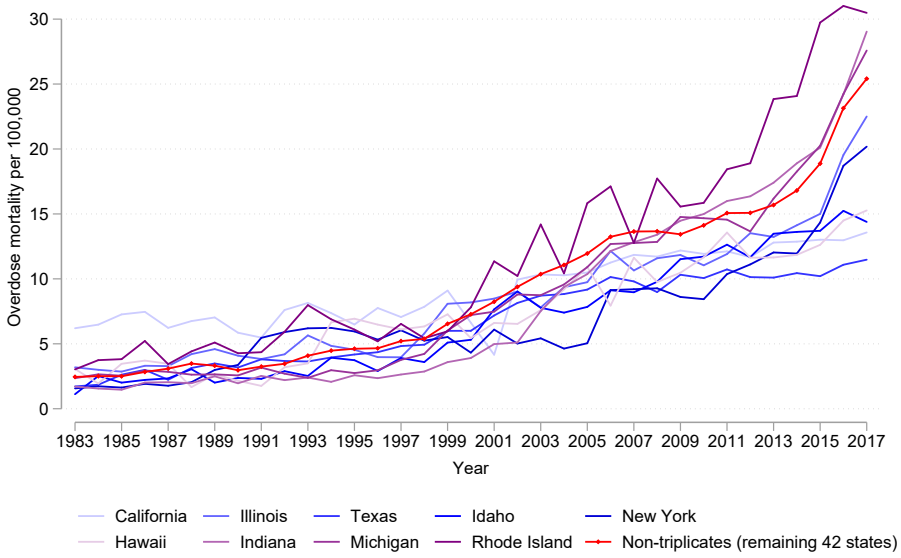
Notes: This figure shows extracts of the internal email from the opioid litigation with details on the list of triplicate states. This figure is referenced in Appendix C.3.

Figure C4: All Drug Overdose Mortality by Triplicate Status.

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



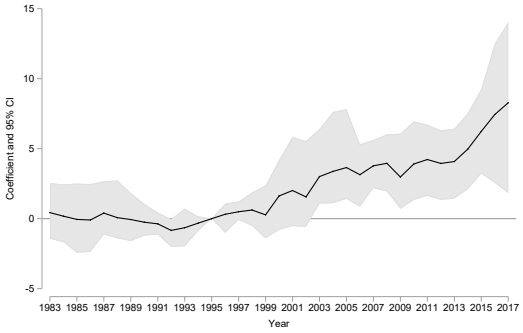
(b) Alternative triplicate definition



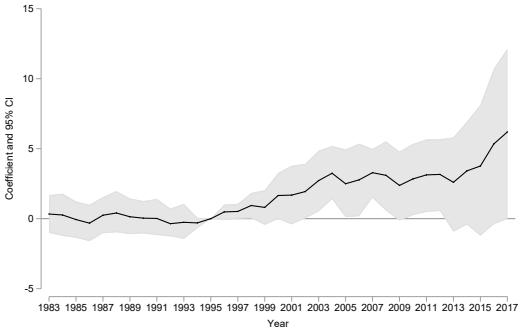
Notes: Time series for all drug overdose mortality. Panel (a) defines triplicates as California, Idaho, Illinois, New York, and Texas. Panel (b) adds Hawaii, Indiana, Michigan, and Rhode Island for a total of 9 triplicate states. This figure is referenced in Appendix C.3.

Figure C5: All Drug Overdose Mortality By Triplicate Status - Unweighted analysis.

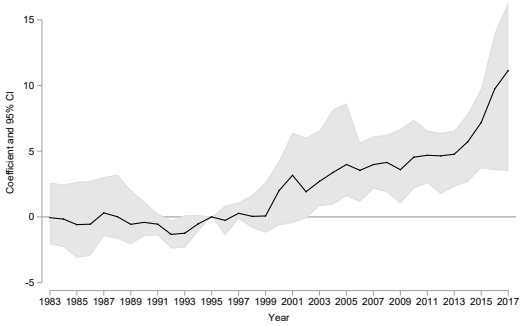
(a) 5 Triplicates unweighted



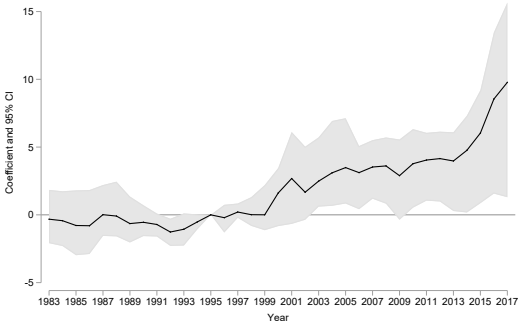
(b) 9 Triplicates unweighted



(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.3.

Table C1: Distribution of the Minimum Detectable Effect for Alternative Specifications and Distributions of the Outcome Variables

	Outcome variable		Minimun effect size							
	Mean	SD	Min	1^{st} pctile	5^{th} pctile	Mean	Median	95^{th} pctile	99^{th} pctile	Max
Distribution	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Panel A: Alpert et al. (2022) model										
Beta (2, 2)	0.50	0.22	0.36	0.41	0.46	0.62	0.60	0.85	0.96	1.24
Beta (1, 3)	0.25	0.19	0.33	0.38	0.44	0.61	0.59	0.82	1.05	1.34
Gamma (1, 2)	2.00	1.99	0.28	0.33	0.38	0.60	0.54	0.95	1.53	3.03
Gamma (2, 2)	4.00	2.82	0.31	0.36	0.40	0.61	0.58	0.90	1.31	1.85
Normal (0, 1)	0.00	1.00	0.32	0.39	0.46	0.63	0.60	0.91	1.08	1.58
Log-normal (2.5, 0.5)	2.50	0.50	0.30	0.39	0.46	0.62	0.59	0.92	1.12	1.59
Log-normal (7, 5)	7.01	5.02	0.24	0.31	0.39	0.59	0.53	1.00	1.64	3.87
Log-normal (8.85, 3.58)	8.80	3.56	0.27	0.38	0.44	0.61	0.57	0.94	1.32	2.26
Log-normal (8.85, 7.15)	8.84	7.14	0.24	0.29	0.36	0.58	0.51	1.01	1.77	4.40
Log-normal (8.85, 14.3)	8.86	14.28	0.12	0.17	0.22	0.51	0.39	1.09	2.51	8.92
Log-normal (0.02, 0.04)	0.02	0.04	0.07	0.11	0.17	0.48	0.33	1.14	2.85	11.16
Panel B: Arteaga and Barone (2023) model										
Beta (2, 2)	0.50	0.22	0.13	0.14	0.14	0.15	0.15	0.15	0.16	0.16
Beta (1, 3)	0.25	0.19	0.13	0.13	0.14	0.14	0.14	0.15	0.15	0.15
Gamma (1, 2)	2.00	2.00	0.12	0.12	0.12	0.13	0.13	0.14	0.15	0.15
Gamma (2, 2)	4.00	2.83	0.12	0.13	0.13	0.14	0.14	0.15	0.15	0.15
Normal (0, 1)	0.02	0.04	0.13	0.13	0.14	0.14	0.14	0.15	0.15	0.15
Log-normal (2.5, 0.5)	2.50	0.50	0.13	0.13	0.14	0.14	0.14	0.15	0.15	0.15
Log-normal (7, 5)	7.00	5.00	0.11	0.11	0.12	0.13	0.13	0.14	0.14	0.15
Log-normal (0.02, 0.02)	0.02	0.02	0.09	0.10	0.10	0.12	0.12	0.13	0.13	0.14
Log-normal (0.02, 0.04)	0.02	0.04	0.04	0.06	0.07	0.09	0.09	0.10	0.11	0.12
Log-normal (0.02, 0.08)	0.02	0.08	0.01	0.02	0.04	0.06	0.06	0.08	0.09	0.09
Log-normal (8.85, 7.15)	8.83	7.11	0.10	0.11	0.12	0.13	0.13	0.14	0.14	0.14

Notes: This table presents summary statistics for the distribution of the minimum detectable effect. Panel A considers the model proposed by Alpert et al. (2022) and panel B considers the model proposed in this paper. Columns (1) and (2) present the mean and standard deviation of the simulated outcome of interest (y and Δy respectively). Columns (3) to (10) present moments of the distribution of the minimum detectable effect, pctile stands for percentile. This table is referenced in Appendix C.2.

Table C2: Replication of Table 1 in Alpert et al. (2022)

Triplicate state group (n)	Nine	Five	Nine	Five
Nontriplicate ×	(1)	(2)	(3)	(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 Appendix C.3.

D Instrumental Variable Analysis

In this appendix we implement an instrumental variable strategy with the goal of scaling our reduced-form results by the increase in prescription opioids. This strategy is given by the following equations, which are run over our sample of commuting zones for the period 1999-2018:

First Stage:

$$\Delta \ Presc. \ Opioids_{ct} = \alpha_1 + \phi \ CancerMR_{ct_0} + \alpha \ \Delta \ X_{ct} + \gamma_{st} + \upsilon_{ct} \ . \tag{D.1}$$

Second Stage:

$$\Delta \ y_{ct} = \tau_1 + \beta \ \Delta \widehat{Presc. \ Opioids}_{ct} + \tau \ \Delta \ X_{ct} + \lambda_{st} + \varepsilon_{ct} \ , \tag{D.2}$$

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 corresponds to the long-change of variable W_{ct}. Regarding Equation (D.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 (D.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.

Next we take Equations D.1 and D.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 D1 are statistically significant using t-ratio inference, Anderson-Rubin weak instrument robust inference, and the tF procedure suggested by Lee et al. (2020).[60] Our results imply that when doses per capita increase from the 25th to the 75th percentile—i.e., a

[60] Lee et al. (2020) suggest that the standard practice of relying on the first-stage F exceeding some threshold (e.g., 10) delivers tests of incorrect size. They propose to construct the "tF 0.05 standard error", which inflates the usual standard errors to take into account the strength of the first stage. 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.

5.02 dose increase—mortality from prescription opioids increases by 88.6% and all opioid mortality increases by 39.3%.[61]

The ordinary least squares (OLS) estimates (columns 1 and 4 of Table D1) 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 downward 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.

Alternative instrumental variable approach. 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 D5, 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.

[61] 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.

Table D1: 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 in long changes 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 Appendix D.

Table D2: 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 in long changes 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 D3: Effects of the Opioid Epidemic on the Share of Social Insurance and Welfare Programs Recipients

Dependent var:	SSDI			SSI		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.000444***		0.00574***	0.0000137		0.00184**
	[0.0000985]		[0.00132]	[0.0000896]		[0.000841]
tF 0.05 se			(0.0018)			(0.0012)
t-stat using tF 0.05 se			3.1250			1.5612
AR p-value			0.0000			0.0107
Cancer MR 94-96		0.00619***			0.00198**	
		[0.000385]			[0.000803]	
Effect size (%)	5.36		76.39	0.27		38.43
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 in long changes 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 D4: Effects of the Opioid Epidemic on Infant and Fertility Outcomes

Dependent var:	Infant Mortality Rate			Sh. Low Birth Weight		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.0511**		-0.0232	0.000169*		0.000905
	[0.0242]		[0.140]	[0.000102]		[0.000640]
tF 0.05 se			-0.19643			-0.0009
t-stat using tF 0.05 se			-0.11811			1.002273
AR p-value			0.8678			0.1272
Cancer MR 94-96		-0.0250			0.000976	
		[0.157]			[0.000665]	
Effect size (%)	4.06		-1.84	0.62		5.55
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)			(0.026100
t-stat using tF 0.05 se			1.92663			-1.87378
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. Control variables in long changes 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 D.

Table D5: Baseline Results under a Shift-share Instrument

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

Dependent var:	SSDI	SSI	Infant Mortality Rate	Fertility rate
	(5)	(6)	(7)	(8)
Presc. Opioids pc	0.00553***	0.00319**	-0.0218	0.00149***
	[0.00127]	[0.00158]	[0.120]	[0.000548]
Model	IV	IV	IV	IV

Notes: Column 1 reports the estimated coefficient for the first stage. Columns 2 to 8 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.