The Opioid Epidemic: Causes and Consequences

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Abstract

This paper studies the origins and consequences of the opioid epidemic. Drawing on recently unsealed documents from state litigation against Purdue Pharma, we instrument for the supply of prescription opioids by exploiting features of the initial marketing of OxyContin. We find that moving from the 25th-to-the-75th percentile in the distribution of prescription opioid supply increases deaths from prescription opioids by 89% and deaths from all opioids by 39%. This corresponds to over 200,000 deaths.

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I. Introduction

Over the last two decades, mortality from opioid overdoses in the United States has increased at an alarming rate. Since 1999, opioid overdoses have claimed the lives of almost 400,000 (Centers for Disease Control and Prevention, 2019), and have contributed to the longest sustained decline in life expectancy in the last century, excluding the influenza and Covid pandemics (Dyer, 2018). Prescription opioids not only contributed directly to the increase in overdose deaths, but also indirectly by initiating opioid addiction, which can lead to the use of heroin and fentanyl, and by affecting one's ability to work, recover from illness, and care for children, among other daily activities. During this period disability claims have increased (Park and Powell, 2021); birth outcomes have worsened (Lynch et al., 2018); and a record number of children are living in foster care as a result of a parent's drug use (Meinhofer and Angleró-Díaz, 2019; Buckles, Evans and Lieber, 2020).

In 2017, 35% of adults in the US had a prescription for opioid painkillers, and 4.1% had used them for nonmedical purposes (NSDUH, 2017). Opioids are highly addictive, with rapid progression to physiological dependence with tolerance and withdrawal, even at prescribed doses and within a short time (Sharma et al., 2016; Hah et al., 2017).

In this paper, we first study the origins of the opioid crisis and, given the scope and scale of the epidemic, we estimate its effects on a broad range of health and economic outcomes. Multiple hypotheses have been put forth regarding the initial causes of the opioid crisis. Demand-side hypotheses suggest that deteriorating cultural and economic conditions may have induced a surge of "deaths of despair" by increasing drug overdoses (Case and Deaton, 2017). Alternative hypotheses consider the role of supply-side factors, such as the dramatic increase in opioid access, changes in physician prescribing attitudes, and the aggressive marketing of prescription opioids (Fernandez and Zejcirovic, 2018; Alpert et al., 2019; Eichmeyer and Zhang, 2020, among others).

The challenge in tracing the origins of the opioid crisis and its effects lies in the fact that the variation in the level of prescription opioids across geographies and over time is not random (Ruhm, 2019). On the one hand, deteriorating socioeconomic conditions at the community or individual level could be the initial cause of an increase in demand for opioids (Carpenter, McClellan and Rees, 2017), and can also explain subsequent negative outcomes. On the other hand, the supply of prescription opioids is positively linked to access to health care and to the number of physicians per capita, so that areas with higher access to opioids are positively selected along health indicators.

To address this challenge, we exploit detailed features of the initial marketing of prescription opioids, which we obtained from recently unsealed court records from state litigation against Purdue Pharma, the manufacturer of OxyContin, a prescription opioid

at the center of the drug epidemic.[1] We document that because of its marketing and for regulatory reasons, OxyContin was initially promoted for cancer patients, with the plan to quickly expand to non-cancer patients and doctors in these same high-cancer-incidence communities. This led to an increase in the promotion of and exposure to OxyContin in areas with higher cancer incidence at the time it was introduced, which persisted over time and opened the door for other pharmaceutical companies to promote their prescription opioids beyond the cancer market. We exploit this geographic variation in exposure to OxyContin as an instrument for the supply of prescription opioids. We provide empirical support for the strategy by showing that (i) before the launch of OxyContin, cancer incidence is not related to opioid mortality, and areas with higher cancer mortality are not on a differential trend with respect to education, income, or health variables; (ii) the evolution of cancer incidence is parallel over time in low- and high-incidence regions and does not account for the differences that appear over time as the opioid epidemic unfolds; and (iii) communities with high rates of cancer at the time of launch experienced a substantial influx of prescription opioids, which was mostly driven by prescribed oxycodone, the active ingredient in OxyContin. This rapid trend was not observed in low-cancer communities.[2]

We quantify the effects of the marketing of OxyContin on drug mortality and a host of economic and health variables: all-cause mortality, birth and fertility outcomes, and demand for social insurance. We leverage data from multiple sources, including administrative data from the Drug Enforcement Administration (DEA) to measure prescription opioid distribution across the country and restricted-access data from the National Vital Statistics System (NVSS) to measure opioid deaths, cancer deaths, and birth and fertility outcomes. We use data from the Food and Nutrition Service of the Department of Agriculture and the Social Security Administration to construct demand for the Supplemental Nutrition Assistance Program (SNAP), Supplemental Security Income (SSI), and Social Security Disability Insurance (SSDI). Our analysis is conducted at the commuting-zone level, an aggregation that encompasses all metropolitan and non-metropolitan areas in the US. This is a natural geographic unit for measuring exposure and access to the local market for prescription opioids. 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. Our final dataset consists of 590 commuting zones, with data from 1999 to 2018.

In terms of the direct effects of the marketing of OxyContin, we estimate that commuting zones with the highest cancer incidence—the 95th percentile relative to the 5th percentile—at the time of the launch of OxyContin received 1.96 doses more of opioids per capita, which amounts to 64% of the average change from 1999 to 2018. We use

[1] These court documents are from Case 07-CI-01303 Commonwealth of Kentucky v. Purdue Pharma.

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

this increase as an exogenous variation in the supply of prescription opioids and find that increasing this supply from the 25th to the 75th percentile caused an increase of prescription opioid deaths of 89% and of all opioid deaths of 39%, which corresponds to approximately 200,000 deaths. However, we do not find evidence that prescription opioids increased death despair, such as suicides or deaths from alcohol-related diseases, as defined by Case and Deaton (2017). This work adds to the literature that documents the importance of supply-side factors (Alpert, Powell and Pacula, 2018; Fernandez and Zejcirovic, 2018; Finkelstein, Gentzkow and Williams, 2018; Schnell and Currie, 2018; Alpert et al., 2019;Evans, Lieber and Power, 2019; Eichmeyer and Zhang, 2020; Powell, Pacula and Taylor, 2020) in explaining the opioid epidemic relative to demand-side factors (Case and Deaton, 2015, 2017). We also build on Alpert et al. (2019), who use variation in state-level regulations regarding the prescription of Schedule II drugs.[3] They show that the five states that, at the time of the launch of OxyContin, had a more cumbersome process for prescribing opioids—e.g., requiring triplicate prescriptions—were not targeted by Purdue Pharma in their initial marketing plans, and subsequently reported a lower level of prescription opioids and overdose deaths. We exploit a different dimension of the marketing of OxyContin that allows us to shed light on within-state variation in prescription rates, which is as large as the between-state variation. In addition, our empirical strategy alleviates the power-related issues that arise when researchers estimate effects on opioid mortality using longitudinal data and exploiting state-level variation, as Griffin et al. (2020) point out.[4]

This paper also contributes to the literature on the effects and economic costs of the opioid epidemic on the demand for social assistance benefits, and birth and maternal outcomes. The paper not only adds the estimation of these effects to the literature, but is also the first to provide estimates that exploit the same source of variation across multiple outcomes. The strength of this approach is that it provides a complete picture of the impact of the opioid epidemic and sheds light on the mechanisms through which the epidemic unravelled.

Demand for social assistance benefits: There is significant policy interest in understanding the drivers of the recent increase in demand for social assistance and its connection to the opioid crisis. Studying the effects of opioid prescriptions for workers on short-term disability directly, Savych, Neumark and Lea (2019) find that an increase in long-term opioid prescribing leads to considerably longer duration of temporary disability. Park and Powell (2021) exploit the rise in heroin and fentanyl use as a result

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

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

of OxyContin's reformulation and find that states with a one-standard-deviation higher rate of non-medical OxyContin use before reformulation experienced a 7% relative increase in disability applications after. We find that the supply of prescription opioids deteriorated socioeconomic conditions substantially by increasing claims for SNAP and disability benefits. Specifically, a change from the 25th to the 75th percentile in the growth of prescription opioids per capita caused a 57% increase in the share of SNAP recipients, a 47% increase in the share of the population receiving SSI, and a 76% increase in the share receiving SSDI.

Birth and maternal outcomes: From 2000 to 2007, one in five women filed a prescription for an opioid during pregnancy (Desai et al., 2014). Also according to the CDC, between 2008 and 2012, on average, 39% of women of reproductive age covered by Medicaid obtained a prescription for an opioid during a year (Ailes et al., 2015). This naturally raises concerns about the risks of opioid abuse in this population and its effects on infant health. Ziedan and Kaestner (2020) exploit changes in the policy environment across states—PDMP (Prescription Drugs Monitoring Program) and "pill mill" legislation—to estimate the effect of prescription opioids on infant health.[5] They estimate that a 100% increase in opioid sales is associated with a 22-gram decrease in birth weight, a 0.3 percentage-point increase in the share of low-birth-weight babies, and no statistically significant effects on gestational age. Regarding maternal behaviors, they document that state policies that reduce prescription opioid sales result in small improvements in the start date and quality of prenatal care. In this paper, we contribute to the literature by examining directly the effects of the opioid epidemic on birth and maternal outcomes. We find that a 25th-to 75th-percentile increase in the supply of prescription opioids decreases birth weight by 0.7%, and deteriorates APGAR scores by 0.9%.[6] We estimate that there is no effect on infant mortality or on the share of low-birth-weight infants, but we find an increase in the APGAR score of infants who died in the first year, meaning that healthier infants died. We find an increase in the incidence of preterm births—but this estimate is not statistically significant—and a decline in pregnancy duration of 0.24 weeks. Overall these results point to a general decline in health at birth. Finally, we estimate an increase in fertility rates of 9%, mostly driven by women 25-29 years old.

The rest of the paper is structured as follows. Section II provides background on the marketing of OxyContin and other opioids. Section III describes the data and provides summary statistics. Section IV explains our identification strategy, provides empirical evidence to support our approach, and assesses threats to the validity of the instrument. Section V presents our results along with robustness checks. Section VII concludes.

[5]The term "pill mill" is typically used to describe a doctor, clinic, or pharmacy that prescribes or dispenses controlled prescription drugs inappropriately (Malbran, 2007).

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

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

In 1996, Purdue Pharma introduced OxyContin to the market. OxyContin is the brand-name for the extended-release formulation of oxycodone. When patented, OxyContin was described as a controlled-release oxycodone compound that substantially reduces the time and resources needed to titrate patients who require pain relief on opioid analgesics (Oshlack et al., 1996). Two key technological innovations are responsible for its success. First, its long-acting formula provided 12 hours of continuous pain relief, an improvement over the standard practice of pain relief every 6-8 hours. Second, it is a single-agent narcotic, so there is no ceiling on the amount of oxycodone per tablet.[7] 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 tablets of oxycodone. In contrast, the most common forms of OxyContin were 20 mg and 40 mg tablets of oxycodone, while 80 mg and 160 mg tablets were also available. Furthermore, OxyContin users rapidly learned that crushing or dissolving the pill causes the oxycodone to be delivered all at once—instead of the slow release over 12 hours—which causes strong euphoric effects.

Prior to the introduction of OxyContin, pain management focused on cancer and end-of-life pain treatment. Patients who suffered from debilitating chronic pain but who do not have a fatal illness were excluded from long-term therapy with opioids, based on care providers' fear that patients would become addicts (Melzack, 1990). MS Contin, 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. OxyContin was intended to take over MS Contin's market and gain ground in the much larger non-cancer pain treatment market, in which opioids were almost absent. Nonetheless, establishing the use of OxyContin for moderate and chronic pain was not an easy task; it was clear to Purdue that they were going to face pushback when expanding to the non-cancer market. Specifically, based on physicians' focus groups in 1995, Purdue concluded that *"there is not the same level of enthusiasm toward this drug for use in non-cancer pain as we identified in cancer pain"* (Purdue Pharma, 1995). The two main barriers Purdue Pharma faced were (i) the stigma related to the use of opioids for non-terminal or non-cancer pain and (ii) the administrative barriers physicians and pharmacies had to overcome to prescribe and sell Schedule II drugs.

[7] 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.

To overcome these obstacles, Purdue deployed a comprehensive marketing strategy based on three main pillars. First, to effectively change physician prescribing behaviors, Purdue Pharma implemented an aggressive marketing plan that pushed the message of an untreated pain epidemic that affected millions of Americans on a daily basis. Pain was introduced as the fifth vital sign, with the goal of encouraging the standardized evaluation and treatment of pain symptoms (Jones et al., 2018). This messaging also included misleading statements—for instance, that opioid addiction rates were lower than 1% and that oxycodone was weaker than morphine, when it is 50% more potent.[8]

Second, OxyContin was promoted directly to physicians by the largest and highest-paid sales force in the industry.[9] The continuous promotion of OxyContin through advertisements, gifts, and promoted medical literature was delivered through repeated visits and calls to physicians. At the same time, the marketing team carefully tracked physician prescription habits to concentrate on the highest prescribers (Van Zee, 2009); OxyContin's annual budget plans state that they will focus on physicians in the top 3 deciles of prescriptions (OxyContin Launch Plan, September 1995, OxyContin Budget Plan, 1996).[10]

Third, Purdue focused their initial marketing efforts on physicians and pharmacies who faced less stigma and paperwork when prescribing opioids. Purdue targeted cancer patients and oncologists who had experience with prescription opioids, with a plan whereby *"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 oncologists and cancer patients to introduce its newest product to the broader market. This strategy also solved additional logistical problems related to the sales of Schedule II drugs, such as OxyContin. At the time of launch, only about half of the pharmacies in the country had the paperwork required to sell Schedule II drugs, and because *"pharmacists are generally reluctant to stock Class II opioids,"* Purdue decided that their *"initial targets will be the 25,000 stores who stock MS Contin,"* where there was no additional paperwork or training required for pharmacies to stock OxyContin.

Purdue's marketing strategy succeeded in (i) making OxyContin a blockbuster drug; OxyContin sales grew from $48 million in 1996 to almost $1.1 billion in 2000 (Van Zee,

[8] *"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 deposition, August 28, 2015.

[9] 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).

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

2009) and yielded $35 billion in revenue for Purdue Pharma (Keefe, 2017), and (ii) making the use of opioids standard practice in the treatment of moderate and chronic pain for a wide range of non-terminal 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 with the objective of growing by reducing OxyContin's market share: *"Success means increasing Duragesic share at the expense of OxyContin"* (Sales Force Memorandum, 2001, Exhibit S0510, State of Oklahoma v. Purdue Pharma et al.)[11] For our purposes, this strategy means that areas with a higher incidence of cancer at the time of the launch of OxyContin would receive a disproportionate amount of marketing and prescriptions for OxyContin and other opioids. This allows us to exploit the differential promotion of OxyContin and its competitors across geographies as a source of exogenous variation in the supply of opioids to quantify the effects of the opioid epidemic on a broad range of outcomes.

III. Data and Summary Statistics

A. Prescription Opioids

We digitize historical records from the Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA). These reports contain the distribution records of all Schedule II substances by active ingredient (e.g., oxycodone, hydrocodone, and morphine). These data are available at the 3-digit ZIP code level from 1997 to 2018.[12] 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 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. 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

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

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

morphine. On average, the shipment of oxycodone to a commuting zone is 3.15 doses per capita in a given year. This figure is 1.6 times as much hydrocodone shipped (1.93 doses per capita) and 3.3 times as much morphine shipped in a given year (0.94 doses per capita). There is wide variation among commuting zones in the levels of opioid prescriptions per capita: 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, and Table A1 shows the evolution of doses per capita over the last two decades. In 1997, the first year with available data, oxycodone and morphine average doses per capita were 0.31 and 0.35, respectively. A decade later, oxycodone doses were 3.26 on average per capita—three times higher than morphine doses per capita. To provide a reference number, consider that in 2016 the CDC established guidelines suggesting that a prescription of 3 days or less, at the lowest effective dose, should be sufficient to treat acute pain (Dowell, Haegerich and Chou, 2016). Thus, by 2007 the average prescription per capita was already at the prescribing limit the CDC would suggest 9 years later.

B. Opioids, Cancer, and Birth Outcomes

We use restricted data from the National Vital Statistics System (NVSS) to construct mortality measures and birth outcomes at the commuting zone level. Mortality measures come from Detailed Multiple Cause of Death (MCOD) files from 1989 to 2018. These 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.[13]

We construct two main measures of opioid-related deaths: prescription opioids and all opioid deaths. The prescription opioids category captures deaths whose underlying cause is substances usually found in prescription painkillers such as hydrocodone, methadone, morphine, and oxycodone, among others.[14] We also consider a broader measure of opioid-related deaths, in which we include deaths from heroin and synthetic opioids; e.g., fentanyl.[15] The CDC reports that the transition from the ICD-9 to ICD-10 resulted in a

[13]Data from the MCOD files and the Linked Birth and Infant Death Data files are provided with county-level identifiers. 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. These crosswalks enable a probabilistic matching of sub-state geographic units, defined by the US Census, to commuting zones.

[14]We use identification codes T40.2 and T40.3 to identify these deaths in the ICD-10 data and codes 965.00, 965.02, 965.09, E850.1, and E850.2 in the ICD-9 data. We follow recommendations from the CDC to construct comparable measures of prescription deaths over time; see CDC (2013).

[15]We use identification codes T40.0-T40.4, X42, X62, and Y12 to count deaths from any opioid in the ICD10-data and codes 965.00, 965.01, 965.02, 965.09, E850.0, E850.1, and E850.2 in the ICD-9 data; see CDC (2013).

small increase in poison-related deaths of 2% (Warner et al., 2011). Appendix Figure A1 shows the time series for the US for these two measures.

Table 1 reports summary statistics on opioid mortality. There were 4 deaths from prescription opioids and 7 deaths from any opioids per 100,000 residents, on average, per year between 1999 and 2018. Prescription opioid deaths vary from no deaths to as many as 106 per 100,000 residents in the most affected commuting zones. Map 2 shows this geographical variation.[16]

We also study how the marketing of prescription opioids affected deaths of despair. Following Case and Deaton (2015), we define deaths of despair as deaths by drug and alcohol poisonings, suicide, and chronic liver diseases and cirrhosis.[17] Although deaths of despair are related to opioid use; on average 90% of deaths counted as deaths of despair are not counted as opioid deaths.[18] We also present separate results for deaths from alcoholic liver diseases and cirrhosis, and suicide; for these categories at least 95% of deaths are not counted as opioids deaths.

We measure cancer incidence by computing cancer mortality in a given commuting zone from the MCOD files. For our purposes, a direct measure of cancer incidence would be to compute the rate of cancer patients in the population. Unfortunately, these data are not available. Incidence measures reported by the CDC and the Surveillance, Epidemiology, and End Results (SEER) program are aggregated at the state level, and are more likely to be affected by variation in diagnosis rates, especially for early-stage cancers. In contrast, cancer mortality is available at county level and has a closer connection to the rates of cancer patients who are using opioid pain-killers (e.g., MS Contin) to manage cancer pain, especially in the later stages of cancer treatment. Cancer mortality is likely a lagged measure of cancer incidence in the population, as cancer deaths at t, are cancer patients at $t-1$. We measure cancer incidence at the time of OxyContin's launch as the average cancer mortality rate between 1994 and 1996.

Summary statistics on cancer mortality for the pre-OxyContin period are presented in the second panel of Table 1, along with cancer mortality rates for the years 1999-2018. Map 3 shows the variation in average cancer mortality in 1994 and 1996. On average, there were 2.52 cancer deaths. The commuting zone with the lowest cancer mortality experienced 1 death for every 1,000 residents, and the commuting zone with the highest mortality experienced 60 deaths per 1,000 residents. These figures are comparable to

[16]We restrict our sample to commuting zones with a population higher than 25,000 in 1999. These commuting zones represent 99.8% of all opioid deaths and 99.3% of the total population. In Appendix Table A11 we present results for different population cuts.

[17]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 and drug poising are counted using codes X40-45, Y10-15, Y45, Y47, and Y49 in the ICD10-data and codes E850-E858, E860, and E980.1 in the ICD-9 data.

[18]In 2000, 91% of deaths of despair were not counted in the all opioids deaths category, by 2015 this share decreased to 84% of deaths of despair.

those documented for the years 1999-2018, when there were 2.48 cancer deaths on average.

Data on birth outcomes come from the Linked Birth and Infant Death Data of the NVVS of the National Center for Health Statistics. 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.[19] We construct infant mortality as the ratio of infant deaths to live births in a given calendar year. The Linked Birth and Infant Death Data also include data on the infant's condition at birth, such as weight and length of gestation. The main measures of infant health we compute from the birth files are the commuting-zone-level (i) average birth weight for all live births, (ii) share of low-birth-weight newborns, (iii) share of preterm births, (iv) APGAR score of all births, (v) APGAR score of deceased infants, and (vi) median pregnancy duration. We also use the birth files to compute the average fertility rate at the commuting-zone level, defined as the ratio of the number of single pregnancies to the female population aged 15 to 44 years old.[20,21]

C. Demand for social assistance benefits

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. When information at the local level is not available, we impute the state-level share of SNAP recipients.[22] We include two measures of disability benefits recipiency, constructed as the share of the population 18 to 65 that receives Supplemental Security Income (SSI) and who is blind or disabled, and the share of the population 18 to 65 that receives Social Security Disability Insurance (SSDI). Information on the total number of SSI recipients in each county is based on SSI Annual Statistical Reports and Old Age, Survivors and Disability Insurance (OASDI) reports prepared by the National Social Security Administration, which we aggregate at the commuting-zone level.[23]

[19] 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.

[20] 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.

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

[22] Table A12 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.

[23] 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

IV. Empirical Strategy

The level of prescription opioids in a given place and time is an equilibrium object determined by supply and demand factors. Supply factors, such as the density of the healthcare network, and demand factors, such as the incidence of pain in the population, affect the level of prescription opioids and may also affect the evolution of our outcome variables. Table 2 shows that the distribution of opioids is not random across space, but rather is related to the demographic composition of the commuting zone and its economic performance. A greater share of the white population and higher median income at the commuting-zone level have a positive correlation with prescription opioids per capita; the share of the Hispanic population, the employment rate, and the demand for social insurance have a negative correlation with the opioid supply.[24] This is in line with Finkelstein, Gentzkow and Williams (2018), who estimate that areas with more physicians per capita, higher levels of income and education, lower Medicare spending per capita, and higher scores on a healthcare quality index have higher opioid abuse rates.

To identify the effect of prescription opioids on opioid-related mortality and our outcomes of interest we use an instrumental variable strategy that exploits geographical variation in the promotional efforts for OxyContin and other prescription opioids as an exogenous variation in the opioid supply. We estimate the causal effects of the supply of prescription opioids via the following equations, which are run over our sample of commuting zones for the period 1999-2018:

First Stage:

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

Second Stage:

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

where c indexes commuting zones, t indexes years, s indexes states, and t_0 is defined as the average of the pre-OxyContin period, i.e., 1994-1996. The operator Δ works as follows: For any random variable W_{ct}, ΔW_{ct} equals the difference $W_{ct} - W_{ct_0}$; we refer to this operation as the long-change of variable W_{ct}. Regarding equation (1), *Presc. Opioids*$_{ct}$ corresponds to doses of opioids per capita shipped to commuting zone c in year t and $CancerMR_{ct_0}$ is the cancer mortality rate in commuting zone c in 1994-1996 (t_0). In equation (2), y_{ct} refers to one of our outcomes of interest, e.g., a measure of opioid-

change in the stock is due to people entering more quickly or receiving benefits for longer time.

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

related mortality. Both equations include a vector ΔX_{ct} that represents the long-changes in the time-varying control variables. The control variables included are contemporaneous cancer mortality, share of the population over 66, share of the population 18-65, share of the population under 1 year, shares of the white and black populations, share of females, and share of Hispanic population. We add state times year fixed effect represented by the term γ_{st} (and λ_{st} in the second-stage equation). These fixed effects control for the variation in outcomes over time that is common to all commuting zones within state s, and purge the variation in the supply of prescription opioids that results from a change in state-level policies, such as the implementation of a PDMP. The variables υ_{ct} and ε_{ct} are idiosyncratic error terms. We cluster standard errors at the commuting-zone level, which is the level of exogenous variation.

We have defined our main specification using a long-changes form—i.e., by computing the change relative to a baseline year for each variable in the estimation. This approach has two advantages. First, it allows us to control for unobservable characteristics at the commuting-zone level. Since our exogenous variation is at the commuting-zone level, we cannot include commuting-zone fixed effects in the regression. However, by expressing our variable in changes, we can partially absorb some of the variation that is specific to the commuting zone. Second, we argue that *how* the supply of opioids per capita evolves relative to the base year is more indicative of the exposure to opioids than its variation in levels. The opioid epidemic has evolved in three waves, with each one characterized by the highest levels of misuse and abuse of a given substance.[25] The misuse and abuse of prescription opioids were the main drivers of deaths until 2010. Nonetheless, research has also found that prescription opioids play an important role in the initiation and use of heroin and fentanyl (American Psychiatric Association, 2017).

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

[25]The first stage reflected massive increases in the use of prescribed opioids and dates from the mid-1990s through 2010. The second wave, from 2010 to 2013, was distinguished by extensive growth in heroin use and associated deaths. The third and current wave, beginning in 2013, has been characterized by surging deaths and problems related to the use of synthetic opioids, particularly fentanyl and its analogs (Maclean et al., 2020)

empirical evidence to support this empirical strategy and assess threats to the validity of the instrument.

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

We start by providing graphical evidence in Figure 1. We divide commuting zones into quartiles according to their level of cancer mortality before the launch of OxyContin and trace the evolution of all prescription opioids, oxycodone, hydrocodone, and morphine in these communities. Panel A of Figure 1 shows the evolution of oxycodone per capita in commuting zones in the bottom and top quartiles of cancer mortality in 1994-1996 and, panel B shows the analogous exercise for the aggregate of prescription opioids.[26] 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 A2.

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

The literature on weak instruments has developed a variety of tests and confidence sets that remain valid whether or not the instruments are weak, in the sense that their probability of incorrectly rejecting the null hypothesis and covering the true parameter value, respectively, remains well controlled. We implement these procedures and present weak-instrument-robust inference. We follow Andrews, Stock and Sun (2019) recommendations and present the effective first-stage F statistic proposed by Olea and Pflueger (2013) to assess the instrument's strength. In the rest of this paper, we refer to this as the *effective F-stat*. The value of the F-statistic testing the null hypothesis that the

[26] In Appendix Figure A3 we present the analogous analysis, but we split the data based on 8 octiles of cancer mortality and observe the same pattern.

instrument is equal to zero in the first stage is always greater than 10, suggesting that we can reject the null hypothesis. Nonetheless, Lee et al. (2020) suggest that this standard practice of relying on the first-stage F exceeding some threshold (e.g., 10) delivers tests of incorrect size. Thus, to assess the statistical significance of our estimates, we (i) compute the "tF 0.05 standard error" proposed by Lee et al. (2020), which inflates the usual standard errors to take into account the strength of the first stage, and (ii) present *p-values* based on Anderson-Rubin Test (Anderson, Rubin et al., 1949).[27]

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

Variation in cancer mortality across locations is not random; rather, it depends on demographic and socioeconomic variables. This could be a threat to our identification strategy since our baseline regression links cancer mortality in commuting zone c at time t_0 with the changes in an outcome variable (e.g., drug mortality) in commuting zone c at time t_0. 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 growth as areas with lower cancer mortality in t_0 in terms of our outcome variables (Goldsmith-Pinkham, Sorkin and Swift, 2020).

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

$$\Delta\ y_{ct} = \alpha_0 + \sum_{t=1989}^{2018} \phi_t\ CancerMR_{ct_0}\mathbf{1}(Year_t) + \alpha\ \Delta\ X_{ct} + \gamma_{st} + \upsilon_{ct} \tag{3}$$

where Δ is the long change operator, and X_{ct} is a vector of time-varying control variables defined previously. In this specification, the coefficients for the pre-OxyContin period; e.g., ϕ_{1989}, ϕ_{1990}, to ϕ_{1995}, test whether the outcome of interest y_{ct} in high and low cancer mortality areas followed similar trends before OxyContin was introduced to the market in 1996. Figure 2 shows the results of this estimation. We find that areas with higher cancer mortality in the mid-nineties were not on a differential trend along: opioid-related

[27]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.

mortality, all-cause mortality, despair mortality, infant mortality, birth weight, fertility, or share of population using SNAP.[28]

Second, in Table 4, we test whether cancer mortality is related to changes in other socio-economic variables such as employment, education, income, or industry composition. Column 1 shows regression results of socio-economic variables on our instrument: 94-96 cancer mortality, and Column 2 repeats this exercise for average cancer mortality in 89-90, the first years in our data. We find that higher cancer incidence is not related to changes in these socio-economic variables.

V. Results

A. Effects on Opioid-related Mortality

We start by inspecting the raw data; in 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 for both prescription opioids and all opioids.[29] Second, following the reduce-form approach from E.q 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 (a) and (b) of Figure 2.

Next we take equations 1 and 2 to the data. Commuting zones with the highest cancer incidence at the time of OxyContin 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 increase, we estimate that an additional dose of prescription opioids per capita caused an increase in prescription opioid mortality of 0.0068 points and in all opioid mortality of 0.0065 points. The estimates presented in columns 3 and 6 of Table 5 are statistically significant using t-ratio inference, Anderson-Rubin weak instrument robust inference, and the recent tF procedure suggested by Lee et al. (2020). Our results imply that when doses per capita increase from the 25th to the 75th percentile—i.e., a 5.02 dose increase—mortality from prescription opioids increases by 88.6% and all opioid mortality increases by 39.3%.[30]

The ordinary least squares (OLS) estimates (columns 1 and 4 of Table 5) differ considerably from the IV estimates. We find a positive correlation between opioid supply and opioid mortality rate, but the difference in magnitude between the OLS and the IV

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

[29]In Appendix Figure A4 we present the analogous analysis, but we split the data based on 8 octiles of cancer mortality and observe the same pattern.

[30]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.

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

Heterogeneous effects. The excess opioid-related mortality induced by the marketing of OxyContin is by and large coming from middle-age white adults. In Appendix Table A2, we repeat our main regression, but change the group for whom we estimate opioid related mortality. Our results imply that when doses per capita increase from the 25th to the 75th percentile—i.e., a 5.02 dose increase—mortality from prescription opioids increases by 58.8% among those aged less than 50 years old, while the estimates for those above 50 years old are not statistically indistinguishable from zero. We find analogous results when we restrict our sample to white population.

The opioid crisis can be viewed as having occurred in three waves (Maclean et al., 2020). The strong relation between mid-nineties cancer mortality and the supply of prescription opioids is present in all the stages of the crisis—Panel A of Table A3 reproduces the estimates of the first stage for different starting and ending year. Our results suggest that the increase in the supply of prescription opioids had a stronger impact on opioid-related mortality in the first wave of the epidemic. However, these differences across periods are not statistically significant.

B. Indirect Effects of the Marketing of Prescription Opioids.

Prescription opioids not only contributed directly to the increase in overdose deaths, but also indirectly deteriorating the living conditions of adults and children by an increase in disability claims (Park and Powell, 2021); worsening birth outcomes (Lynch et al., 2018); and record numbers of children living in foster care as a result of a parent's drug use (Meinhofer and Angleró-Díaz, 2019; Buckles, Evans and Lieber, 2020). In this section, we document the cost of the increase in opioid supply on non-cancer-related mortality, the demand for social insurance, and infant and maternal outcomes.

Aggregated Mortality. Areas with high- and low-cancer-incidence were comparable in terms of non-cancer-related mortality before the introduction of OxyContin—as shown in Panel (c) of Figure 2. We find no relationship between this measure of 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. (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. In panel (c) of Figure 2 and panels (b) and (c) of Figure A5, however, we show that there is no evidence of an effect of the opioid crisis on deaths of despair such as suicides or alcohol-related deaths beyond the direct effect on drug overdoses documented before. Table 7 shows the instrumental variables results for these outcomes. We estimate a positive but small increase in overall deaths from despair and deaths from alcoholic liver diseases and cirrhosis significant only at the 10% level and no effect on suicides. This last result also speaks to a recent literature on the connection between access to opioids and suicides (Tibbitts and Cowan, 2021).

Demand for Social Insurance. Addiction to and misuse of prescription opioids could reduce work capacity and put people at risk of permanently reducing their labor supply; in this context, disability insurance applications are a useful proxy for socioeconomic conditions and longer-term labor force attachment. We document a tight link between the opioid epidemic and an increase in disability beneficiaries. These results are presented in Panel A of Table 6. We find positive and significant effects for measures of both disability programs. A change from the 25th to the 75th percentile in the growth of opioids per capita caused a 47% increase in the share of the population receiving SSI and a 76% increase in the share receiving SSDI. [31]

SNAP is designed to act as a safety net for low-income workers. In our context, applications to SNAP are a useful proxy for deteriorating economic conditions. We find a positive effect on the share of SNAP beneficiaries: Our estimates suggest that a change from the 25th to the 75th percentile in the growth of oxycodone per capita caused a 57% increase in the share of the population enrolled in SNAP.[32] These results point to a substantial worsening of economic conditions. The effects we observe on SSDI and SNAP are particularly strong during the third wave of the epidemic, when the incidence of illicit drug use, such as of heroin and fentanyl, increased (Table A4).

Birth, Pregnancy, and Fertility outcomes: The opioid epidemic among adults could affect the well-being of infants through various channels. In this paper, we explore how the epidemic has impacted infant health and maternal outcomes (Panel B of Table 6).

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

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

We find evidence that an increase in opioid prescriptions caused a worsening of birth outcomes; a 25th-to-75th-percentile increase in the supply of prescription opioids decreases birth weight by 0.7%, and deteriorates APGAR scores by 1% relative to its mean value. Although not statistically significant, we estimate increases in the share of low-weight births. We also find an increase in the APGAR score of infants who died in the first year, which means that healthier infants died. However, in aggregate terms, we do not find any increase in the infant mortality rate.

We also explore maternal outcomes. We find a 0.62% reduction in the median gestation period when the opioid supply increases from the 25th to the 75th percentile. This result translates to a reduction in the median length of pregnancy of 0.24 weeks, although the increase in the incidence of preterm births is not statistically significant. We estimate an increase in fertility, a 25th-to-75th percentile increase in opioids increases fertility by 9%. This is the result of an increase in fertility for women 25 to 29 years old, which compensates a decline in fertility for those over 35 years old. These results are presented in Appendix Table A5. Using survey data, others have documented that opioid use is linked to lower adherence to contraceptive methods (Terplan et al., 2015), and that the increase in fertility is only present for non-marital births (Caudillo and Villarreal, 2021).

In summary, our results suggest that the opioid epidemic, while not affecting directly the infant mortality rate, contributes to the worsening of birth outcomes through reductions in pregnancy duration and infant health at birth. This deterioration in birth outcomes, could have been compensated for by the change in the composition of mother's age in favor of younger mothers. Nonetheless, our estimated declines in birth weight are not small in magnitude. For a reference, Almond, Hoynes and Schanzenbach (2011) estimate an increase in birth weight of 0.5 percentage point as a result of the roll-out of food stamps, and Hoynes, Miller and Simon (2015) find a 0.3% increase in birth weight from the expansion of the Earned Income Tax Credit (EITC). This is particularly important in light of evidence on the importance of birth weight and health at birth for future health, schooling, and earnings (Behrman and Rosenzweig, 2004).

VI. Robustness Checks

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

A. First Stage

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, Sorkin and Swift, 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 A6, 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, Sorkin and Swift (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.

A potential concern with our choice of instrument is that mid-nineties cancer mortality may be capturing demographic variation along the age distribution. Our baseline regression already controls for the change in the share of the population over 65, but our instrument is expressed in levels, so some of this variation may still be important. We directly test this by including the share of population over 65, the size of the population over 65, and total population as additional control variables. Table A7 shows the results of this exercise. We find that the first stage regression is as strong as in our baseline regression.

We test whether the positive relationship in our first stage is driven by a state or a group of states. Figure A6 presents the estimate of the first stage coefficient restricting the sample to (i) all non-triplicate states, (ii) only triplicate states, and (iii) to the exclusion of all states, one at the time. We find that the relationship between mid-nineties cancer mortality and the supply of opioids is not only present in non-triplicate states or driven by one particular state.

B. Placebo checks

Are other mid-1990s mortality rates predictive of future prescription opioids per capita distribution? Our identification strategy connects mid-1990s cancer mortality to future growth in the supply of prescription opioids through the targeted marketing of Purdue Pharma. As a result, 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. However, 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 (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 A8 we show placebo instrument regressions for two mortality rates that

are less likely to be affected by the previous concern: Cerebrovascular disease and transit accidents. We find that none of these measures predict future distribution of opioids (Columns 1 and 2) or change the predicted power of our instrument (Columns 3 and 4).

An additional ideal placebo check would be to estimate the relationship between cancer mortality and prescription opioids supply in the pre-period. Unfortunately, ARCOS data only starts in 1997 so this test is unfeasible. An alternative version of this test is to study directly the relationship between mortality from opioids and cancer before the launch of OxyContin. Columns 1 and 2 of Table A9 report these results. We find that different from the period after the launch of OxyContin lagged cancer mortality is unrelated to future opioid mortality. This suggests that the connection between cancer and opioids exists only as a result of the marketing of OxyContin, and is not the result of other underlying mechanisms.

C. Alternative Definitions: Opioid Supply and Opioid Mortality

Many pharmaceutical companies—Janssen, Endo, Cephalon-Teva, Actavis, Insys, and Mallinckrodt—promoted their prescription opioids beyond the cancer market following Purdue's leadership. Nonetheless, Purdue Pharma was the leader in the cancer-pain treatment market. So, as an additional check, we use data on Oxycodone—the active ingredient in OxyContin—as an alternative measure of opioid supply. We find a positive relationship between cancer mortality rates and this measure of opioid supply. In Table A9, columns (4) and (5) we estimate that an additional dose of oxycodone per capita caused an increase in prescription opioid mortality of 91% and in all opioid mortality of 40%.

Drug overdose deaths can be hard to categorize. Since we use data that record deaths using both the ICD-9 and ICD-10 codes, we construct an additional outcome measure for opioid mortality, the drug-induced mortality rate, and present the results using this measure in Table A10. The drug-induced category has the advantage that comparisons across years are less affected by changes in the ICD classification, but this comes at the cost of being less linked to our main outcome of interest—i.e., deaths from prescription opioids.[33] Exploiting this measure, we arrive at similar conclusions: An additional dose of opioids per capita caused an increase in the drug-induced mortality rate of 0.0112 points. An increase from the 25th to the 75th percentile of prescription opioids per capita increases drug-induced mortality by 47%.

[33]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.

D. Alternative Sample Restrictions

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 A11 we reproduce our analysis using alternative restrictions on the size of commuting zones. We arrive at analogous conclusions to the main analysis; there is a strong and positive relation between mid-nineties cancer mortality and supply of prescription opioids which translates to (i) increases in opioid-related mortality, and (ii) deteriorating economic conditions and health outcomes.

Finally, SNAP benefit recipiency rates at the commuting-zone level required imputations for some commuting zones with no available data at the local level. Table A12 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.

VII. Policy Implications and Conclusions

This paper studies the effects of the introduction and marketing of OxyContin on the subsequent opioid epidemic. We exploit geographical variation in the initial promotion of OxyContin that targeted the cancer patients and physicians market. We document that this initial targeting had long-term effects on opioid mortality, along with a deterioration in socioeconomic conditions measured by the demand for SSDI, SSI, and SNAP; and a worsening of birth outcomes. Overall, we find strong evidence that the marketing practices for OxyContin were central to the opioid epidemic. In this paper, we sought to provide a complete picture of the effects of the opioid epidemic. However, data access limitations have prevented us from speaking to some important topics, such as the effects on children's living arrangements and environments, foster care referrals, and the demand for and use of healthcare.[34] We hope that future research will shed light on these subjects.

Our results have direct policy implications regarding the desirability of promotional efforts by pharmaceutical companies that target physicians, pharmacies, and patients. We document the devastating consequences of aggressive and deceitful marketing. Although marketing expanded over the 25 years since the introduction of OxyContin, regulatory oversight remains relatively limited.[35] Some regulatory initiatives constitute small steps in the right direction, such as the Sunshine Act of 2010 that required the reporting of payments from the pharmaceutical industry to physicians, with a recent expansion

[34]Data on these outcomes are available for a shorter window of time than our analysis—e.g., the American Community Survey provides data on living arrangements of children starting in 2010—or at a more aggregated geography level—e.g., foster care placements are available at the state level or only for a subset of large counties.

[35]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). Direct-to-consumer prescription drug advertising is only permitted in the US and New Zealand (Schwartz and Woloshin, 2019).

that includes payments to physician assistants, nurse practitioners, nurses, pharmacists, and dietitians. Furthermore, a growing segment of the medical community has spoken out against the pharmaceutical industry's effort to influence doctors, and a number of teaching hospitals have enacted policies that restrict or ban visits from pharmaceutical representatives. However, most of these initiatives are concerned with the rising costs of prescription drugs, and not with the risks of abuse and addiction. More can be done to restrict the pharmaceutical promotion that carries this risk.

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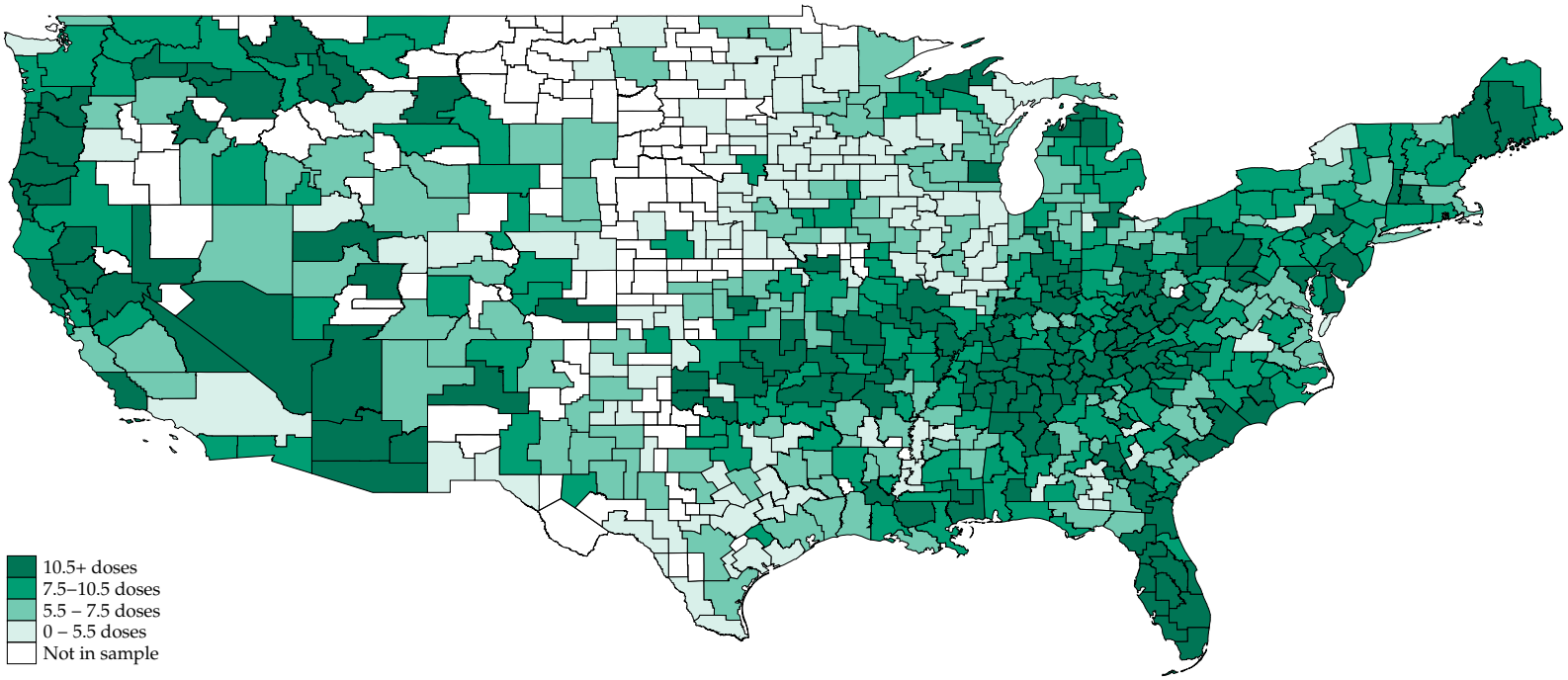
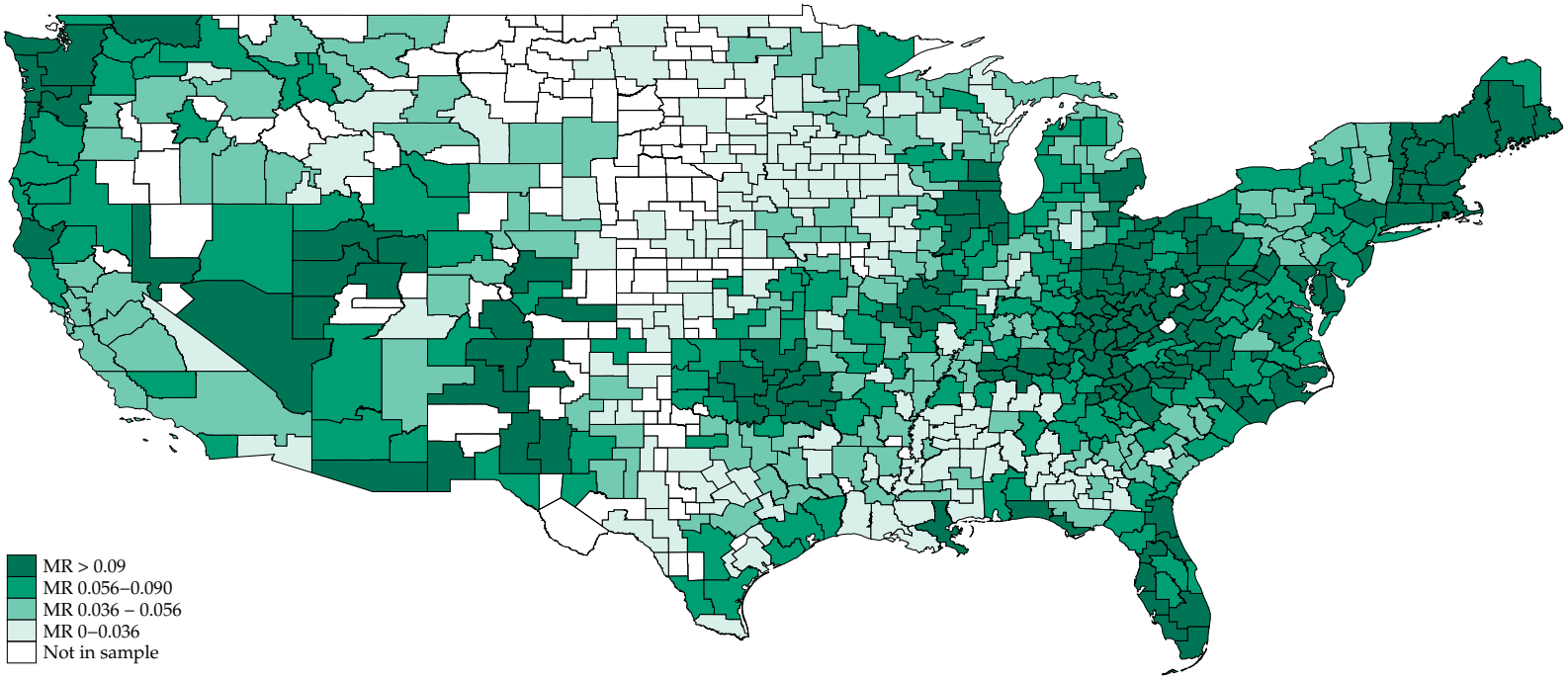
VIII. Maps and Figures

Map 1: Prescription Opioids Distribution in 2010



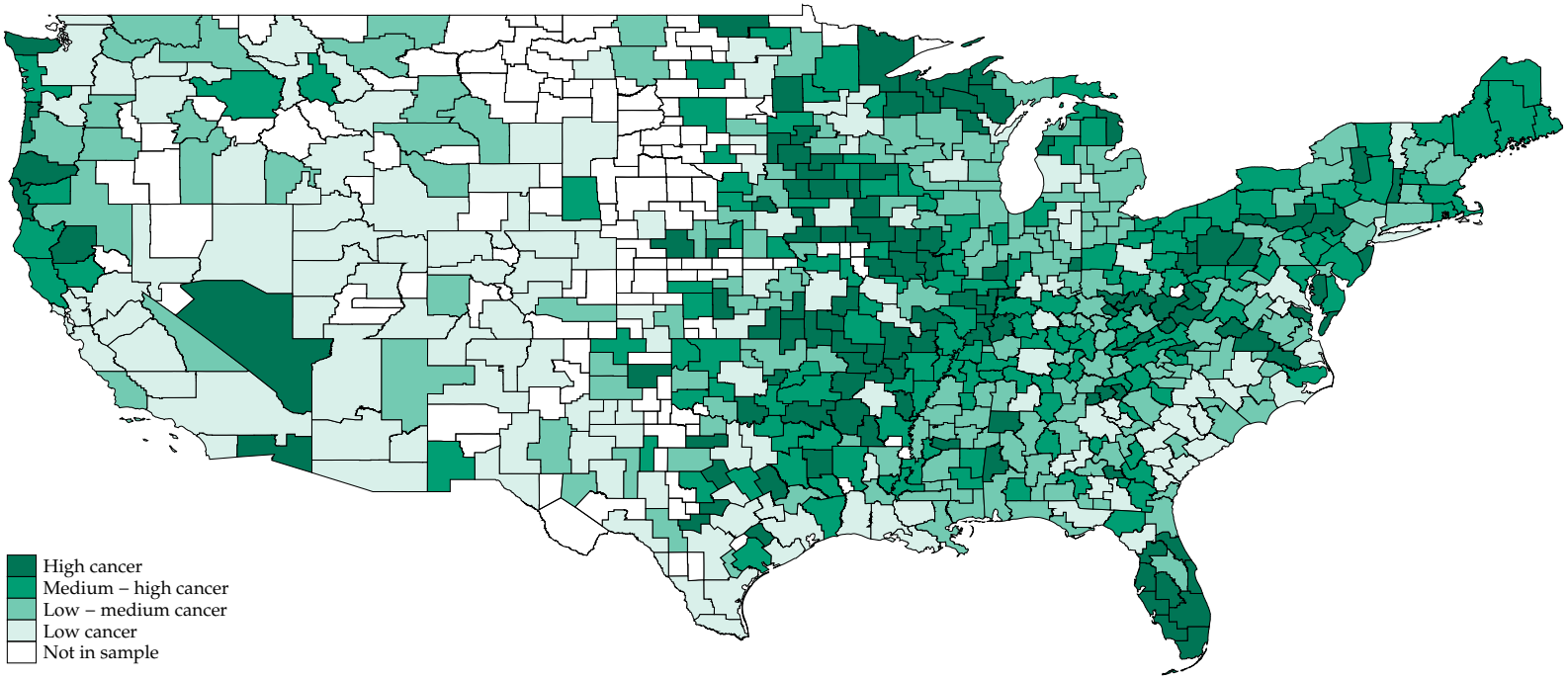
Notes: This map shows the distribution of prescription opioids in 2010. Lighter shades indicate commuting zones with a lower supply and darker shades indicate commuting zones with a higher supply. Each group corresponds to one quartile of the prescription opioids distribution; i.e., each color accumulates 25% of the mass of this distribution. This figure is referenced in Section III.A.

Map 2: Any Opioid Mortality Rate 1999 - 2018



Notes: This map shows the distribution of opioid mortality 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. This figure is referenced in Section III.B.

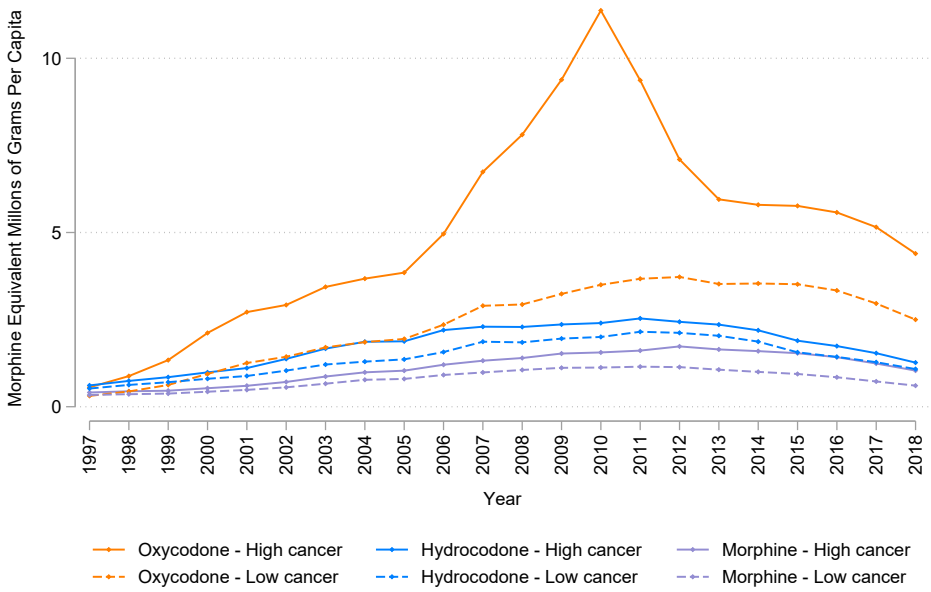
Map 3: Distribution of Cancer Mortality 1994 - 1996



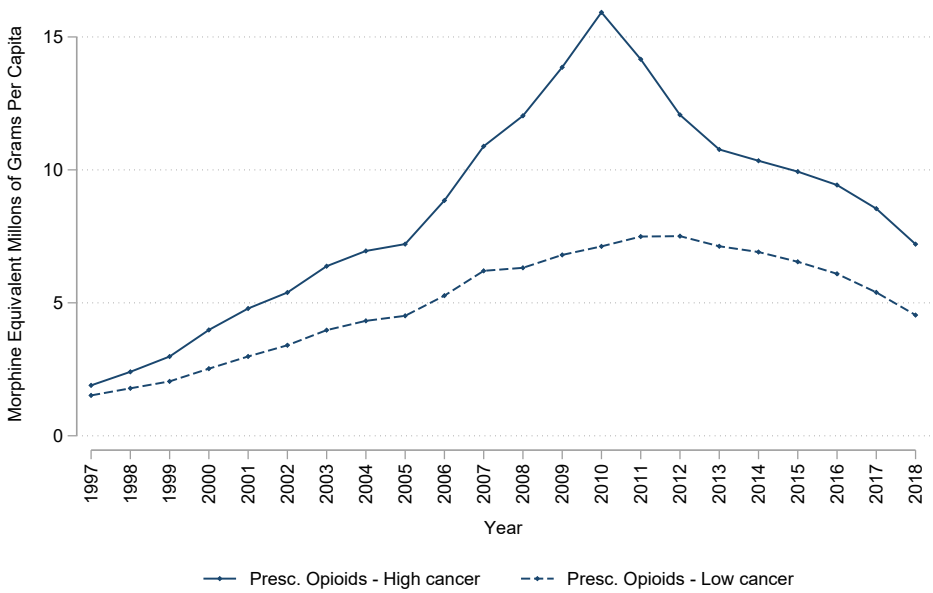
Notes: This map shows the cancer mortality rate at the commuting-zone level in 1994 - 1996. Lighter shades indicate commuting zones with lower cancer prevalence, while darker shades indicate commuting zones with higher cancer prevalence. Each group corresponds to one quartile of the cancer mortality distribution; i.e., each color accumulates 25% of the mass of this distribution. This figure is referenced in Section III.B.

Figure 1: Evolution of Prescription Opioids by 1994-1996 Cancer Prevalence

(a) Main Prescription Opioids



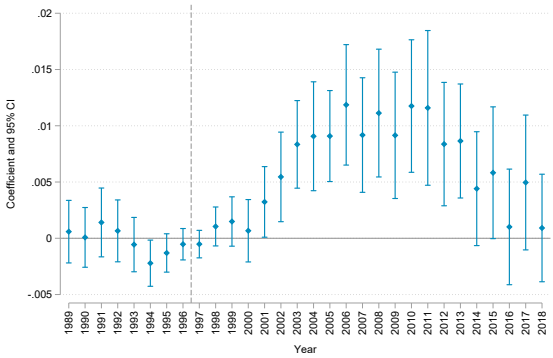
(b) All Prescription Opioids



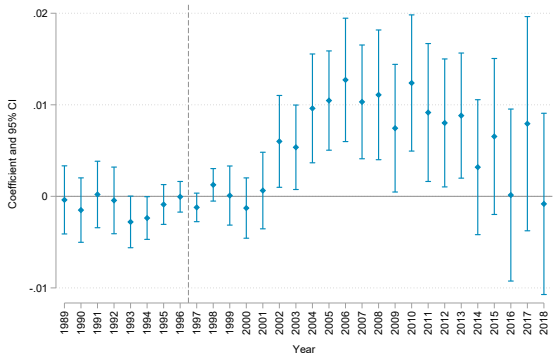
Notes: This figure shows the evolution of oxycodone, hydrocodone, and morphine (panel a) and all prescription opioids (panel b) in the forth quartile (solid lines) and first quartile (dashed lines) of the cancer mortality rate distribution before the launch of OxyContin. Between 1997 and 2010, areas in the highest quartile of cancer incidence saw an increase in oxycodone gm per capita of 2,900%, while areas in the lowest quartile experienced a growth that was one-third that. Oxycodone, hydrocodone, and all prescription opioids are measured in morphine-equivalent mg. This figure is referenced in Section IV.A.

Figure 2: Dynamic Reduced Form Estimates

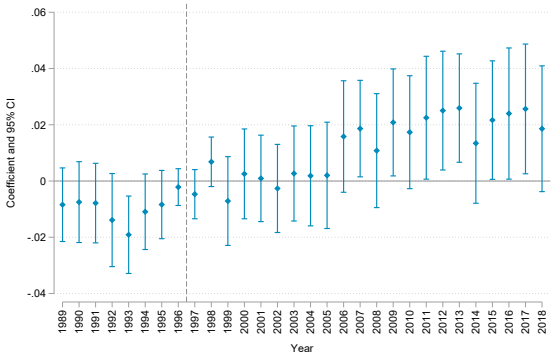
(a) Prescription Opioids Mortality



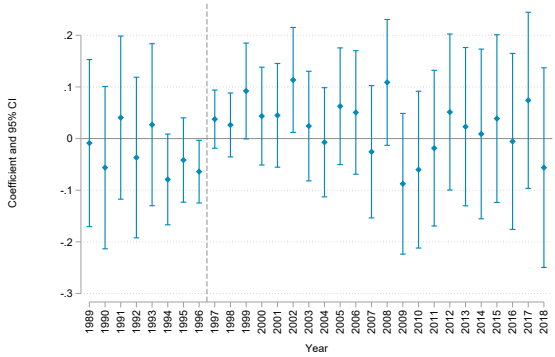
(b) All Opioid Mortality



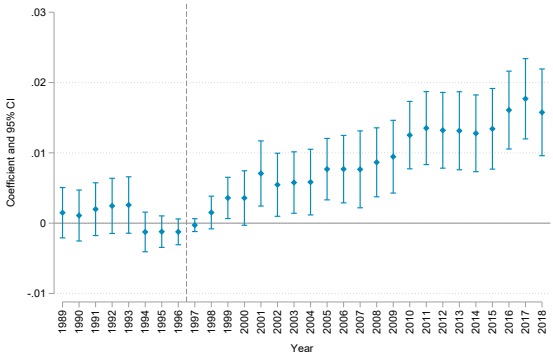
(c) Deaths of Despair



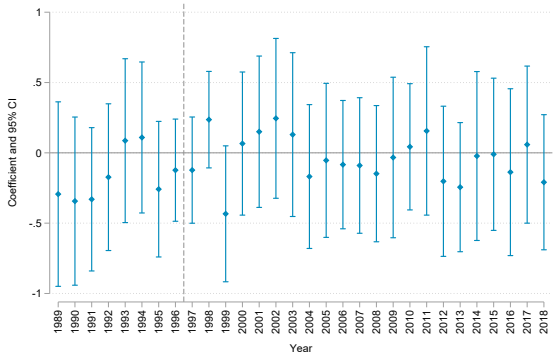
(d) All-cause Mortality



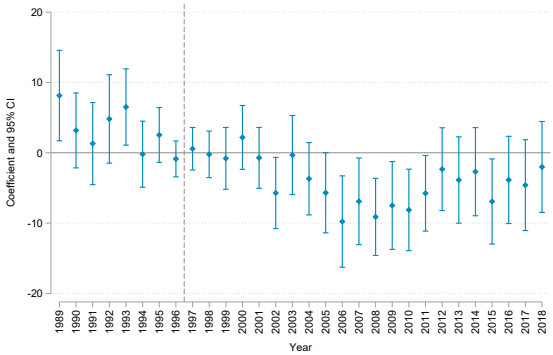
(e) SNAP



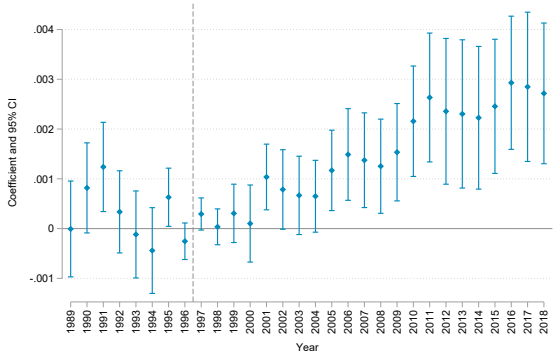
(f) Infant Mortality Rate



(g) Birth Weight



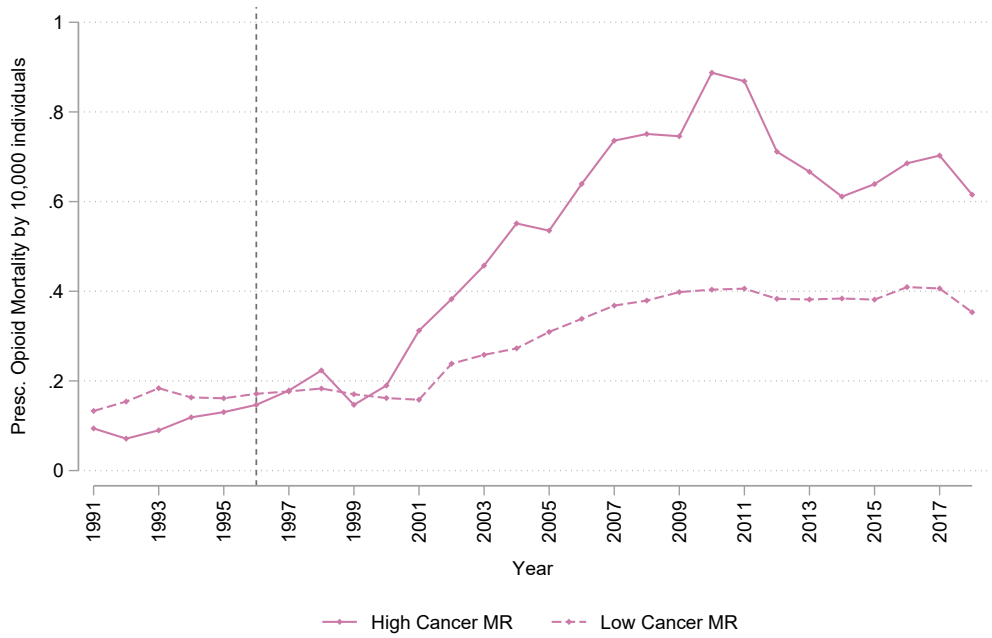
(h) Fertility Rate



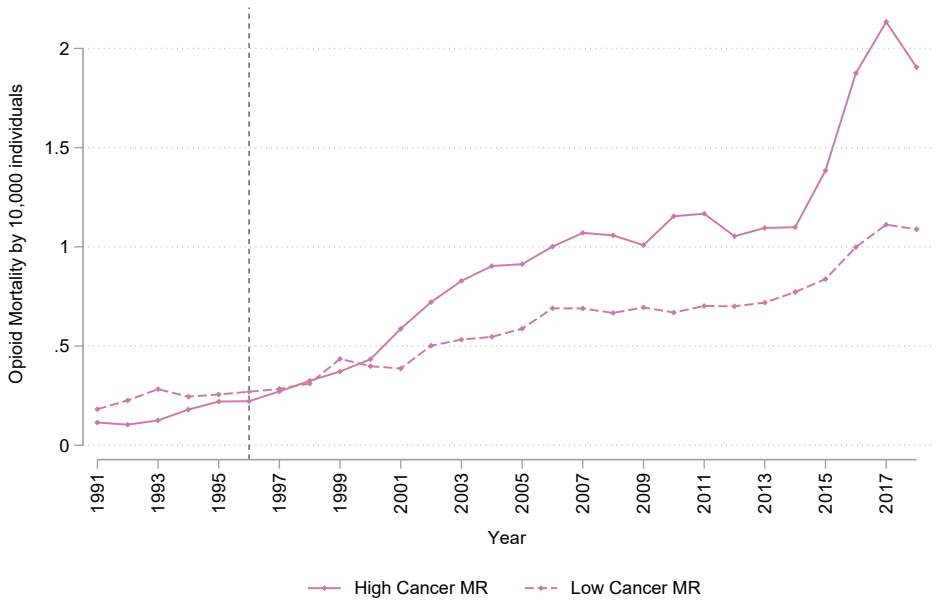
Notes: This figure shows the dynamic reduced-form relationship between outcomes of interest and our instrument—cancer mortality in 1994 - 1996. Each coefficient corresponds to the estimate of ϕ_t in Equation 3. This figure is referenced in Section IV.B., in Section V.A., and in Section V.B.

Figure 3: Opioid Mortality Rate by 1994-1996 Cancer Prevalence

(a) Prescription Opioids



(b) All Opioids



Notes: This figure shows the evolution of prescription opioid mortality (panel a) and the evolution of all opioid mortality (panel b) by 1994-1996 cancer prevalence. The high-cancer mortality rate corresponds to the group of commuting zones in the fourth quartile of cancer mortality in 1994-1996 and low cancer corresponds to the first quartile. The vertical line at 1996 indicates the year OxyContin was launched. Prescription opioid mortality captures deaths whose underlying cause is substances usually found in prescription painkillers such as hydrocodone, methadone, morphine, and oxycodone, among others; see data section for details on the codes used to construct this measure. This figure is referenced in Section IV.A.

IX. Tables

Table 1: Summary Statistics, 1999-2018

	Mean	Median	SD	Min	Max	Obs
Opioid Prescriptions: Doses per capita						
All 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
Outcomes of interest						
Opioid mortality						
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						
Deaths of despair	0.37	0.34	0.15	0.02	1.96	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
All-cause mortality (+20 years old)	9.87	9.93	2.06	2.79	20.92	11,800
Demand for social insurance						
Share SSI	0.04	0.03	0.02	0.00	0.30	11,800
Share SSDI	0.05	0.04	0.02	0.01	0.16	11,800
Share SNAP	0.12	0.11	0.07	0.00	1.20	11,800
Infant and maternal outcomes						
Infant MR (per 1,000 births)	6.86	6.54	2.87	0.00	30.61	11,800
Birth weight	3,274.25	3,276.53	79.47	2,930.28	3,569.76	11,800
Share low birth weight	0.08	0.08	0.02	0.02	0.20	11,800
Share preterm	0.12	0.12	0.03	0.05	0.62	11,800
APGAR score - all infants	8.82	8.84	0.19	5.00	10.00	11,800
APGAR score - dead infants	5.62	6.00	2.28	0.00	10.00	11,460
Median gestation	38.95	39.00	0.24	35.00	40.00	11,800
Fertility rate	0.08	0.08	0.01	0.04	0.19	11,800

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

Table 2: Determinants of the Opioid Distribution in 2000

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

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

Table 3: First-stage Results

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

Notes: The long change in prescription opioids per capita uses as a baseline the year 1997, the first year ARCOS data is available. Control variables are contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years, share of Black, White, and Hispanic population, and share of female population. Effect size is computed as the predicted changes in doses of prescription opioids per capita from an increase in cancer mortality that would change a commuting zone in the 5th percentile of the cancer distribution to the 95th percentile. Standard errors are clustered at the CZ level. * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is referenced in Section IV.A.

Table 4: Mid-1990s Cancer — Exclusion restriction

Independent variable:	Cancer MR 89-90	Cancer MR 94-96
Dependent variables		
Income per capita	19.42	16.93
	[62.24]	[66.42]
Share with some college	0.0063	0.00686
	[0.00386]	[0.00458]
Share with high school or less	0.00257	0.00183
	[0.00420]	[0.00505]
Share working in manufacturing	0.0063	0.00686
	[0.00386]	[0.00458]
Prescription Opioids Mortality Rate	-0.000795	-0.000251
	[0.000580]	[0.000617]
Any Opioid Mortality Rate	-0.00101	0.0000191
	[0.000671]	[0.000732]
Infant Mortality Rate	-0.0989	-0.0378
	[0.154]	[0.151]
Labor Force Participation	-0.00153*	0.0000537
	[0.000821]	[0.000727]
Employment rate	-0.000781	-0.000594
	[0.000489]	[0.000507]
Share SSDI	-0.000523	-0.000305
	[0.000890]	[0.000684]
Share SSI	0.000151	-0.000628
	[0.000345]	[0.00101]
Share SNAP	-0.000529	0.000678*
	[0.000840]	[0.000402]
Fertility rate	-0.641	-0.604
	[0.490]	[0.585]

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 IMR, we run a panel regression; for the other variables, where yearly data are not available, we run one cross-sectional regression. All regressions include as control variables: cancer mortality rate, share of population under 1 year, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. In panel-level regressions, standard errors are clustered at the commuting-zone level; in cross-sectional regressions, standard errors are robust to heteroskedasticity. * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is referenced in Section IV.B.

Table 5: Direct Effects on Opioid Mortality

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

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

Table 6: Indirect Effects: Consequences of the Opioid Epidemic

Panel A. All-cause mortality and social insurance outcomes.						
Dependent var:	All-cause mortality			SSDI		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.0213		0.0286	0.000444***		0.00574***
	[0.0136]		[0.0469]	[0.0000985]		[0.00132]
tF 0.05 se			(0.06580)			(0.00182)
t-stat using tF 0.05 se			0.4346			3.1250
AR p-value			0.5319			0.0000
Cancer MR 94-96		0.0309			0.00619***	
		[0.0515]			[0.000385]	
Effect size (%)	3.68		4.94	5.36		76.39
Model	OLS	RF	IV	OLS	RF	IV
Dependent var:	SSI			SNAP		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.00000709		0.00311**	0.000144		0.00982***
	[0.000147]		[0.00144]	[0.000285]		[0.00299]
tF 0.05 se			(0.00196)			(0.00407)
t-stat using tF 0.05 se			1.5833			2.4134
AR p-value			0.0114			0.0000
Cancer MR 94-96		0.00335**			0.0106***	
		[0.00137]			[0.00227]	
Effect size (%)	0.11		46.88	0.58		56.70
Model	OLS	RF	IV	OLS	RF	IV
Panel B: Infant and maternal outcomes.						
Dependent var:	IMR			Birth Weight		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.0511**		-0.0232	-0.552*		-4.490**
	[0.0242]		[0.140]	[0.331]		[2.143]
tF 0.05 se			(0.19643)			(3.00676)
t-stat using tF 0.05 se			-0.1181			-1.4933
AR p-value			0.8678			0.0163
Cancer MR 94-96		-0.0250			-4.843**	
		[0.157]			[2.127]	
Effect size (%)	4.06		-1.84	-0.08		-0.69
Model	OLS	RF	IV	OLS	RF	IV

(continued)

Table 6: Indirect Effects: Consequences of the Opioid Epidemic *(continued)*

Panel B: Infant and maternal outcomes (continued).						
Dependent var:	Share low birth weigth			Preterm births		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.000169*		0.000905	0.000270*		0.00141
	[0.000102]		[0.000640]	[0.000150]		[0.000937]
tF 0.05 se			(0.00090)			(0.00131)
t-stat using tF 0.05 se			1.0023			1.0649
AR p-value			0.1272			0.1126
Cancer MR 94-96		0.000976			0.00152	
		[0.000665]			[0.00100]	
Effect size (%)	0.62		5.55	0.84		5.90
Model	OLS	RF	IV	OLS	RF	IV
Dependent var:	APGAR Score - All Infants			APGAR Score - infant casualties		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	-0.000501		-0.0169*	0.0155		0.282*
	[0.00188]		[0.00994]	[0.0179]		[0.153]
tF 0.05 se			(0.01395)			(0.21467)
t-stat using tF 0.05 se			-1.2118			1.3137
AR p-value			0.0674			0.0383
Cancer MR 94-96		-0.0189*			0.319*	
		[0.0107]			[0.164]	
Effect size (%)	-0.03		-0.96	1.38		25.17
Model	OLS	RF	IV	OLS	RF	IV
Dependent var:	Fertility rate			Gestation		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.0000665		0.00153***	-0.000164		-0.0489***
	[0.0000621]		[0.000566]	[0.00304]		[0.0186]
tF 0.05 se			(0.00079)			(0.02610)
t-stat using tF 0.05 se			1.9266			-1.8738
AR p-value			0.001			0.0011
Cancer MR 94-96		0.00165***			-0.0527***	
		[0.000482]			[0.0171]	
Effect size (%)	0.43		9.85	0.00		-0.63
Model	OLS	RF	IV	OLS	RF	IV

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

Table 7: Effects of the Opioid Epidemic on Deaths of Despair

Dependent var:	Deaths of Despair		
	(1)	(2)	(3)
Prescription opioids pc	0.00626***		0.0127*
	[0.00182]		[0.00715]
tF 0.05 se			0.0100
t-stat using tF 0.05 se			1.266
AR p-value			0.0542
Cancer MR 94-96		0.0137*	
		[0.00751]	
Effect size (%)	8.44		17.13
Model	OLS	RF	IV

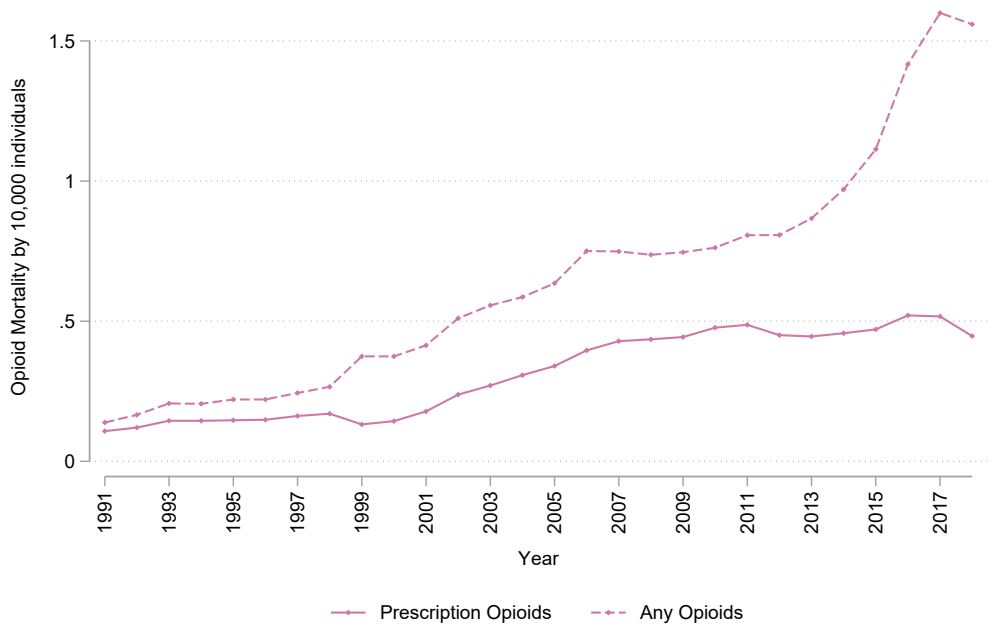
Dependent var:	Alcoholic Liver Diseases and Cirrhosis		
	(1)	(2)	(3)
Prescription opioids pc	0.000765**		0.00552*
	[0.000353]		[0.00292]
tF 0.05 se			0.0041
t-stat using tF 0.05 se			1.3473
AR p-value			0.0351
Cancer MR 94-96		0.00596**	
		[0.00302]	
Effect size (%)	3.23		23.34
Model	OLS	RF	IV

Dependent var:	Suicide		
	(1)	(2)	(3)
Prescription opioids pc	-0.0000460		-0.00582
	[0.000430]		[0.00378]
tF 0.05 se			0.0053
t-stat using tF 0.05 se			-1.0974
AR p-value			0.1065
Cancer MR 94-96		-0.00628	
		[0.00402]	
Effect size (%)	-0.16		-19.80
Model	OLS	RF	IV

Notes: All regressions include state times year fixed effects. Each regression is run over a sample of 11,800 observations with 590 clusters (commuting zones). Control variables are contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. 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.

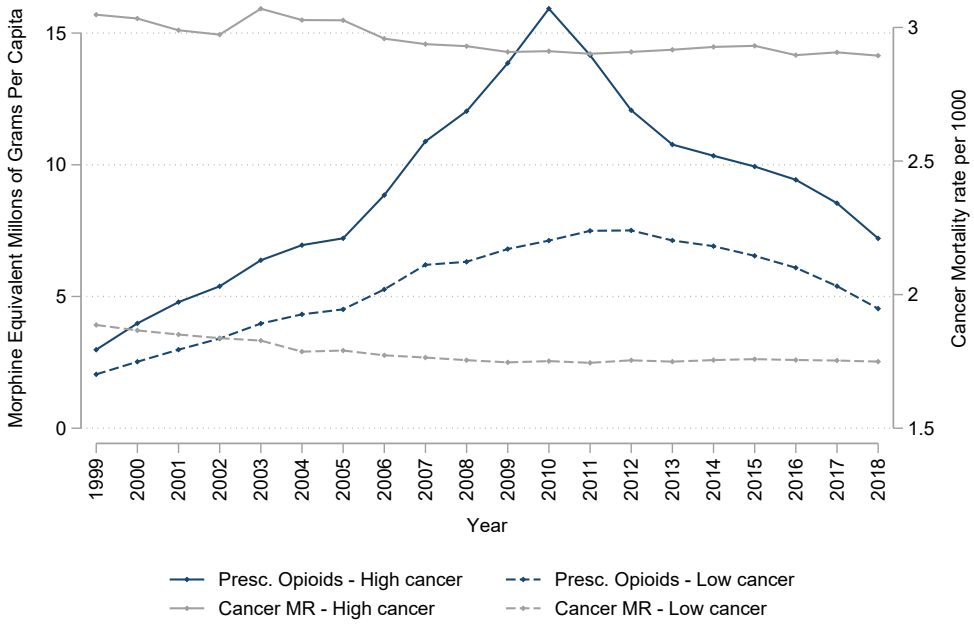
A Extra Figures

Figure A1: Evolution of Prescription Opioid and All Opioid Mortality Rates



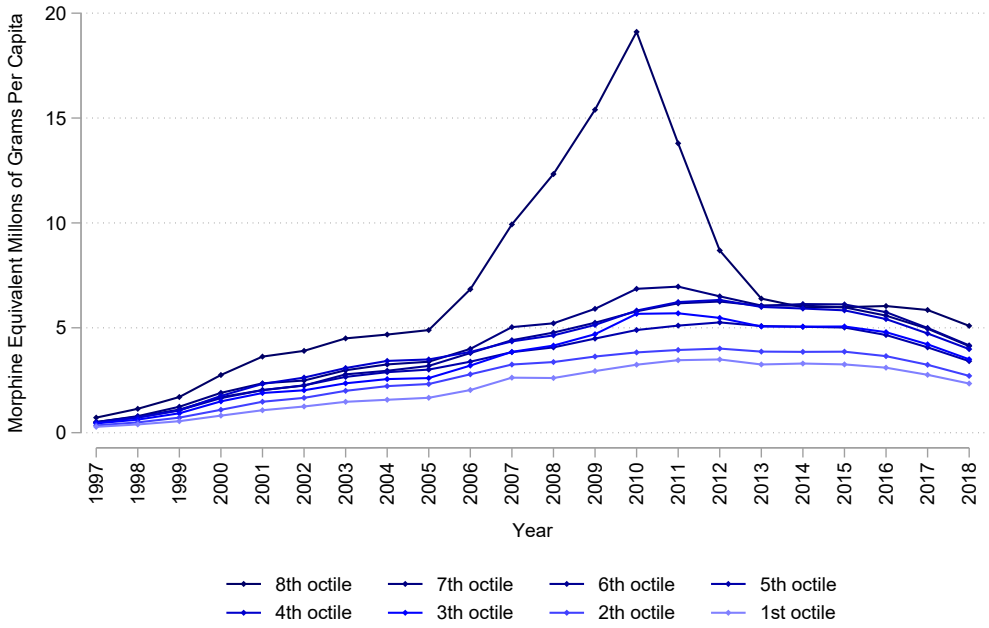
Notes: This figure shows the evolution of prescription opioid and all opioid mortality rates from 1991 to 2018. The 1991-1998 data use ICD-9 codes to categorize the cause of death, and the 1999-2018 data use ICD-10 codes. The time series show that the transition from ICD-9 to ICD-10 classifications resulted in a small increase in poison-related deaths; this is consistent with what the CDC reports (Warner et al., 2011). This figure is reference in Section III.B.

Figure A2: Evolution of Cancer Mortality and Oxycodone by 1994-1996 Cancer Prevalence



Notes: The left-hand axis of this figure shows the evolution of oxycodone in the forth quartile (solid lines) and first quartile (dashed lines) of the cancer mortality rate distribution before the launch of OxyContin. The right-hand axis of this figure shows the evolution of cancer mortality in the top and bottom quartiles of the cancer mortality distribution before the launch of OxyContin. Oxycodone is measured in morphine-equivalent mg. This figure is reference in Section IV.A.

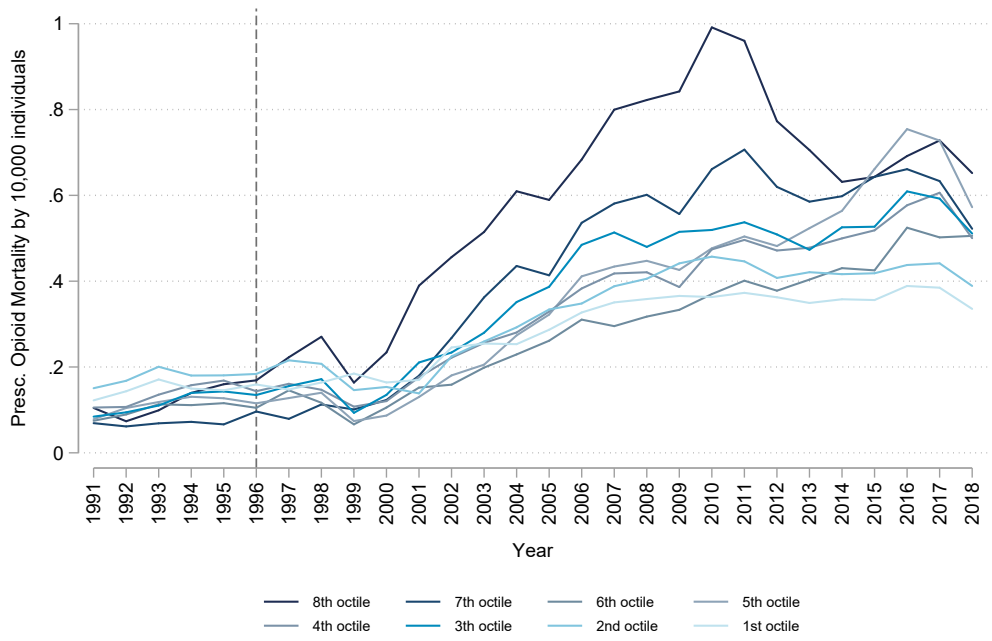
Figure A3: Evolution of Oxycodone by Octiles of the 1994-1996 Cancer Prevalence



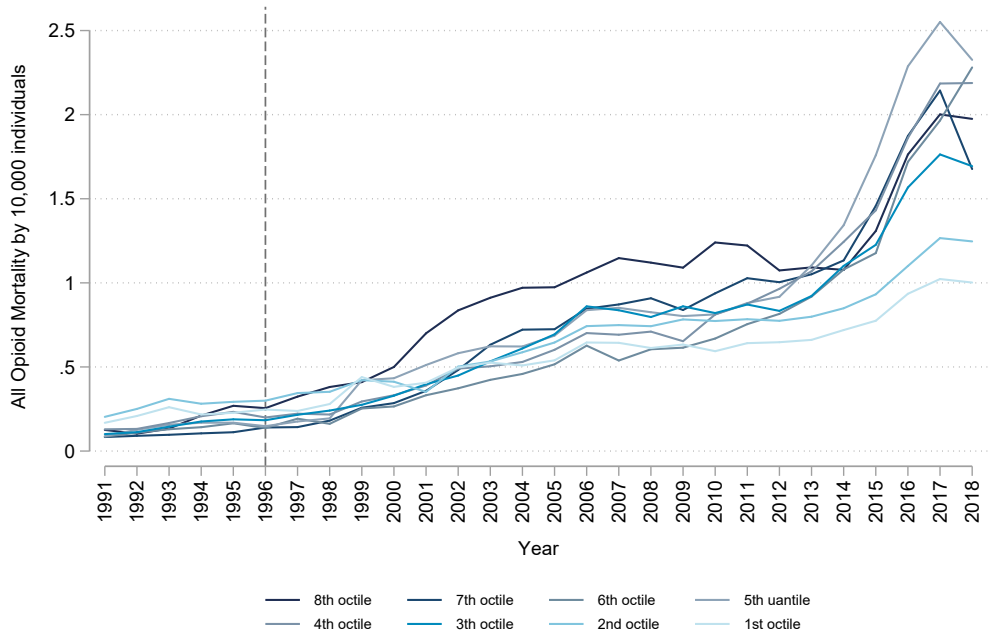
Notes: This figure shows the evolution of oxycodone in eight groups of commuting zones. Each group is composed of those commuting zones in the *n-th* octile of the cancer mortality rate distribution before the launch of OxyContin. Darker colors indicate groups with higher cancer prevalence (e.g., the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

Figure A4: Opioid Mortality Rate by Octiles of the 1994-1996 Cancer Prevalence

(a) Prescription Opioids



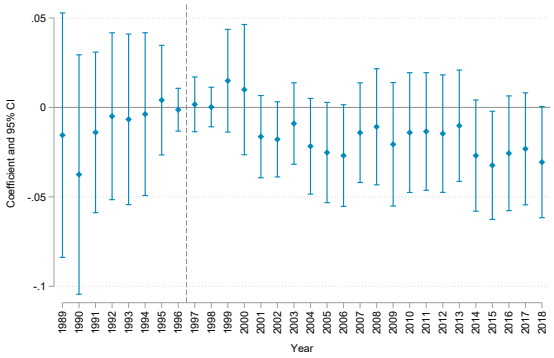
(b) All Opioids



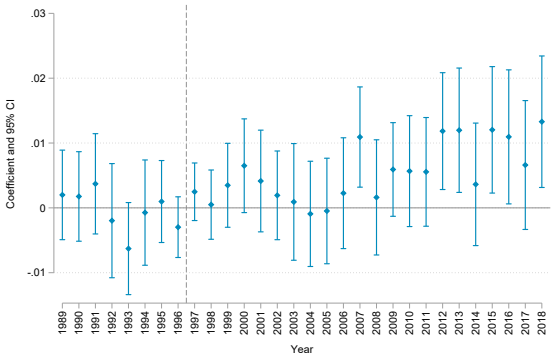
Notes: This figure shows the evolution of prescription opioid (panel a) and all opioids (panel b) mortality in eight groups of commuting zones. Each group is composed of those commuting zones in the *n-th* octile of the cancer mortality rate distribution before the launch of OxyContin. Darker colors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

Figure A5: Dynamic Reduced Form Estimates - Additional Outcomes

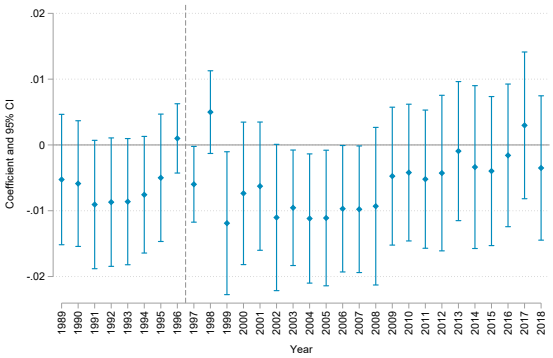
(a) APGAR Score - All Infants



(b) Alcoholic Liver Diseases and Cirrhosis

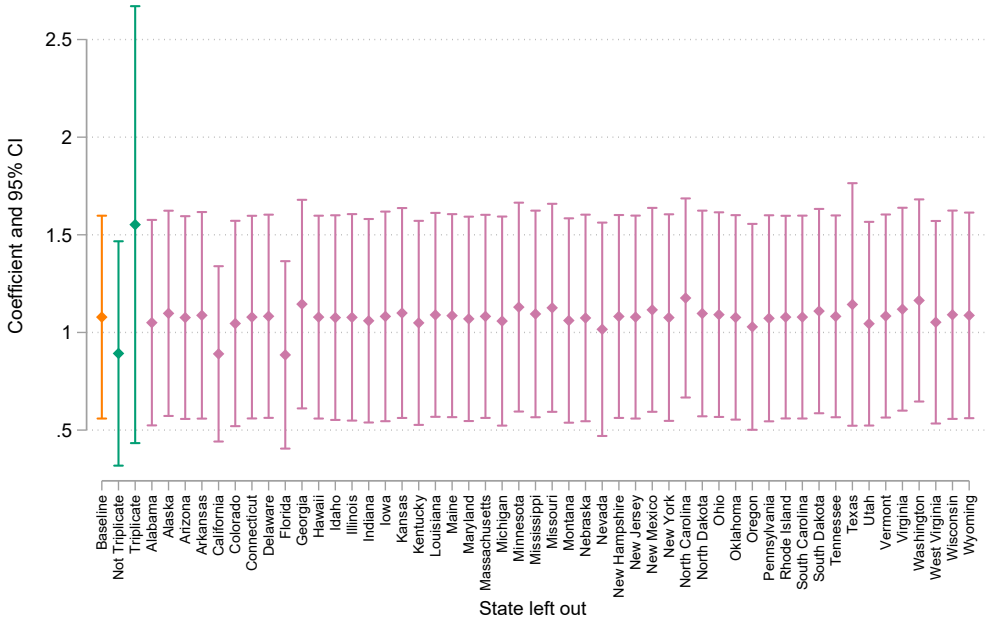


(c) Suicide



Notes: This figure shows the dynamic reduced-form relation between outcomes of interest and our instrument—cancer mortality in 1994 - 1996. Each coefficient corresponds to the estimate of ϕ_t in Equation 3. This figure is referenced in Section V.B.

Figure A6: Estimates of the First-stage Coefficient



Notes: This graph reports the estimated coefficient of the first stage (ϕ) and the corresponding 95% confidence interval. The first coefficient and confidence interval replicate the result from column 6 of Table 3. Each of the subsequent coefficients are computed by excluding all commuting zones in the state indicated on the horizontal axis. This figure is reference in Section VI.A.

B Extra 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 reference in Section III.A.

Table A2: Direct Effects on Opioid Mortality by Age and Race

Dependent var:	Prescription opioids			All Opioids		
	Less than 50 yo	More than 50 yo	White	Less than 50 yo	More than 50 yo	White
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.0155***	0.00184	0.00528***	0.0185***	-0.000391	0.0168***
	[0.00435]	[0.00133]	[0.00201]	[0.00530]	[0.00193]	[0.00486]
tF 0.05 se	(0.0061)	(0.0019)	(0.0028)	(0.0074)	(0.0027)	(0.0067)
t-stat using tF 0.05 se	2.5396	0.9860	1.8439	2.4878	-0.1125	2.4945
Effect size (%)	58.81	15.08	60.31	31.04	-1.25	64.28
Model	IV	IV	IV	IV	IV	IV
Observations	11,800	11,800	11,800	11,800	11,800	11,800
Clusters	590	590	590	590	590	590
Effective F-stat	16.63	16.63	16.63	16.63	16.63	16.63
Cragg-Donald Wald F-stat	358.58	358.58	358.58	358.58	358.58	358.58

Notes: Control variables are contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. 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 reference in Section V.A.

Table A3: Baseline Results with Different Time Periods

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

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

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

Table A4: Baseline Results with Different Time Periods. IV Estimates.

	SNAP			SSDI		
	(1)	(2)	(3)	(4)	(5)	(6)
Presc. Opioids pc	0.00455*	0.00487**	0.00680***	0.00584***	0.00605***	0.00718***
	[0.00250]	[0.00219]	[0.00205]	[0.00144]	[0.00141]	[0.00135]
Effective F	15.22	17.06	25.70	15.22	17.06	25.70
Sample	**1999-2010**	**1999-2013**	**2010-2018**	**1999-2010**	**1999-2013**	**2010-2018**
	SSI			IMR		
	(1)	(2)	(3)	(4)	(5)	(6)
Presc. Opioids pc	0.00226*	0.00248*	0.00320*	0.0458	0.0512	0.0846
	[0.00133]	[0.00141]	[0.00174]	[0.185]	[0.160]	[0.113]
Effective F	15.22	17.06	25.70	15.22	17.06	25.70
Sample	**1999-2010**	**1999-2013**	**2010-2018**	**1999-2010**	**1999-2013**	**2010-2018**
	Birth weight			Fertility		
	(1)	(2)	(3)	(4)	(5)	(6)
Presc. Opioids pc	-5.989**	-5.093**	-2.915*	0.00210***	0.00233***	0.00350***
	[2.811]	[2.316]	[1.623]	[0.000696]	[0.000674]	[0.000778]
Effective F	15.22	17.06	25.70	15.22	17.06	25.70
Sample	**1999-2010**	**1999-2013**	**2010-2018**	**1999-2010**	**1999-2013**	**2010-2018**

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

Table A5: Effects on Fertility Rate by Age

Age group:	10-19	20-24	25-29	30-34	35-39	40-44
	(1)	(2)	(3)	(4)	(5)	(6)
Presc. Opioids pc	-0.00038	-0.00107	0.00327***	0.0000223	-0.00123**	-0.0000851**
	[-1.40]	[-0.96]	[2.83]	[0.05]	[-2.47]	[-2.08]
Effective F-stat	16.63	16.63	16.63	16.63	16.63	16.63
Model	IV	IV	IV	IV	IV	IV
Observations	11,800	11,800	11,800	11,800	11,800	11,800
Clusters	590	590	590	590	590	590

Notes: This table presents results of the effect of the prescription opioids supply on the fertility rate of women age 10 to 44 years by age group. Standard errors in square brackets are clustered at the CZ level; using these standard errors, we report * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is reference in Section V.B.

Table A6: Baseline Results under a Shift-share Instrument

Dependent var:	Presc. Opioids pc	Presc. Opioids MR	Any Opioids MR	SNAP	SSDI
	(1)	(2)	(3)	(4)	(5)
Shift Share	0.00417***				
	[0.000997]				
Effective F	17.47				
Presc. Opioids pc		0.00644***	0.00635***	0.00927***	0.00553***
		[0.00188]	[0.00219]	[0.00277]	[0.00127]
Model	FS	IV	IV	IV	IV
Dependent var:		SSI	Infant Mortality Rate	Fertility rate	Birth weight
		(6)	(7)	(8)	(9)
Presc. Opioids pc		0.00319**	-0.0218	0.00149***	-4.344**
		[0.00158]	[0.120]	[0.000548]	[1.964]
Model		IV	IV	IV	IV

Notes: Column 1 reports the estimated coefficient for the first stage. Columns 2 to 9 present results from IV regressions using the shift-share instrument. Our preferred specification restricts the sample to commuting zones with population higher than 25,000 residents. 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 reference in Section VI.A.

Table A7: 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 CZ level. * $p<0.10$, ** $p<0.05$, *** $p<0.01$. This table is reference in Section VI.A.

Table A8: Placebo Check - Alternative Instruments

Dependent variable:	Prescriptions Opioids pc			
	(1)	(2)	(3)	(4)
Cardiovascular disease 94-96	0.372		-2.023**	
	[0.611]		[0.822]	
Transit accidents 94-96		1.621		-0.991
		[1.546]		[1.528]
Cancer 94-96			1.381***	0.954***
			[0.347]	[0.243]
Model	FS	FS	FS	FS
Observations	11,800	11,800	11,800	11,800
Rsquared	0.588	0.587	0.602	0.598
Clusters	590	590	590	590

Notes: Columns 1-2 report first-stage regression with alternative instrument. Columns 3-4 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 reference in Section VI.B.

Table A9: Out-of-sample Reduce Form and Alternative Measure of Opioid Supply.

Dependent var:	Presc. opioids MR	All opioids MR	Oxycodone pc	Presc. opioids MR	All opioids MR
	(1)	(2)	(3)	(4)	(5)
Cancer MR 89-90	-0.000122	-0.000208			
	[-0.16]	[-0.22]			
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	RF	RF	FS	IV	IV
Observations	3,540	3,540	11,800	11,800	11,800
Clusters	590	590	590	590	590
Adjusted R^2	0.065	0.13	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. Columns (3) to (5) reproduce the main analysis using Oxycodene shipments as the measure of opioid supply. Effect size in column (3) 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 (4) and (5) 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 reference in Section VI.B. and in Section VI.C.

Table A10: 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 A11: 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.B. and in Section VI.D.

Table A12: 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.