The Marketing of Prescription Opioids and Its Enduring Effects

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Abstract

This paper exploits the role of the marketing of OxyContin in the expansion of the prescription opioids supply to study the origins and effects of the opioid epidemic. We obtained recently unsealed documents from state litigation against Purdue Pharma and accessed confidential documents related to the initial marketing targets of OxyContin. We exploit detailed features of the initial marketing of OxyContin to instrument for the supply of prescription opioids. We find that moving from the 25th to the 75th percentile in the distribution of prescription opioids supply, increases deaths from prescription opioids by 89% and deaths from all opioids by 39%. This corresponds to over 200,000 deaths. We estimate that the opioid crisis did not have an effect on labor market outcomes, such as labor force participation or employment rates, but deteriorated socioeconomic conditions by increasing claims from SNAP and disability and it increased crime. We estimate small decreases in birth weight but no effect on infant mortality, a small increase in fertility rates, and a small decrease in pregnancy duration.

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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. Opioid overdoses claimed the lives of almost 400,000 since 1999 (Centers for Disease Control and Prevention, 2019), and have contributed to the longest sustained decline in life expectancy in the last century, outside from the influenza and covid pandemics (Dyer, 2018). Furthermore, the rise has been accompanied by stagnation in labor force participation (Krueger, 2017); an increase in disability claims; worsening of 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).

Prescription opioids not only contributed directly to the increase in overdose deaths, but also indirectly by initiating opioid addiction which can lead to the abuse of heroin and fentanyl, and by affecting one's ability to work, recover from illness, and care for children, among other daily activities. In 2017, 35% of adults in the US had a prescription for opioid painkillers, and 4.1% had used them for nonmedical purposes in the past year (NSDUH, 2017). Opioids are highly addictive, with rapid progression to physiological dependence with tolerance and withdrawal. Physical dependence can occur even at prescribed doses and within a short period (Hah et al., 2017; Sharma et al., 2016).

In this paper, we study the origins of the opioid crisis and 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 aggressive marketing of prescription opioids (Alpert, Dykstra and Jacobson, 2020; Fernandez and Zejcirovic, 2018 and 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, and can also explain subsequent negative outcomes. On the other hand, the supply of prescription opioids is positively linked to access to healthcare 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 that 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 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 and exposure to OxyContin in areas with higher-cancer-incidence from the time it was introduced, which persisted over time and opened the doors 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 this 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 along 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 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: the labor market, demand for social insurance, crime, and a broad range of birth and fertility outcomes. We leverage data from multiple sources, including administrative data from the Drug Enforcement Administration (DEA) to measure prescription opioids 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 Local Area Unemployment Statistics from the Bureau of Labor Statistics to measure our labor market outcomes, and 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). Finally, we build our measures of crime from the Uniform Crime Reports from the Federal Bureau of Investigation. 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, and 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

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

[2] Oxycodone is a semisynthetic opioid, 50% more potent than morphine, indicated for the management of acute pain.

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 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 opioids deaths of 89% and of all opioids deaths of 39%. This work adds to the literature that documents the importance of supply-side factors (Alpert et al., 2019; Powell, Pacula and Taylor, 2020; Fernandez and Zejcirovic, 2018; Finkelstein, Gentzkow and Williams, 2018; Schnell and Currie, 2018; Eichmeyer and Zhang, 2020; Evans, Lieber and Power, 2019; Alpert, Powell and Pacula, 2018) in explaining the opioid epidemic relative to demand-side factors (Case and Deaton, 2015, 2017). We also build on the seminal work of 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 labor market, demand for social assistant benefits, crime, 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.

Labor market outcomes. Recent studies have connected the opioid crisis to the decline in labor force participation (Krueger, 2017). On the one hand, opioid use could improve labor market outcomes if it enhanced work capacity by helping workers alleviate chronic pain, but on the other, labor market outcomes could worsen if addiction or other prescription opioid-related problems reduce work capacity. Which channel dominates is an empirical question for which researchers have obtained different answers. Using variation in the rates of prescription opioids across time and over space, Harris et al. (2020);

[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).

Aliprantis, Fee and Schweitzer (2019); and Beheshti (2019) find that access to opioids reduces labor force participation. Park and Powell (2021), who study how the 2011 reformulation of OxyContin and the subsequent transition to heroin and fentanyl affected labor market outcomes, find it had negative effects on traditional labor supply measures.[5] On the other hand, Currie and Schwandt (2020) argue that there is little relationship between the opioid crisis and labor market outcomes. This literature, however, relies on the exogeneity of the variation of prescription opioids across space and over time. With our instrumental variable approach, we estimate that the opioid crisis did not affect labor market outcomes such as labor force participation or employment rates.

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 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 socio-economic 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 opiods 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.

Crime. Drug epidemics often induce a rise in crime. The heroin wave of the 1970s and the crack cocaine crisis of the 1980s were each accompanied by major gun violence, including large numbers of murders and violent and property crimes (Szalavitz and Rigg, 2017). Policies intended to curb the opioid epidemic have been documented to reduce crime. Dave, Deza and Horn (2020) exploit the differential timing in the introduction of prescription drug monitoring programs (PDMP) across states and find that when a PDMP is put in place, the overall crime rate declines by 5%; these reductions are associated with both violent and property crimes. Ours is the first paper to study the direct effects of the supply of opioids on crime. We find that the availability of prescription opioids increased crime across the board. A change from the 25th to the 75th percentile in the growth of prescription opioids per capita caused an increase in crime incidents by 60% relative to the mean, with property crimes increasing 65% and violent crime increasing by 39%.

[5] In 2010, the FDA approved a reformulated, abuse-deterrent version of OxyContin designed to make the pill difficult to crush or dissolve. Alpert, Powell and Pacula (2018) and Evans, Lieber and Power (2019) document how the substantial reduction in the supply of abusable prescription opioids impacted overdoses involving heroin and other types of opioids.

Birth and maternal outcomes. From 2000 to 2007 one of five women filled 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 the year (Ailes et al., 2015). This naturally raises concerns about the risks of abuse in this population and its effects on infant health. Ziedan and Kaestner (2020) exploit changes in the policy environment across states (PDMP and "pill mill" legislation) to estimate the effect of prescription opioids on infant health.[6] 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 find that a 25th-to 75th- percentile increase in the supply of prescription opioids decreases birth weight by 1%, and deteriorated APGAR scores by 1%.[7] We estimate that there is no effect on infant mortality and 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 babies died. We find no effects on the incidence of preterm births, but a decline in pregnancy duration of 0.24 weeks. Finally, we estimate an increase in fertility rates of 9%, mostly driven by women 25-29 years old, and we do not find an effect on the quality of prenatal care.[8]

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

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. Two key technological innovations are responsible for its success. First, its long-acting formula provided 12 hours

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

[7]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.

[8]We measure quality of prenatal care as the share of mother with an adequate level of the Kessner Index of prenatal care, which includes information about both the timing of prenatal care initiation and prenatal care visits after initiation.

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.[9] Both of these factors significantly increased patients' access to potent doses of opioids and augmented the risk of dependency and abuse. For example, Percocet was the most common oxycodone product on the market before 1996, and it mostly sold in the form of tablets of 2.5 mg of oxycodone. In contrast, the most common forms of OxyContin were tablets of 20 mg and 40 mg 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 slowly over 12 hours, creating strong euphoric effects.

Previous to the introduction of OxyContin, pain management focused on cancer and end-of-life pain treatment. 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 physician 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, 1995). The two main barriers Purdue Pharma faced were (i) the stigma related to the use of opioids for non-terminal or non-cancer pain and (ii) the administrative barriers physicians and pharmacies had to overcome to prescribe and sell Schedule II drugs.

To overcome these obstacles, Purdue deployed a comprehensive marketing strategy based on three main pillars. First, to effectively change physician prescribing behaviors, Purdue Pharma implemented an aggressive marketing plan that pushed the message of an untreated pain epidemic that affected millions of Americans on a daily basis. Pain was introduced as the fifth vital sign with the goal of encouraging the standardized evaluation and treatment of pain symptoms (Jones et al., 2018). This messaging also included misleading statements —for instance, that opioid addiction rates were lower than 1% and that oxycodone was weaker than morphine, when it is 50% more potent.[10] Second,

[9] 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.

[10] *"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.

OxyContin was promoted directly to physicians by the largest and highest-paid sales force in the industry. 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.[11] Third, Purdue focused their initial marketing efforts on physicians and pharmacies who faced less stigma and paperwork when prescribing opioids. Purdue initially targeted cancer patients and oncologists 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 1996). 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.

This strategy succeeded in making OxyContin a blockbuster drug that yielded $35 billion rendering in revenue for Purdue Pharma (Keefe, 2017) and in making the use of opioids standard practice in the treatment of moderate and chronic pain for a wide range of non-terminal conditions. It opened the doors 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 law suits for their role in the opioid epidemic, shadowed closely OxyContin 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 vs Purdue Pharamet al.)[12] For our purposes, this strategy meant that areas with a higher incidence of cancer would receive a disproportionate amount of marketing and of 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.

[11] OxyContin annual budget plans specifically state that they will focus on physicians in the top 3 deciles of prescriptions.

[12] Duragesic is a Fentanyl patch manufactured by Janssen.

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 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.[13] 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 meperdine in morphine equivalente mg. We construct a geography 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 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 opioids 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. Appendix Table A1 shows the evolution of doses per capita over the last two decades. In 1997, the first year of available data, oxycodone and morphine average doses per capita were 0.31 and 0.35, respectively. A decade later, oxycodone doses were 3.26 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. Opioid, Cancer and Birth Outcomes

We use data from the National Vital Statistics System (NVSS) to construct mortality measures and birth outcomes. We use restricted data to access county identifiers. Mortality measures come from Detailed Multiple Cause of Death (MCOD) files from 1991 to 2018. These record every death in the US along with the county of residence, the

[13]The ARCOS system data is available online from 2000 to 2018, we used the WayBack Machine application to collect earlier data for 1997 to 1999, which is the oldest period available.

underlying cause of death, and up to 20 additional multiple causes and thus represent a census of deaths in the US. The 1991-1998 data use ICD-9 codes to categorize the cause of death, and the 1999-2018 data use ICD-10 codes.

We construct two main measures of opioid-related deaths: prescription opioid 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 small increase in poison-related deaths of 2% (Warner et al., 2011). Appendix Figure A2 shows the time series for the US of 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.[16]

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, and incidence measures reported by the CDC and the Surveillance, Epidemiology, and End Results (SEER) 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, especially in the later stages of cancer treatment, using opioid pain-killers (e.g., MS Contin) to manage cancer pain.

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. On average, there were 2.52 cancer deaths in a commuting zone in 1994-1996. The commuting zone with the lowest cancer mortality experienced 1 death for every 1,000 residents, and the commuting zone with the highest mortality experience 60 deaths per 1,000 residents. These figures are comparable to those documented for the years 1999-

[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).

[16]One challenge in working with granular data on opioid mortality is that a higher fraction of geographies would not have reported any death from opioids in a given year, giving rise to a distribution that exhibits skewness and a large proportion of zeros. Thus, when computing a change in the mortality rate from year t relative to the base year, even a small increase in the number of deaths would imply a huge change. To alleviate this concern, we restrict our sample to commuting zones with a population higher than 25,000 in 1999. In Appendix Table A3 we present results that include all commuting zones with population greater than or equal to 20,000 in 1999.

2018 when there were 2.48 cancer deaths on average. We present further evidence on the determinants of cancer in Section 4.

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.[17] 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 births files are the (i) commuting-zone-level average birth weight for all live births, (ii) share of preterm births, (iii) APGAR score of all births, (iv) APGAR score of deceased infants and (v) median pregnancy duration at the commuting-zone level. We also use the births file 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.[18] Finally as measure of pregnancy care, we compute the share of mothers with an adequate prenatal care using the Kessner Index.[19]

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. These crosswalks provide a probabilistic matching of sub-state geographic units, defined by the US Census, to commuting zones.

C. Other Outcome Variables

Labor market outcomes. Labor market variables are constructed based on county-level labor force data from the Local Area Unemployment Statistics program of the Bureau of Labor Statistics. In particular, we construct measures of labor force participation and employment for the period spanning 1990-2018, by aggregating county-level annual averages for each commuting zone.

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

[17] 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 infants deaths were successfully linked while in 1998, 98.4% of deaths records were linked.

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

[19] The Kessner Index takes into account three factors: month in which prenatal care begin, number of prenatal care visits, and length of gestation. Importantly, the Kessner Index can be computed for all years under analysis.

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.[20] We include two measures of disability benefits recipiency, constructed as the share of the population 18-65 that receives Supplemental Security Income (SSI) who are blind or disabled, and the share 18 to 65 receiving Social Security Disability Insurance (SSDI). Information on the total number of SSI recipients in each county is based on the 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.

Crime outcomes. To create our crime variables, we use data from the yearly files of the Federal Bureau of Investigation's Uniform Crime Reports for the period 1996-2018. We use the Offenses Known and Clearances by Arrest dataset, which records yearly reported violent and property crimes at the law enforcement agency level. Because several agencies are inconsistent in their reporting frequency, we restrict the data to law enforcement agencies that reported crimes for all years in the period, and for which December was the last month of reporting in each year.[21] Finally, we aggregate the data at the commuting-zone level and construct a measure of total reported crimes per 100,000 residents, by type of offense: overall, violent, and property crime.

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 indeed the distribution of opioids is not random across space but is related to the demographic composition of the commuting zone and its economic performance. A greater share of white population and higher median income at the commuting zone level have a positive correlation with prescription opioids per capita; while the share of Hispanic population, the employment rate, and the demand for social insurance have a negative correlation with opioid suply.[22] This is in line with Finkelstein, Gentzkow and Williams (2018), who estimate that areas with more physicians per capita, higher levels

[20] For commuting zones crossing state lines and for which local-level data is missing we calculate an average of the corresponding state-level shares, weighted by the number of counties in the commuting zone, belonging to each state.

[21] Alternatively we restrict the data to law enforcement agencies that reported crimes for all years in the period, and for all months in each of these years and the results are the same.

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

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 outcomes of interests we use an instrumental variable strategy that exploits geographical variation in the promotional efforts for OxyContin and other prescription opioids as an exogenous supply shifter. We estimate the causal effects of the supply of prescription opioids via the following equations, which are run over the sample of commuting zones for the period 1999-2018:
First Stage:

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

Second Stage:

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

where the operator Δ is the difference between t and t_0, and t_0 is defined as the average of the pre-OxyContin period, i.e., 1994-1996. c indexes commuting zones, t indexes years, and s indexes states. y_{ct} refers to one of our outcomes of interest, e.g., a measure of opioid-related mortality. $Presc.\ Opioids_{ct}$ corresponds to doses of opioids per capita shipped to commuting zone c in year t. $CancerMR_{ct_0}$ is the cancer mortality rate in 1994-1996. X_{ct} are time-varying covariates at the commuting-zone level: contemporaneous cancer mortality, share of the population over 66, share of the population 18-65, share of the population under 1 year, share of white and black population, share of females and share of Hispanic population. We add state times year fixed effect, represented by the term $\gamma_s \Delta t$; this controls for the variation in outcomes over time that is common to all commuting zones within state s. This fixed-effects specification would purge the variation in the supply of prescription opioids that results from a change in state-level policy, such as implementation of a PDMP. The variable ε_{ct} is an idiosyncratic error term. 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, the opioid epidemic has evolved in three waves, each one characterized by the highest levels of misuse and abuse of a given substance.[23] The misuse

[23]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

and abuse of prescription opioids were the main driver of deaths until 2010. Nonetheless, research also has found that prescription opioids play an important role in the initiation and use of heroin and fentanyl (APA, 2017). In this context, how the supply of opioids per capita evolves relative to the base year is more indicative of the exposure to opioids than the variation in levels.

Our instrumental variable approach is similar to a shift-share instrument, where the shares are cancer rates in the mid nineties, and the shift is the national growth of prescription opioids. We choose to only use as instrument our measure of mid nineties cancer mortality to highlight that this is our only source of exogenous variation. We show results using the shift share instrument in Appendix Table A2, and the results are quantitatively indistinguishable.

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 (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: (i) strongly correlated with the opioids supply—i.e., the coefficient ϕ must be statistically different from zero, and (ii) uncorrelated with the error term in the second-stage equation 2. Evidence supporting our strategy was first presented in Section 2, in which we discussed Purdue Pharma's marketing strategy and its rationale for focusing on the cancer market as the place to start and expand from. Next, we provide empirical evidence to support this empirical strategy and assess threats to the validity of the instrument.

A. Does cancer mortality in the mid-nineties 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 quartile of cancer mortality in 1994-1996, panel B shows the analogous exercise for the aggregate of prescription opioids.[24] 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

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)

[24]In Appendix Figure A1 we present the analogous analysis, but we split the data based on 8 octiles of cancer mortality and see the same pattern.

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 2.

Table 3 shows the results of the first-stage regression defined in equation 1. Column one 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 6, where 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-nineties 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 33% relative to the base period. Furthermore, this positive relationship is robust to the exclusion of all states, one at a time (see, Figure A3), for other opioids, specifically oxycodone (see, column 3 of Table 6) and is also present in the cross-section for all years.

B. What relates to cancer mortality in the mid-nineties and is it related to our outcomes variables?

Variation in cancer mortality across locations is not random; 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 that in the abscense of OxyContin's marketing areas with higher cancer mortality in the pre-OxyContin period (t_0) exhibit the same trend as areas with lower cancer mortality in t_0 in terms of our outcome variables.

We provide evidence to support this assumption. We estimate one regression for each outcome variable in which we replicate our main reduced-form specification in the pre-period. We regress the changes in y at t relative to 1989-1990 on the level of cancer mortality in 1989-1990. That is, for each of our outcome variables, we consider the following specification:

$$\Delta y_{ct} = \mu_0 + \mu_1 \, CancerMR_{ct_0} + \mu\Delta \, X_{ct} + \theta_s \Delta t + \omega_{ct}, \tag{3}$$

where the Δ operator refers to the change between 1996 and 1990 i.e., we estimate this regression in an out-of-sample period to avoid any effects induced by the opioid epidemic

on our outcome variables. $CancerMR_{ct_0}$ is the cancer mortality rate in 1989-1990 and X_{ct} are our time-varying covariates at the commuting-zone level. Table 4 shows the results of this estimation. We estimate that areas with higher cancer mortality are not on a differential trend along education, income or health variables. Moreover, with the exception of a weak relationship to labor force participation, the evolution of our outcome variables is unrelated to lagged cancer mortality. As an additional robustness check, we replicate our main analysis adding labor market controls to our set of covariates and our results remain unchanged; see Table A4.

We also estimate whether lagged cancer mortality (1989-1990) predicts changes in opioid-related mortality from 1991 to 1996. Column 1 and 2 of Table 6 show the results of this estimation. We find that, different from the period after the launch of OxyContin, lagged cancer mortality is unrelated to future opioid mortality suggesting 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. Is cancer mortality in the mid-nineties predictive of future mortality from opioids?

Figures 3 and 4 show our reduced-form results on drug-related mortality. We follow the same strategy as in Figure 1, and split commuting zones based on the cancer mortality distribution. Before the launch of OxyContin, opioid deaths are very similar in high and low cancer areas, for both prescription opioids and all opioid mortality. Consistent with what we found in the first-stage graph, the marketing of OxyContin had a positive effect on opioid-related mortality. 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.

In regression form, we estimate the following reduced-form specification:

$$\Delta Y_{ct} = \pi_0 + \zeta CancerMR_{ct_0} + \pi \Delta\ X_{ct} + \psi_s \Delta t + \nu_{ct}, \tag{4}$$

where Y corresponds to prescription opioid mortality and mortality from all opioids, $CancerMR$ is the cancer mortality rate in 1994-1996 and X_{ct} is our set of covariates. Columns (2) and (5) of Table 5 show the results of this estimation. We find that there is a strong and positive relationship between mid-nineties cancer mortality and future increases in opioid mortality.

V. Results

A. Direct effects: prescription and all opioid mortality

Commuting zones with the highest cancer incidence at the time of launch of OxyContin received 64% more opioids per capita than their counterparts—the 95th percentile relative to the 5th percentile. Using this increase as a supply shifter, we estimate that an additional dose of prescription opioids per capita caused an increase on prescription opioid mortality of 0.0068 points and on all opioid mortality of 0.0065 points. These estimates are presented in columns 3 and 6 of Table 5. Our results imply that when doses per capita increase from the 25th to the 75th percentile, i.e., a 5.02 doses increase; mortality from prescription opioids increases by 88.6% and all opioids mortality rate increases in 39.3%.[25]

The ordinary least squares estimates (columns 1 and 4 of Table 5), differ considerably from the IV estimates. We find a positive correlation between opioids supply and opioids mortality rate but, the difference in magnitude between the OLS and the IV estimates suggests that the former suffers from a negative bias. Put another way, by looking at the correlation between opioids supply and opioids deaths we would underestimate the role of the supply of prescription opioids in explaning the rise in mortality. The negative bias in the OLS estimates is consistent with commuting zones receiving 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 that 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 have higher opioid abuse rates.

Drug overdose deaths can be hard to categorize, since we use data that records deaths using both, the ICD-9 and ICD-10 codes, we also construct an additional outcome measure for opioid mortality, drug-induced mortality rate; and present results using this measure in columns 6 and 7 of Table 6. Drug-induced category has the advantage that comparisons across years are less affected by the change in the ICD classification, but this comes at the cost of being less linked to our main outcome of interest that are deaths from prescription opioids.[26] Exploiting this measure, we arrived to similar conclusions than with our main definitions of drug overdose deaths: an additional dose of opioids per capita caused an increase on drug-induced mortality rate of 0.0112 points. An increase

[25]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.

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

from the 25th to the 75th percentile of prescription opioids per capita, increases drug induced mortality by 51%.

B. Labor market and social assistance benefits

Commuting zones with higher exposure to prescription opioids did not see a worsening in their labor market outcomes as a result of the opioid epidemic. The first panel of Table 7 presents these results. We do not detect a statistically significant deterioration in employment and we find a positive but imprecisely estimated increases in labor force participation as a consequence of the differential increase in prescription opioids supply driven by the marketing practices of Purdue Pharma and its competitors.

Addiction to and misuse of prescription opioids could reduce work capacity and put people at risk of permanently reducing the labor supply; in this context, disability insurance applications are a useful proxy for 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 columns (2) and (4) of the second panel of Table 7. We find positive and significant effects for both measures. 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.

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 that are not necessarily reflected by direct labor market outcomes. 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.[27] Overall, we find no evidence of an effect on labor supply or employment. However, these aggregated statistics mask the effects on a population of interest, those with poor health, a weak attachment to the labor market, and who are at risk of abuse and addiction. For this population we find a substantial worsening of economic conditions.

C. Crime

Soon after the launch of OxyContin, there was a surge of demand for the drug in the illegal markets, situation that fuelled illegal drug dealers with thousands of dollars and placed users in dangerous situations (Meier, 2018). This situation worsen during later

[27]The receipt of benefits from multiple programs is not uncommon. SNAP program 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 can not be entirely driven by dual applicants. Under the assumption that the 20 percent of SNAP recipients are SSI recipients too, 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.

stages of the opioid crisis when rates of use of illegal drugs such as heroin increased. We are the first to estimate the causal effect of the supply of prescription opioids on crime rates. The bottom panel of Table 7 shows our results. We find large increases in crime across the board but mostly driven by property crimes. Specifically, a change from the 25th to the 75th percentile in the growth of prescription per capita caused a 61% increase in total crime rates, a 39% in violent crime, and 65% increase in property crime.

D. Birth and maternal 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 infants' health and maternal outcomes (Table 8). We find evidence that an increase in opioid prescriptions caused a slight worsening of birth outcomes; a 25th-to 75th-percentile increase in the supply of prescription opioids decreases birth weight by 1%, and deteriorated APGAR scores by 1%, relative to its mean value. We also find an increase in the APGAR score of infants who died in the first year, but we do not estimate any increase in infant mortality rate, or in the share of low-weight births.

Opioid use during pregnancy is not uncommon; e.g., from 2000 to 2007 one of five women filled a prescription for an opioid during pregnancy (Desai et al., 2014). The bottom panel of Table 8 presents our main estimates on maternal outcomes. We find a 0.62% reduction in the median gestation period when 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 we find no effects on the incidence of pre-term births. We estimate an increase in fertility, a 25th- to-75th increase in opioids increases fertility by 9%. This is the result of an increase in fertility from women 25 to 29 years old, that compensates a decline in fertility for those over 35 years old.

In summary, our results suggest that the opioid epidemic, while not affecting directly infant mortality rate, contributed to the worsening of birth outcomes through reductions in pregnancy duration and infants health at birth.

VI. Policy Implication and Conclusions

This paper studies the effects of the marketing and the introduction of OxyContin on the subsequent opioid epidemic. We exploit geographical variation in the initial promotion of OxyContin that targeted the cancer market. We document that this initial targeting had long-term effects on opioid mortality as well as a deterioration in socioeconomic conditions measured as demand for SSDI, SSI, SNAP, an increase in crime and, and a slight worsening of birth outcomes. Overall, we find strong evidence that the marketing practices of OxyContin were central to the unraveling of the opioid epidemic.

Our results have direct policy implications regarding the desirability of promotional efforts from pharmaceutical to physicians, pharmacies, and patients. We document the devastating consequences that result from aggressive and deceitful marketing. Although marketing expanded over the past 25 years since the introduction of OxyContin, regulatory oversight remains relatively limited.[28] There have been regulatory initiatives that constitute small steps in the right direction, such as the Sunshine Act of 2010 that required reporting of payments from industry to physicians, with a recent expansion that includes payments to physician assistants, nurse practitioners, nurses, pharmacists, and dietitians. Furthermore, a growing segment of the medical community has spoken out against the pharmaceutical industry effort to influence doctors. A number of teaching hospitals have enacted policies that restrict or ban visits from pharmaceutical representatives. Most of these initiatives, however, are concerned with the rising costs of prescription drugs, and not with the risks of abuse and addiction. More can be done in terms of restrictions to pharmaceutical promotion that carries this risk.

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[28]Currently, prescription drug marketing practices in the US include direct-to-consumer and professional branded advertising, detailing vis-its, free drug samples, direct physician and hospital payments (e.g., speaker fees, food, travel accommodations).Direct-to-consumer prescription drug advertising is only permitted in the United States and New Zealand (Schwartz and Woloshin, 2019).

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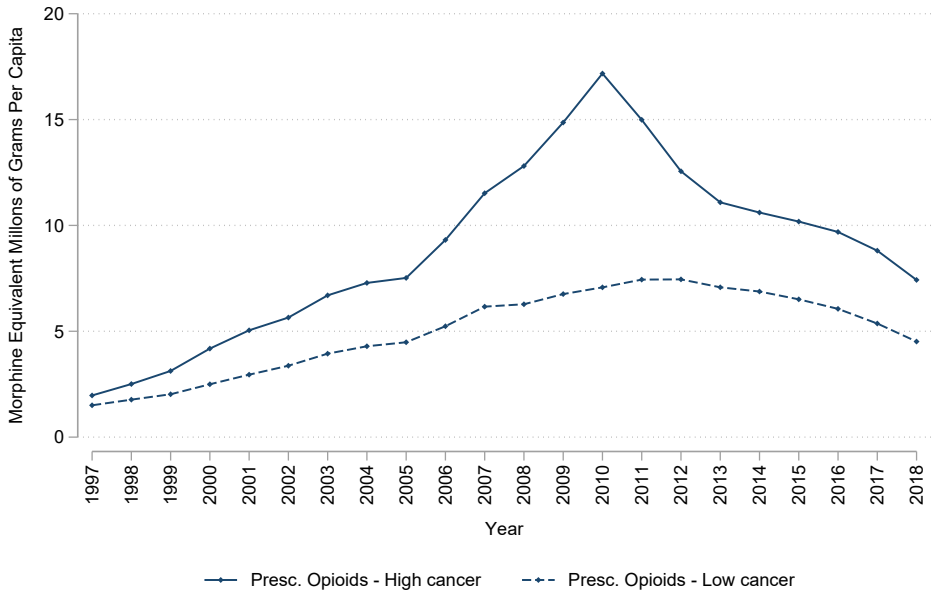
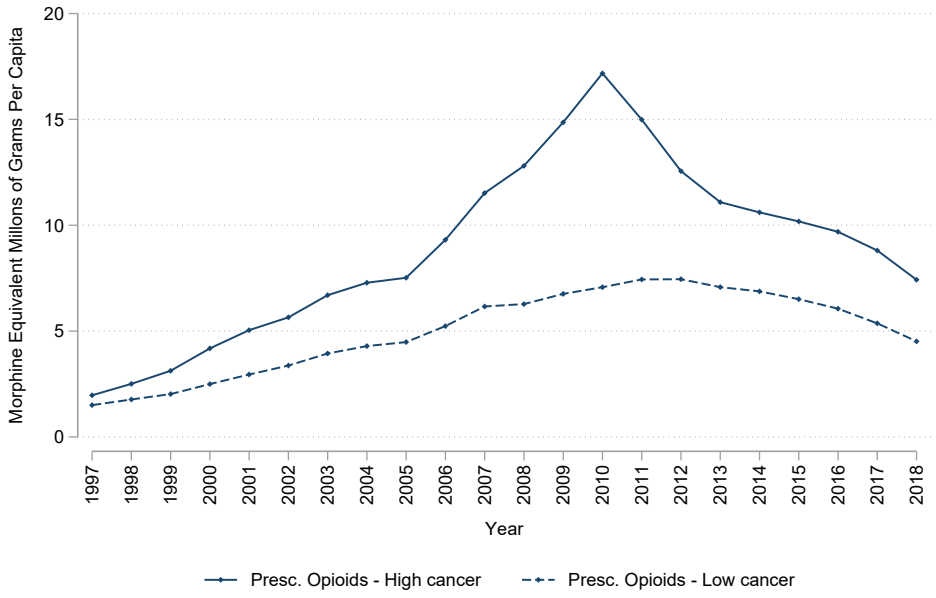
VII. Figures

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

(a) Main Prescription Opioids

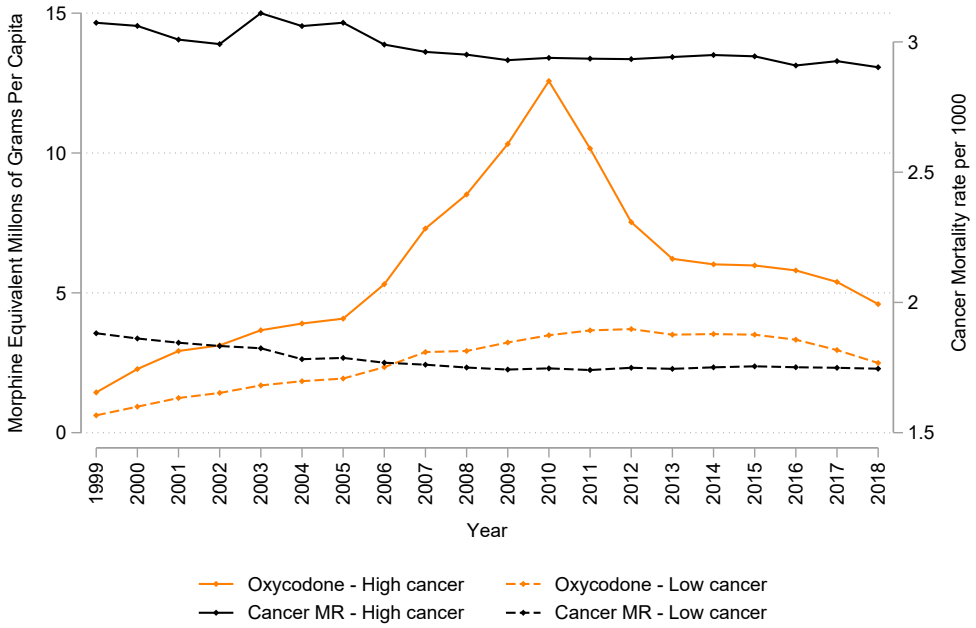


(b) All Prescription Opioids



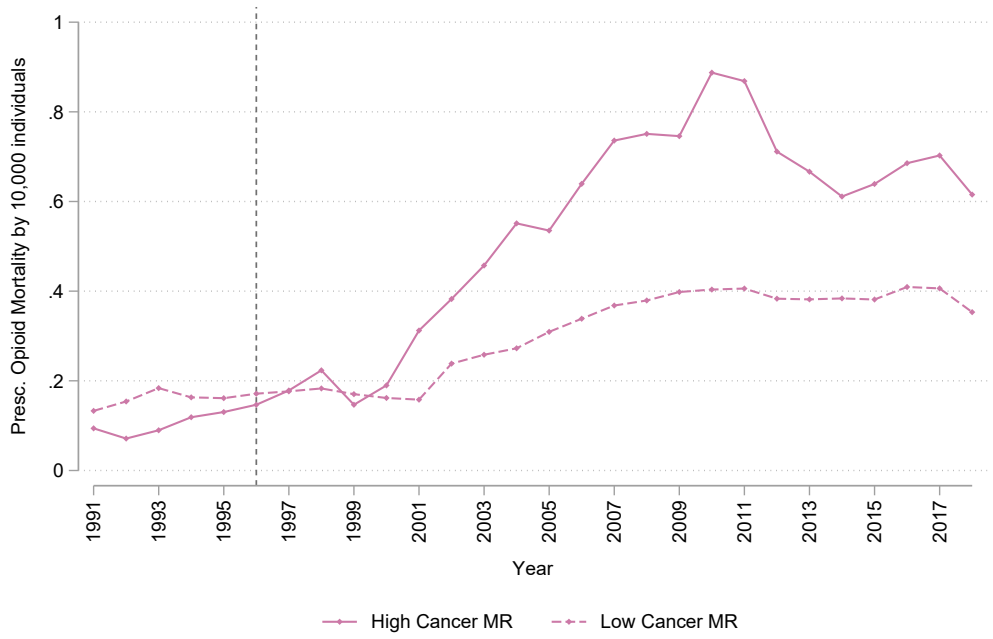
Notes: This figure shows the evolution of oxycodone, hydrocodone, and morphine (panel a) and all prescription opioids (panel b) in the forth quartile (solid lines) and first quartile (dashed lines) of the cancer mortality rate distribution before the launch of OxyContin. Between 1997 and 2010 areas in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

Figure 2: Evolution of Cancer Mortality and Oxycodone by 1994-1996 Cancer Prevalence



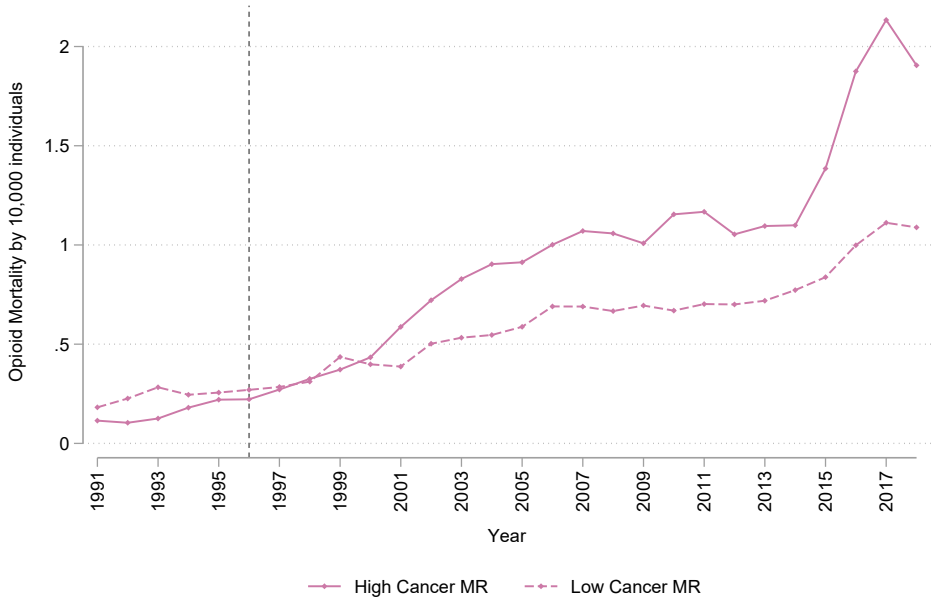
Notes: The left-hand axis of this figure shows the evolution of oxycodone in the forth quartile (solid lines) and first quartile (dashed lines) of the cancer mortality rate distribution before the launch of OxyContin. The right-hand axis of this figure shows the evolution of cancer mortality in the top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

Figure 3: Prescription Opioids Mortality Rate by 1994-1996 Cancer Prevalence



Notes: This figure shows the evolution of prescription opioid mortality by 1994-1996 cancer prevalence. High cancer mortality rate corresponds to the group of commuting zones in the forth 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 opioids morality 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 codes used to construct this measure.

Figure 4: All Opioids Mortality Rate by 1994-1996 Cancer Prevalence



Notes: This figure shows the evolution of all opioid mortality by 1994-1996 cancer prevalence. High cancer mortality rate corresponds to the group of commuting zone in the forth 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. All opioids mortality captures deaths whose underlying cause is subtances found in prescription painkillers as well as heroin and synthetic opioids; e.g., fentanyl;see data section for details on codes used to construct this measure.

VIII. Tables

Table 1: Summary Statistics, 1999-2018

	Mean	Median	SD	Min	Max	Obs
Opioids Prescription: Doses per capita						
All Opioids	6.42	5.48	4.32	0.00	57.65	11,876
Oxycodone	3.15	2.52	2.60	0.00	51.31	11,876
Hydrocodone	1.93	1.55	1.50	0.00	16.66	11,876
Morphine	0.94	0.77	0.69	0.00	10.67	11,876
Cancer Mortality per 1,000						
Cancer MR 94 -96	2.52	2.53	0.58	0.11	6.04	590
Cancer MR	2.48	2.49	0.55	0.59	4.75	11,876
Outcomes: Mortality per 1,000						
Prescription opioids	0.04	0.03	0.05	0.00	1.06	11,876
Any opioids	0.07	0.05	0.07	0.00	1.22	11,876
Outcomes: Labor Market						
Labor Force Participation (LFP)	0.48	0.49	0.06	0.02	1.00	11,800
Employment	0.94	0.94	0.02	0.73	0.99	11,800
Outcomes: Social Assitance						
Sh. SSI	0.04	0.03	0.02	0.00	0.30	11,800
Sh. SSDI	0.05	0.04	0.02	0.01	0.16	11800
Sh SNAP	0.12	0.11	0.06	0.00	0.57	11,800
Outcomes: Crime rates per 100,000						
Total crime rate	1574.51	1383.37	1372.12	0.00	6849.93	11,800
Violent CR	168.38	122.09	174.31	0.00	1249.73	11,800
Propoerty CR	1406.14	1235.60	1221.13	0.00	6462.62	11,800
Birth and Maternal Outcomes						
Infant MR (per 1,000 births)	6.86	6.54	2.87	0.00	30.61	11,880
Birth weight	3274.4	3276.9	79.7	2930.3	3569.8	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	35.0	40.0	11,800
Fertility rate	0.08	0.08	0.01	0.04	0.19	11,800
Adequacy of care	0.80	0.82	0.09	0.02	0.97	11,800

Notes: This table presents summary statistics for our main outcomes, measures of prescription opioids 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 Local Area Unemployment Statistics from the BLS to measure labor market outcomes, and 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). Crime data come from the Uniform Crime Reports from the FBI.

Table 2: Determinants of Opioid Distribution in 2000

Dependent variable: All prescription opioids per capita			
	(1)		(2)
Demographics		*Crime*	
Share white	3.526***	Overall	-0.0000622
	[0.961]		[0.0000752]
Share Hispanic	-2.055	Violent	0.00160***
	[2.426]		[0.000614]
Share female	6.709	*Economic characteristics*	
	[9.973]	Ln income	2.517***
Share 18-65	21.67***		[0.922]
	[4.348]	Sh. below poverty line	0.0521
Share +66	6.211		[0.0625]
	[7.665]	Sh. employed in manufacturing	-0.0374***
Share under 1	-100.8*		[0.0105]
	[56.42]	Sh. with some college education	0.00938
Labor market			[0.0135]
Employment rate	-16.18***	*Health outcomes*	
	[6.031]	Cancer mortality rate	-0.164
LFP	-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	Sh. 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 var			5.9901
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 assistant demand, crime outcomes, economic characteristics, and health outcomes at the commuting zone level. Data on economic characteristics comes from county-level tabulations of the Decennial Census Data. The variable share with some college measures the share of 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

Table 3: First Stage

Dependent variable: All 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
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. R2	0.019	0.524	0.559	0.533	0.564

Notes: control variables are contemporaneous cancer mortality rate, share of population under one 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 is computed as the predicted changed on 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

Table 4: Mid-nineties Cancer Selection

Independent variable:	Cancer MR 89-90
Dependent variables	
Income per capita	19.42
	[62.24]
Share with some college	0.0063
	[0.00386]
Share with HS or less	0.00257
	[0.00420]
Share Manufacturing	0.0063
	[0.00386]
Prescription Opioids MR	-0.000795
	[0.000580]
Any Opioids MR	-0.00101
	[0.000671]
IMR	-0.0989
	[0.154]
Labor Force Participation	-0.00153*
	[0.000821]
Employment rate	-0.000781
	[0.000489]
Share SNAP	-0.000529
	[0.000840]
Share on Disability	-0.000523
	[0.000890]
Share SSI	0.000151
	[0.000345]
Total crime rate	44.5
	[28.63]
Fertility rate	-0.641
	[0.490]

Notes: Each coefficient corresponds to a separate regression where the dependent variables is measured as the change with respect to 1989-1990. For prescription opiods, any opiods, labor market variables, crime, SNAP and IMR we run a panel regression, for the other variables where yearly data is not available we run one cross-sectional regression. All regressions include as controls variables: cancer mortality rate, share of population under one 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. 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.

Table 5: Direct Effects on Opioid Mortality

Dependent var:	Long change in mortality from Prescription opioids			Long change in mortality from All Opioids		
	(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]
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
Obs	11,800	11,800	11,800	11,800	11,800	11,800
Clusters	590	590	590	590	590	590
Adj R2	0.4304	0.3908		0.5368	0.5144	
Kleibergen-Paap Wald 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 one 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 are clustered at the CZ level. * p<0.10, ** p<0.05, *** p<0.01

Table 6: Robustness Checks and Alternative Specifications

Dependent var:	Presc. opioids MR	All opioids MR	Oxycodone pc	Presc. opioids MR	All opioids MR	Drug Induced MR	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
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]		
Prescription Opioids pc						0.0121***	0.0112***
						[0.00314]	[0.00369]
Effect size			38.00	91.50	40.37		50.71
Model	RF	RF	FS	IV	IV	RF	IV
Observations	3,540	3,540	11,800	11,800	11,800	11,800	11,800
Clusters	590	590	590	590	590	590	590
Adj R2	0.065	0.13	0.526			0.569	

Notes: Regressions in columns (3) to (7) include state times year fixed effects. Control variables are contemporaneous cancer mortality rate, share of population under one 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 in column (3) is computed as the predicted changed on 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. Effect size in columns (4),(5) and (7): 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 are clustered at the CZ level. * p<0.10, ** p<0.05, *** p<0.01

Table 7: Labor Market and Social Assistance Outcomes

Panel A: Labor Market Outcomes

Dependent var:	Employment rate		Labor Force Participation	
	(1)	(2)	(3)	(4)
Prescription opioids pc	-0.000108	-0.00181	0.000290	0.00348
	[0.000171]	[0.00214]	[0.000388]	[0.00239]
Effect size	-0.66	-11.12	2.46	29.53
Model	OLS	IV	OLS	IV

Panel B: Social Assistance Programs

Dependent var:	SSDI		SSI		SNAP	
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.000444***	0.00574***	0.00000709	0.00311**	0.000144	0.00982***
	[0.0000985]	[0.00132]	[0.000147]	[0.00144]	[0.000285]	[0.00299]
Effect size	5.95	76.39	0.11	46.88	0.83	56.58
Model	OLS	IV	OLS	IV	OLS	IV

Panel C: Crime Outcomes

Dependent var:	Aggregate		Violent		Property	
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	12.78*	275.8***	1.236	23.22***	11.43*	254.1***
	[6.567]	[71.92]	[1.118]	[7.455]	[5.980]	[66.55]
Effect size	2.82	60.90	2.08	39.07	2.90	64.58
Model	OLS	IV	OLS	IV	OLS	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 one 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 are clustered at the CZ level. * p<0.10, ** p<0.05, *** p<0.01

Table 8: Birth and Maternal Outcomes

Panel A: Birth outcomes

Dependent var:	Infant Mortality		Birth weight		Preterm births	
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.0511**	-0.0232	-0.552*	-4.490**	0.000270*	0.00141
	[0.0242]	[0.140]	[0.331]	[2.143]	[0.000150]	[0.000937]
Effect size	4.057	-1.826	-0.085	-0.687	0.836	5.852
Model	OLS	IV	OLS	IV	OLS	IV

Panel B: Birth outcomes

Dependent var:	APGAR score - all infants		APGAR score - dead infants	
	(1)	(2)	(3)	(4)
Prescription opioids pc	-0.000501	-0.0169*	0.0155	0.282*
	[0.00188]	[0.00994]	[0.0179]	[0.153]
Effect size	0.000	-0.910	1.383	25.169
Model	OLS	IV	OLS	IV

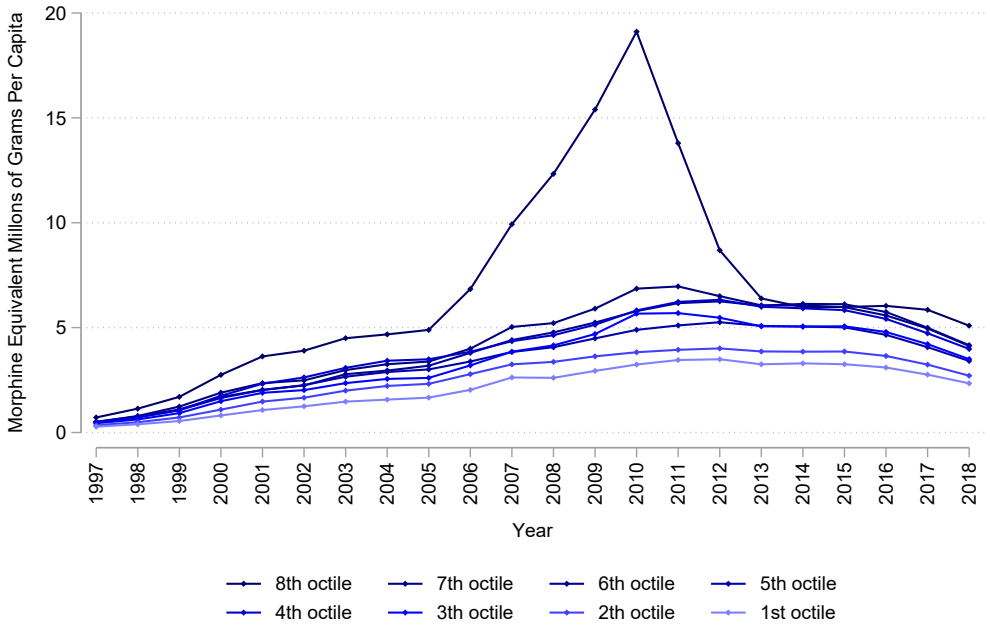
Panel C: Maternal outcomes

Dependent var:	Gestation		Fertility rate		Adequacy of care	
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	-0.000164	-0.0489***	0.0000665	0.00153***	-0.00104	0.00292
	[0.00304]	[0.0186]	[0.0000621]	[0.000566]	[0.000811]	[0.00531]
Effect size	0.000	-0.618	0.000	9.405	-0.627	1.818
Model	OLS	IV	OLS	IV	OLS	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 one 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 are clustered at the CZ level. * p<0.10, ** p<0.05, *** p<0.01

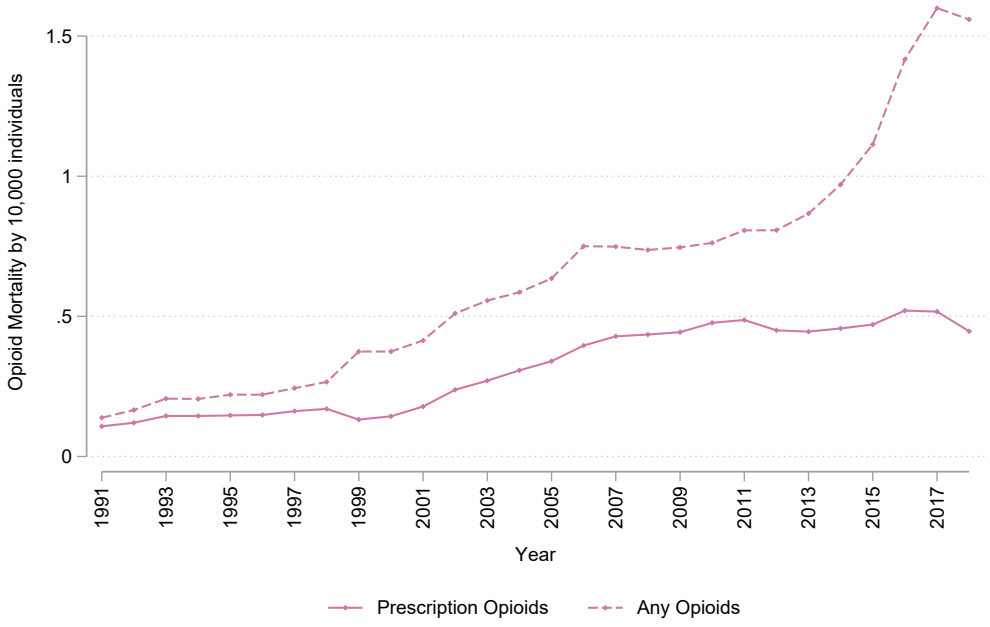
A Extra Figures

Figure A1: 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 by those commuting zones in the *nth* 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 picked in 2010 at 19 morphine equivalent millions of gm per capita). Lighter colors indicate groups with lower cancer prevalence.

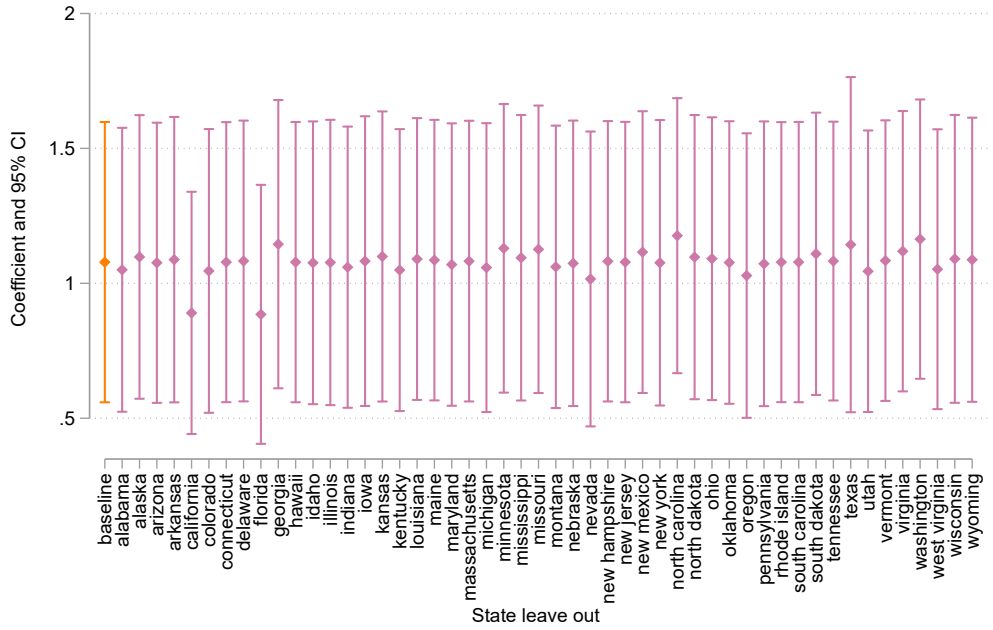
Figure A2: Evolution Prescription Opioid and All Opioid Mortality Rates



Notes: This figure shows evolution of prescription opioid and all opioid mortality rates since 1991 till 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 the 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)

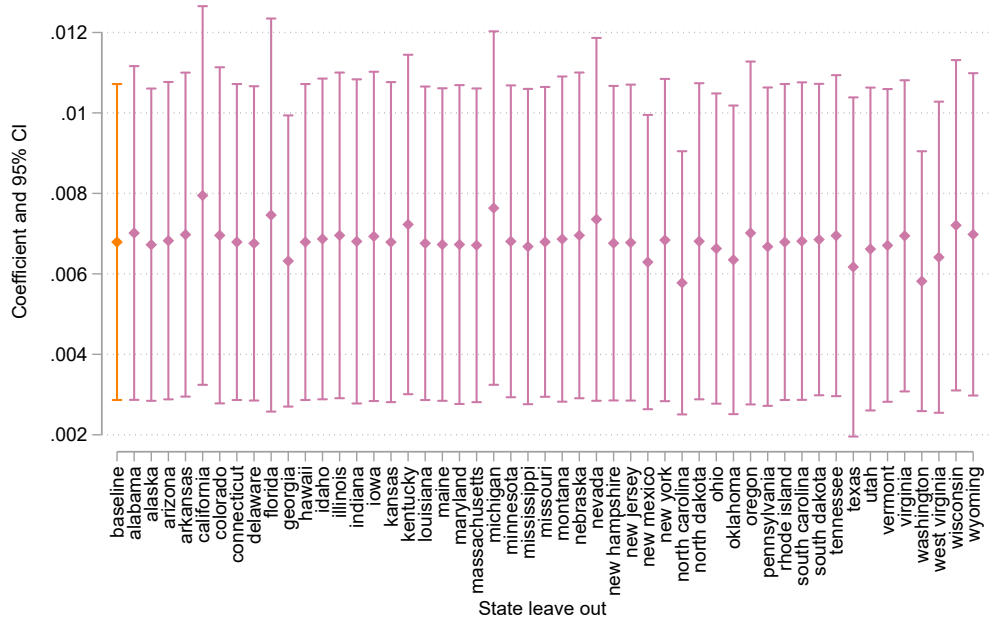
A. Robustness Check: Leave Out on State at the Time

Figure A3: Estimates of the First-stage Coefficient



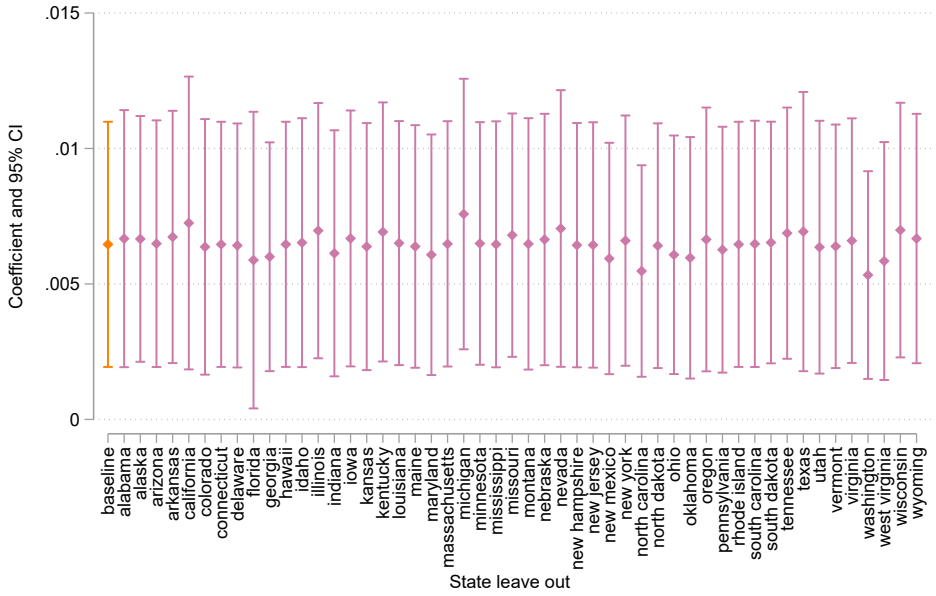
Notes: This graphs reports the estimated coefficient of the first stage (ϕ) and the corresponding 95% confidence interval. The first coefficient and confidence interval replicate the result from column 6 of Table 3, each of the subsequent coefficients are computed by excluding all commuting zones in the state indicated on the horizontal axis.

Figure A4: IV Specification Estimates of the Effect on Prescription Opioids Mortality



Notes: This graphs shows the estimated coefficient of the IV regression on prescription opioids mortality, instrumenting oxycodone shipments with cancer mortality in 1994-1996. The first coefficient and confidence interval replicate the result from column 3 of Table 5, each of the subsequent coefficients are computed by excluding all commuting zones in the state indicated on the horizontal axis.

Figure A5: IV Specification Estimates of the Effect on All Opioids Mortality



Notes: This graphs shows the estimated coefficient of the IV regression on all opioids mortality, instrumenting oxycodone shipments with cancer mortality in 1994-1996. The first coefficient and confidence interval replicate the result from column 6 of Table 5, each of the subsequent coefficients are computed by excluding all commuting zones in the state indicated on the horizontal axis.

B Extra Tables

Table A1: Additional Summary Statistics: Opioids Prescription, doses per capita

	Mean	Median	SD	Min	Max	Obs
1997						
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						
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						
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 distribution of oxycodone, hydrocodone and morphine for the years 1997, 2007 and 2017. Data on distribution comes from the DEA and is expressed in morphine mg equivalents.

Table A2: Baseline Results Under Shift-Share Instrument

Dependent var:	Presc. Opioids pc	Presc. Opioids MR	Any Opioids MR	SNAP	SSDI	SSI	Crime Rate	IMR	Fertility rate
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Shift Share	0.00417***								
	[4.18]								
Effective F	17.47								
Presc. Opioids pc		0.00644***	0.00635***	0.00927***	0.00553***	0.00319**	258.7***	-0.0218	0.00149***
		[3.44]	[2.91]	[3.35]	[4.34]	[2.02]	[3.87]	[-0.18]	[2.71]
Obs	11,800	11,800	11,800	11,800	11,800	11,800	11,800	11,800	11,800
Clusters	590	590	590	590	590	590	590	590	590

Notes: Column 1 reports the estimated coefficient for the first stage. Columns 2 to 9 present results from IV regressions usigng 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 one 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

Table A3: Baseline Results Under Alternative Sample Restrictions

Panel A: First Stage			
Dependent variable: Prescription Opioids pc			
	(1)	(2)	(3)
Cancer MR 94-96	1.191***	1.055***	1.018***
	[4.79]	[3.55]	[3.54]
Sample	**15,000+**	**40,000+**	**55,000+**
R squared	0.467	0.568	0.608

Panel B: Instrumental Variables Results						
Dependent variable:	Prescription Opioids MR			Any Opioids MR		
	(1)	(2)	(3)	(4)	(5)	(6)
Presc. Opioids pc	0.00355***	0.00684***	0.00826***	0.00152	0.00697**	0.00885***
	[2.65]	[2.96]	[3.08]	[0.89]	[2.56]	[2.69]
Sample	**15,000+**	**40,000+**	**55,000+**	**15,000+**	**40,000+**	**55,000+**
Observations	12,820	10,880	9,620	12,820	10,880	9,620
Clusters	641	544	481	641	544	481

Notes: Panel A presents results for the first stage regression using alternative sample definitions. Panel B presents results from a regression of 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 5 under alternative sample restrictions. 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 one 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

Table A4: Baseline Results with Labor Market Controls

Dependent var:	Presc. Opioids pc	Presc. Opioids MR	Any Opioids MR	SNAP	SSDI	SSI	Crime Rate	IMR	Fertility rate
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Cancer MR 94-96	1.072***								
	[0.264]								
Presc. Opioids pc		0.00674***	0.00639***	0.0103***	0.00587***	0.00313**	277.0***	-0.0326	0.00148***
		[0.00200]	[0.00231]	[0.00308]	[0.00136]	[0.00141]	[72.58]	[0.138]	[0.000562]
Observations	11,800	11,800	11,800	11,800	11,800	11,800	11,800	11,800	11,800
Clusters	590	590	590	590	590	590	590	590	590

Notes: Column 1 reports the estimated coefficient for the first stage. Columns 2 to 9 present results from regressing the depend variable 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 5 under alternative set of control variables. 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 one 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