

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

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March 16, 2022

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Abstract

This paper studies the origins and consequences of the opioid epidemic. Drawing on recently unsealed records from state litigation against Purdue Pharma, we exploit detailed features of the marketing of OxyContin, which initially targeted the cancer pain market, to assess the role of supply side factors and to instrument for the level of prescription opioids. We document a strong link between Purdue Pharma's promotional targeting and future increases in the supply of prescription opioids and overdose deaths. Also we estimate the epidemic triggered a large increase in disability and SNAP claims and was accompanied by worsening of infant health and increased non-marital fertility rates.

JEL No. I12, I18, I30, J13

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†Department of Economics, University of California, Los Angeles (mvbarone@g.ucla.edu). This project was supported by an SSHRC Institutional Grant (SIG), University of Toronto Mississauga Research and Scholarly Activity Fund (RSAF), and funding from the UC Network on Child Health, Poverty and Public Policy provided through the UC Office of the President's Multicampus Research Programs and Initiatives. We thank Adriana Lleras-Muney, Sarah Reber, Catherine Maclean, Marcella Aslan, Kory Kroft, Roman Zarate, Emily Weisburst, Clementine Van Effenterre, David Price, and Laura Wherry for their comments and helpful conversations. We thank seminar participants at the Council of Economic Advisers, Central Bank of Colombia, Electronic Health Economics Colloquium (EHEC), EGSC, ICESI, LACEA, Rice University, Simon Fraser University, Universidad Catolica de Uruguay, University of Houston, and the University of Toronto. Natalia Vigezzi and Bisma Khan provided excellent research assistance. This paper was previously circulated as "The Opioid Epidemic: Causes and Consequences".

I. Introduction

Over the last two decades, mortality from opioid overdoses in the United States has increased at an alarming rate. Since 1999, prescription opioid overdoses have claimed the lives of over 400,000 (CDC, 2019); contributing to the longest sustained decline in life expectancy in the last century, excluding the influenza and Covid pandemics (Dyer, 2018). Opioids are highly addictive, with rapid progression to physiological dependence with tolerance and withdrawal, even at prescribed doses and within a short time (Sharma et al., 2016; Hah et al., 2017). In 2012, the national opioid dispensing rate peaked at 81.3 prescriptions per 100 persons (CDC, 2020). Although the dispensing rate has declined since then; by 2018, there were still an average of 51.4 prescriptions per 100 persons. The potential effects of the rise in the supply of prescription opioids can stretch beyond the increase in overdose deaths, and include the transition to the use of illegal opioids such as heroin and fentanyl, a decline in one’s ability to work, recover from illness, and care for children, among other daily activities (Alpert, Powell and Pacula, 2018, Lynch et al., 2018, and Meinhofer and Angleró-Díaz, 2019).

Tracing the effects of the opioid crisis and its origin is challenging because the variation in the level of prescription opioids across geographies and over time is not random (Ruhm, 2019). On the one hand, deteriorating socioeconomic conditions could cause an increase in demand for opioids, and can also explain the subsequent decline in outcomes, which would lead to negatively biased estimates (Carpenter, McClellan and Rees, 2017 and Case and Deaton, 2017). On the other hand, the origin of the epidemic coincides with dramatic supply-side changes such as the increase in opioid access, a shift in physician prescribing attitudes, and the aggressive marketing of prescription opioids.¹ It has been documented that such increase is positively linked to access to health care and the number of physicians per capita so that areas with higher access to opioids are positively selected along indicators of healthcare access (Finkelstein, Gentzkow and Williams, 2018), which could, in turn, attenuate the estimates of the effects of the epidemic.

In this paper, we provide new evidence of the central role that the initial marketing of prescription opioids played in the unfolding of the opioid epidemic. We also document its consequences on the well-being of adults and its intergenerational effects. 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 opioid epidemic.² We document that OxyContin was initially promoted to the cancer pain market with the

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

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

plan to quickly expand to the much larger and more profitable non-cancer pain market. This targeting implied that physicians and patients in high-cancer areas were first exposed to OxyContin promotion and gained access to potent prescription opioids to treat moderate and chronic pain. That is, these high-cancer areas constituted the gateway of OxyContin to the non-cancer pain market. Furthermore, Purdue Pharma’s later strategy to target top prescribers—those in the highest three deciles of the opioid dispensing distribution—created a path dependency from where the promotion started to where it expanded to. Drawing on these insights, we exploit the geographic variation in cancer mortality in the mid-nineties—as a proxy for the cancer pain market served by Purdue Pharma—to assess the role of supply-side factors in the unfolding of the opioid epidemic. We use this variation as an instrument for the supply of prescription opioids and estimate its effect on a broad range of outcomes.

We collect data from multiple sources and construct a panel of commuting zones covering the United States from 1999 to 2018.³ We use data on the distribution of prescription opioids to measure the supply of opioids at the commuting zone level. We measure adults’ well-being using data on mortality from opioids and other causes, and the demand for social safety net programs—Supplemental Nutrition Assistance Program (SNAP), Supplemental Security Income (SSI), and Social Security Disability Insurance (SSDI). To capture the intergenerational effects of the epidemic we exploit linked data on births and maternal outcomes.

We find three key results. In terms of opioid-related mortality, increasing the supply of opioids from the 25th-to-the-75th percentile caused an 89% increase in prescription opioids deaths and a 39% increase in deaths from all opioids. This corresponds to approximately 200,000 deaths. These deaths are concentrated in young and middle-aged adults, with no effects on those 55 and older. We do not find effects of the rise in opioid supply on deaths of despair, or other causes of death.⁴

Second, the increase in prescription opioid supply had large indirect effects on communities. The demand for social safety net programs increased: A change from the 25th to the 75th percentile of prescriptions caused an increase of 57% 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. Third, we document large intergenerational effects. We estimate an increase in fertility rates of 10%, which is driven entirely by increases in non-marital births, and it is concentrated in women of ages 25-29. We find a decline in pregnancy duration of 0.24 weeks, a reduction in birth weight of 0.7%, and a worsening

³Commuting zones is a unit of aggregation that encompasses all metropolitan and non-metropolitan areas in the US. While less granular than counties, commuting zones are much more granular than states.

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

of APGAR scores by 0.9%.⁵ We estimate that there is no effect on infant mortality, but we find an increase in the APGAR score of infants who died in the first year, meaning that healthier infants died. Taken together, these results point to a general decline in health at birth.

Our identification strategy relies on the assumption that communities with higher cancer mortality in the mid-nineties, received larger influxes of prescription opioids after the launch of OxyContin. We show that in fact there is a strong and positive relationship between these two variables and the growth in prescription opioids is mostly driven by prescribed oxycodone, the active ingredient in OxyContin.⁶ Commuting zones with the highest cancer incidence—the 95th percentile relative to the 5th percentile—at the time of the launch of OxyContin received 1.96 more doses of opioids per capita. To put this result into context, an extra 1.96 doses of opioids per capita correspond to 64% of the average change in the distribution of prescription opioids from 1999 to 2018. This relationship is robust to alternative specifications and is not driven by a particular group of states. We also show that the evolution of cancer incidence is parallel over time in low- and high-incidence areas and does not account for the differences in opioid influx and opioid mortality that appear as the epidemic unfolds.

Crucially, we also require that in the absence of OxyContin’s marketing, areas with higher cancer mortality would exhibit the same *trends* as areas with lower cancer mortality in terms of our outcome variables (Goldsmith-Pinkham, Sorkin and Swift, 2020). To test this we use an event-study approach and investigate the presence of pre-trends. We do not find any evidence of a relationship between mid-nineties cancer mortality and the growth of outcomes of interest before the launch of OxyContin. In addition, we document that areas with higher cancer mortality are not on a differential trend with respect to socio-economic variables such as education, income, or other health variables. For example, we find that high- and low-cancer mortality commuting zones were on the same trend regarding suicide mortality and the share of employment in manufacturing and mining industries. These results suggest that deterioration in socio-economic conditions is not different in high and low cancer mortality places. This is not to say that the variation in cancer mortality across space is randomly distributed. In fact, we find strong demographic predictors of cancer such as the share of the population over 65 and the share non-Hispanic. What we require and provide evidence in favor of is that high and low cancer areas are on the same trends along our health and economic outcomes.

Finally, we propose two placebo exercises. First, we show that mid-1990s mortality rates from other causes, such as cerebrovascular mortality, are not predictive of the future

⁵The 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.

⁶Oxycodone is a semi-synthetic opioid that is 50% more potent than morphine and prescribed for the management of acute pain.

prescription opioids distribution. In a second placebo exercise, we relate cancer mortality in 1989-1990—the first year of our data—to the evolution of outcomes of interest before the launch of OxyContin. That is, we test if there is a relationship between the level of cancer and the growth of our outcomes outside the analysis period, and find no evidence of such link. Both of these exercises suggest that the connection between cancer mortality and prescription opioid distribution is not driven by other underlying health trends, but by the link created by Purdue Pharma through the marketing of OxyContin.

The contribution of this paper is threefold. First, this work adds to the literature that documents the importance of supply-side factors in explaining the origins and evolution of the opioid epidemic. This literature documents the role of physicians (Eichmeyer and Zhang, 2020; Schnell and Currie, 2018), access to healthcare (Powell, Pacula and Taylor, 2020), and pharmaceutical promotions (Fernandez and Zejcirovic, 2018; Miloucheva, 2021) as drivers of the increase in prescriptions and overdose deaths. This paper is closest to Alpert et al. (2021), who use state-level variation in the regulations regarding the prescription of Schedule II drugs.⁷ They show that the five states that, at the time of the launch of OxyContin, had a more cumbersome process for prescribing opioids were not as targeted by Purdue Pharma in their initial marketing plans. Subsequently, these five states reported lower levels of prescription opioids and overdose deaths. We improve and extend their work in multiple dimensions. Exploiting commuting-zone level variation in the initial marketing of OxyContin, we confirm its role in the origin of the crisis and quantify its impact on multiple measures of adult wellbeing and intergenerational outcomes. Our research design allows us to control for state-specific trends and state-level policy changes, which were common during this period—e.g., the implementation of Prescription Drug Monitoring Programs (PDMP), the regulation of “pill mill” clinics, and the availability of naloxone.^{8,9} Furthermore, the use of commuting-zone level variation improves power. Griffin et al. (2020) document that empirical strategies exploiting state-level variation to estimate effects on opioid mortality have very low statistical power to detect a significant policy effect.¹⁰

Second, this paper is the first to document the direct effects of the increase in access to prescription opioids on the demand of disability benefits and on one of the largest anti-

⁷The 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.

⁸The term “pill mill” is typically used to describe a doctor, clinic, or pharmacy that prescribes or dispenses controlled prescription drugs inappropriately (Malbran, 2007).

⁹Naloxone is a drug that can reverse an opioid overdose if administered quickly. The level of naloxone access varies by state and over time. Between 2001 and 2017 every U.S. state has passed a law that facilitates widespread distribution and use of naloxone (Doleac and Mukherjee, 2019).

¹⁰Griffin 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).

poverty programs in the United States, SNAP, which has not been studied before. Our work is related to [Savych, Neumark and Lea \(2019\)](#) who find evidence that an increase in long-term opioid prescribing leads to a considerably longer duration of temporary disability, and to [Park and Powell \(2021\)](#) who document that the rise in access and consumption of illicit opioids—such as heroin and fentanyl—increase disability applications by 7%.

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

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

In 1996, Purdue Pharma introduced OxyContin to the market. 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.¹¹ Both of these factors significantly increased patients' access to potent doses of opioids and augmented the risk of dependency and use disorder. For example, Percocet was the most common oxycodone product on the market before 1996 and was mostly sold in the form of 2.5 mg of oxycodone per tablet. In contrast, the most common forms of OxyContin were 20 mg and 40 mg tablets of oxycodone, while 80 mg and 160 mg tablets were also available. Furthermore, OxyContin users rapidly learned that crushing or dissolving the pill causes the oxycodone to be delivered all at once—instead of the slow release over 12 hours—which causes strong euphoric effects.

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' fears of the risk of addiction ([Melzack, 1990](#)). MS Contin, also produced

¹¹Other 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.

by Purdue Pharma, was the gold standard for cancer pain treatment. OxyContin’s development was in response to the generic competition Purdue Pharma expected to face when MS Contin’s patent protection expired in 1996. In their words: *“Because a bioequivalent AB rated generic control-release morphine sulfate is expected to be available sometime during the later part of 1996, one of the primary objectives is to switch patients who would have been started on MS Contin onto OxyContin as quickly as possible”* (OxyContin Launch Plan, September 1995).

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

To overcome these obstacles, Purdue deployed a comprehensive marketing strategy based on three main pillars. First, to effectively change physician prescribing behaviors, Purdue Pharma implemented an aggressive marketing plan that pushed the message of an untreated pain epidemic that affected millions of Americans on a daily basis. Pain was introduced as the fifth vital sign, with the goal of encouraging the standardized evaluation and treatment of pain symptoms (Jones et al., 2018). This messaging also included misleading statements—for instance, that opioid addiction rates were lower than 1% and that oxycodone was weaker than morphine when it is 50% more potent.¹²

Second, OxyContin was promoted directly to physicians by the largest and highest-paid sales force in the industry.¹³ 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

¹² *“We are well aware of the view held by many physicians that oxycodone is weaker than morphine. We all know that this is the result of their association of oxycodone with less serious pain syndromes. This association arises from their extensive experience with and use of oxycodone combinations to treat pain arising from a diverse set of causes, some serious, but most less serious. This ‘personality’ of oxycodone is an integral part of the ‘personality’ of OxyContin.”* Exhibit 11 from Richard Sackler’s—chairman and president of Purdue Pharma—deposition, August 28, 2015.

¹³The 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).

Plan, 1996).¹⁴

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

Purdue’s marketing strategy succeeded in making the use of opioids the standard practice in the treatment of moderate and chronic pain for a wide range of non-terminal conditions, expanding the use of opioids to the non-cancer pain market. By 2003, nearly half of all physicians prescribing OxyContin were primary care physicians (Van Zee, 2009). This strategy also opened the door for other pharmaceutical companies to promote their prescription opioids beyond the cancer market following Purdue’s leadership. These companies—Janssen, Endo, Cephalon-Teva, Actavis, Insys, and Mallinckrodt—who are also part of dozens of lawsuits for their role in the opioid epidemic, closely shadowed OxyContin’s marketing intending to grow by reducing OxyContin’s market share: “*Success means increasing Duragesic share at the expense of OxyContin*” (Sales Force Memorandum, 2001, Exhibit S0510, State of Oklahoma v. Purdue Pharma et al.).¹⁵ Furthermore, Purdue’s later strategy to promote only to top opioid prescribing physicians, those in the highest three decile of the distribution (Figure A1), meant that areas with high initial promotion as a result of the cancer market focus, also observed higher future promotion when Purdue’s plan shifted to top prescriber.¹⁶ This created a path dependency that

¹⁴From 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).

¹⁵Duragesic is a fentanyl patch manufactured by Janssen.

¹⁶This strategy is also followed by other pharmaceutical companies. For example, Janssen refers to

made initial targets always relevant as the distribution of opioids expanded.

For our purposes, Purdue’s marketing strategy means that areas with a higher incidence of cancer at the time of the launch of OxyContin would receive a disproportionate amount of marketing and prescriptions for OxyContin and other opioids. Thus, the ideal instrument is a measure of the cancer market Purdue Pharma was serving with MS Contin prior to the introduction of OxyContin. Hypothetically, there are multiple ways to proxy this market. One is to use mid-nineties MS Contin prescription rates as this was Purdue’s gateway to the non-cancer pain market. However, for the period of analysis these data are not available at the county or commuting zone level.¹⁷ Another approach would be to exploit a direct measure of Purdue Pharma’s marketing efforts—e.g., payments to physicians, areas served by sales representatives, and the number of visits of these representatives—unfortunately, these data are not available to the public.¹⁸ Thus, our measure of the cancer market in the mid-nineties is cancer mortality between 1994 and 1996.¹⁹ 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 2018.²⁰ Our main independent variable is grams of prescription opioids per capita at the commuting-zone level; this corresponds to the sum of oxycodone, codeine, mor-

high decile prescribers as their *highmost important customers* in a Sales Force Memorandum for Duragesic in 2001.

¹⁷From reading court litigation’s documents we know that at that time, Purdue had access to extremely granular prescription drugs data through a firm called IMS (later called Xponent and today called IQVIA). We have contacted IQVIA to inquire about these data and they stated they do not keep any records of historical data. Additionally, State Drug Utilization Data (SDUD) reports the number of prescriptions paid by Medicaid agencies at the state level, which does not allow us to exploit within-state variation.

¹⁸Court litigation’s documents refer to lists of sales representatives and visits to physicians but we could not access these files; only extracts of these lists are available in the courts’ documents. Open Payments Data collected by the Centers for Medicare & Medicaid Services (CMS) are available starting in 2014, eight years after the introduction of OxyContin and four years after the introduction of the abuse-deterrent OxyContin.

¹⁹An alternative plausible instrument is the number of oncologists per capita. However, this measure is far too concentrated in the largest commuting zones.

²⁰ARCOS 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.

phine, 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 morphine. Oxycodone represents around half of all prescription opioids shipments, and the average commuting zone receives 3.15 doses per capita in a given year. This number masks substantial geographical variation. While some commuting zones received no doses, others report as much as 51.31 oxycodone doses per capita in a given year, Map 1 shows this variation. Figure A2 shows the rapid growth of prescription opioids over time and the dominant role of oxycodone in such growth.

B. Cancer Mortality

We proxy cancer incidence by computing cancer mortality in a given commuting zone. Cancer mortality is likely a lagged measure of cancer incidence in the population since cancer deaths at time t are cancer patients in previous periods. Nonetheless, cancer mortality has a closer connection to the rates of cancer patients who are using opioid painkillers to manage cancer pain, such as MS Contin, especially in the later stages of cancer treatment.²¹ We measure cancer incidence at the time of OxyContin’s launch as the average cancer mortality rate between 1994 and 1996 using a restricted-access version of the Detailed Multiple Cause of Death (MCOd) files.²² Map 2 shows large variation in average cancer mortality in 1994 and 1996.

C. Outcome measures

Opioid mortality. We use restricted-access data from the MCOd files from 1989 to 2018 to construct mortality measures. These files record every death in the US along with the county of residence, the underlying cause of death, and up to 20 additional causes

²¹An additional measure of cancer incidence is the rate of cancer patients in the population. Unfortunately, incidence measures reported by the CDC and the Surveillance, Epidemiology, and End Results (SEER) program are aggregated at the state level and are more likely to be affected by variation in diagnosis rates, especially for early-stage cancers. In contrast, cancer mortality is available at the county level. Importantly, the two measures are highly correlated: the correlation coefficient is 0.88.

²²We describe these files in more detail in the next subsection. We also consider age-adjusted cancer mortality and test if our results are sensitive to any of the years used as our baseline cancer mortality measure. We find very similar and strong first-stage estimates across these alternative measures.

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.

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.²³ We also consider a broader measure of opioid-related deaths, in which we include deaths from heroin and synthetic opioids; e.g., fentanyl.²⁴ Map 3 shows this geographical variation.²⁵ Prescription opioid deaths vary from no deaths to as many as 106 per 100,000 residents in the most affected commuting zones.

Deaths of Despair. We also study how the marketing of prescription opioids affected deaths of despair. Case and Deaton (2015) define deaths of despair as deaths by drug and alcohol poisonings, suicide, and chronic liver diseases and cirrhosis. Our measure of deaths of despair does not include drug poisonings as these are counted in prescription and any opioids deaths. That is, our measure is limited to deaths from suicide, chronic liver disease, cirrhosis, and poisonings that are attributable to alcohol—these deaths amount to, on average, 79% of the deaths studied by Case and Deaton (2017).²⁶

Demand for social assistance benefits. We construct a measure of SNAP benefit reciprocity 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.²⁷ We include two measures of disability benefits reciprocity, 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

²³We use identification codes T40.2 and T40.3 to specify prescription-opioid-related overdoses in the ICD-10 data and codes 965.00, 965.02, 965.09, E850.1, and E850.2 in the ICD-9 data.

²⁴We 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.

²⁵The 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 A3 shows the time series for the US for these two measures.

²⁶We 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 poisoning are counted using codes X45 and Y15 in the ICD10-data and codes E850-E858, E860, and E980.1 in the ICD-9 data.

²⁷Table A14 shows the result for the sample of commuting zones that do not require state-level imputation. Our results are not sensitive to this sample restriction.

(OASDI) reports prepared by the National Social Security Administration, which we aggregate at the commuting-zone level.²⁸

Maternal and birth outcomes. Data on birth outcomes come from the Linked Birth and Infant Death Data of the National Vitals Statistic System (NVSS). The microdata for each year between 1995 and 2018 include the deaths of all infants born in that calendar year for which the death certificate can be linked to a birth certificate and all births occurring in a given calendar year.²⁹ We construct infant mortality as the ratio of infant deaths to live births in a given calendar year. The Linked Birth and Infant Death Data also include data on the infant’s condition at birth, such as weight and length of gestation. The main measures of infant health we compute from the birth files are the commuting-zone-level (i) average birth weight for all live births, (ii) share of low-birth-weight newborns, (iii) share of preterm births, (iv) APGAR score of all births, (v) APGAR score of deceased infants, and (vi) median pregnancy duration. Finally, we use the birth files to compute the average fertility rate at the commuting-zone level, defined as the ratio of the number of single pregnancies to the female population aged 15 to 44 years old.^{30,31}

In sum, we build a data set at the commuting-zone level, covering the period from 1989 to 2018 for our outcome variables and the instrument. ARCOS data are available since 1997, so analyses using this measure are restricted to a later period.³² We restrict our sample to areas with more than 25,000 residents. This represents 99.8% of all opioid deaths and 99.3% of the total population. Our final dataset consists of 17,110 observations from 590 commuting zones.

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

²⁸We observe the number of beneficiaries at a given point in time but do not observe the number of beneficiaries entering or exiting the programs. Thus, we cannot speak to the question of whether a change in the stock is due to people entering more quickly or receiving benefits for a longer time.

²⁹At 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.

³⁰We 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.

³¹Data for the period 1989-1994 come from the Natality Birth Files. These files provide demographic and health data for all births occurring during the calendar year that we use to construct infant mortality rates, birth weight, fertility rate, and APGAR scores for the analysis we perform in Section IV.B.

³²We 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.

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.³³ 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 source of variation in the opioid supply. We estimate the causal effects of the supply of prescription opioids via the following equations, which are run over our sample of commuting zones for the period 1999-2018:

First Stage:

$$\Delta \text{Presc. Opioids}_{ct} = \alpha_0 + \phi \text{CancerMR}_{ct_0} + \alpha \Delta X_{ct} + \gamma_{st} + v_{ct} . \quad (1)$$

Second Stage:

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

where c indexes commuting zones, t indexes years, s indexes states, and t_0 is defined as the average of the pre-OxyContin period. The operator Δ works as follows: For any random variable W_{ct} , ΔW_{ct} equals the difference $W_{ct} - W_{ct_0}$; we refer to this operation as the long-change of variable W_{ct} . Regarding Equation (1), $\text{Presc. Opioids}_{ct}$ corresponds to doses of opioids per capita shipped to commuting zone c in year t and CancerMR_{ct_0} is the cancer mortality rate in commuting zone c in 1994-1996 (t_0). In Equation (2), y_{ct} refers to one of our outcomes of interest, e.g., a measure of opioid-related mortality. Both equations include a vector 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 effects represented by the term γ_{st} (and λ_{st} in the second-stage equation). These fixed effects control for the variation in outcomes over time that is common to all commuting zones within state s , and purge the

³³We also find a small negative correlation between the share of employment in the manufacturing industry and opioid prescription rates.

variation in the supply of prescription opioids that results from a change in state-level policies—such as the implementation of a PDMP, access to naloxone, and regulation of “pill mills”. The variables v_{ct} and ε_{ct} are idiosyncratic error terms. We cluster standard errors at the commuting-zone level, which is the level of exogenous variation.

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

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

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

We start by providing graphical evidence in Figure 1. We divide commuting zones into quartiles according to their level of cancer mortality before the launch of OxyContin and trace the evolution of all prescription opioids, oxycodone, hydrocodone, and morphine in these communities. Panel (a) of Figure 1 shows the evolution of the aggregate of prescription opioids per capita in commuting zones in the bottom and top quartiles of cancer mortality in 1994-1996, as well as the evolution of oxycodone—the active ingredient of OxyContin, which accounts for the largest share of this growth.³⁴ 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

³⁴In Appendix Figure A5 we present the analogous analysis, but we split the data based on 8 octiles of cancer mortality and observe 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 A4.

Table 3 shows the results of the first-stage regression defined in Equation 1. Column 1 is a bivariate regression of prescription opioids per capita on cancer mortality at t_0 . Columns to the right add time-varying controls and different specifications of fixed effects. Our preferred specification is the one in column 5, in which we control for state-times-year fixed effects and our covariates. For all specifications, there is a positive and strong relationship between cancer rates in the mid-1990s and the change in opioids per capita. A one-unit (one-standard-deviation) increase in 1994-1996 cancer mortality increases the change in prescription opioids per capita relative to 1997 by 1.1 (0.13 standard deviation). To put this figure in context, a change from a commuting zone in the 5th percentile of the cancer distribution to the 95th percentile increases opioids per capita by 64% relative to the base period. We can see the strength of this relationship graphically in panel (b) of Figure 1 where we plot the first stage coefficients by year. We find that starting in 1998, the second year in our data, and until 2018, the last year in our data, there is a positive and statistically significant relationship between cancer rates and prescription opioids per capita.

The literature on weak instruments has developed a variety of tests and confidence sets that remain valid whether or not the instruments are weak, in the sense that their probability of incorrectly rejecting the null hypothesis and covering the true parameter value, respectively, remains well controlled. We implement these procedures and present weak-instrument-robust inference. We follow Andrews, 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 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).³⁵

³⁵Based 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.

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. Specifically, in Table A3 we find that cancer mortality is: strongly related to share of the population over 65, negatively associated with the share of Hispanic population and positively associated with mortality from other causes of death. There is not, however, a strong correlation with our outcome variables: opioid mortality, shares in SNAP and disability, IMR or fertility. Regardless, 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., prescription opioid mortality) in commuting zone c at time t_0 , which could be affected by demographic characteristics. Nonetheless, the validity of our identification strategy does not require that cancer be randomly distributed across areas, but rather that in the absence of OxyContin marketing, areas with higher cancer mortality in the pre-OxyContin period (t_0) exhibit the same *trend* as areas with lower cancer mortality in t_0 in terms of our outcome variables (Goldsmith-Pinkham, Sorkin and Swift, 2020).

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

$$\Delta y_{ct} = \alpha_0 + \sum_{t=1989}^{2018} \phi_t \text{CancerMR}_{ct0} \mathbf{1}(\text{Year}_t) + \alpha \Delta X_{ct} + \gamma_{st} + v_{ct} , \quad (3)$$

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. Figures 2, 3, and 4 show the results of this estimation on main outcomes of interest.³⁶ We find that areas with higher cancer mortality in the mid-nineties were not on a differential trend along: opioid-related mortality, despair mortality, infant mortality, birth weight, fertility, or share of population using SNAP.³⁷ There is no evidence of pre-trends, i.e., the estimated coefficients for the pre-OxyContin period are jointly statistically indistinguishable from zero. After the introduction of OxyContin in 1996,

³⁶Appendix Figures A7, A11, and A12 complement this analysis.

³⁷Data on SSDI and SSI are not available at the county level before 1996 so we can not conduct this exercise for such outcomes.

strong patterns appear, and mid-nineties cancer mortality starts to predict opioid-related mortality, demand for SNAP, increased fertility, and worsening birth outcomes.

We also provide evidence that higher cancer mortality places were not on a differential trend along economic outcomes. In Appendix Figure A13, we test for a relationship between the share of employment in the manufacturing and mining industry and cancer mortality before the launch of OxyContin and find no evidence of a differential trend in these variables. Second, we perform an out-of-sample dynamic reduced-form analysis. That is, we run Equation 3 over a sample of commuting zones for the years 1989 to 1995 and estimate if lagged cancer mortality—average cancer mortality rate in 1989 and 1990, the first years in our data—predicts our outcome variables. We present the results of this analysis in Figure 5 and Figure A14. These results demonstrate that before the introduction of OxyContin there is no relationship between our outcome measures and lagged cancer mortality—the estimated coefficients are statistically indistinguishable from zero.

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

V. Results

A. Effects on Opioid-related Mortality

We start by inspecting the raw data; in panel (a) of Figure 2 we split commuting zones based on the cancer mortality distribution and document that early in the 2000s, a wedge starts to appear between high- and low-cancer-incidence groups, and by the end of the sample opioid mortality in high-cancer areas is 75% higher.³⁸ Second, following the reduced-form approach from Eq. 3, we estimate that after the launch of OxyContin a strong relationship emerges between mid-nineties cancer mortality and opioid-related mortality as shown in Panel (b) of Figure 2.³⁹

³⁸In Appendix Figure A6 we present the analogous analysis, but we split the data based on 8 octiles of cancer mortality and observe the same pattern.

³⁹In Appendix Figure A7 we replicate this analysis for any opioid mortality and document similar trends.

Next we take equations 1 and 2 to the data. Commuting zones with the highest cancer incidence at the time of OxyContin’s launch received 64% more opioids per capita than their counterparts—i.e., the 95th percentile relative to the 5th percentile. Using this increase as an exogenous 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%.⁴⁰

The ordinary least squares (OLS) estimates (columns 1 and 4 of Table 5) differ considerably from the IV estimates. We find a positive correlation between opioid supply and opioid mortality rate, but the difference in magnitude between the OLS and the IV estimates suggests that the former suffers from attenuation bias. Put another way, by looking at the correlation between opioid supply and opioid deaths, we would underestimate the role of the supply of prescription opioids in explaining the rise in mortality. The negative bias in the OLS estimates is consistent with commuting zones that receive a disproportionate amount of marketing being positively selected on observable characteristics: Areas initially targeted by OxyContin campaigns had better access to healthcare and a larger number of physicians per capita, which served as OxyContin initial network. These results are consistent with Finkelstein, 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 young and middle-aged adults and is driven mainly by white adults at the beginning of the epidemic. In Figure 6, we present the interactive-reduced-form analysis for three age groups (panel a) and for white vs non-white middle-age mortality (panel b). The analysis by age shows (i) no evidence of pretrends on opioid mortality for any of these groups, and (ii) opioid mortality increases that are concentrated among individuals aged less than 55 years old. For those 55 and older we see no effects. This pattern also alleviates concerns that our results are driven by underlying health trends that correlate with min-nineties cancer mortality. When studying the effects by race, we find that estimates for whites are positive and statistically significant starting soon after the launch of OxyContin. For non-whites it takes around

⁴⁰The 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.

a decade for estimates to be positive and statistically significant. Finally, we find the epidemic affected men and women similarly (Appendix Figure A9).

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

B. Adult Wellbeing and Intergenerational effects

We quantify the effects of the increase of opioid supply in three groups of outcomes. First, we look at direct measures of opioid mortality and despair mortality. Then, we ask whether the access to potent opioids has deteriorated the well-being of adults by looking at the demand for social insurance programs.

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.

Other Mortality Measures. We ask whether the dramatic increase in opioid supply affected all-cause mortality, excluding cancer deaths. These results are presented in Table 6. We find no relationship between overall mortality and the increase in prescription opioids. To put this result into context, note that at their peak in 2017, opioid-related deaths accounted for 1.8% of all deaths. The introduction of very effective pain medication could have improved the well-being of individuals with high incidence of pain and low risks of addiction. To assess if there is any indication of such improvements we estimate our reduced-form exercise on mortality rate for those 75 and older, but find no evidence of any reduction or increase in mortality (Appendix Figure A10).

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 Appendix Figure A11 we show that there is only a weak link between the increase in the supply of opioids and deaths of despair during the last wave of the opioid epidemic and that this driven by alcohol-related deaths. We estimate a positive but small increase in deaths from alcoholic liver diseases and cirrhosis significant only at the 10% level and no effect on suicides, see Table 6. The category alcoholic liver diseases includes causes of deaths such as hepatitis and related conditions, that may be directly affected by opioid use (Ruhm, 2021), so it is possible this small effect is directly driven by opioid use. Furthermore, the fact that we do not find an effect on suicides

(Figure A11), suggests that first, there are no pre-trends between our instrument and this measure of despair, and second, that the marketing of OxyContin did not trigger further despair. Similarly, we do not find evidence of changes in smoking rates (Figure A15).

Demand for Social Insurance. Addiction to and misuse of prescription opioids could reduce work capacity and put people at risk of permanently reducing their labor supply; in this context, disability insurance applications are a useful proxy for socioeconomic conditions and longer-term labor force attachment. We document a tight link between the opioid epidemic and an increase in disability beneficiaries. These results are presented in Table 7. We find positive and significant effects for measures of both disability programs. A change from the 25th to the 75th percentile in the growth of opioids per capita caused a 47% increase in the share of the population receiving SSI and a 76% increase in the share receiving SSDI.⁴¹ We do not have data for SSI or SSDI claims in the pre-period, but we can estimate our reduced-form event-study after the introduction of OxyContin. Figure A8 shows the strong positive pattern between mid-nineties cancer mortality and disability claims.

SNAP is designed to act as a safety net for low-income 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.⁴² These results point to a substantial worsening of economic conditions. The effects we observe on SSDI and SNAP are particularly strong during the third wave of the epidemic, when the incidence of illicit drug use, such as of heroin and fentanyl, increased (Table A5). Figure 3 shows the dynamic evolution of these effects.

Maternal and birth outcomes. Given the high levels of prescription opioid use in women of reproductive age and the staggering increase in the incidence of neonatal abstinence syndrome (NAS) (Patrick et al., 2015), it is policy relevant to study the effect of the epidemic on fertility and maternal and birth outcomes.⁴³ To the best of our knowledge, we are the first to document a causal rise in fertility as a result of the opioid epidemic. Specifically, a 25th-to-75th percentile increase in opioids increases fertility by 10% (Table 8). This result is entirely explained by non-marital births as we can see in column 1

⁴¹SSDI uses 1996 data as the baseline year, and SSI uses 1998 as the baseline year.

⁴²The 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 reciprocity 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.

⁴³Neonatal abstinence syndrome is a result of the sudden discontinuation of fetal exposure to medicine or drugs that were used or abused by the mother during pregnancy.

of Appendix Table A6. By age, we find that most of the increase in fertility is coming from women 25 to 29 years old, which compensates a decline in fertility for those over 35 years old. [Terplan et al., 2015](#) document that the higher rates of unwanted pregnancies in the population of women who take opioids is mostly driven by the lack of adherence to contraception.

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

Our estimated declines in birth weight are not small in magnitude. For a reference, [Almond, 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 relevant in light of evidence on the importance of birth weight and health at birth for future health, schooling, and earnings ([Behrman and Rosenzweig, 2004](#)).

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

C. Complier Analysis

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

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

VI. Robustness Checks

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

A. First Stage

A potential concern with our choice of instrument is that mid-nineties cancer mortality may be capturing demographic variation along the age distribution. Our baseline regression already controls for the change in the share of the population over 65, but our instrument is expressed in levels, so some of this variation may still be important. We directly test this by including the share of population over 65, the size of the population over 65, and total population as additional control variables. Table A8 shows the results of this exercise. We find that the first stage regression is as strong as in our baseline regression. Additionally, we test the robustness of the first stage to alternative choices of instruments. Column 1 of Table A9, replicates the first stage with age adjusted cancer mortality and we find a very similar and strong first-stage estimates. In column five we estimate a population weighted regression and find similar results. As an additional

robustness check, we test whether the relationship between future opioid supply and mid-nineties cancer mortality is sensitive to any of the years used as our baseline cancer mortality measure. Columns two to four show there is a strong first-stage for 1994, 1995 and 1996 cancer mortality. In column six we use mid-nineties cancer mortality for those over 65 in order to reduce variation in access to healthcare. For this alternative instrument we find a positive and statistically significant effect.

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 A7, we show results using the shift-share instrument. To construct this instrument, we use the national growth rate of prescription opioids as the shift component. The results are quantitatively indistinguishable from our preferred specification. As Goldsmith-Pinkham, 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.

Finally, we test whether the positive relationship in our first stage is driven by a state or a group of states. Figure A16 presents the estimate of the first stage coefficient restricting the sample to (i) all non-triplicate states, (ii) only triplicate states, and (iii) to the exclusion of all states, one at the time. We find that the relationship between mid-nineties cancer mortality and the supply of opioids is present in both triplicate and non-triplicate states, and is robust to the exclusion of any state.

B. Placebo checks

Are other mid-1990s mortality rates predictive of future prescription opioids per capita distribution? Our identification strategy connects mid-1990s cancer mortality to future growth in the supply of prescription opioids through the targeted marketing of Purdue Pharma. This implies that we can test the validity of our design by estimating first-stage regressions for placebo instruments—i.e., mid-1990s mortality from causes unrelated to cancer. Finding a good placebo instrument is challenging, given that the causes that underlie the incidence of cancer and other conditions, such as heart disease are not independent (Honoré and Lleras-Muney, 2006). As a result, there is substantial overlap across underlying causes and the correlation across measures is very high. With this caveat, in

Table A10 we show placebo instrument regressions for three mortality rates that are less likely to be affected by the previous concern: Cerebrovascular disease (CVD), transit accidents and homicide.⁴⁴ We find that none of these measures predict future distribution of opioids (Columns 1 to 3) or change the predicted power of our instrument (Columns 4 to 6).

C. Alternative Definitions: Opioid Supply and Opioid Mortality

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

Drug overdose deaths can be hard to categorize, specially when using data that spans more than one version of the ICD codes. We construct an additional outcome measure for opioid mortality and present the results using this measure in Table A12. This measure has the advantage that comparisons across years are less affected by changes in the ICD classification, but this comes at the cost of including a broader set of drugs as the cause of deaths.⁴⁵ Exploiting this measure, we arrive at similar conclusions: An additional dose of opioids per capita caused an increase in the drug-induced mortality rate of 0.0112 points. An increase from the 25th to the 75th percentile of prescription opioids per capita increases drug-induced mortality by 47%.

D. Alternative Sample Restrictions and Specifications

In our main specification, we restrict our sample to areas with more than 25,000 residents, which represents 99.8% of all opioid deaths and 99.3% of the total population. In Table A13 we reproduce our analysis using alternative restrictions on the size of commuting zones. We arrive at analogous conclusions to the main analysis; there is a strong and positive relation between mid-nineties cancer mortality and supply of prescription opioids which translates to (i) increases in opioid-related mortality, and (ii) deteriorating economic conditions and health outcomes.

⁴⁴A good candidate for this placebo check is mortality from external causes of deaths. External causes are defined as intentional and unintentional injury and poisoning (including drug overdose). From this category, we construct measures of mortality that do not include any of our outcome measures: accidental poisoning and suicide.

⁴⁵Drug-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.

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

VII. Policy Implications and Conclusions

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

Finally, our results have direct policy implications regarding the desirability of promotional efforts of addictive drugs by pharmaceutical companies that target physicians, pharmacies, and patients. We document the devastating consequences of aggressive and deceitful marketing. Although marketing expanded over the 25 years since the introduction of OxyContin, regulatory oversight remains relatively limited.⁴⁶ Some regulatory initiatives constitute small steps in the right direction, such as the Sunshine Act of 2010 that required the reporting of payments from the pharmaceutical industry to physicians, with a recent expansion that includes payments to physician assistants, nurse practitioners, nurses, pharmacists, and dietitians. Furthermore, a growing segment of the medical community has spoken out against the pharmaceutical industry’s effort to influence doc-

⁴⁶Currently, 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).

tors, 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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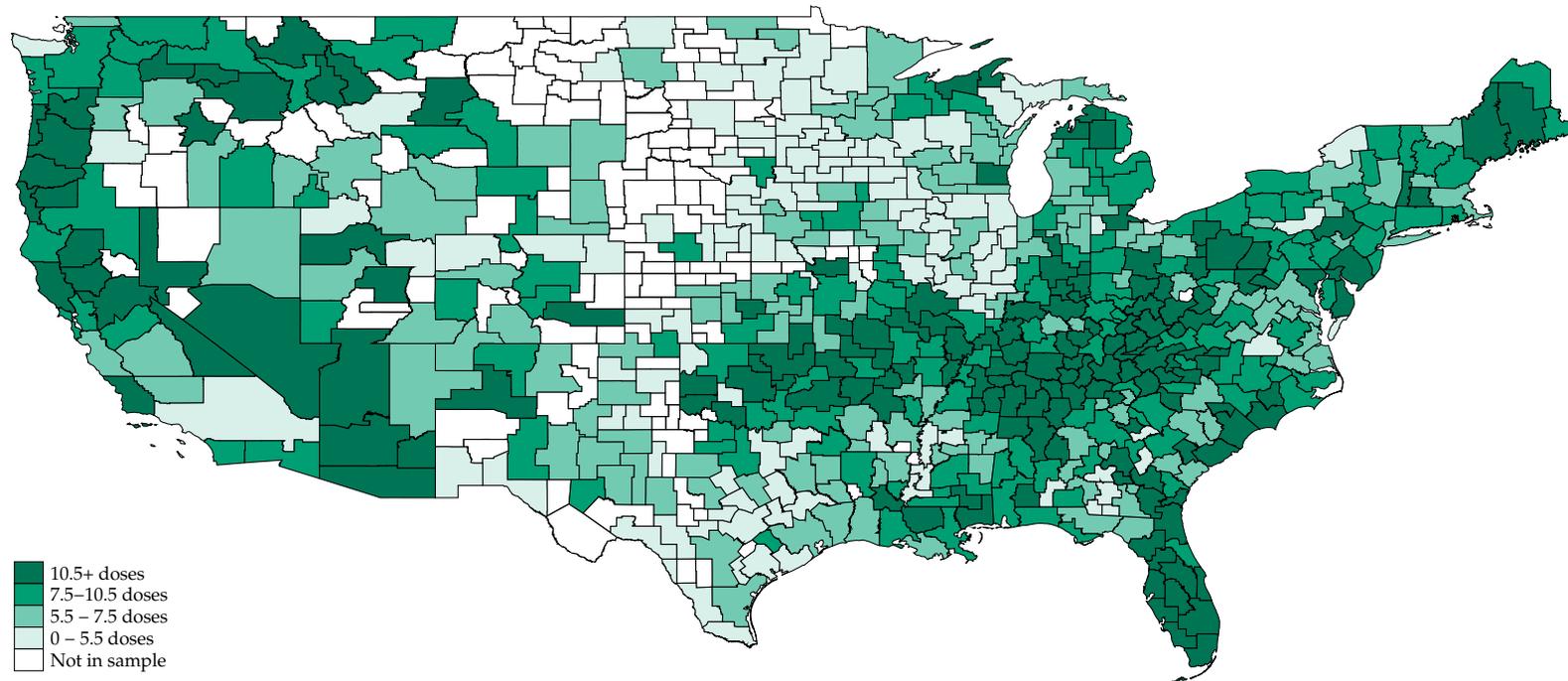
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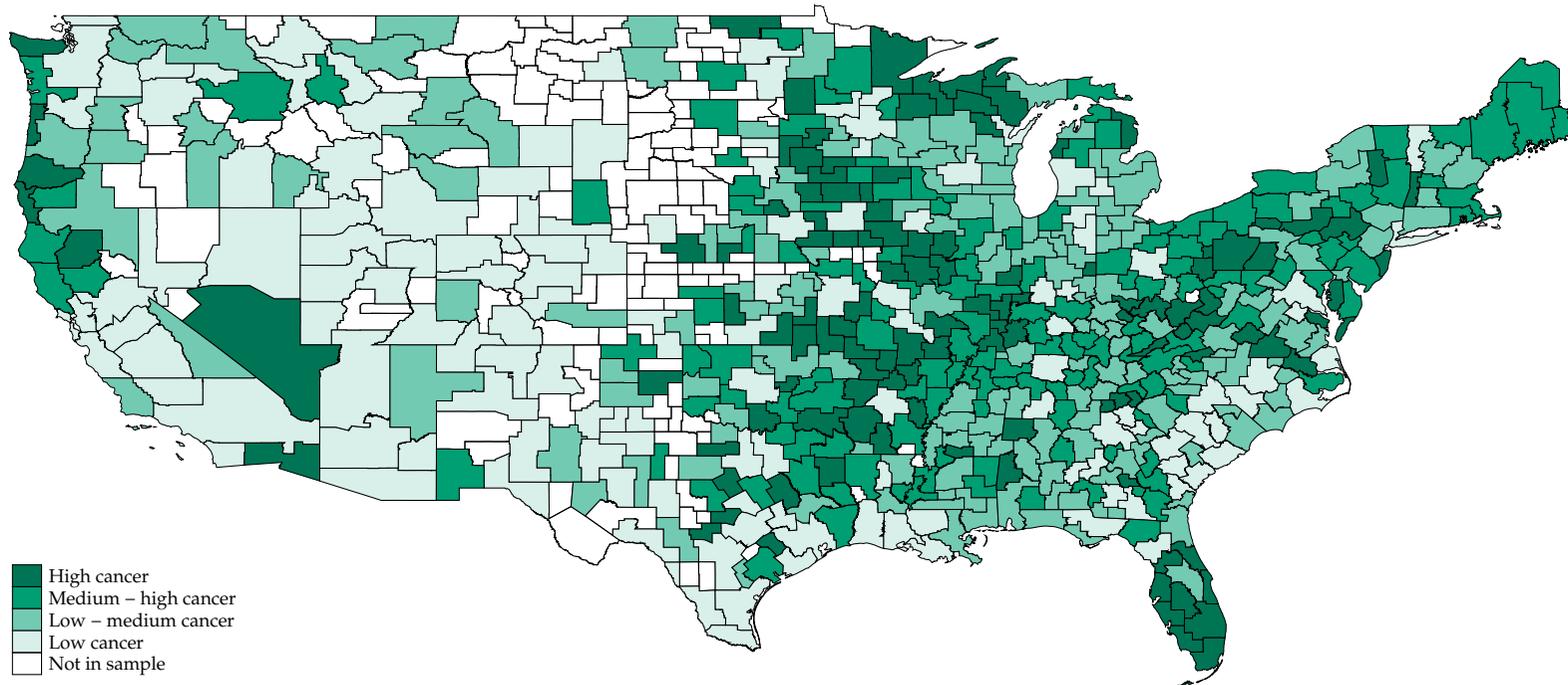
VIII. Maps and Figures

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



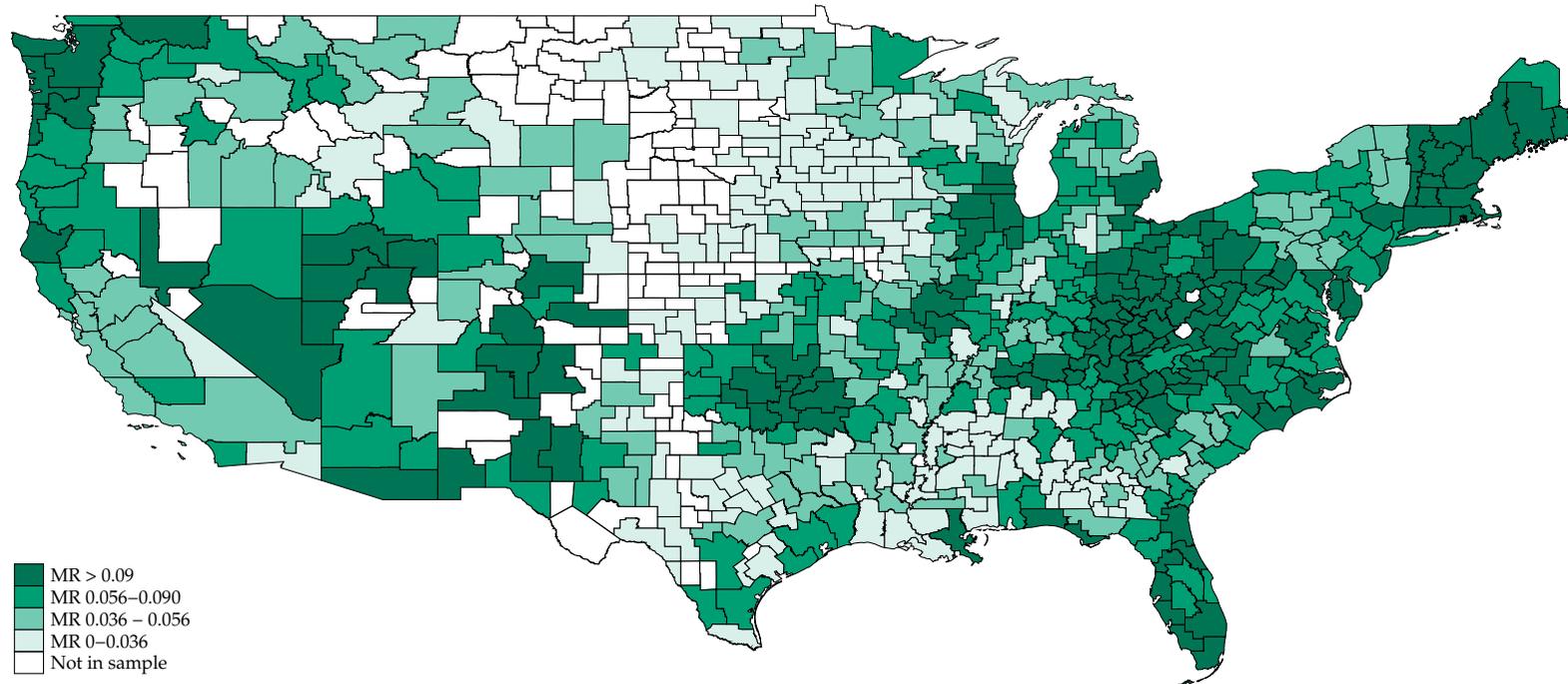
Notes: This map shows the distribution of prescription opioids at the commuting zone level in 2010, the year when the distribution of prescription opioids peaked as shown in Figure 1. Lighter shades indicate commuting zones with a lower prescription-opioid supply and darker shades indicate commuting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

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



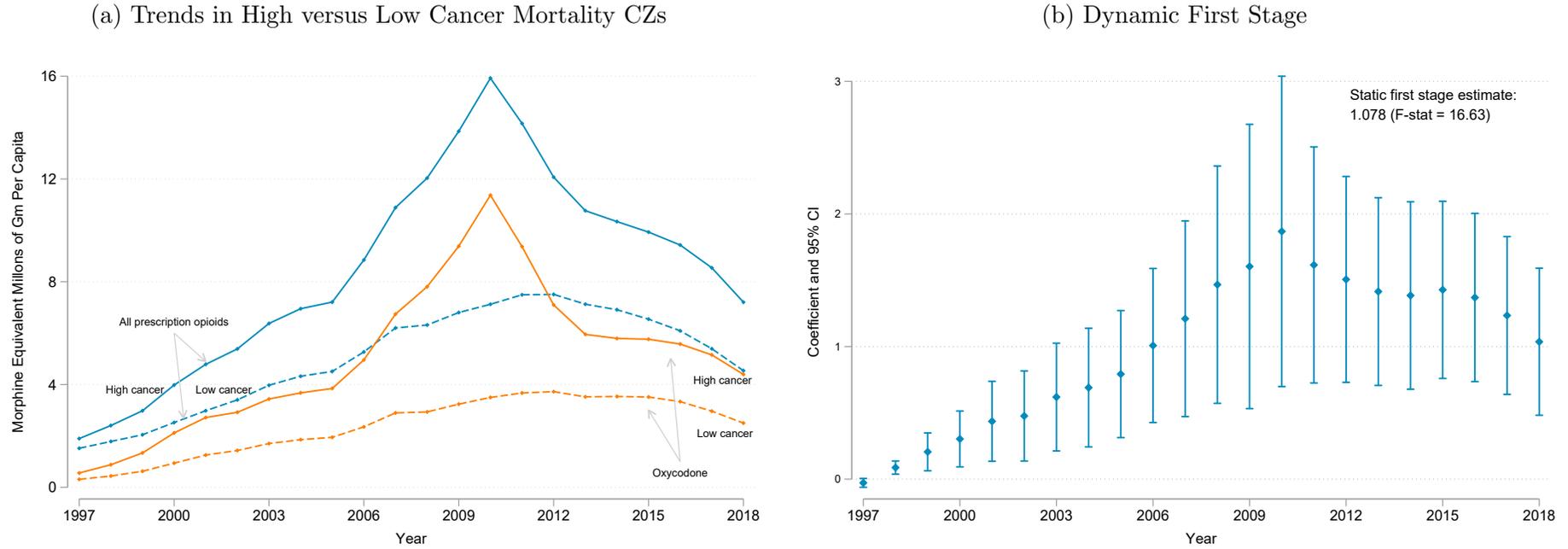
Notes: This map shows the cancer mortality rate at the commuting-zone level for the year 1994 - 1996, before OxyContin was introduced to the market. Lighter shades indicate commuting zones with lower cancer prevalence, while darker shades indicate commuting zones with higher cancer prevalence. Each group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

Map 3: Prescriptions Opioid Mortality Rate 1999 - 2018



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

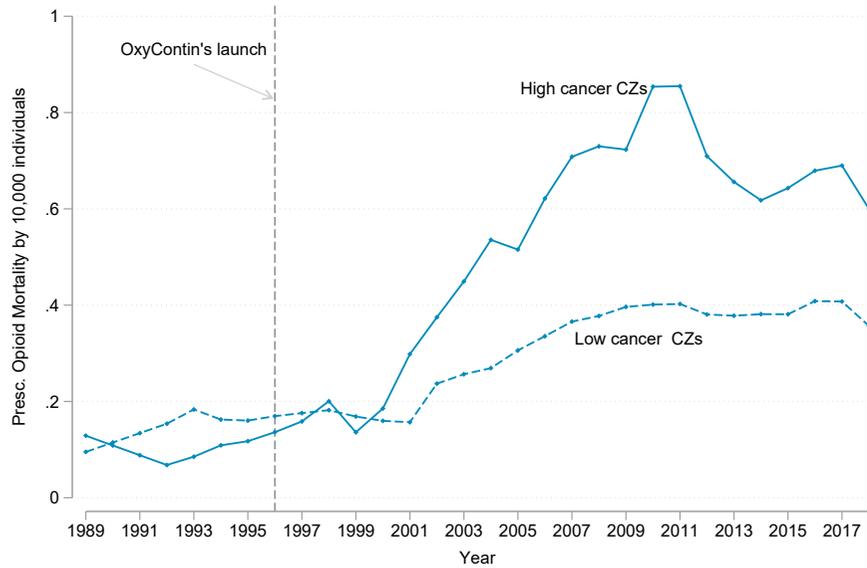
Figure 1: Prescription Opioids Distribution by Cancer Prevalence



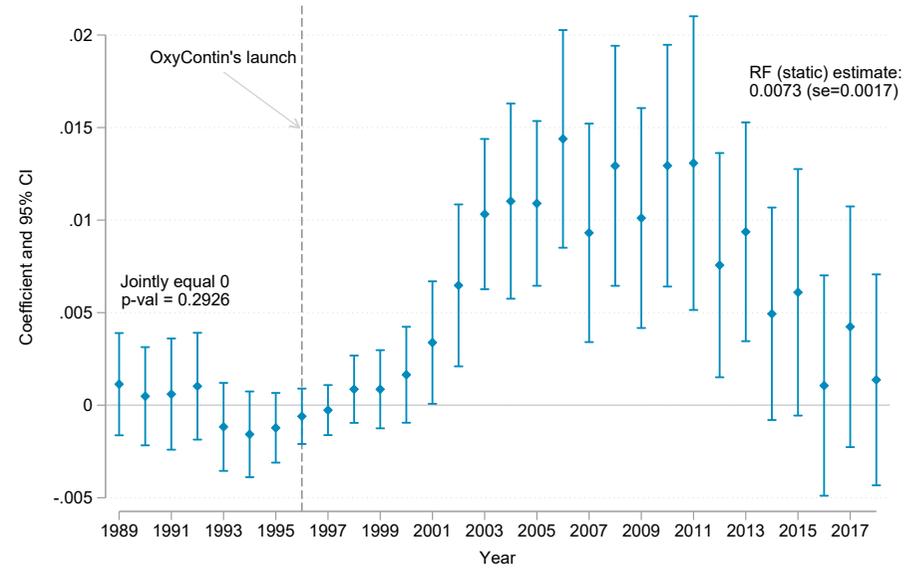
Notes: Panel (a) shows the evolution of all prescription opioids (blue lines) and oxycodone (orange line) in commuting zones in the bottom (dashed lines) and top (solid lines) quartiles of cancer mortality before the launch of OxyContin. Oxycodone is OxyContin's active ingredient. Between 1997 and 2010,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

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

(a) High versus Low Cancer Mortality CZs

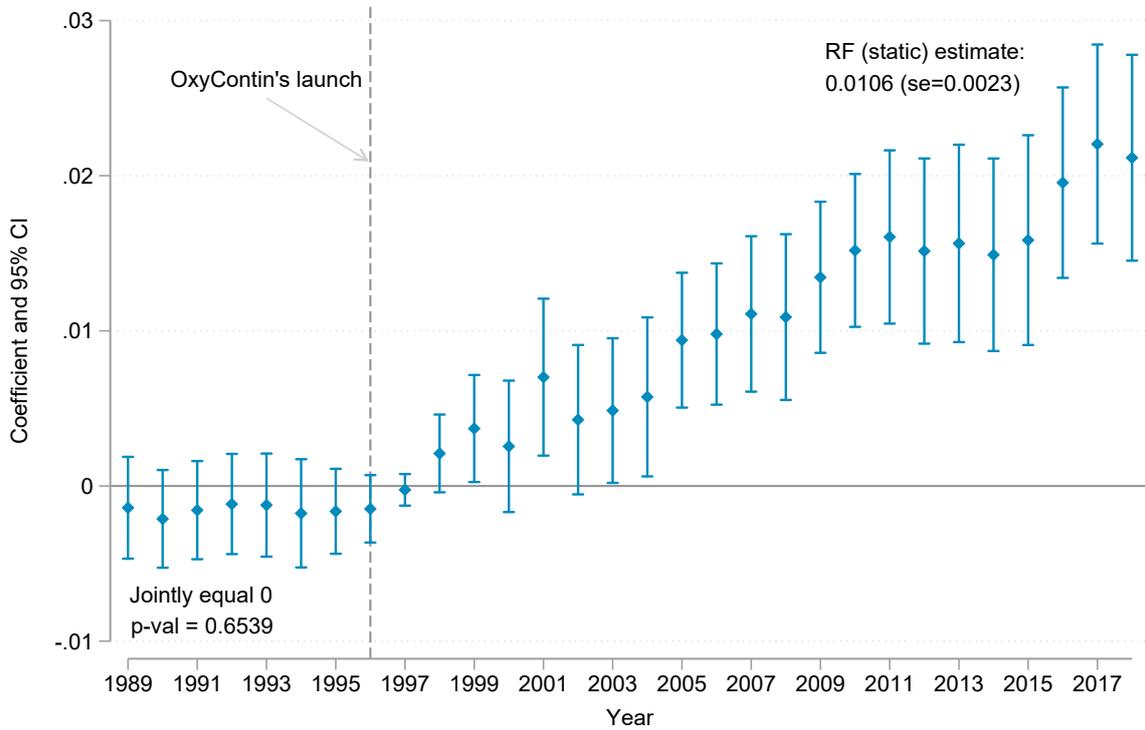


(b) Reduced Form - Event Study Approach



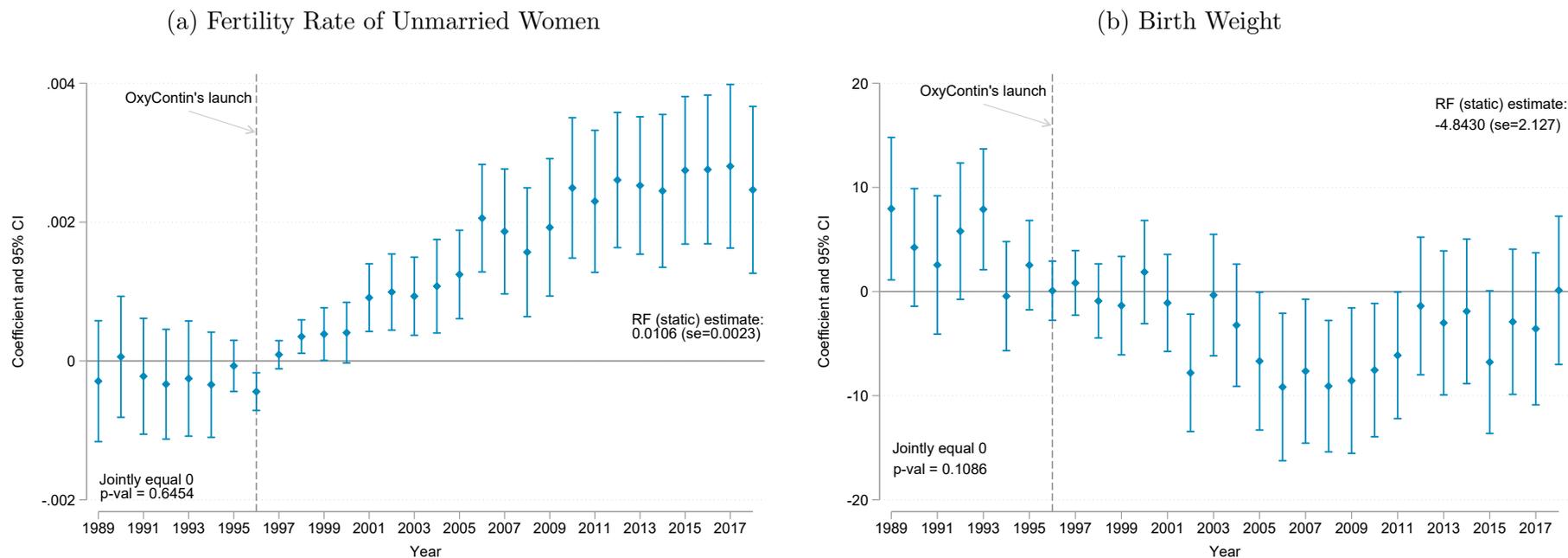
Notes: This figure shows the effects of the increase in prescription opioid supply in prescription opioid mortality. Panel (a) shows the raw data, early in the 2000s, a wedge starts to appear between high- and low-cancer-incidence groups, and by 2018 prescription opioid mortality in high-cancer areas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

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



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

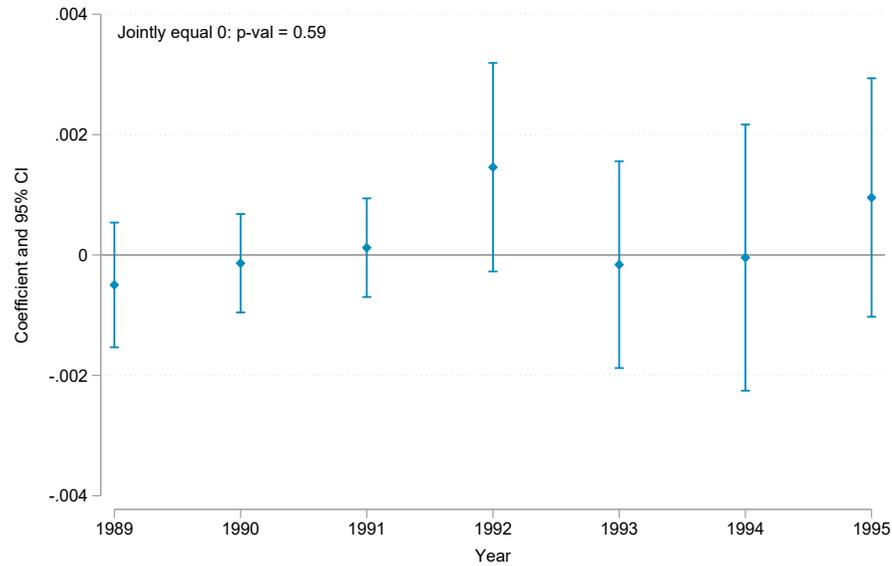
Figure 4: Effects of Purdue Pharma’s Mid-nineties Cancer-market Targeting on Fertility Rates and Birth Outcomes



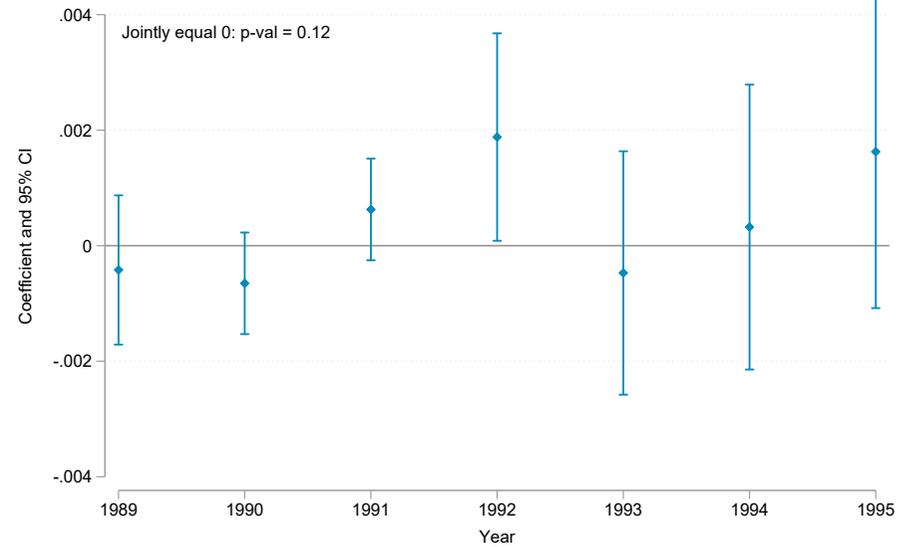
Notes: This figure shows the effects of the increase in prescription opioid supply in the fertility rate of unmarried women (panel a) and in birth weight (panel b). We present the results of a dynamic reduced-form estimation where we regress these outcomes on a set of year-dummy variables interacted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

Figure 5: Robustness Check: Dynamic Reduced Form for Out-of-sample Opioid-Mortality

(a) Prescription Opioids Mortality

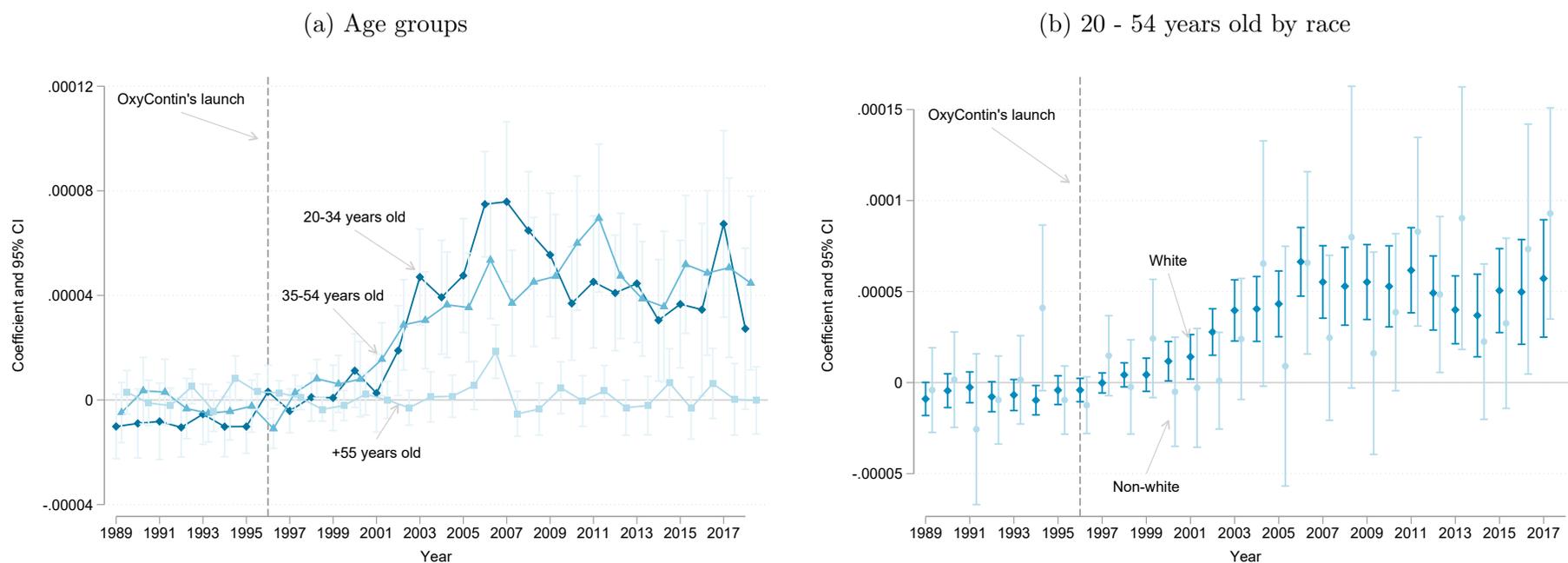


(b) All Opioid Mortality



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

Figure 6: Effects of Purdue Pharma’s Mid-nineties Cancer-market Targeting on Opioid Mortality by Age and Race



Notes: This figure shows the effects of the increase in prescription opioid supply in opioid related mortality by age group (panel a) and by race for individuals aged 35-54 years old (panel b). We present the results of a dynamic reduced-form estimation where we regress these outcomes on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. These coefficients correspond to the estimate of ϕ_t in Equation 3. We use this specification to test for the presence of pre-trends in the relation between opioid mortality and mid-nineties cancer mortality; we do not reject the null hypothesis that the estimated coefficients before 1996 are jointly equal to zero, the p values of these tests are: 0.4946 (20-34 years old); 0.7302 (35-54 years old); 0.1934 (+55 years old) for the estimates presented in panel (a), and 0.2551 (white) and 0.3021 (non-white) for the estimates presented in panel (b). This figure is referenced in Section V.A.

IX. Tables

Table 1: Summary Statistics for 1999-2018

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

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

Table 2: Determinants of the Opioid Distribution in 2000

Dependent variable: Prescription opioids per capita			
	(1)		(2)
<i>Demographics (in shares)</i>		<i>Crime (in rates)</i>	
White	3.526*** [0.961]	Overall	-0.0000622 [0.0000752]
Hispanic	-3.323*** [0.807]	Violent	0.00160*** [0.000614]
Female	6.709 [9.973]	<i>Economic characteristics</i>	
Aged 18-65	21.67*** [4.348]	Ln income	2.517*** [0.922]
Aged +66	6.211 [7.665]	Share below poverty line	0.0521 [0.0625]
Infants	-100.8* [56.42]	Share employed in manufacturing	-0.0374*** [0.0105]
<i>Labor market</i>		Share with some college education	0.00938 [0.0135]
Employment rate	-16.18*** [6.031]	<i>Health outcomes</i>	
Labor Force Participation	-1.805 [2.493]	Cancer mortality rate	-0.164 [0.330]
<i>Social assistance</i>		Infant mortality rate	-0.0117 [0.0199]
SSDI	48.45*** [9.821]	Birth weight	0.000336 [0.00127]
SSI	5.740 [8.944]	Share preterm births	2.330 [4.796]
SNAP	-1.914 [3.848]	Gestation	-0.200 [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***
<i>se</i>	[0.210]	[0.222]	[0.231]	[0.258]	[0.264]
<i>t-stat</i>	4.571	4.914	4.593	4.388	4.083
<i>Effective F-stat</i>	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 \times Year	State Year	State \times 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. *t-stat* corresponds to the *t-statistic* for the null hypothesis that the coefficient on cancer mortality rate is equal to zero. *Effective F-stat* corresponds to the the effective first-stage F statistic proposed by [Olea and Pflueger \(2013\)](#). Standard errors are clustered at the CZ level. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. This table is referenced in Section [IV.A](#).

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

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

Notes: Each coefficient corresponds to a separate regression where the dependent variable is measured as the change with respect to 1989-1990. For prescription opioids, any opioids, labor market variables, SNAP, and 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*** [0.00117]		0.00679*** [0.00200] (0.00281)	0.00419*** [0.00139]		0.00646*** [0.00231] (0.00324)
<i>tF 0.05 se</i>			2.3876			1.9747
<i>t-stat using tF 0.05 se</i>			0.0000			0.0019
<i>AR p-value</i>						
Cancer MR 94-96		0.00732*** [0.00167]			0.00697*** [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 tF 0.05 se*, and the *AR p-value* correspond to weak-instrument-robust inference procedures. This table is referenced in Section V.A.

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

Dependent var:	All cause mortality			Deaths of Despair		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.0213		0.0286	-0.000442		-0.00494
	[0.0136]		[0.0469]	[0.000732]		[0.00621]
<i>tF 0.05 se</i>			(0.0658)			(0.0087)
<i>t-stat using tF 0.05 se</i>			0.4346			-0.459
<i>AR p-value</i>			0.5319			0.4311
Cancer MR 94-96		0.0309			-0.00533	
		[0.0515]			[0.00699]	
Effect size (%)	3.68		4.94	-0.74		-7.39
Model	OLS	RF	IV	OLS	RF	IV
Dependent var:	Alcoholic Liver Diseases and Cirrhosis			Suicide		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.000765**		0.00552*	-0.0000460		-0.00582
	[0.000353]		[0.00292]	[0.000430]		[0.00378]
<i>tF 0.05 se</i>			(0.0041)			(0.0053)
<i>t-stat using tF 0.05 se</i>			1.3473			-1.0974
<i>AR p-value</i>			0.0351			0.1065
Cancer MR 94-96		0.00596**			-0.00628	
		[0.00302]			[0.00402]	
Effect size (%)	3.23		23.34	-0.16		-19.80
Model	OLS	RF	IV	OLS	RF	IV

Notes: 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 tF 0.05 se*, and the *AR p-value* correspond to weak-instrument-robust inference procedures. This table is referenced in Section V.B.

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

Dependent var:	SSDI			SSI		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.000444***		0.00574***	0.00000709		0.00311**
	[0.0000985]		[0.00132]	[0.000147]		[0.00144]
<i>tF 0.05 se</i>			(0.0018)			(0.0020)
<i>t-stat using tF 0.05 se</i>			3.1250			1.5833
<i>AR p-value</i>			0.0000			0.0114
Cancer MR 94-96		0.00619***			0.00335**	
		[0.000385]			[0.00137]	
Effect size (%)	5.36		76.39	0.11		46.88
Model	OLS	RF	IV	OLS	RF	IV
Dependent var:	SNAP					
	(1)	(2)	(3)			
Prescription opioids pc	0.000144		0.00982***			
	[0.000285]		[0.00299]			
<i>tF 0.05 se</i>			(0.0041)			
<i>t-stat using tF 0.05 se</i>			2.4134			
<i>AR p-value</i>			0.0000			
Cancer MR 94-96		0.0106***				
		[0.00227]				
Effect size (%)	0.58		56.70			
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 tF 0.05 se*, and the *AR p-value* correspond to weak-instrument-robust inference procedures. This table is referenced in Section V.B.

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

Dependent var:	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]
<i>tF 0.05 se</i>			(0.19643)			(3.00676)
<i>t-stat using tF 0.05 se</i>			-0.1181			-1.4933
<i>AR p-value</i>			0.8678			0.0163
Cancer MR 94-96		-0.0250			-4.843**	
		[0.157]			[2.127]	
Effect size (%)	4.06		-1.84	-0.08		-0.69
Model	OLS	RF	IV	OLS	RF	IV
Dependent var:	Share low birth weight			Preterm births		
	(1)	(2)	(3)	(4)	(5)	(6)
Prescription opioids pc	0.000169*		0.000905	0.000270*		0.00141
	[0.000102]		[0.000640]	[0.000150]		[0.000937]
<i>tF 0.05 se</i>			(0.00090)			(0.00131)
<i>t-stat using tF 0.05 se</i>			1.0023			1.0649
<i>AR p-value</i>			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]
<i>tF 0.05 se</i>			(0.01395)			(0.21467)
<i>t-stat using tF 0.05 se</i>			-1.2118			1.3137
<i>AR p-value</i>			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]
<i>tF 0.05 se</i>			(0.00079)			(0.02610)
<i>t-stat using tF 0.05 se</i>			1.9266			-1.8738
<i>AR p-value</i>			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 tF 0.05 se*, and the *AR p-value* correspond to weak-instrument-robust inference procedures. This table is referenced in Section V.B.

Table 9: Complier Analysis

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

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

A Extra Figures

Figure A1: Purdue Pharma Budget Plan 1997: Target Audiences

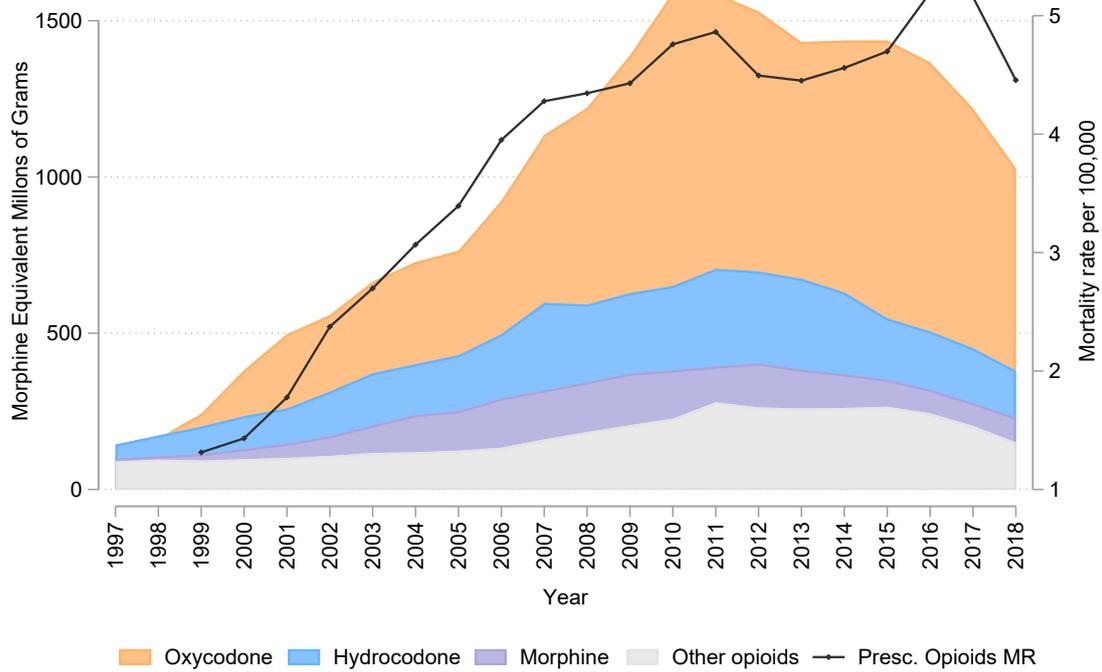
C. Target Audiences

1. Primary Audiences

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

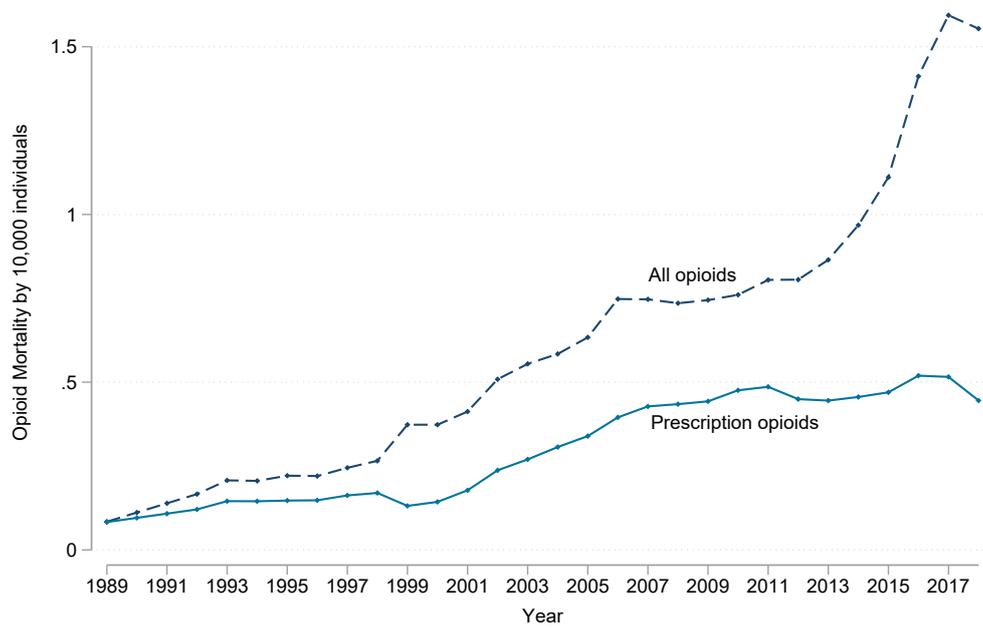
Notes: [Purdue Pharma Budget Plan 1997](#), p.25. This figure is referenced in Section II.

Figure A2: Evolution of Prescription Opioid Distribution



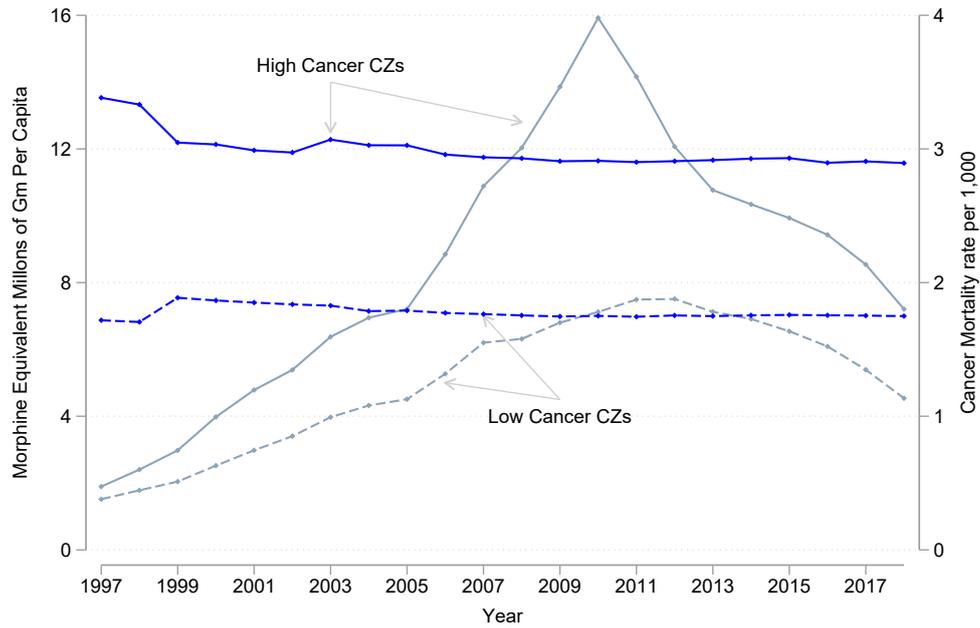
Notes: This figure shows the evolution of shipments of all prescription opioids and the three main components: oxycodone, hydrocodone and morphine. Oxycodone is the active ingredient of OxyContin. Shipments of prescription opioids are expressed in morphine-equivalent doses. Data on opioids distribution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

Figure A3: Evolution of Prescription Opioid and All Opioid Mortality Rates



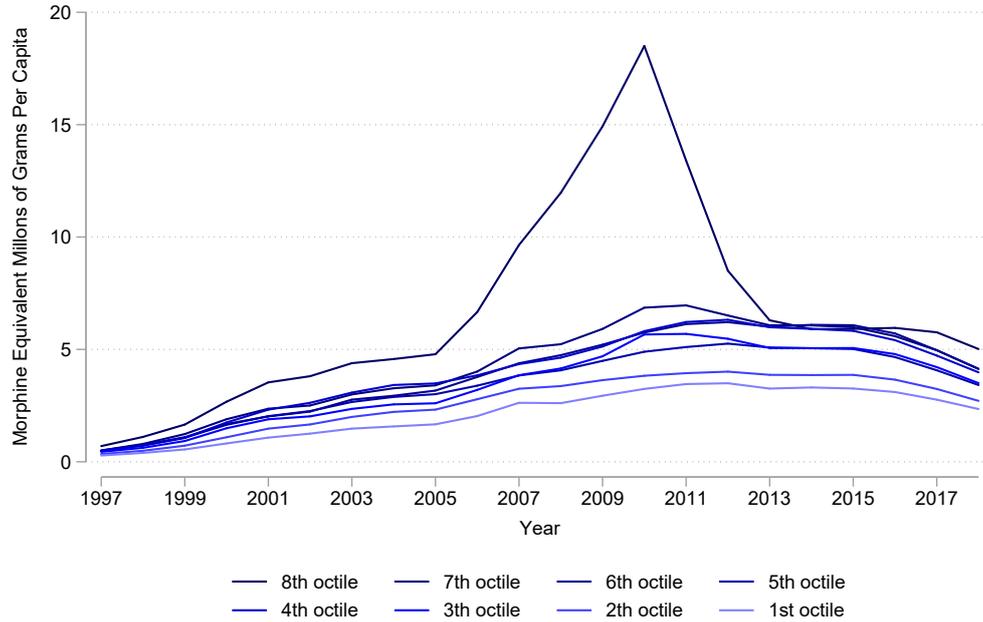
Notes: This figure shows the evolution of prescription opioid and all opioid mortality rates from 1989 to 2018. The 1989-1998 data use ICD-9 codes to categorize the cause of death, and the 1999-2018 data use ICD-10 codes. The time series show that the transition from ICD-9 to ICD-10 classifications resulted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

Figure A4: Evolution of Cancer Mortality and Prescription Opioid Supply



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

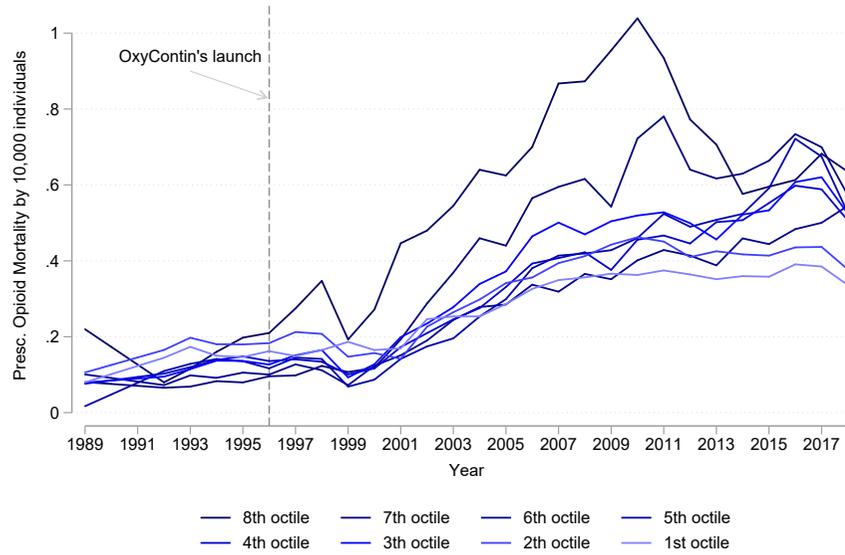
Figure A5: Evolution of Oxycodone by Octiles of the 1994-1996 Cancer Prevalence



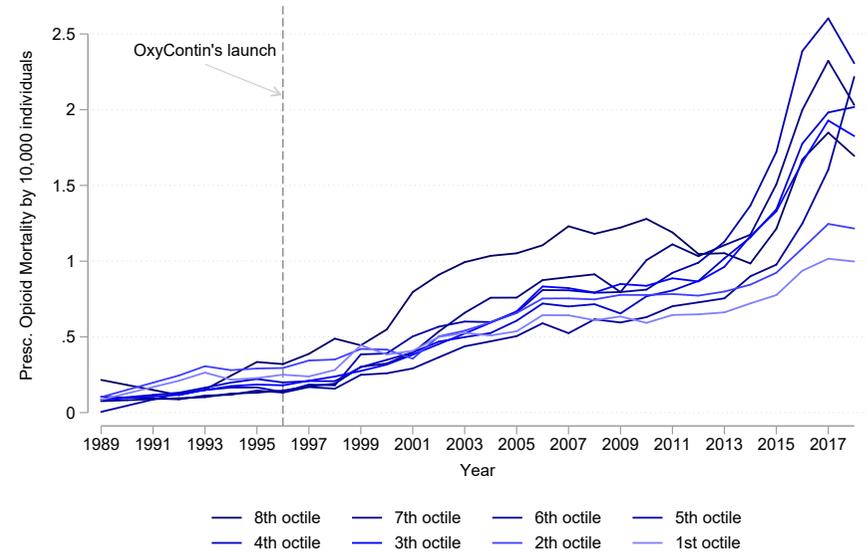
Notes: This figure shows the evolution of oxycodone in eight groups of commuting zones. Each group is composed of those commuting zones in the n -th octile of the cancer mortality rate distribution before the launch of OxyContin. Darker colors indicate groups with higher cancer prevalence (e.g., the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

Figure A6: Opioid Mortality Rate by Octiles of the 1994-1996 Cancer Prevalence

(a) Prescription Opioids



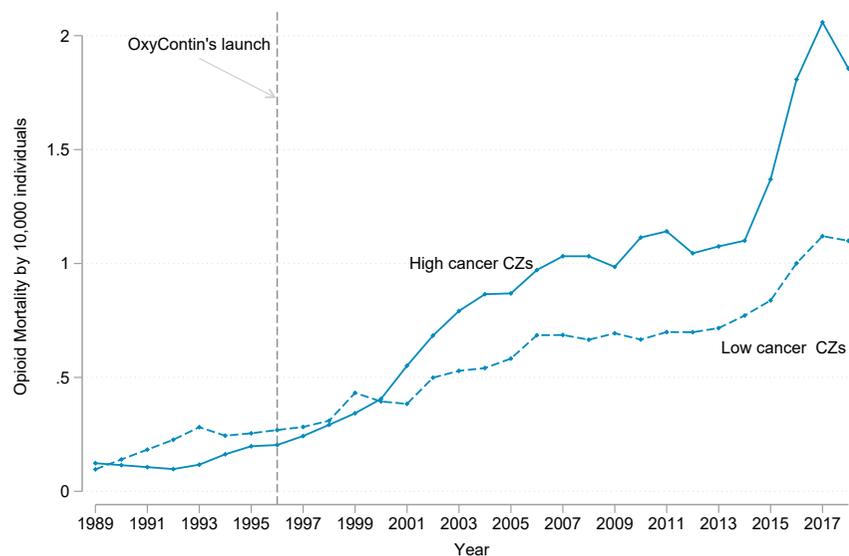
(b) All Opioids



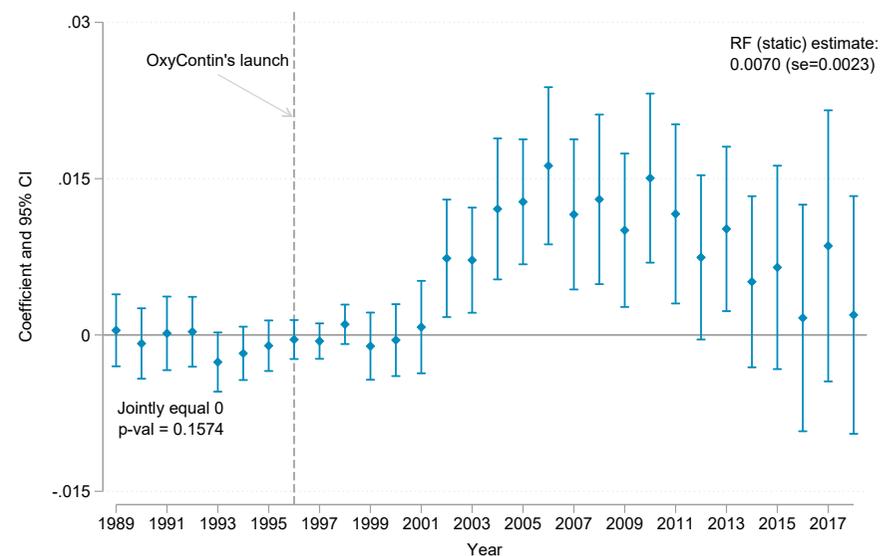
Notes: This figure shows the evolution of prescription opioid (panel a) and all opioids (panel b) mortality in eight groups of commuting zones. Each group is composed of those commuting zones in the n -th octile of the cancer mortality rate distribution before the launch of OxyContin. Darker colors indicate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

Figure A7: Effects of Purdue Pharma’s Mid-nineties Cancer-market Targeting on All-Opioid Mortality

(a) High vs Low Cancer Mortality CZs



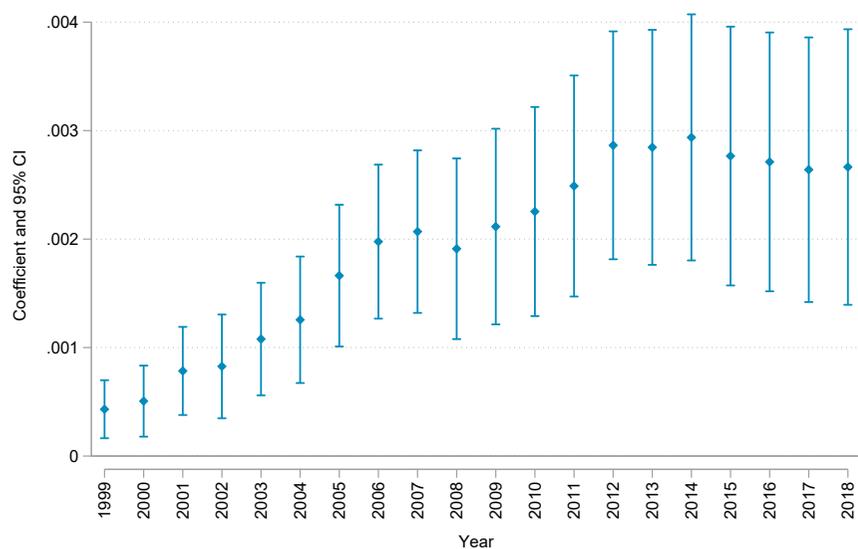
(b) Reduced Form - Event Study Approach



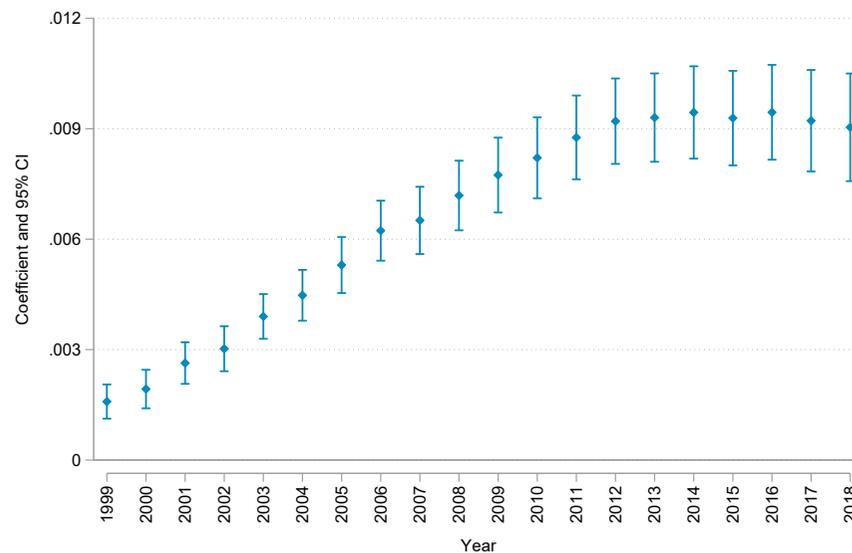
Notes: This figure shows the effects of the increase in prescription opioid supply in birth weight (panel a) and in the fertility rate of unmarried women (panel b). We present the results of a dynamic reduced-form estimation where we regress these outcomes on a set of year-dummy variables interacted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

Figure A8: Effects of Purdue Pharma's Mid-nineties Cancer-market Targeting on Disability Claims

(a) SSI

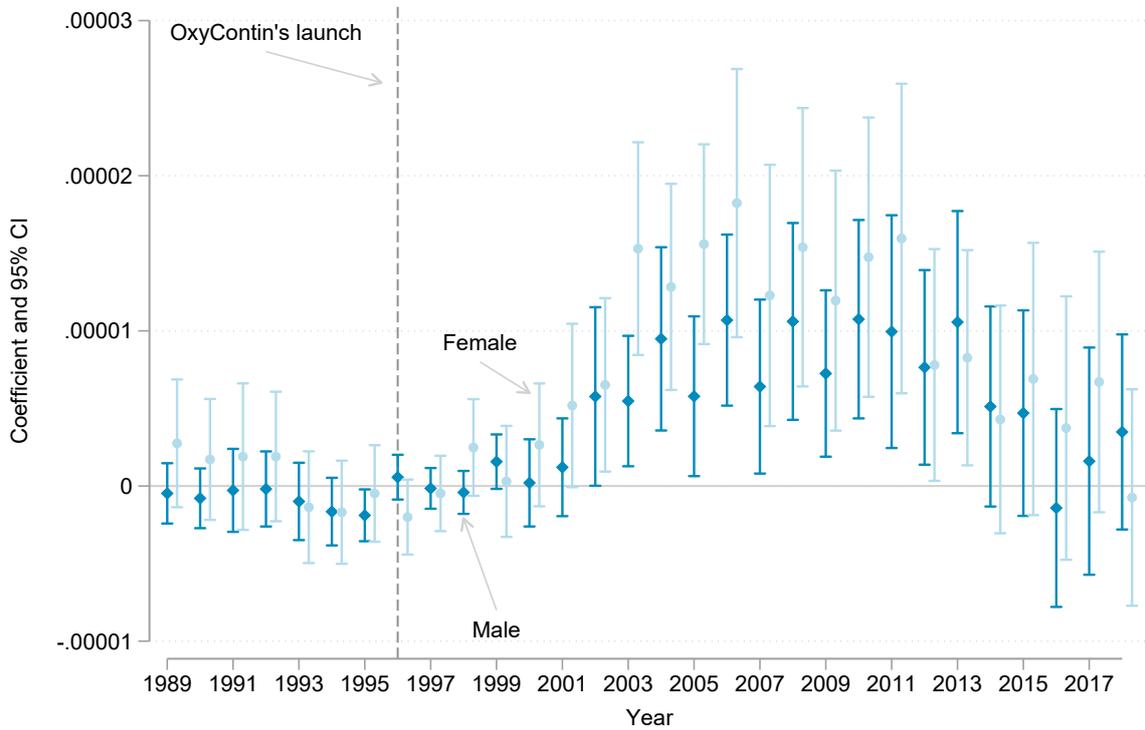


(b) SSDI



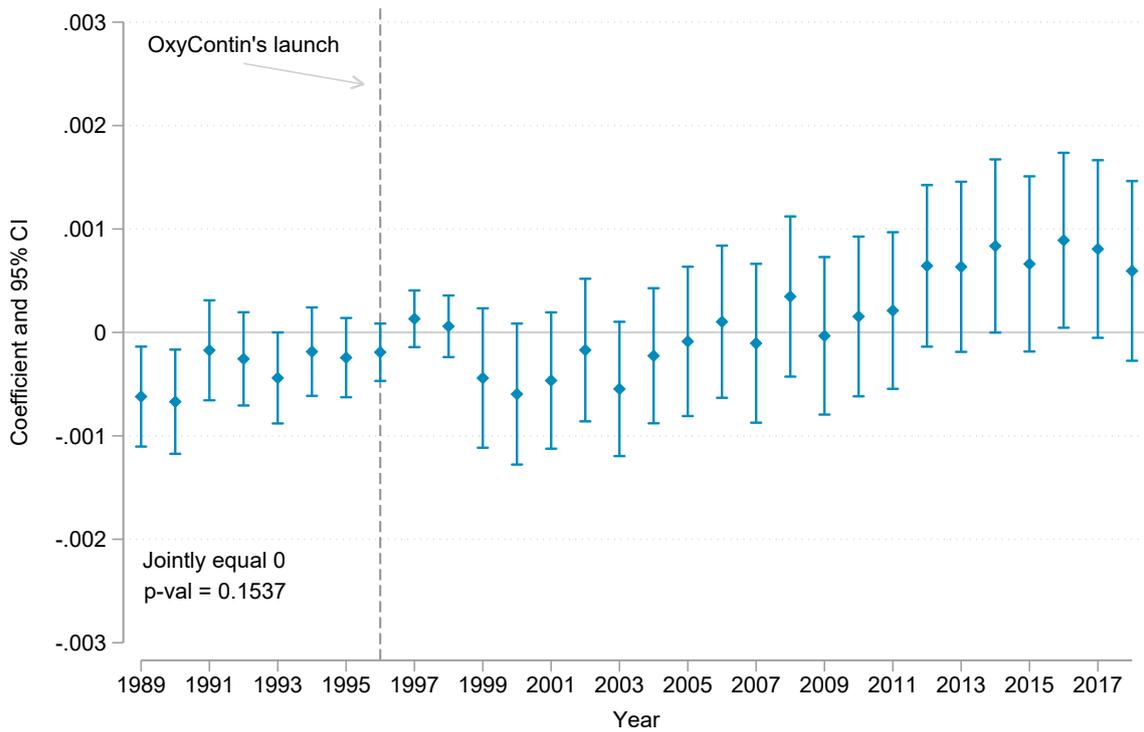
Notes: We present the results of a dynamic reduced-form estimation where we regress these outcomes on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. These coefficients corresponds to the estimate of ϕ_t in Equation 3. This figure is referenced in Section V.B.

Figure A9: Effects of Purdue Pharma’s Mid-nineties Cancer-market Targeting on Opioid Mortality by Gender



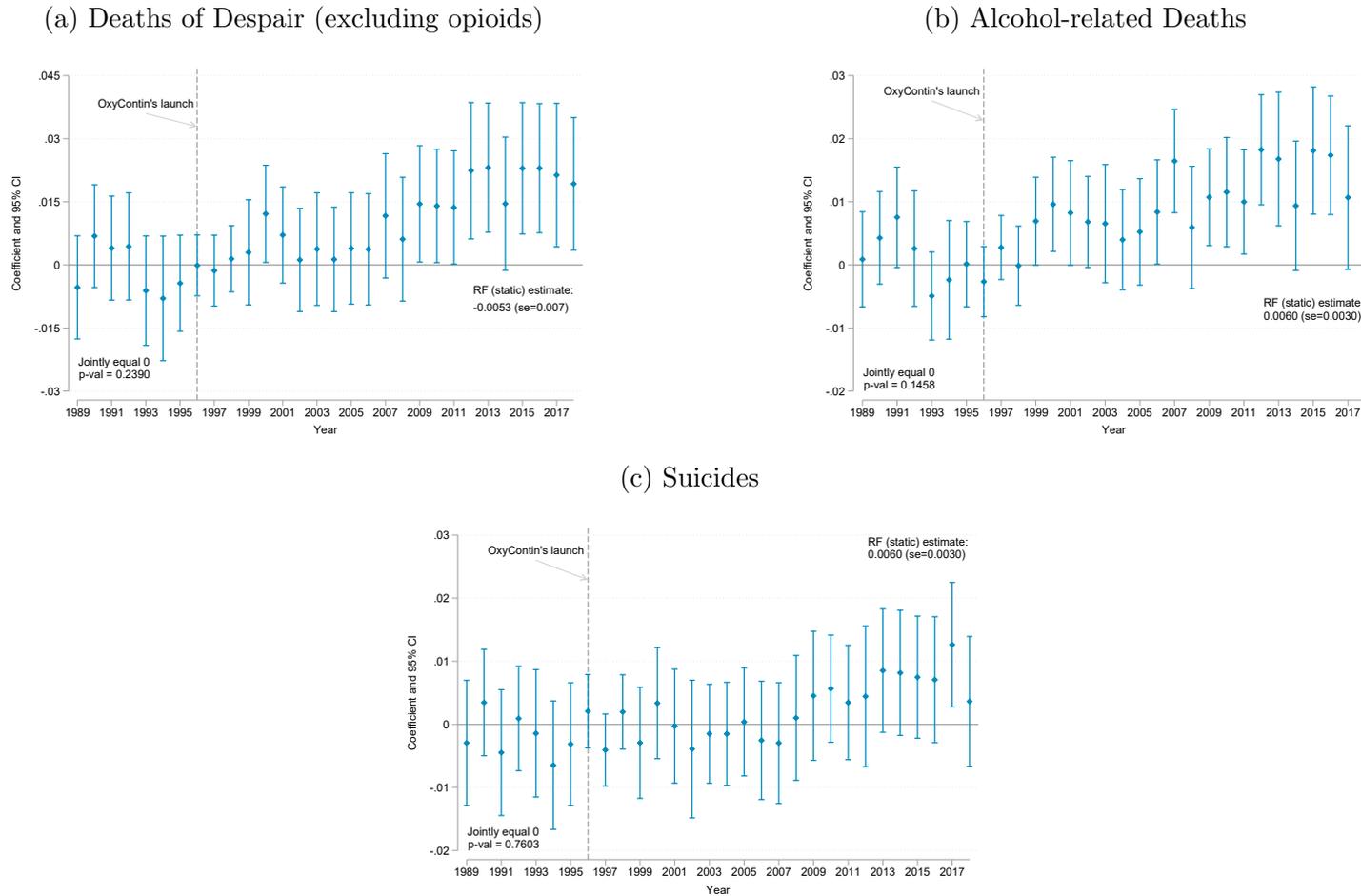
Notes: This figure shows the effects of the increase in prescription opioid supply in opioid related mortality by gender. We present the results of a dynamic reduced-form estimation where we regress these outcomes on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996.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

Figure A10: Trends in Non-cancer Mortality for Individuals Aged +75 Years Old.



Notes: This figure shows the effects of the increase in prescription opioid supply in non-cancer mortality for individuals older than 75 years old. We present the results of a dynamic reduced-form estimation where we regress these outcomes on a set of year-dummy variables interacted with our instrument—cancer mortality in 1994-1996. These coefficients corresponds to the estimate of ϕ_t in Equation 3. We use this specification to test for the presence of pre-trends in the relation between opioid mortality and mid-nineties cancer mortality; we do not reject the null hypothesis that the estimated coefficients before 1996 are jointly equal to zero, the p values of this 0.1537. This figure is referenced in Section V.B.

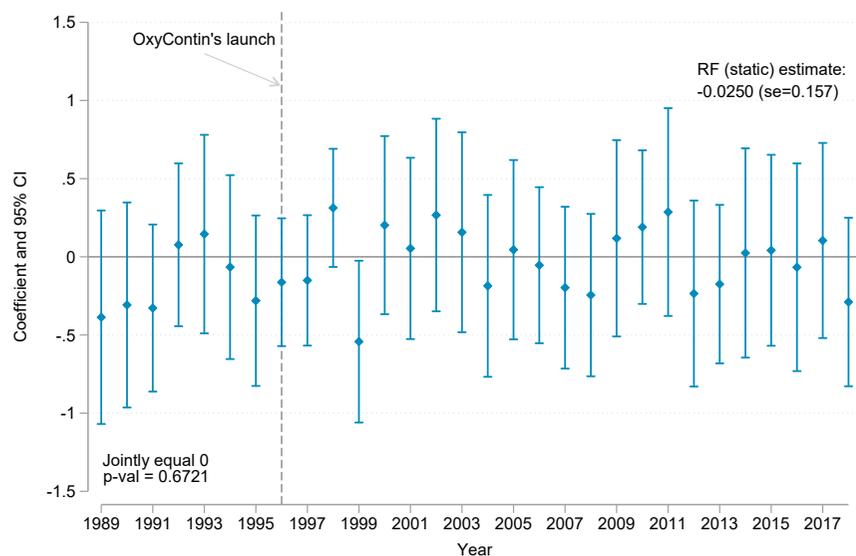
Figure A11: Effects of Purdue Pharma's Mid-nineties Cancer-market Targeting on Deaths of Despair



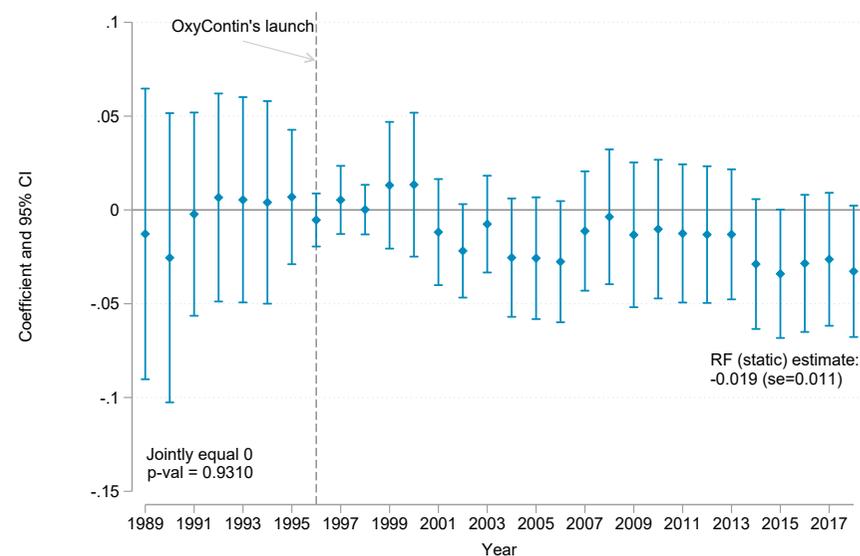
Notes: This figure shows the effects of the increase in prescription opioids supply in various measures of deaths of despair; excluding deaths which cause is opioid poisoning. We present the results of a dynamic reduced-form estimation were we regress these outcomes on a set of year-dummy variables interacted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

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

(a) Infant Mortality Rate



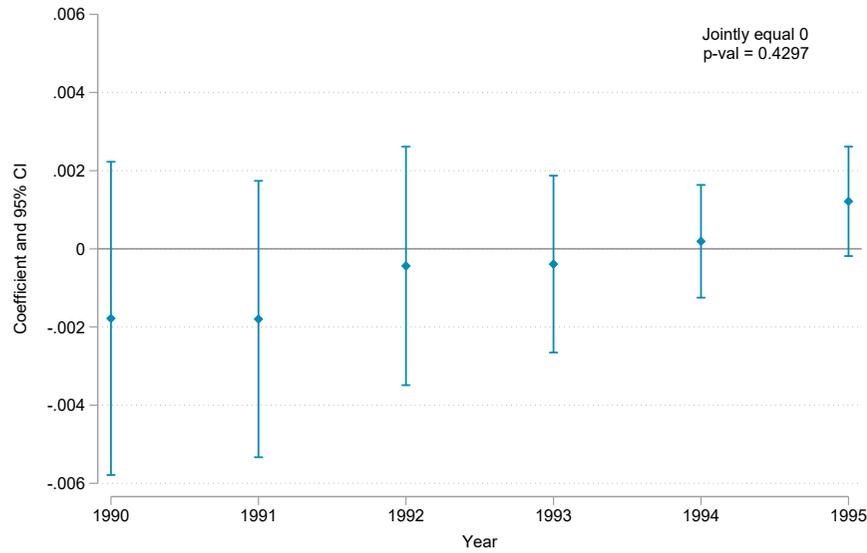
(b) APGAR Score



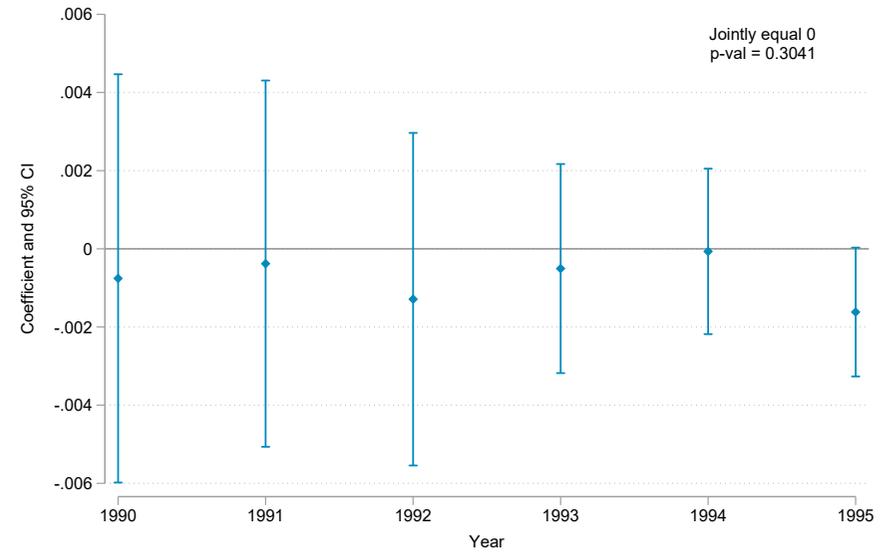
Notes: This figure shows the effects of the increase in prescription opioids supply in infant mortality rate (panel a) and in APGAR score (panel b). The APGAR score is a measure of the physical condition of a newborn infant. It varies from 0 to 10, a score of 10 represents the best possible condition.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

Figure A13: Dynamic Reduced Form Estimates - Employment in Manufacturing and Mining Industries.

(a) Manufacturing



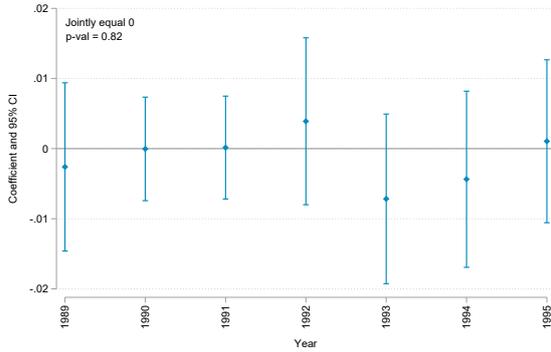
(b) Mining



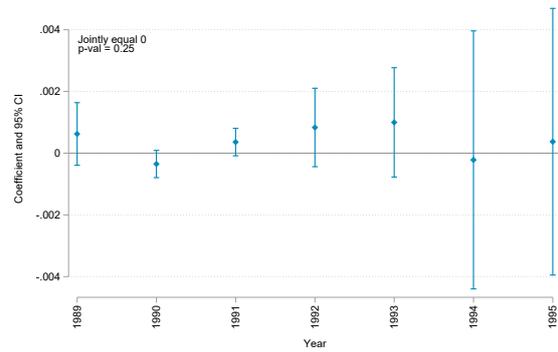
Notes: This figure shows the dynamic reduced-form relationship between the share of employment in the manufacturing and mining industries and our instrument before the launch of OxyConting. The first year of available data is 1990. We use this specification to test for the presence of pre-trends and do not reject the null hypothesis that the estimated coefficients up to 1995 are jointly equal to zero. This figure is referenced in Section IV.B.

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

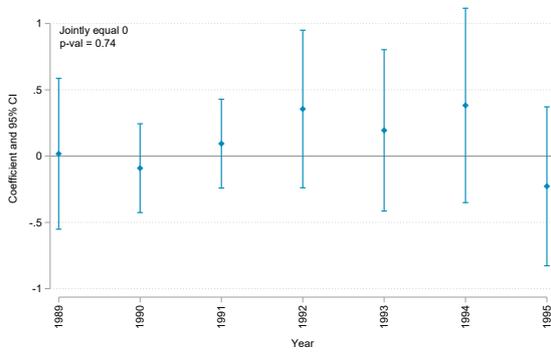
(a) Deaths of Despair



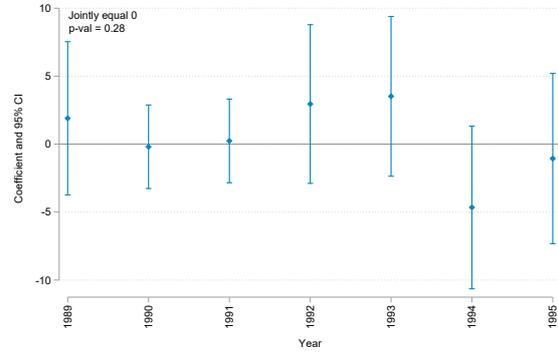
(b) SNAP



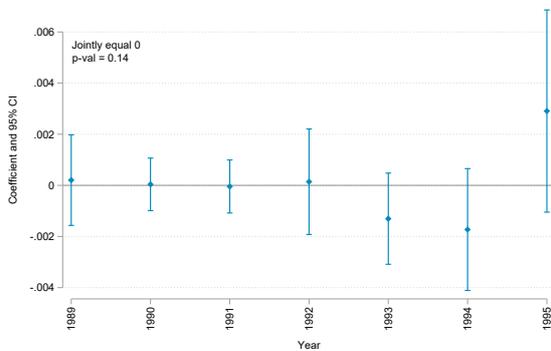
(c) Infant Mortality Rate



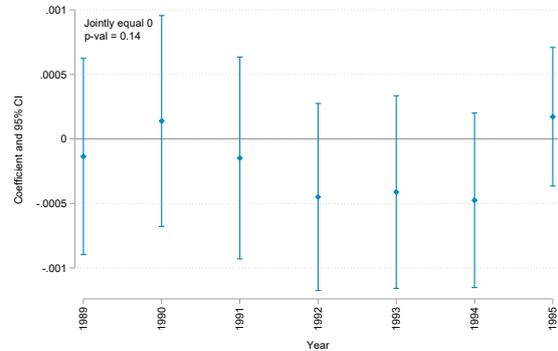
(d) Birth Weight



(e) Fertility Rate - 25 to 29 years old

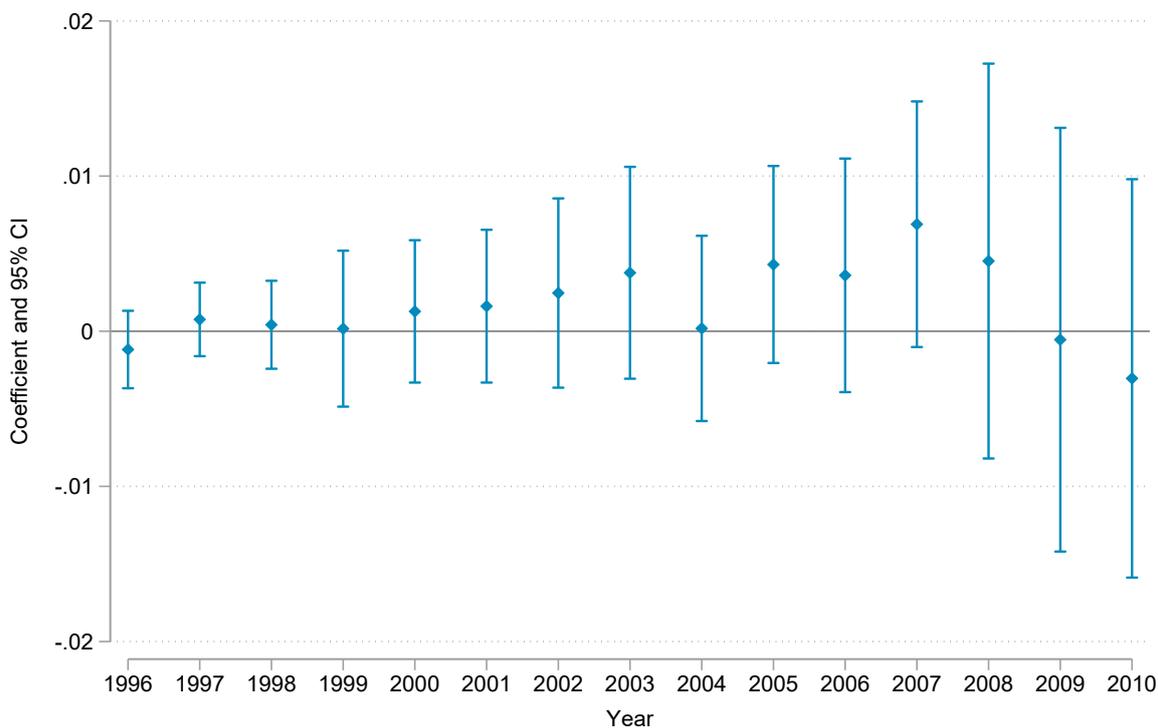


(f) Fertility Rate - unmarried woman



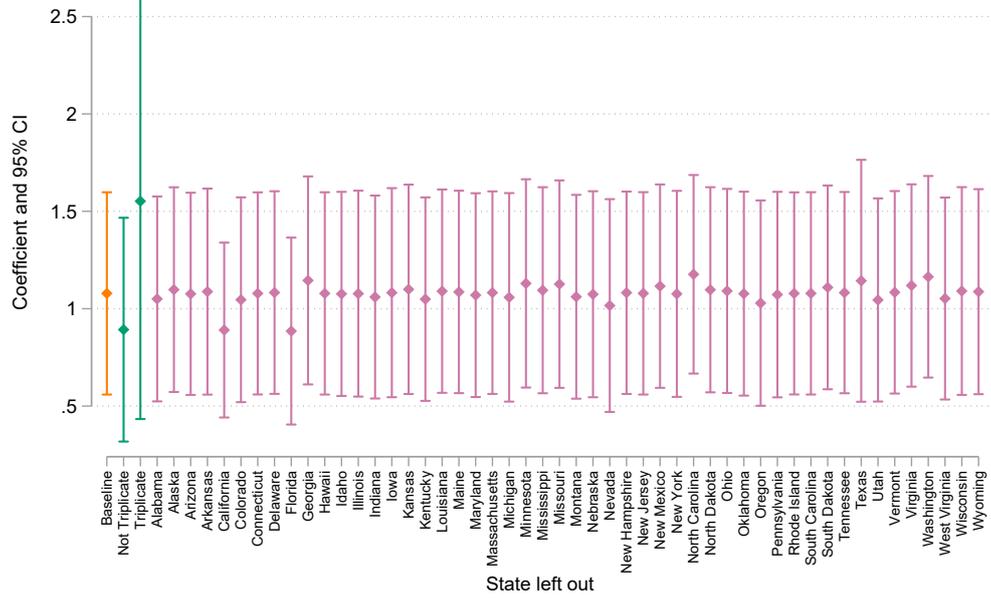
Notes: This figure shows the dynamic reduced-form relationship between outcomes of interest and our instrument in a out-of-sample period. That is, we replicate our dynamic reduced-form analysis in the pre-OxyContin period. We regress each outcome on a set of year-dummy variables interacted with the out-of-sample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

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



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

Figure A16: 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 referenced 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 referenced in Section III.A.

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

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

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

Table A3: Determinants of Cancer Mortality Rate 94-96

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

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

Table A4: Baseline Results with Different Time Periods

<i>Panel A: First Stage</i>				
Dependent variable:	Prescription Opioids pc			
	(1)	(2)	(3)	(4)
Cancer MR 94-96	1.078***	0.916***	1.047***	1.474***
<i>se</i>	[0.264]	[0.258]	[0.277]	[0.330]
<i>t-stat</i>	4.08	3.55	3.78	4.46
<i>Effective F-stat</i>	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
<i>Panel B: Instrumental Variables</i>				
Dependent variable:	Prescription Opioids Mortality Rate			
	(1)	(2)	(3)	(4)
Presc. Opioids pc	0.00679***	0.00785***	0.00769***	0.00533***
	[0.00200]	[0.00259]	[0.00230]	[0.00169]
Observations	11,800	7,080	8,850	5,310
Sample	All	1999-2010	1999-2013	2010-2018
Dependent variable:	Any Opioid Mortality Rate			
	(1)	(2)	(3)	(4)
Presc. Opioids pc	0.00646***	0.00677***	0.00672***	0.00562**
	[0.00231]	[0.00256]	[0.00232]	[0.00237]
Observations	11,800	7,080	8,850	5,310
Sample	All	1999-2010	1999-2013	2010-2018

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

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

	SNAP			SSDI		
	(1)	(2)	(3)	(4)	(5)	(6)
Presc. Opioids pc	0.00455* [0.00250]	0.00487** [0.00219]	0.00680*** [0.00205]	0.00584*** [0.00144]	0.00605*** [0.00141]	0.00718*** [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* [0.00133]	0.00248* [0.00141]	0.00320* [0.00174]	0.0458 [0.185]	0.0512 [0.160]	0.0846 [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** [2.811]	-5.093** [2.316]	-2.915* [1.623]	0.00210*** [0.000696]	0.00233*** [0.000674]	0.00350*** [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 ?? under alternative periods. Columns (1) and (4) present estimates for the first wave of the opioid epidemic, columns (2) and (5) present estimates for the first and second waves pooled together, and columns (3) and (6) present estimates for the after-OxyContin reformulation period. All regressions include state times year fixed effects and a set of control variables: contemporaneous cancer mortality rate, share of population under 1 year old, share of population between 18 and 65, share of population over 66 years old, share of Black, White, and Hispanic population, and share of female population. Standard errors are clustered at the CZ level. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. This table is referenced in Section V.B.

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

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

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

Table A7: Baseline Results under a Shift-share Instrument

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

Notes: Column 1 reports the estimated coefficient for the first stage. Columns 2 to 9 present results from IV regressions using the shift-share instrument. 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 referenced in Section VI.A.

Table A8: First Stage Results with Population Size Controls

Dependent variable: Prescription opioids per capita					
	(1)	(2)	(3)	(4)	(5)
Cancer MR 94-96	1.078***	1.635***	1.072***	1.046***	1.608***
<i>se</i>	[0.264]	[0.483]	[0.276]	[0.266]	[0.490]
<i>t-stat</i>	4.08	3.39	3.88	3.94	3.28
<i>Effective F-stat</i>	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 referenced in Section VI.A.

Table A9: First Stage: Alternative choices of instrument

Dependent variable: Prescription opioids per capita						
	(1)	(2)	(3)	(4)	(5)	(6)
Age-adjusted Cancer MR 94-96	0.743*** [0.194]					
Cancer MR 1994		1.044*** [0.245]				
Cancer MR 1995			0.962*** [0.240]			
Cancer MR 1996				0.738*** [0.199]		
Cancer MR 94-96 (weighted)					1.865*** [0.408]	
Above-65-years-old Cancer MR 94-96						0.210** [0.0988]
Observations	11,800	11,800	11,800	11,800	11,800	11,800
Clusters	590	590	590	590	590	590

Notes: All regressions include state times year fixed effects and a set of control variables: 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.A.

Table A10: Placebo Check - Alternative Instruments

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

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

Table A11: Alternative Measure of Opioid Supply.

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

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

Table A12: Direct Effects. Alternative Measure of Opioid Mortality

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

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

Table A13: Baseline Results under Alternative Sample Restrictions

Dependent var:	Presc. Opioids pc			Prescription Opioids MR		
	(1)	(2)	(3)	(4)	(5)	(6)
Cancer MR 94-96	1.191*** [0.249]	1.055*** [0.297]	1.018*** [0.288]			
Presc. Opioids pc				0.00355*** [0.00134]	0.00684*** [0.00231]	0.00826*** [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 [0.00171]	0.00697** [0.00273]	0.00885*** [0.00329]	0.0137 [0.0361]	0.0515 [0.0477]	0.102 [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*** [0.00106]	0.00586*** [0.00155]	0.00652*** [0.00173]	0.00204** [0.000851]	0.00339** [0.00169]	0.00438* [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*** [0.00248]	0.00997*** [0.00336]	0.00919*** [0.00307]	0.175 [0.130]	-0.0297 [0.142]	0.0604 [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*** [1.852]	-3.770* [2.240]	-6.480** [2.624]	0.00108*** [0.000404]	0.00156** [0.000632]	0.00160** [0.000706]
Sample	15,000+	40,000+	55,000+	15,000+	40,000+	55,000+

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

Table A14: Alternative Sample Results for SNAP

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

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

Table A15: Alternative Specifications

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

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

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