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Abstract

This paper studies how opioid analgesic sales are related to socioeconomic conditions in France. Using the *OpenHealth* database on prescription opioid retail sales at the district level from 2008 to 2017, we show that increases in the poverty rate induce more sales: a one percentage point increase in poverty produces, approximately, a ten percent increase in opioid sales. Our analysis further shows that opioid sales are positively related to the share of middle-aged people and the share of individuals with basic education only, while they are negatively related to population density. We identify the causal effects of economic conditions on opioid sales by using two alternative strategies. First, we implement a Two-Stage Least Squares (2SLS) approach, where we instrument for poverty by exploiting a reform aimed at reducing poverty of low-income individuals. Second, we use a three-dimensional panel model that allows us to control for a large pool of potential confounding factors. We are among the first to address potential reverse causality issues in this context. Our results suggest that middle-aged individuals and people with lower education levels are mostly at risk and should be carefully screened before and monitored after being treated. Pharmacovigilance should be more intensively addressed towards poor and rural areas. We conclude that a combination of policies aimed at improving economic prospects and strictly monitoring access to opioid medications would be beneficial for reducing opioid-related harm.

JEL Codes: I11, I15, I18
Keywords: Prescription Opioids, Socioeconomic Conditions, France.

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1 Introduction

The opioid crisis is a major public health problem in the US. It calls for the rapid implementation of remedies aimed at containing and monitoring abuse and misuse of narcotic medications.

During the last decades, the US has experienced a drastic increase in the number of individuals who became addicted to opioids used to treat chronic pain. This has caused an epidemic that counts 116 deaths per day in 2016, more than those caused by weapons and road accidents together (HHS, 2019). Approximately forty percent of opioid overdose deaths seem to be the result of prescription opioid abuse (HHS, 2019). These medicines are often the first substances that individuals consume before switching to heroin (Cicero et al., 2017 and Mars et al., 2014) and the vast majority of opioid misusers misemploy opioid analgesics (SAMHSA, 2017). Overdoses are now the predominant cause of death of middle-aged people and the crisis has been declared a public health emergency in October 2017.

In some European countries, a similar alarming increase in prescription opioid use is observed, though consumption has not reached the US levels yet (Van Amsterdam and Van den Brink, 2015). The abuse and misuse of opioids have remarkable economic and social costs. These encompass reduced productivity at work, declined labor force participation, increased health spending, higher criminal justice costs, increased number of newborns with Neonatal Abstinence Syndrome (NAS), besides the loss of human lives and reduced life expectancy. After 1993, the US is witnessing its first major reduction in life expectancy that results from a large number of opioid-related overdoses. The Council of Economic Advisers (CEA, 2017) estimates that the cost of the US opioid crisis reaches 504 billion dollars, that is, 2.8 percent of the GDP in 2015. The importance of opioids for palliative care prevents, however, from giving up on opioid pain-killers altogether and requires, instead, suitable policies that permit access to opioid analgesics, while limiting their addiction risks.

To provide policy-makers with guidance on appropriate regulations, it is first necessary to identify the mechanisms giving rise to the crisis as well as factors favoring opioids prescribing. Empirical evidence suggesting that both opioid use and socioeconomic conditions tend to be highly heterogeneous across regions has led several researchers to postulate the existence of a relationship between opioid consumption and socioeconomic status, though the direction of causality is controversial. On the one hand, living in disadvantaged socioeconomic conditions induces feelings such as detachment from the labor force, social isolation, depression, and marginalization, which push people to seek drugs (including prescription opioids) in search of emotional relief. Furthermore, living in poor conditions may induce individuals to sell these drugs on the black market for raising cash. This is the so-called 'deaths of despair' hypothesis. On the other hand, experiencing pain and/or consuming (and abusing) drugs may drive individuals out of the labor force and eventually lead them into the poverty trap.

The causal relationship between socioeconomic status and opioid consumption is an important theme to be investigated because any such study can provide policy-makers with guidance on how to address pharmacovigilance efforts and services for addiction treatment, support studies

on abuse and misuse and help protect the most vulnerable people. In addition, studying the causal link from economic status to opioid use helps predicting the impact of new regulations applied at the national level: any policy aimed, for instance, at limiting access to these narcotics is likely to have a different impact across different geographical areas.

In this paper, we aim at shedding light on the magnitude of opioid analgesics use in Europe, by focusing on France, where the dangers of overconsumption are much smaller than in the US, but consumption is nevertheless increasing. According to Degenhardt et al. (2019), the consumption of opioids (measured in *DDDs*[1] per million people per day) is approximately 5.5 times larger in the US than in France in 2016. The number of opioid-related deaths per million people is equal to 91.1 in the US in 2017 (22.4 in 1999), which is 23 times larger than the 3.8 in France in 2016 (1.3 in 2000) (CDC, 2019 and CépiDc-Inserim, 2019).[2] We investigate sales trends at the national level, whether there are local variations in opioid use and whether these variations are caused by variations in economic opportunity while controlling for socio-demographic indicators. This was made possible by using the *OpenHealth* database that enables access to high-resolution, high-frequency retail sales data for all opioid active ingredients available on the French market between 2008 and 2017.

Although similar studies have been performed in the US, the French health, economic and social systems, as well as laws regulating access to narcotic medications, are deeply different from those in the US. This may induce relevant differences in consumption behavior, prescribing patterns and the way opioid use relates to indicators of economic opportunity. Moreover, research on the *causal relationship* between opioid use and economic conditions is still scarce. We are the first to investigate this research question in a European environment. Compared to previous research, our long panel and the granularity of our data enable us to control for a large pool of unobserved factors. Moreover, the recent release of a law aimed at reducing poverty allows us to isolate exogenous variations in the local poverty rate. We exploit these features to address potential reverse causality issues, by using two alternative strategies: a Two-Stage Least Squares (2SLS) approach and a three-dimensional panel model.

The paper is organized as follows. Section 2 summarizes the existing literature on the opioid crisis. Section 3 discusses consumption trends and substitution patterns among several opioid analgesics on the French market. Subsection 3.1 describes the data provided by *OpenHealth* and the methodology used to measure opioid consumption,[3] while Subsection 3.2 discusses our descriptive results. Section 4 includes an econometric analysis aimed at assessing the relationship between opioid consumption and socioeconomic factors. Subsections 4.1, 4.2 and 4.3 describe our econometric specifications and discuss the results. Section 5 offers a focus on Oxycodone, a strong opioid molecule, which caused many deaths in the US, and whose consumption has significantly increased in France. Section 6 concludes.

[1] The reader can refer to Subsection 3.1 for a more detailed definition of *DDD*.

[2] See Appendix D for a more detailed overview of opioid-related deaths and hospitalizations in France.

[3] Note that, throughout the paper, we use the terms 'opioid sales', 'opioid use' and 'opioid consumption' interchangeably, even though we do not observe actual consumption by individual patients. This is a limitation of the present study.

2 Literature Review

The expression 'deaths of despair' was first introduced by Case and Deaton (2017) and refers to the idea that living in a disrupted socioeconomic environment induces individuals to consume more licit and illicit substances, such as tobacco, alcohol, and drugs, which results in impoverished health outcomes and increased mortality. In the context of the opioid crisis, the direction of causality between economic status and the use of prescription pills is still largely debated.

Some studies seem to corroborate the 'deaths of despair' hypothesis, by suggesting that economic variables play a role in fueling the epidemic. Hollingsworth et al. (2017) show how macroeconomic fluctuations, as proxied by variations in the unemployment rate, are related to measures of opioid-related harm and how the latter increases in periods of economic distress. Similarly, Ghertner and Groves (2018) claim that prescription opioid sales and opioid-related harm are more common in areas characterized by poor economic conditions, while Venkataramani et al. (2019) find a significant association between automotive assembly plant closures and opioid overdose deaths. In a European setting, Nordmann et al. (2013) study opioid abuse, as measured by doctor-shopping, in three French regions and find that there exist geographical variations in the prevalence of this practice. The authors observe that doctor-shopping[4] is more prevalent in the region with the most unfavorable socioeconomic environment (in terms of poverty, unemployment, number of crimes), even though they do not offer an econometric analysis that supports this statement.

Other papers cast doubt on the assumption that economic impairment leads to increased opioid use and suggest that the causal link may run in the opposite direction. Krueger (2017) shows how the decline in the US labor force participation is positively associated with the increased use of opioid pain relievers. He estimates that increased opioid prescriptions could be responsible for as much as 20 percent of the fall in labor force participation for males and 25 percent for females, between 1999 and 2015. Based on the observation that shifts in the type of drugs (opioid analgesics versus illicit opioids) causing overdose deaths have been contextual to changes in the composition of deaths, Ruhm (2018) concludes that the driving forces of the epidemic need not be found in worsening economic conditions, but should rather be linked to specific characteristics of the public health environment. As a consequence, he sustains that policy interventions aimed at improving economic prospects would have a limited impact if any, and proposes instead to push more on remedies aimed at affecting the drug environment (such as prescription drugs monitoring programs, development of abuse-deterrent drugs and improved education for healthcare professionals).

Perhaps strikingly, none of these papers uses econometric techniques aimed at addressing the reverse causality question. To the best of our knowledge, this issue has only been addressed by Currie et al. (2019), who focus on employment as a proxy for economic status and find ambigu-

[4]Doctor-shopping is defined as the practice of visiting multiple physicians to illicitly obtain multiple prescriptions. Likewise, pharmacy-shopping is defined as the practice of visiting multiple pharmacies to obtain more medications.

ous results. The authors conclude that the relationship between opioid use and instrumented employment is rather weak and, hence, the roots of the crisis need to be found in reasons other than economic disruption.

Besides socioeconomic factors, the recent literature on the opioid crisis identifies a few additional elements related to the US epidemic, which are worth mentioning here.

First, the epidemic is partially due to the exponential increase in the number of prescriptions by general practitioners (GPs). Since 1986, the World Health Organization (WHO) has encouraged healthcare professionals to take cancer and non-cancer pain treatment more seriously into account and this, combined with the industry's marketing effort, has eventually led to overprescribing opioids. In the economics literature, Schnell (2017) tries to rationalize this phenomenon and shows that physicians prescribe at least 20 percent more than what would be optimal.

The aggressive marketing by pharmaceutical companies is another major ingredient of the epidemic. In the US, for example, Purdue Pharma (the manufacturer of OxyContin, a strong opioid analgesic) has been sued several times for distributing advertising material that overstated the benefits of opioids, while understating their addiction risks (e.g., a promotional video distributed to general practitioners claimed that the risk of getting addicted to OxyContin was as low as one percent). Pharmaceutical companies' marketing strategies have been shown to be effective in influencing physicians' prescribing habits. Handland et al. (2018, 2019) show how direct-to-physician advertising of opioids is associated with increased prescribing and positively related to opioid-related overdoses. Fernandez and Zejcirovic (2018) take a step further, by uncovering the causal link from opioid product promotion to opioid overdose deaths.

Finally, over-consumption is exacerbated by the presence of a secondary black market and by patients' specific behaviors (such as doctor-shopping and pharmacy-shopping). The National Survey on Drug Use and Health (SAMHSA, 2017) reveals that, in 2016, 53 percent of individuals misusing opioid pain relievers obtained them from a friend or a relative (for free, by paying or stealing), 6 percent bought them from a drug dealer and 1.4 percent are prescriptions given by more than one doctor.

3 Descriptive Analysis

This section provides a descriptive analysis of sales trends and substitution patterns among different classes of opioid analgesics in France from 2008 to 2017. Even though descriptive studies on opioid use in France exist (Chenaf et al., 2019), research in this field is scant and, here, we contribute by showing what our data document. Describing and monitoring sales trends of analgesics is already an important task *per se*, in that it allows us to determine for which substances consumption has increased the most and whether there have been changes in their use. Consequently, this enables us to identify which drugs require further surveillance, to support studies on problematic use and to provide guidance on measures aimed at promoting safe usage of these narcotics.

3.1 Consumption Data and Methodology

The *OpenHealth* database contains information on opioid retail sales in France since 2008, both in terms of turnover and in terms of consumer units sold, where consumer units indicate the number of packs sold for each product. Sales data concern the 94 French departments composing Metropolitan France.[5] Data are provided at the national, regional and department levels and on a monthly, quarterly and yearly basis. For our investigation, we exploit annual data both at the national and at the department level.

For each item, the database indicates the product's denomination, the name of the pharmaceutical company marketing it, the number of packs sold, the number of pills in each pack and the quantity of the active ingredient (in milligrams) contained in each pill. This is important since one can compute the total quantity (in mg) sold of each active ingredient and convert this to the number of *DDDs* consumed, which is the methodology recommended by the WHO for drug consumption studies. *DDD* means *Defined Daily Dose* and is defined by the WHO as "the assumed average maintenance dose per day for a drug used for its main indication in adults", that is the amount (in mg) of an active ingredient that should be administered to an average weight adult patient (70 kilograms) daily for a drug's main indication. Using this metric allows comparing consumption trends across different products as well as aggregating consumption data for different active ingredients.

Throughout the paper, drug usage is measured in terms of number of *DDDs* per 1000 inhabitants per day, by exploiting the following formula:

$$DU = \frac{1000 * n * p * mg/p}{365 * DDD * h}$$

where DU denotes drug usage, n is the number of packs sold, p is the number of pills in a pack, mg/p is the number of milligrams per pill, h is the number of inhabitants in the geographical area of interest and 365 is the number of days in a year. Finally, DDD refers to the official measure for each active substance as provided on the WHO website.[6] Note that, when we discuss results at a more aggregate level for the sets of mild, strong and all opioids, DU is given by the sum of the $DDDs$ consumed for each active ingredient in the set.

3.2 Consumption and Substitution Patterns

This subsection is aimed at describing consumption trends and substitution patterns (2008-2017) for the main opioids sold in France. We discuss our results both for each active ingredient individually and, at a more aggregate level, for the sets of mild and strong opioids. The distinction between mild and strong opioids is done according to WHO's three-step ladder for

[5] The *OpenHealth* database provides data on sales by community pharmacies only (retail sales), thus neglecting hospital usage. Corsica and overseas departments are not included in our database. Note also that 'departments' is the denomination France uses for districts.

[6] When the *DDD* for a particular active ingredient was not mentioned on this website (this happens most frequently for Codeine combinations), we contacted the WHO directly and applied the *DDD* that they suggested.

treatment of chronic pain, which classifies analgesics as (i) non-opioids, such as non-steroidal anti-inflammatory drugs (NSAIDs), Paracetamol and Ibuprofen; (ii) mild opioids, such as Codeine combinations and Tramadol (alone or in combination);[7] (iii) strong opioids, such as Oxycodone, Fentanyl and Morphine. Appendix Tables A1 to A3 list the names of all active ingredients and product denominations sold, as well as all the companies active in the country.[8]

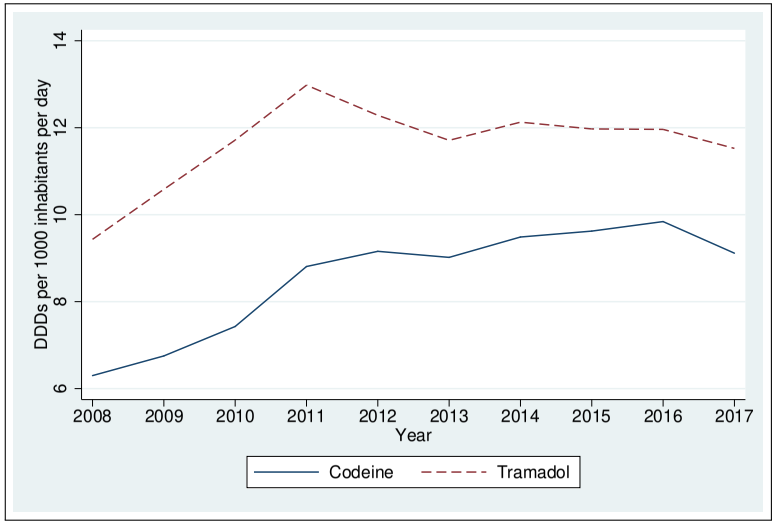
The most commonly used analgesics are mild opioids. Figure 1 panel (a) shows that Tramadol, alone or in combination, is more frequently administered than Codeine, which is only available in combination on the market. Consumption of both these active ingredients increases during the 10 years. Codeine consumption rises by 45 percent, from 6.3 *DDDs* per 1000 inhabitants per day in 2008 to 9.1 in 2017. Tramadol retail sales also increase, even though at a slower pace, from 9.4 to 11.5 *DDDs* (a 22 percent increase). Tramadol peaks in 2011 and, then, slightly declines between 2011 and 2013. By contrast, Codeine consumption keeps rising during the whole period under examination. Overall, mild opioid sales rise by 31 percent. Figure 1 panel (b) shows that the shares of Codeine and Tramadol remained stable over time.

In the group of strong opioids (panels (c) and (d)), oral Morphine remains the most widely used analgesic, although its consumption falls from 0.97 to 0.66 *DDDs*. Injectable Morphine slightly decreases from 0.12 to 0.10. Transdermal Fentanyl is the second most commonly used strong opioid. Its sales remain approximately constant over time, even though they experience a slight decline: overall, consumption for this substance drops by 11 percent.

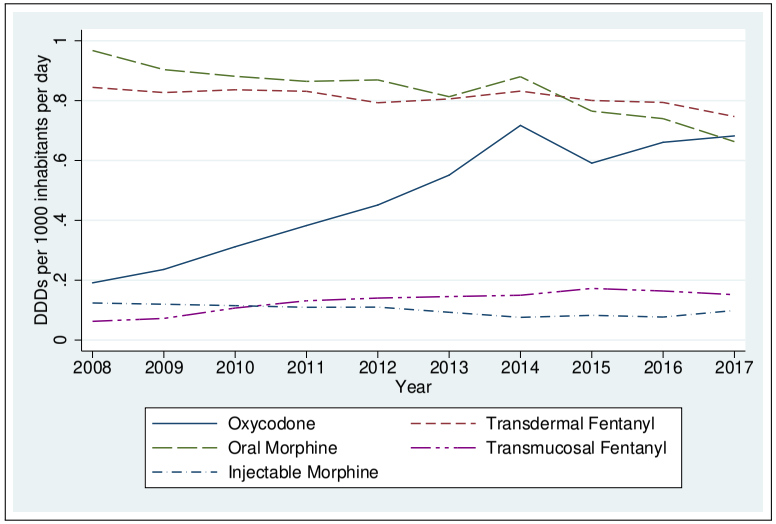
Oxycodone consumption, instead, exhibits a spectacular increase, reaching and even overcoming Morphine in 2017. Its sales rise from 0.19 to 0.68 *DDDs*, a 257 percent variation. Trends also show that Oxycodone retail sales slow down between 2014 and 2015. Interestingly, this is the period during which generics started to enter the Oxycodone market. Before this date, the market was a monopoly, where the only manufacturer was Mundipharma (the European name of Purdue Pharma). Panel (d) in Figure 1 reveals that the fall in Oxycodone sales between 2014 and 2015 has been mainly absorbed by Fentanyl (in part by transdermal, in part by transmucosal Fentanyl). This observation seems to be in accordance with previous findings in the literature. Specifically, Castanheira et al. (2019) find that, when a molecule experiences generic entry, its overall consumption (originator+generics) counterintuitively decreases because part of the demand switches to the generic version of the substance, while part of the patients switches to its closest substitute (Fentanyl, in this case). The authors explain this in terms of changes in the advertising effort by the incumbent firm: as the patent comes close to its expiration date, the incumbent monopolist foresees generic entry, which sensibly reduces its profits, and, consequently, stops investing in promotion.

[7] It is important to mention that, even though Codeine and Tramadol are considered mild opioids, the addiction risks linked to their use remain serious. Indeed, concerns related to the problematic use of these substances has recently led French authorities to shorten the duration of Tramadol prescriptions from twelve to three months.

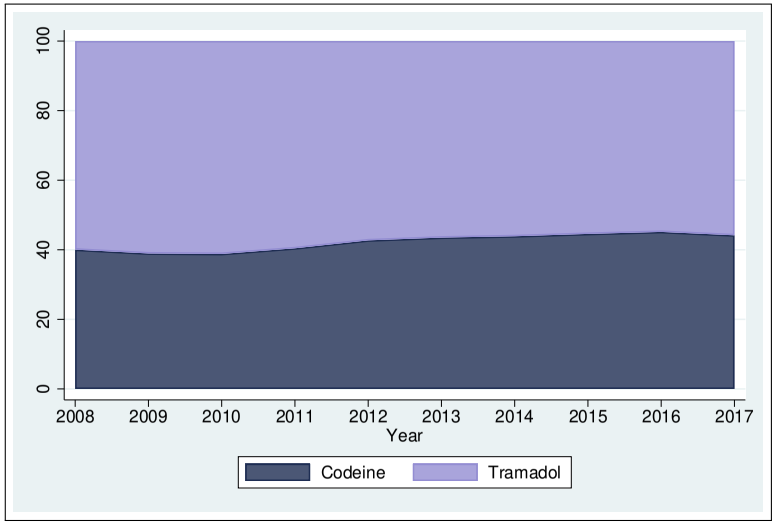
[8] We include the following active substances in our analysis: Tramadol (alone or in combination), Codeine combinations, Oxycodone, Fentanyl and Morphine. Note that results for transdermal and transmucosal Fentanyl as well as for oral and injectable Morphine are discussed separately. This is because different routes of administration require different *DDDs* for these ingredients.



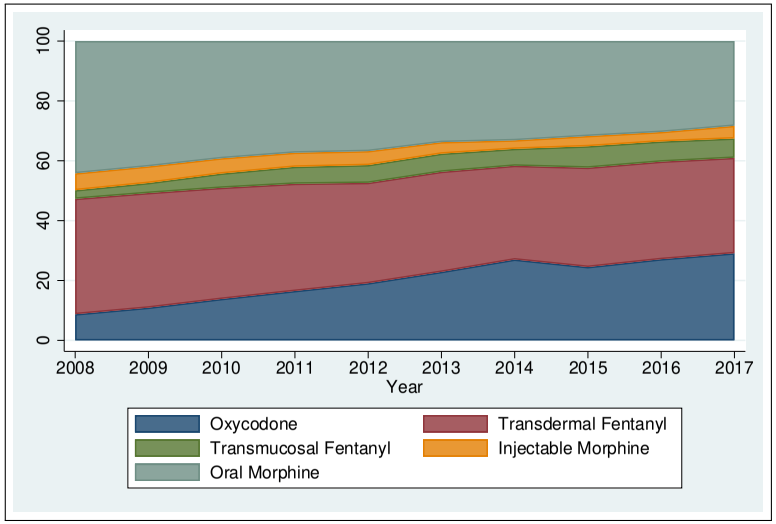
(a). Mild Opioid Consumption by Active Ingredient (in *DDDs*)



(c). Strong Opioid Consumption by Active Ingredient (in *DDDs*)



(b). Mild Opioid Market Shares (in percentage)



(d). Strong Opioid Market Shares (in percentage)

Sources: OpenHealth database; authors' calculations.

Figure 1. Opioid Analgesic Sales in France: Trends and Market Shares

Finally, transmucosal Fentanyl registers the second highest variation rate, from 0.06 to 0.15 *DDDs*: a 142 percent increase. Overall, strong opioid consumption increases by approximately 7 percent, from 2.19 *DDDs* in 2008 to 2.34 in 2017. Panel (d) further suggests that Morphine is increasingly being replaced by Oxycodone and, to a lesser extent, by Fentanyl. This pattern may raise some concerns since Fentanyl and Oxycodone are claimed to be stronger than Morphine.

In summary, this descriptive analysis highlights the following stylized facts: mild opioids are the most consumed in France; Tramadol is the most widely used; Morphine is the most commonly administered among strong opioids; Oxycodone experiences the largest expansion in sales. These findings are particularly meaningful if we consider that, according to the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM, 2019), Tramadol, Morphine, and Oxycodone are the substances most frequently involved in intoxications. The high consumption of Fentanyl may also raise concerns due to its strength (10 times stronger than Morphine).

4 Econometric Analysis

In this section, we assess the responsiveness of local per capita opioid analgesic sales to changes in socioeconomic indicators. To do this, we run a series of panel regressions of per capita opioid use on socioeconomic determinants in 94 French departments (Metropolitan France) for the years between 2008 and 2017. Our main focus is on the relationship between opioid consumption and economic conditions.

Retail sales data are extracted from the *OpenHealth* database, while data used to proxy department socioeconomic status are collected from the Institut National de la Statistique et des Études Économiques (INSEE) and Organization for Economic Cooperation and Development (OECD) websites. Appendix B offers a detailed description of these data. Table 1 provides a list of the variables, together with summary statistics. Opioid Consumption is measured, as above, in *DDDs* per 1000 inhabitants per day. Poverty Rate indicates the share of individuals living with less than 60 percent of the national median income, while Unemployment Rate is the share of unemployed people in the active population. Age Group refers to the share of individuals aged between 40 and 59 years old, whereas (Only) Basic Education represents the share of individuals with up to high school level diploma. Doctors and Pharmacists densities are measured as the number of these healthcare professionals per 100,000 inhabitants, while Population Density is the number of inhabitants per square kilometer.

We report the mean, standard deviation, minimum and maximum for each variable included in the econometric analysis, but also for each opioid active ingredient individually. For some variables, the difference between the minimum and the maximum is staggering:[9] this is true, for instance, for Oxycodone consumption and, to a lesser extent, for the totals of mild and strong opioids. A considerable part of this variation is due to nationwide increasing trends in opioid

[9]The summary statistics in Table 1 are computed by considering the value for each variable in each time period as a single observation. Hence, for example, the minimum for Oxycodone consumption represents the minimum across all departments and across all time periods.

use (as shown in Figure 1), but, even neglecting this time dimension, variability in opioid use across departments persists. This may appear surprising, given the French 'centralized culture', according to which rules governing the healthcare system are invariant across geographical areas. This evidence suggests that national policies determining the availability of opioid medications are not the only responsible for opioid consumption and spark our interest in investigating the role played by demand-side determinants of opioid use.

Variable	No. of Obs.	Mean	Std. dev.	Min	Max
Mild Opioids (DDDs)					
Codeine	940	9.269	3.197	1.371	25.844
Tramadol	940	12.614	4.320	2.052	38.689
Total Mild	940	21.882	7.442	3.423	64.534
Strong Opioids (DDDs)					
Oxycodone	940	.573	.711	.004	8.170
Transdermal Fentanyl	940	.881	.315	.184	3.467
Transmucosal Fentanyl	940	.140	.056	.014	.340
Oral Morphine	940	.956	.948	.057	13.285
Injectable Morphine	940	.116	.216	0	4.034
Total Strong	940	2.667	1.776	.361	22.081
All Opioids (DDDs)					
Total	940	24.549	8.610	3.784	82.763
Socio-Economic Covariates					
Poverty Rate (%)	940	.143	.030	.073	.29
Unemployment Rate (%)	940	.091	.019	.04	.155
Age Group (%)	940	.273	.090	.243	.295
(Only) Basic Education (%)	940	.581	.062	.300	.687
Population Density	940	571.46	2468.87	14.67	21347.01
Doctors Density	940	301.07	83.70	170.15	852.85
Pharmacists Density	940	111.80	17.00	74.00	187.00
GDP (per head)	940	27655.68	10573.55	18340	97479
Gini Coefficient	940	.272	.025	.227	.433

Table 1. Summary Statistics

4.1 Econometric Specification

We first run a series of linear panel regressions, where the unit of analysis is department-year. Our econometric specification is:

$$logY_{dt} = \beta_0 + \beta_1 X_{dt} + \alpha_d + \delta_t + u_{dt}, \tag{1}$$

where Y_{dt} is consumption of active ingredients in department d and year t, and u_{dt} is an idiosyncratic error term, which is clustered at the department level. X_{dt} is a vector containing our main variables of interest: unemployment and poverty rate, as well as socio-demographic factors, such as the share of individuals aged between 40 and 59, the share of individuals with basic education and population density.[10] β_1 is the vector of parameters to be estimated. We also include department, α_d and year, δ_t, fixed effects to control for department-specific time-invariant characteristics and shocks or unexpected events common to all departments, but varying across time.

We use a log-level specification, in which consumption is logged, while the right-hand side variables are kept in levels since they are already expressed in percentage terms. Given the presence of department fixed effects and our log-level specification, the estimated coefficients should be interpreted as the percentage change in consumption associated with a percentage point change in the independent variables, within a department and across time. The regressions are run for all opioids together and for mild and strong opioids separately.

Table 2 reports the results obtained when using Ordinary Least Squares (OLS). The poverty rate is positively and significantly associated with the use of opioid pain relievers. This holds true especially for the class of mild opioids, where the coefficient associated with poverty is significant at the one percent confidence level and larger in magnitude than the one obtained for strong opioids. This result suggests that, when the poverty rate increases by one percentage point within a department and across time, mild and strong opioid use rises by approximately 7 and 5 percent, respectively.

Higher shares of middle-aged individuals, as well as higher shares of individuals with basic education only, are associated with higher levels of opioid use, and this finding is consistent across different classes of opioid analgesics. In addition, population density is negatively associated with opioid use, suggesting that consumption is more prevalent in rural areas. The number of doctors and pharmacists in a department, instead, are not correlated with opioid use.

Finally, the R-squared of the regressions for mild opioids are larger than those of the regressions for strong opioids because the relationship between consumption and some of the socioeconomic covariates (especially poverty) is weaker for the class of strong opioids. The R-squared of the regressions for all opioids lie between the two, but they are closer to those for mild opioids. This is because consumption for mild opioids is much larger (in terms of *DDD*s) than for strong opioids. Analogous reasoning applies to the magnitude of the estimated coefficients.

[10] See Table 1 for details

	All Opioids			Mild Opioids			Strong Opioids		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Poverty Rate	6.1869*** (2.3250)	7.6816*** (2.1871)	7.3732*** (2.2764)	6.4121*** (2.3187)	7.9385*** (2.1568)	7.5909*** (2.2422)	3.3181 (2.5092)	4.6845* (2.6143)	4.6548* (2.7398)
Unemployment Rate		-2.1837 (4.9636)	-1.7502 (4.9182)		-2.4136 (4.8510)	-1.9362 (4.7575)		-.1776 (6.5715)	-.0261 (6.7898)
Age (40-59)		20.0620** (8.3311)	20.2170** (8.3604)		19.6976** (8.1377)	19.8656** (8.1631)		20.6229* (10.8930)	20.7036* (10.9027)
(Only) Basic Education		7.8347* (4.5411)	7.8263* (4.4531)		7.4713* (4.4872)	7.4594* (4.3823)		10.8858* (5.6378)	10.9085* (5.6337)
Population Density		-.0005*** (.0001)	-.0004** (.0002)		-.0005*** (.0001)	-.0004** (.0002)		-.0004** (.0002)	-.0004 (.0002)
Doctors Density			-.0003 (.0014)			-.0003 (.0014)			.0003 (.0017)
Pharmacists Density			.0035 (.0042)			.0038 (.0041)			.0012 (.0053)
R^2	.3896	.4307	.4330	.4234	.4637	.4665	.1048	.1390	.1393
N	940	940	940	940	940	940	940	940	940

Note: Robust standard errors clustered at the department level in parentheses. Each regression includes department and year fixed effects and is weighted by department population. $^{*}p < 0.1$,$^{**}p < 0.05$,$^{***}p < 0.01$.

Table 2. Opioid Consumption (Ordinary Least Squares)

The OLS estimates highlight the magnitude and sign of correlations between opioid consumption, economic conditions, and other socio-demographic factors, but do not identify causal effects. Indeed, by including department fixed-effects, the model in equation (1) allows controlling for a large set of unobservables, thus considerably reducing the risk of spurious correlations. However, we are not able to control for time-varying department-specific characteristics, other than those included in the analysis as covariates. As a consequence, an omitted variable problem may persist. Moreover, we are not able to infer whether living in poor conditions leads people to consume more opioids or whether drug consumption keeps individuals out of the labor market and eventually drives them into poverty (reverse causality).

We now address these endogeneity issues, by implementing a Two-Stage Least Square (2SLS) approach, which allows us to isolate the exogenous variation in poverty and draw conclusions on the causal relationship from poverty to opioid consumption.

The French government recently introduced a new law with the explicit purpose of fighting poverty of low-income individuals and providing them with higher monetary incentives for finding an occupation.[11] The new system was experimented in 34 departments as of June 2007 and entered into force at the national level (in all departments) in June 2009.[12] This is considered the most important social experiment that ever took place in France (Allègre, 2009).

We use a difference-in-difference strategy to isolate the exogenous variation in the poverty rate induced by the reform. This is the first equation in our Two-Stage Least Squares (2SLS) estimation procedure. In the second stage, opioid consumption is regressed on the predicted values for poverty from the first stage and the remaining socioeconomic covariates, as in equation (1). For the diff.-in-diff. estimation, the 34 departments that have been experimenting with the new system since the beginning of our study period (year 2008) represent our comparison group, while the remaining departments form the treatment group.

We estimate the following system of simultaneous equations:

$$Poverty_{dt} = \gamma_0 + \gamma_1 REFORM_{dt} + \gamma_2 Z_{dt} + \gamma_3 W_{dt} + \epsilon_d + \phi_t + v_{dt} \tag{2}$$

$$logY_{dt} = \beta_0 + \beta_1 \widehat{Poverty}_{dt} + \beta_2 W_{dt} + \alpha_d + \delta_t + u_{dt} \tag{3}$$

In equation (2), the observed poverty rate is regressed on the binary variable, $REFORM_{dt}$ (our diff.-in-diff. instrument), that takes value 1, if department d receives treatment in period t, 0

[11] Essentially, this law (Loi n. 2008-1249 du 1er Décembre 2008) was aimed at reforming the system of the so-called *minima sociaux*, by substituting two old instruments, called *Revenu Minimum d'Insertion (RMI)* and *Allocation de Parent Isolé (API)*, with a new one, the *Revenu de Solidarité Active (RSA)*. The *Minima sociaux* represent the system of social benefits paid to individuals in precarious conditions, in order to ensure them a minimum income.

[12] The "Loi n. 2007-1223 du 21 aout 2007", so-called "Loi TEPA", defined the terms of the experimentation. The first department to experiment was Eure in June 2007, followed by 9 departments starting the experimentation between November and December 2007. The major part joint the experiment between January and February 2008, while a few (8 departments) joint later, between March and April 2008. It should be noted that, among the 34 departments experimenting with the new system since the end of 2007/ beginning 2008, only two (Creuse and Mayenne) applied the reform over the whole department territory, while the remaining departments experimented in some selected areas. See Appendix C for further details on the reform.

otherwise. Poverty is additionally regressed on a set of excluded (Z_{dt} contains Doctors and Pharmacists density, GDP per head and Gini coefficient) and included (W_{dt} contains Unemployment rate, Age (40-59), Education level and Population density) instruments, as well as on department, ϵ_d, and year, ϕ_t, fixed effects. Because the 34 experimenting departments were only partially treated before June 2009, the coefficient γ_1 underestimates the full effect of the reform. However, this is not too relevant here, since the goal is rather finding a source of exogenous variation that allows instrumenting for poverty.[13] Equation (3) is the main equation, which explains the log consumption of opioids by instrumented poverty, the set of controls W_{dt} and the department, α_d, and year, δ_t, fixed effects.

The main results are shown in Table 3. The first stage regression in column (7) of Table 3 is the same for all opioids and shows that the coefficient associated with $REFORM$ is negative and significantly different from zero at the 5 percent confidence level. This indicates that the reform had a stronger impact in those departments that were not experimenting before it was applied at the national level than in those that were already experimenting before this date. Unemployment is, as expected, positively and significantly associated with poverty, while the estimate for the Gini coefficient indicates that more inequality is associated with more poverty.

In the first two columns of Table 3, the dependent variable is the log-consumption of all opioids, while, in columns from (3) to (6), we consider mild and strong opioids separately. To facilitate comparison, we report in columns (1), (3) and (5) of Table 3 the OLS estimates of columns (2), (5) and (8) in Table 2.

The estimated coefficient for the poverty rate is positive and significantly different from zero at the one percent level for mild and for all opioids. This relationship becomes, however, weaker for strong opioids. OLS estimates are, in general, lower in magnitude than 2SLS estimates. For all and mild opioids, a one percentage point increase in the poverty rate causes, approximately, an 11 percent increase in opioid use, within a department and across time. This effect is, instead, only 6 percent for strong opioids. Population density is negatively associated with opioid use, suggesting that the latter is more common in rural than in urban areas. Basic education is positively associated with opioid use, even though this relationship is significant at the 10 percent level only. Finally, middle-aged individuals tend to consume more pain-killers.

In Appendix Table E1, we repeat the same analysis by using data for the poverty rate when the poverty threshold is set at 50% of the national median income. This may serve as a robustness check, but also yields useful insights on the role played by the 'intensity' of poverty. In this specification, the estimated coefficients for poverty are larger in magnitude than those in Table 3, confirming that, if the share of the 'poorest' increases, opioid consumption increases by more. The coefficients for the other covariates remain very close to those of Table 3.

[13] The 34 departments were not randomly chosen, but volunteered to implement the experimentation, and were poorer than the others, to begin with. Our diff.-in-diff. approach allows controlling for potential self-selection bias.

	All Opioids		Mild Opioids		Strong Opioids		
	OLS (1)	IV 2nd Stage (2)	OLS (3)	IV 2nd Stage (4)	OLS (5)	IV 2nd Stage (6)	IV 1st Stage (7)
Poverty Rate	7.6816*** (2.1871)	10.9801*** (3.6767)	7.9385*** (2.1568)	11.6145*** (3.6635)	4.6845* (2.6143)	6.1483 (4.3096)	
Unemployment Rate	-2.1837 (4.9636)	-3.9583 (5.2597)	-2.4136 (4.8510)	-4.3914 (5.1420)	-.1776 (6.5715)	-.9652 (6.7845)	.5020*** (.1231)
Age, 40-59	20.0620** (8.3311)	17.8707** (8.4914)	19.6976** (8.1377)	17.2555** (8.3080)	20.6229* (10.8930)	19.6504* (11.1393)	.1349 (.2447)
(Only) Basic Education	7.8347* (4.5411)	8.4928* (4.3642)	7.4713* (4.4872)	8.2048* (4.2968)	10.8858* (5.6378)	11.1778** (5.5816)	.0756 (.1230)
Population Density	-.0005*** (.0001)	-.0006*** (.0002)	-.0005*** (.0001)	-.0006*** (.0002)	-.0004** (.0002)	-.0004* (.0002)	.0000** (.0000)
REFORM							-.0034** (.0017)
Doctors Density							-.0001* (.0000)
Pharmacists Density							.0002* (.0001)
GDP (per capita)							3.14e-07 (4.04e-07)
Gini							.8225*** (.1910)
R^2	.4307	.4243	.4637	.4558	.1390	.1380	
N	940	940	940	940	940	940	940
F-stat							125.005

Note: Robust standard errors clustered at the department level in parentheses. Each regression includes department and year fixed effects and is weighted by department population. $^{*}p < 0.1$,$^{**}p < 0.05$,$^{***}p < 0.01$.

Table 3. Opioid Consumption (Two-Stage Least Squares)

4.2 Discussion

The results presented in Subsection 4.1 are consistent with previous findings in the US and France that we briefly describe in Section 2 (Ghertner and Groves, 2018 and Nordmann et al., 2013). At the same time, we build on the existing literature by showing that there exists a causal link running from economic conditions, as proxied by the poverty rate, to opioid product sales and by shedding light on the role played by the intensity of poverty.

By including socio-demographic indicators as controls, we also complement previous research. The incidence of pain across age groups in France, for instance, is studied by Hadjiat et al. (2018). They find that chronic pain is more prevalent among adults aged between 45 and 64. In the US, the major part of opioid-related overdose deaths in 2015 occurred among individuals aged between 25 and 55 (CDC, 2019), while Case and Deaton (2017) suggest that the opioid epidemic is an important contributor to the increase in mortality among middle-aged non-Hispanic whites.[14]

Furthermore, the US opioid epidemic seems to have affected more heavily rural communities (Global Commission on Drug Policy, 2017). For example, the Government Accountability Office (GAO, 2003) explains that the first reports of widespread abuse and diversion of OxyContin appeared in rural areas. Cicero et al. (2017) show that prescription opioid misusers are more commonly white, reside in suburban or rural areas and have less than a college education.

The unemployment rate, instead, doesn't seem to play a role in fueling opioid consumption in France: the coefficient associated with unemployment is not statistically different from zero. This is in contrast with some previous studies in the US, which show that unemployment is positively related to opioids use and abuse (Hollingsworth et al., 2017).

Finally, the coefficients associated with the year dummies, which we do not report for space reasons, confirm that consumption has increased over time.

We also looked at the coefficients picked up by the department fixed effects. These are illustrated in Figure 2 after been regrouped into four intervals based on quartiles: $[-2.07, -1.43]$, $[-1.43, -0.95]$, $[-0.95, -0.45]$ and $[-0.45, 11.22]$. The last interval, $[-0.45, 11.22]$, is represented in dark red in Figure 2 (15 departments and Paris including its four surrounding departments) and consists essentially of coefficients that are close to or larger than zero, which means that opioid consumption is larger than the one that results from socioeconomic differences represented by our variables. These departments are essentially located close and along the western coast of the country, in the Parisian region and in the south-east. In all other departments, the regression coefficients picked up by these dummies are negative, which means less opioid consumption. These are located in 13 departments in the mid-southern region of France (in white in Figure 2). This shows that opioid use is, in part, explained by unobserved time-invariant department-specific characteristics.

[14] For further insights on opioid-related deaths in France, see Appendix D

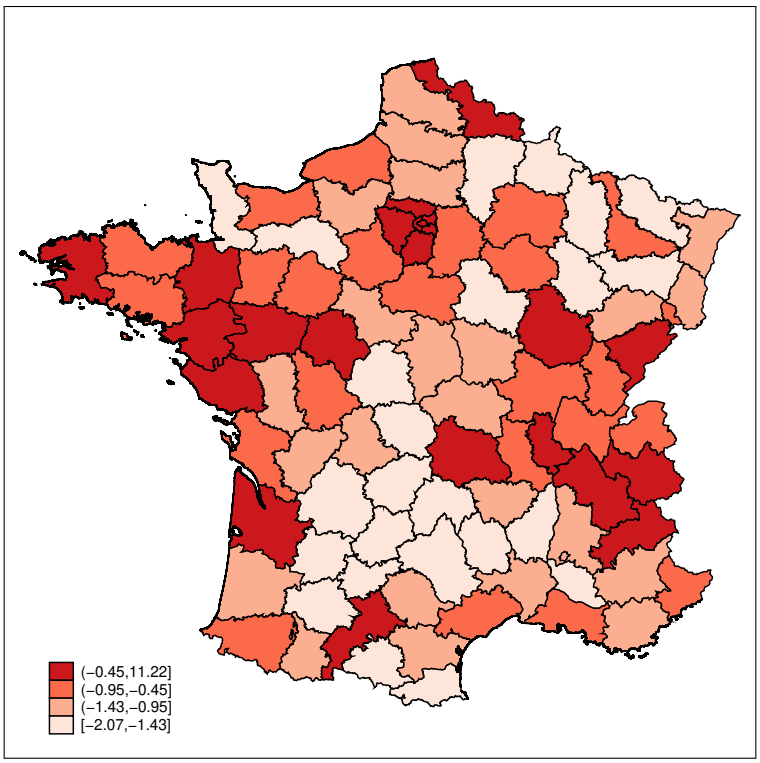


Figure 2. Geographical Opioid Consumption Variability (Department Fixed Effects)

4.3 A Three-dimensional Panel Model: Active Substance, Department and Year

In this subsection, we propose an alternative specification through which we identify causal effects by controlling for a considerably large set of unobservables. We do this by using a three-dimensional panel model, where the three-dimensions are given by active substance, department and year. This model can be written as:

$$logY_{sdt} = \beta_0 + \beta_1 X_{dt} + \eta_s + \alpha_d + \delta_t + \gamma_{sd} + \lambda_{st} + u_{sdt}, \tag{4}$$

where Y_{sdt} represents consumption of an active substance, s, in department, d, and year, t. X_{dt} is the vector of explanatory variables proxying departments' socioeconomic status and β_1 is a vector of parameters to be estimated. η_s, α_d, and δ_t denote, respectively, substance, department and year fixed effects and u_{sdt} is an idiosyncratic error term.[15] We also include department-by-substance, γ_{sd}, and year-by-substance interactions, λ_{st}, which allow us to control for unobserved department-product and time-varying product characteristics. It is possible, for example, that two departments with the same poverty rate are characterized by different levels of consumption for a given active ingredient, simply because they have different medical cultures and different medical practices. Indeed, as is well-known, physicians discuss and exchange opinions about what they think is the best drug to cure a given condition[16]. Controlling for unobserved department-substance factors allows taking into account this type of spillovers (which may be spuriously correlated with poverty).[17]

The results from these regressions are shown in Table 4. In the first two columns, we consider all the active substances, in columns (3)-(4), the focus is on mild opioids, while, in columns (5)-(6), we focus on strong opioids. The coefficients are close in magnitude to those in Table 2. The poverty rate is significantly different from zero at the one percent confidence level for all and for mild opioids. Given our specification, these results should be interpreted as follows: sales for mild, strong and all opioids increase by 6 to 8 percent in response to a one percentage point increase in the poverty rate, when controlling for other observables as well as for unobserved department-product specific factors and time-varying product characteristics. The coefficient associated with age is positive and significant and so is the one associated with education, showing that, as the portion of individuals with basic education increases, opioid consumption also rises. The coefficient for population density remains negatively associated with sales, while the coefficient for unemployment remains insignificant. Doctors and pharmacists densities are again not significantly associated with consumption, whereas their inclusion does not affect the

[15] The error term is clustered at the department-substance level, but results are robust to alternative clusterings.

[16] Previous research has shown that peer effects are important and there exists significant clustering in treatment.

[17] Note that adding department-by-year fixed effects would allow us to also control for department characteristics that vary over time. However, for β_1 to be identified, we would need our independent variables in X_{dt} to vary across active substances, s, for all department-year pairs. In the above model, instead, β_1 can be identified, since, for identification, we need X_{dt} to have non-zero variation over t for at least one department-product pair and non-zero variation over d for some product-year combination (Balazsi et al., 2015).

significance and magnitude of the coefficients associated with the remaining variables.

Finally, these three-dimensional panel regressions use a larger number of observations, thus yielding more precise estimates than the bi-dimensional specifications of Subsection 4.1: the standard errors are lower and the R-squared are higher than those reported in Tables 2 and 3.

Compared to the simple OLS model with only department and year fixed effects, this approach enables us to control for a larger pool of unobserved confounding factors. Nevertheless, there may still exist time-varying department characteristics that are correlated with X_{dt} and, hence, would bias our estimation. If this is the case, the estimated coefficients are not informative about the causal effect of socioeconomic status on opioid consumption. This potential endogeneity issue is addressed through 2SLS estimation in Subsection 3.1, and we avoid repeating it here.

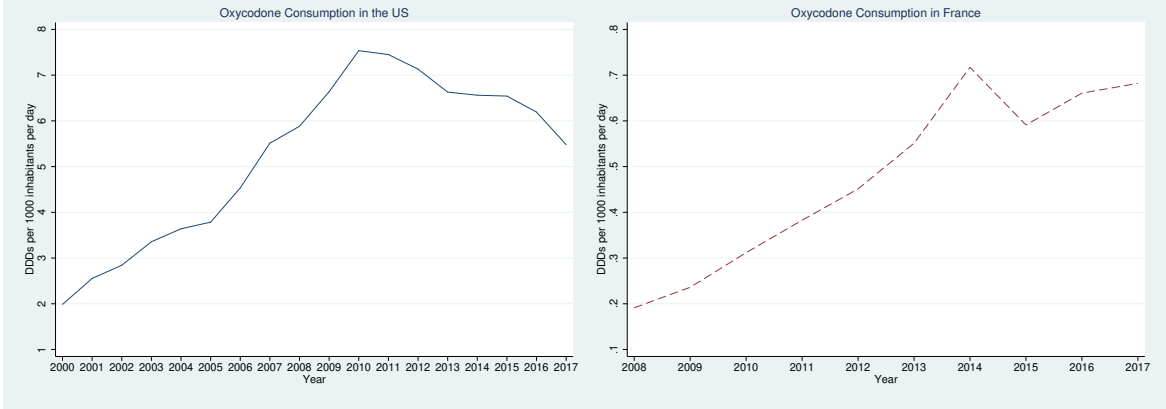
	All Opioids		**Mild Opioids**		**Strong Opioids**	
	(1)	(2)	(3)	(4)	(5)	(6)
Poverty Rate	5.8260***	5.9095***	7.9381***	7.5907***	4.9813**	5.2376**
	(1.6982)	(1.7027)	(1.5189)	(1.5782)	(2.2723)	(2.2763)
Unemployment Rate	-.0848	.0631	-2.4144	-1.9372	.8479	.8638
	(3.6641)	(3.7340)	(3.4161)	(3.3486)	(4.9071)	(5.0215)
Age, 40-59	19.1259***	19.2419***	19.6969***	19.8650***	18.9025**	18.9971**
	(5.8131)	(5.8033)	(5.7302)	(5.7451)	(7.7142)	(7.6876)
(Only) Basic Education	12.1902***	12.2485***	7.4731**	7.4614**	14.0827***	14.1698***
	(2.7792)	(2.7808)	(3.1598)	(3.0842)	(3.6634)	(3.6709)
Population Density	-.0003*	-.0003	-.0005***	-.0004***	-.0002	-.0002
	(.0002)	(.0002)	(.0001)	(.0001)	(.0002)	(.0002)
Doctors Density		.0008		-.0003		.0012
		(.0010)		(.0010)		(.0013)
Pharmacists Density		.0012		.0038		.0001
		(.0031)		(.0029)		(.0041)
R^2	.3277	.3279	.5042	.5068	.3149	.3152
N	6573	6573	1880	1880	4693	4693

Note: Robust standard errors clustered at the department-substance level in parentheses. Each regression includes department, year and substance fixed effects, together with department-by-substance and year-by-substance fixed effects. Regressions are weighted by department population.
$^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$.

Table 4. Opioid Consumption (Three-dimensional Panel)

5 The Case of Oxycodone

The explosive increase in Oxycodone use has been blamed to be one of the major drivers of the opioid crisis in the US and, since it displays the most spectacular increase in consumption over the last ten years in France as well (as shown in Section 3), we further investigate this ingredient in particular. Figure 3 compares Oxycodone retail sales in the US and France and illustrates the rise in sales between 2000 and 2010 in the US and between 2008 and 2017 in France (Oxycodone was launched on the French market in April 2002). The growth rates in the two countries are very close: 279 percent in the US between 2000 and 2010 and around 256 percent in France between 2008 and 2017. In the US, the reduction in Oxycodone consumption after 2010 may be largely due to the introduction of its abuse-deterrent version, while the decline in France between 2014 and 2015 coincides with the entry of generics on the Oxycodone market.



Sources: OpenHealth database; authors' calculations.

Figure 3. Oxycodone Retail Sales: the US versus France

In Table 5, we investigate the relationship between socioeconomic indicators and Oxycodone consumption and compare with their impact on all the remaining strong opioids. We do this by using the three-dimensional panel model discussed in Subsection 4.3 and including a dummy variable for Oxycodone which is equal to one if the active ingredient is Oxycodone, and zero for all the remaining active ingredients (oral Morphine, injectable Morphine, transdermal Fentanyl and transmucosal Fentanyl). We then interact this dummy with each explanatory variable. Hence, our econometric specification becomes:

$$logY_{sdt} = \beta_0 + \beta_1 X_{dt} + \theta D_{Oxy} * X_{dt} + \eta_s + \alpha_d + \delta_t + \gamma_{sd} + \lambda_{st} + u_{sdt}$$

where all the variables are defined as before (Subsection 4.3) and D_{Oxy} is the Oxycodone dummy.

Column (1) in Table 5 reports the results for the model without the Oxycodone dummy. Column (2) adds the interaction terms $D_{Oxy} * X_{dt}$. The coefficients associated with each ex-

planatory variable now represent their effect on all strong opioids except Oxycodone, whereas adding each of these coefficients to the coefficients associated with the interaction terms represents the impact on Oxycodone only. This analysis reveals that poverty has a smaller impact on Oxycodone consumption than on other strong opioids, though the estimated parameter equal to -9.55 is hardly different from zero. None of the other differences is significantly different from zero. In an alternative specification (column (3)), we additionally interact a time trend specific for Oxycodone consumption with each variable in X_{dt} and we find comparable results (the only significant interaction term is the one associated with poverty).

The much higher growth rate characterizing Oxycodone use may then be due to reasons other than socioeconomic factors. These include (1) product positioning since Oxycodone is offered in pills, which makes its administration easy; (2) pharmaceutical companies marketing pressure; (3) psychological factors. Psychological factors, in particular, may well explain the substitution patterns observed in Figure 1 panel (d), and discussed in Subsection 3.2, according to which Morphine seems to be increasingly replaced by Oxycodone and, to a lesser extent, by Fentanyl. This pattern has been observed in several other European countries and some researchers have referred to this phenomenon as *morphinophobia* (Garcia del Pozo et al., 2008): doctors are more and more reluctant to prescribe Morphine because patients often associate Morphine with very severe diseases and with death. By contrast, Oxycodone and Fentanyl seem to be less "psychologically scary" for patients.

	(1) Consumption	(2) Consumption	(3) Consumption
Poverty Rate	4.9813** (2.2723)	6.8938*** (2.4028)	6.8575*** (2.4028)
Unemployment Rate	.8479 (4.9071)	-1.6117 (5.3206)	-1.6454 (5.3220)
Age, 40-59	18.9025** (7.7142)	21.2998** (8.8886)	21.2233** (8.8953)
(Only) Basic Education	14.0827*** (3.6635)	15.8391*** (4.1963)	15.7922*** (4.1972)
Population Density	-.0002 (.0002)	-.0002 (.0003)	-.0001 (.0002)
Oxy*Poverty		-9.5559* (5.1951)	-.0046* (.0026)
Oxy*Unemployment		12.2823 (12.8820)	.0061 (.0063)
Oxy*Age		-11.9718 (16.8227)	-.0056 (.0083)
Oxy*Education		-8.7580 (8.0983)	-.0042 (.0040)
Oxy*Population		-.0004 (.0005)	-2.54e-07 2.73e-07
R^2	.3149	.3177	.3178
N	4693	4693	

Note: Robust standard errors clustered at the department-substance level in parentheses. Each regression includes department, year and substance fixed effects, together with department-by-substance and year-by-substance fixed effects. Regressions are weighted by department population. $^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$.

Table 5. Strong Opioid Consumption (Three-dimensional Panel with Oxycodone Variables)

6 Conclusion and Policy Implications

Our analysis seems to corroborate the so-called 'deaths of despair' hypothesis, which has been put forward by some authors in the US (Case and Deaton, 2017), while criticized by others (Ruhm, 2018 and Currie et al., 2019).

Compared to Ruhm (2018), the specific setting of our analysis allows us to abstract from differences in regulation and policy measures concerning narcotic drugs because, in France (and, more broadly, in the EU), such regulations, policy interventions and rules governing the health-care system are centralized and, hence, homogeneous across French departments. In addition, several important regulations concerning the administration of narcotic drugs were issued before 2008 and remained unchanged during our study period. Yet, our investigation suggests that poverty plays a significant role in driving opioid analgesic sales. In contrast to Ruhm (2018), the effect of our economic proxy becomes sometimes larger and more significant, when controlling for possible fixed and time-varying confounding factors as well as for reverse causality.

In partial accordance with Currie et al. (2019), we find that unemployment is not significantly related to opioid consumption. However, poverty is and, even though unemployment and poverty are often positively correlated, being unemployed does not necessarily mean being poor, and vice versa, especially in France, where considerable monetary support is offered to unemployed people. Consequently, unemployment does not necessarily represent a good proxy of economic disruption and the type of despair mentioned by Case and Deaton (2017) is more likely to be a poor individual than a (temporary) unemployed one.

Having said this, we agree with Ruhm (2018) in stating that regulation and policy interventions play a crucial role in addressing the crisis since the significant discrepancies in mortality rates between France and the US may largely be attributed to deeply different regulatory systems and medical cultures. For example, in Europe, it is strictly forbidden to advertise prescription-only medicines publicly; pharmaceutical companies are not allowed to provide free samples for narcotic medications; the bureaucratic burden associated with opioid prescription is much heavier. Finally, a less liberal medical culture may also make the difference: European doctors are known to be more conservative and more reluctant to use opioids.

An additional crucial aspect to be considered is the interplay between national policies and local economic prospects: any new regulation imposed at the national level is likely to trigger heterogeneous responses across geographical regions and pharmaceutical companies because the final consumers (the patients) will react differently depending on their economic status and the producers (the firms) may, then, have an incentive to revise their marketing strategies. These topics represent the focus of future research.

We conclude that both socioeconomic aspects and regulatory frameworks are crucial for explaining the opioid crisis. They represent two important facets of the same coin and policies aimed at fighting the epidemic should not translate in an *out-out* between improving socioeconomic status or enhancing the regulatory environment, but should rather view these as complementary aspects of the same crisis.

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A Tables and Figures

This appendix contains information about the opioid analgesics on the French market and the pharmaceutical companies marketing them.
Specifically, Table A1 below lists all the active substances, the name of each product, the route of administration and the available dosages.
Table A2 gives the name of the companies selling mild opioids, whether their products are branded or generics and whether sales data for each company are available for the whole period between 2008 and 2017. Table A3 contains the same information for strong opioids.

Active Ingredient	Product Denomination	Administration Route	Dosages
Codeine+Paracetamol	Algicalm, Algisedal, Codoliprane, Compralgyl, Dafalgan codeine, Gaosedal, Klipal codeine, Lindilane, Claradol codeine, Doliprane codeine, and generics	Oral	20, 25, 30, 50 mg
Codeine+Ibuprofen	Antarene codeine	Oral	30, 60 mg
Codeine+Paracetamol+Cafeine	Migralgine, Prontalgine	Oral	20 mg
Codeine+Paracetamol+Aspirine	Novacetol	Oral	10 mg
Codeine+Aspirine+Cafeine	Sedaspir	Oral	20 mg
Tramadol	Biodalgic, Topalgic, Contramal, Monoalgic, Monocrixo, Monotramal, Orozamudol, Predalgic, Takadol, Zamudol, Zumalgic, Trasedal, and generics	Oral	50-100-150-200-300 mg and 100mg/ml
Tramadol+Paracetamol	Ixprim, Zaldiar and generics	Oral	37.5 mg
Tramadol+Dexketoprofene	Skudexum	Oral	75 mg
Dihydrocodeine	Dicodin	Oral	60 mg
Nalbuphine	Generic	Injectable	20mg/2ml
Oxycodone	Oxycontin, Oxynorm, Oxynormoro and generics	Oral	5-10-15-20-30-40-60-80-120 mg
Morphine	Actiskenan, Aguettant, Sevredol, Skenan, Oramorph, Moscontin, Kapanol	Oral	5 mg/ml, 10mg/5 ml, 20mg/1ml, 30mg/5ml, 100mg/5ml and 5-10-20-30-50-60-100-200 mg
Morphine	Lavoisier, Renaudin, Aguettant, Cooper, Meram	Injectable	0.1-1-10-20-40-50 mg/ml, 50mg/5ml, 100mg/5ml
Fentanyl	Durogesic, Matrifen and generics	Transdermal	12-25-50-75-100 μg/hour
Fentanyl	Abstral, Actiq, Breakyl, Effentora, Instanyl, Pecfent, Recivit	Transmucosal	67-100-133-200-267-300-400-533-600-800-1200-1600 μg
Hydromorphone	Sophidone	Oral	4-8-16-24 mg
Buprenorphine	Temgesic	Sublingual	0.2 mg
Pethidine	Pethidine Renaudin	Injectable	50mg/ml

Table A1. Opioid Analgesics on French Market

Active Ingredient	Company	Branded	Generic	Entry	Exit
Codeine + Paracetamol	Cooper	X		<2008	On the market
	Arrow Generiques		X	<2008	On the market
	Bayer Sante Familiale	X		<2008	On the market
	Biogaran		X	<2008	On the market
	Bristol Mayers	X		<2008	On the market
	Cristers		X	Q1-2009	On the market
	EG Laboratoire		X	<2008	On the market
	Gifrer Barbezat	X		<2008	On the market
	Grunenthal	X		<2008	On the market
	Merck Med. Fam. sas	X		<2008	On the market
	Mylan		X	<2008	On the market
	Mylan Medical sas	X		<2008	On the market
	Pierre Fabre Med.	X		<2008	On the market
	Sandoz sas		X	<2008	On the market
	Sanofi Aventis France	X		<2008	On the market
	Teva Sante		X	<2008	On the market
Codeine + Ibuprofen	Elerte	X		Q2-2011	On the market
Codeine (Combinations)	Pharmastra	X		<2008	On the market
	Bride	X		<2008	On the market
	Mc Neil sas			Q1-2008	Q2-2008
	Johnson Johnson	X		<2008	On the market
	Boehringer-Ingelheim France	X		<2008	On the market
Tramadol	Arrow Generiques		X	<2008	On the market
	Biocodex	X		<2008	On the market
	Biogaran		X	<2008	On the market
	Cristers		X	Q2-2014	On the market
	EG Laboratoire		X	<2008	On the market
	Elerte	X		<2008	Q4-2011
	Evolupharm		X	Q3-2013	On the market
	Expanscience	X		<2008	On the market
	GNR Pharma		X	Q2-2008	Q2-2008
	Grunenthal	X		<2008	On the market
	Laboratoire X.O	X		<2008	On the market
	Medapharma	X		Q1-2008	Q4-2008
	Mylan		X	<2008	On the market
	Mylan Medical sas	X		<2008	On the market
	Qualimed		X	<2008	Q3-2013
	RPG Ranbaxy Pharm. Generiq.		X	Q2-2013	On the market
	Sandoz sas		X	<2008	On the market
	Sanofi Aventis France	X		Q1-2008	On the market
	Sanofi Zentiva		X	<2008	On the market
	Teva Sante		X	<2008	On the market
	Therabel Lucien Pharma	X		<2008	On the market
	Zydus France sas		X	<2008	On the market

Table A2. Pharmaceutical Companies (Mild Opioids)

Active Ingredient	Company	Branded	Generic	Entry	Exit
Tramadol + Paracetamol	Arrow Generiques		X	Q2-2013	On the market
	Biogaran		X	Q1-2013	On the market
	Cristers		X	Q2-2013	On the market
	EG Laboratoire		X	Q2-2014	On the market
	Evolupharm		X	Q3-2013	On the market
	Gerda		X	Q2-2018	Q2-2018
	Grunenthal	X		<2008	On the market
	KRKA Pharma		X	Q3-2013	On the market
	Mylan		X	Q1-2013	On the market
	Mylan Medical sas	X		Q3-2014	On the market
	Pharma Reference PHR Lab		X	Q3-2013	Q1-2016
	RPG Ranbaxy Pharm. Gen.		X	Q2-2013	On the market
	Sandoz sas		X	Q1-2013	On the market
	Sanofi Zentiva		X	Q1-2013	On the market
	Teva Sante		X	Q1-2013	On the market
	Zydus France sas		X	Q2-2013	On the market
Tramadol + Dexketoprofene	Menarini France	X		Q2-2017	On the market

Table A2 (cont.). Pharmaceutical Companies (Mild Opioids)

Active Ingredient	Company	Branded	Generic	Entry	Exit
Oxicodone	Mundipharma	X		<2008	On the market
	Arrow Generiques		X	Q2-2017	On the market
	Mylan sas		X	Q4-2014	On the market
	EG Laboratoire		X	Q3-2015	On the market
	Biogaran		X	Q1-2018	On the market
Transdermal Fentanyl	Janssen Cilag sa	X		<2008	On the market
	Takeda	X		Q1-2009	On the market
	Arrow Generiques		X	Q1-2010	On the market
	Biogaran		X	Q4-2009	On the market
	EG Laboratoire		X	Q2-2010	On the market
	Mylan		X	Q4-2013	On the market
	RPG Ranbaxy Pharm. Generiq.		X	Q4-2013	Q4-2015
	Sandoz sas		X	Q3-2009	On the market
	Teva Sante		X	<2008	On the market
	Sanofi Zentiva		X	Q2-2009	On the market
Transmucosal Fentanyl	Kyowa Kirin Pharma	X		Q3-2009	On the market
	Teva Sante		X	<2008	On the market
	Mylan Medical sas		X	Q2-2013	On the market
	Takeda	X		Q2-2010	On the market
	Grunenthal	X		Q3-2014	On the market
Oral Morphine	Ethypharm	X		<2008	On the market
	Aguettant	X		<2008	2008
	GSK	X		<2008	2010
	Mundipharma	X		<2008	On the market
	Kyowa Kirin Pharma	X		<2008	On the market
Injectable Morphine	Aguettant	X		<2008	On the market
	Cooper	X		<2008	On the market
	Chaix et du Marais	X		<2008	On the market
	Renaudin	X		2013	On the market

Table A3. Pharmaceutical Companies (Strong Opioids)

B Data Description

Data for the set of variables used to describe the department's socioeconomic status are downloaded from the INSEE and OCSE websites. These chosen variables are mainly based on the literature that deals with the opioid epidemic in the US, which has identified a few socio-economic factors related to the crisis. The covariates included in the econometric analysis are the following:

1. **Poverty and Unemployment**. The poverty rate is defined by the OECD as the share of individuals living below the poverty line, usually set at 60% of the national median income.
   The poverty rate is analogously defined by the INSEE as follows: *"Le taux de pauvreté correspond à la portion d'individus dont le niveau de vie est inférieur pour une année donnée à un seuil dénommé seuil de pauvreté (exprimé en euros). L'INSEE, comme EUROSTAT et les autres pays européens, mesure la pauvreté monétaire de manière relative. Dans l'approche en termes relatifs, le seuil de pauvreté est déterminé par rapport à la distribution des niveaux de vie de l'ensemble de la population. On privilégie en Europe le seuil de 60% du niveau de vie médian"*. Data for the year 2017 at the department level are missing and, hence, they are interpolated, by replacing them with their 2016 value.
   The unemployment rate is defined, as usual, as the share of unemployed individuals over the active population, that is unemployed people plus individuals currently in the labor force. This is defined by the INSEE as *"Le taux de chômage est le pourcentage de chômeurs dans la population active (actifs occupés+chômeurs)"* .

2. **Population, Age Groups, and Education**. Population and age groups data are available for every year, while education data are only available for the years 1999, 2010 and 2015 (according to the census realized in these years). The INSEE provides the number of individuals older than 16 and no longer attending school ("population non-scolarisée") in each education group, where each group refers to a different diploma level.
   The first group represents the portion of people with no diploma or with a DNB ("Diplôme nationale du brevet") that is awarded after completion of the first cycle of education.
   The second group represents the share of individuals holding a BEP ("Brevet d'étude professionnelle") or CAP ("Certificat d'aptitude professionnelle"). These are obtained after completion of two years of a professional high school ("Lycée").
   The third group represents the share of people owning a "Baccalauréat", which is obtained after completion of high school (professional, technical or general).
   The last group includes individuals with a "Diplome d'études supérieures ", that is a university degree.
   Education data are interpolated as follows. We consider the difference in the number of individuals in each education group between two subsequent censuses and we divide this number by the number of years between the two census, to obtain an average annual varia-

tion. For the years in which data are missing, the number of individuals in each education group is computed based on this annual variation. For the years 2016 and 2017, we apply the same annual variation as for the years between 2010 and 2015. Finally, we divide the number of individuals in each education group by the department population in each year, to obtain the share of people in each group. In the same way, we divide the number of individuals in each age group by the department population each year to obtain the share of people in a given age group.

3. **Population Density as a proxy for Rural/Urban**. For our fixed-effects regressions, we are not allowed to use a dichotomous variable to characterize departments as rural or urban. Hence, we use population density as a proxy for the rural/urban variable, where population density is measured in number of inhabitants per square kilometer and with the understanding that a more densely populated department is "more urban" than a less populated one. This choice is based on the observation that both the OECD and EUROSTAT classify geographical areas by employing a three-step approach mainly based on population density.
   To construct our population density variable, we exploit population data and data on the area of each department (in square kilometers), both provided by INSEE.

4. **Healthcare Professionals**. INSEE also provides data on the number of doctors and pharmacists in each department and each year. Data for doctors and pharmacists are expressed in terms of densities, that is the number of doctors or pharmacists per 100000 inhabitants. Data are available for the whole period (2008-2017) but missing in 2011, for doctors, and in 2011 and 2013, for the pharmacists. These data have been interpolated by taking, respectively, the average between 2010 and 2012 and the average between 2012 and 2014.

5. **GDP per head and Gini Coefficient**. Data for the Gini coefficient are provided by INSEE. They are not available for 2017 at the department level. Hence, they are replaced by using their 2016 value.
   Data on GDP per head are extracted from the OECD website. Data at the department level are missing for the years 2016 and 2017 and are replaced by their 2015 value.

C The French Social System and the "Revenu de Solidarité Active (RSA)" Reform

France, as a country, is characterized by a strong social system and a large variety of benefits paid by public authorities to individuals in precarious situations, to ensure them a minimum revenue.[18] Until June 2009, these included, among others, the "Revenu Minimum d'Insertion (RMI)" and the "Allocation de Parent Isolé (API)". The RMI was created in 1988 to guarantee minimum resources to anyone aged 25 or over and/ or who was responsible for at least one child born or to be born. The API was created in 1976 and it was addressed to individuals who were taking care alone of at least one child born or to be born. Both these instruments have been replaced by the "Revenu de Solidarité Active (RSA)".

In August 2007, a new law in favor of employment and purchasing power (the so-called "loi TEPA"[19]) authorized French departments to experiment the introduction of the RSA for a period no longer than three years, on the totality of their territory or some selected areas. This new instrument was meant to replace the old social minima RMI and API to provide stronger return-to-employment incentives and increase the long-term disposable income of low-income households. Unlike the old system, the mechanism is designed in such a way that any increase in income from a professional activity results in a decrease in the RSA lower than this increase so that the household's disposable income always increases when its activity income increases. The generalized RSA has a cumulation rate of 62% (or a 38% withdrawal rate): the RSA is reduced by 38 cents and the disposable income of the household increases by 62 cents - for each additional euro earned at work. The RSA pursues, therefore, both a redistributive objective and an incentive objective: fighting the poverty of low-wage workers and encouraging the return to work. The RSA is a family-based device whose amount takes into account household income and family status.

The experimentation took place between June 2007 and June 2009 in 34 French departments expressing their interest in experimenting on a voluntary basis. After this period, the law no. 2008-1249 of December 2008 put an end to the experimentation, by imposing the RSA on the whole national territory as of 1st June 2009. According to the text of this law, the RSA is intended to provide its beneficiaries with adequate means, in order to fight poverty, to encourage the exercise or return to a professional activity and to improve social integration.
Table C1 below lists the departments taking part in the experimentation, together with its start date.

[18] The information contained in this section has been retrieved from Allègre, 2009, Comité d'Evaluation des expérimentations, 2008 and DREES, 2019.

[19] Loi n. 2007-1223 du 21 aout 2007 en faveur du travail, de l'emploi et du pouvoir d'achat.

Department	Start Date RSA - RMI	Start Date RSA - API
Aisne	January 2008	January 2008
Allier	January 2008	February 2008
Alpes-Maritimes	April 2008	July 2008
Bouches du Rhone	January 2008	June 2008
Calvados	February 2008	March 2008
Charente	November 2007	November 2007
Charente-Maritime	January 2008	February 2008
Haute-Corse	January 2008	January 2008
Cote-d'Or	December 2007	December 2007
Cote-d'Armor	January 2008	
Creuse	March 2008	March 2008
Dordogne	March 2008	March 2008
Doubs	March 2008	March 2008
Eure	June 2007	November 2007
Gard	February 2008	
Gers	February 2008	February 2008
Hérault	December 2007	January 2008
Ile-et-Vilaine	January 2008	January 2008
Loir-et-Cher	November 2007	November 2007
Loire Atlantique	December 2007	December 2007
Marne	December 2007	

Table C1. Departments Experimenting RSA and Start Date of Experimentation

Department	Start Date RSA - RMI	Start Date RSA - API
Haute-Marne	January 2008	February 2008
Mayenne	March 2008	March 2008
Morbihan	February 2008	March 2008
Nord	January 2008	January 2008
Oise	November 2007	November 2007
Pas de Calais	January 2008	June 2008
Rhone	June 2008	June 2008
Haute-Saone	April 2008	April 2008
Seine-Maritime	January 2008	February 2008
Deux-Sèvres	January 2008	February 2008
Vienne	November 2007	November 2007
Seine-Saint-Denis	March 2008	March 2008
Vald'Oise	November 2007	November 2007

Table C1 (cont.). Departments Experimenting RSA and Start Date of Experimentation

D Opioid-related Harm

D.1 The International Classification of Disease (ICD-10) System

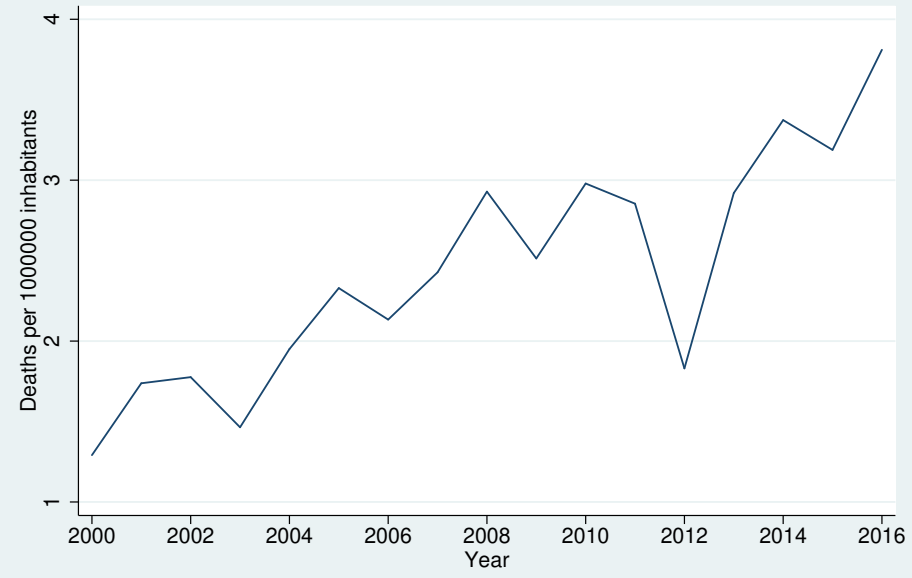
In the International Classification of Disease System, the causes of death are classified by using the Underlying Cause of Death (UCD) codes. The Underlying Cause of Death (UCD) is defined by the WHO as "the disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury". In what follows, we use the ICD tenth revision (ICD-10).
Drug poisonings are defined as fatalities with ICD-10 codes: X40-X42, X60-X64, X85 and Y10-Y12. In addition, the categories F01-F99 identify deaths related to mental and behavioral disorders. We use codes F11, identifying all deaths due to mental and behavioral disorders related to opioid use, X42, identifying deaths due to accidental poisoning by narcotics and psychodysleptics [hallucinogens] and exposure to these products, X62, identifying deaths due to auto-intoxication through narcotics and psychodysleptics [hallucinogens] and exposure to these products, Y12, identifying deaths due to poisoning by narcotics and psychodysleptics [hallucinogens] and exposure to these products, when the intention is not known. For fatal overdoses, the death certificate lists one or more drug categories involved as immediate or contributory causes of death. These are included separately in the Multiple Cause of Deaths (MCOD) files as ICD-10 “T-codes”. All the codes between T36 and T50 concern poisonings by, adverse effect of and underdosing of drugs, medicaments, and biologicals. This includes adverse effects of a correctly administrated substance; poisoning by overdose of substance; poisoning by substance given or taken by mistake; underdosing (intentional or not) by taking less substance than prescribed or instructed. In particular, the code T40 concerns poisonings by narcotics and psychodysleptics [hallucinogens], where the fourth digit indicates the specific substance causing the poisoning: T40.0 for opium, T40.1 for heroin, T40.2 for other opioids (codeine, morphine, natural and semisynthetic opioids), T40.3 for methadone, T40.4 for other synthetic narcotics (pethidine, other synthetic opioids) and T40.6 for other and unspecified narcotics.

D.2 Opioid-related Death

In this subsection, we analyze mortality data related to opioid consumption in France. These data are extracted from the *Centre d'épidémiologie sur les causes médicales de décès* (CépiDc-Inserim, 2019) database on all causes of death in France from 1979 to 2016. In this database, the causes of death are coded and classified according to the International Classification of Diseases (ICD-10) realized by the WHO. In order to identify deaths related to problematic use of opioids, we selected the codes F11, X42, X62 and Y12.[20]
Figure D1 below depicts the trend in opioid-related deaths between 2000 and 2016, where the y-

[20] Unfortunately, in the French database, MCOD T-codes are not available, so that we are not able to determine to which specific substance the death is related. Indeed, the X42, X62 and Y12 codes include poisonings for codeine, heroin, methadone, morphine, opium, but also cannabis, cocaine, LSD, and mescaline.

axis reports the number of deaths per 1000000 inhabitants. For this graph, we restrict attention to data concerning accidental deaths only (codes F11 and X42). In France, opioid-related deaths rose from 1.3 to 3.8 per one million population, which is a 192% increase over the 2000-2016 period and almost 5 deaths per week in 2016. Even though these numbers are still far from those characterizing the opioid crisis in the US, these trends arise safety concerns and induce authorities to reflect on appropriate measures to prevent a potential opioid epidemic in Europe.



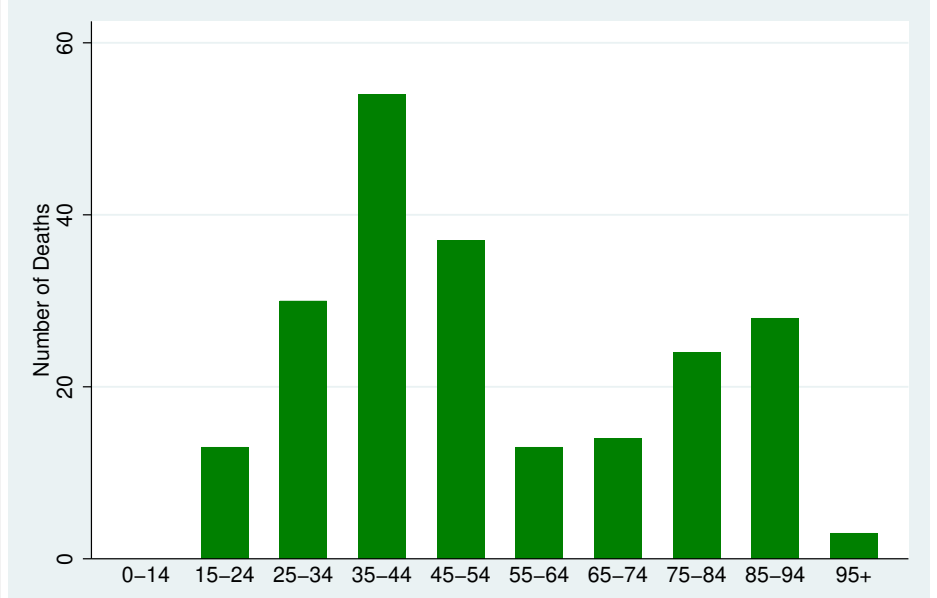
Sources: CépiDc-Inserim database; authors' calculations.

Figure D1. Opioid-related Deaths in France between 2000 and 2016

Figure D2 below describes the partition of deaths across age groups in 2014. The vast majority of opioid-related deaths concerns individuals between 35 and 44 years old: in particular, 25% of deaths involve individuals in this age group, while 17,13% of all opioid-related deaths pertain to those in the 45-54 group so that these two groups alone account for the 37,13% of deaths. If we further include the 25-34 age group, which accounts for 13,89% of deaths, we conclude that about 56% of deaths are related to individuals between 25 and 54 years old. This is consistent with findings in the US (references have been cited in the main text) and with our regression results, according to which individuals between 40 and 59 years old tend to consume more prescription opioids than the rest of the population.

Note however that, despite this consistency, these results need to be interpreted with caution, because, from the mortality data, we cannot distinguish between deaths linked to licit or illicit opioids. This means that we cannot infer from this data how many deaths are related to prescription opioids, even though regressions of opioid-related deaths on prescription opioid sales

reveal a positive and significant association between prescription opioid use and opioid deaths. Results from these regressions are reported in Table D1 below. The independent variable is the natural logarithm of sales for all opioid analgesics, while, for the dependent variable, we use levels, rather than logs, since this variable takes on zero value for some departments in some years. In addition, the dependent variable changes across columns of Table D1, depending on which codes are considered. In particular, the first column considers deaths due to accidental poisoning only (codes F11 and X42), the second adds deaths due to autointoxication (codes F11, X42, and X62), the third column includes accidental deaths plus deaths for which the intention is not known (codes F11, X42, and Y12) and the last column considers all deaths. This dependent variable measures the number of deaths per 100000 inhabitants. Finally, each regression includes department and year fixed effects. The coefficient associated with opioid analgesics sales is always positive and significant, indicating that increases in sales of opioid pain relievers increase opioid-related deaths, even though this association is small. This coefficient is similar, in magnitude, across regressions, even though slightly higher and more significant, when we include auto-intoxication cases. This latter result may be an indicator that prescription opioids are employed by individuals with suicidal intentions. This issue has been raised by a few authors in the US (Oquendo et al., 2018), pointing to its relevance for policy purposes.



Sources: CépiDc-Inserim database; authors' calculations.

Figure D2. Opioid-related Deaths by Age Group in 2014

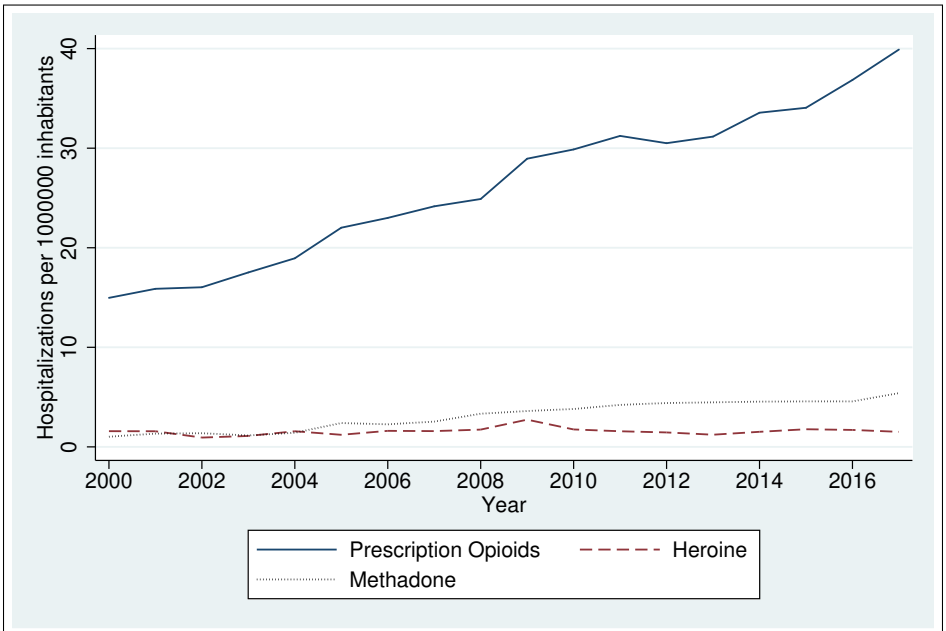
	(1) Deaths F11-X42	(2) Deaths F11-X42-X62	(3) Deaths F11-X42-Y12	(4) Deaths F11-X42-X62-Y12
Log(All)	.106878**	.1307885***	.1048804**	.128791***
	(.0415193)	(.0429159)	(.0418354)	(.0431959)
R^2	.0657136	.0635004	.0656494	.0632717
N	846	846	846	846

Note: Robust standard errors clustered at the department level in parentheses. Each regression includes department and year fixed effects and is weighted by department population.
$^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$.

Table D1. Opioid-related Deaths (Ordinary Least Squares)

D.3 Opioid-related Hospitalizations

In this subsection, we present data on hospitalizations related to intoxications due to opioid use in France. These data are extracted from *ScanSanté* database, realized by the "Agence Technique de l'Information sur l'Hospitalisation" (ATIH) (ScanSanté, 2019). We select data for which the main diagnosis is intoxication due to opioid use, identified by the International ICD-10 system with the codes T400, T401, T402, T403, T404, T406. These codes identify, respectively, intoxications due to opium, heroin, other opioids (codeine, morphine, natural and semisynthetic opioids), methadone, other synthetic opioids (Pethidine and other synthetic opioids, such as Fentanyl) and other and unspecified narcotics.
Figure D4 below depicts the trend in opioid-related hospitalizations between 2000 and 2017, where the y-axis reports the number of hospitalizations per 1000000 inhabitants. In France, opioid-related hospitalizations rose from about 15 to 39.91 per one million population, which is a 166,6% increase over the 2000-2017 period and approximately 7 hospitalizations per day in 2017.



Sources: ScanSanté database; authors' calculations.

Figure D4. Opioid-related Hospitalizations in France between 2000 and 2017

E Robustness Check

In this section, we perform the same analysis as in Subsection 4.1, by exploiting data for the poverty rate when the poverty threshold is set at the 50% (instead of 60%) of the national median income. The purpose of this exercise is two-fold: first, it can serve as a robustness check for the results obtained in Table 3; second, it can provide us with useful insights on the role played by the 'intensity' of poverty in determining opioid use. Results are shown in Table E1.

Interestingly, the estimated coefficients for the poverty rate are larger in magnitude than those reported in Table 3. This holds true both in the OLS and in the 2SLS specification and across different classes of opioid analgesics. Moreover, the coefficients remain significant at the one percent confidence level for all and mild opioids. This means that, as the share of the poorest individuals in a department increases, opioid consumption rises by more and suggests that the higher the intensity of poverty, the larger opioid use. The magnitude of the coefficients associated with the remaining socioeconomic covariates, as well as their statistical significance, are very similar to those in Table 3.

	All Opioids		Mild Opioids		Strong Opioids		
	OLS	IV 2nd Stage	OLS	IV 2nd Stage	OLS	IV 2nd Stage	IV 1st Stage
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Poverty Rate	9.8290***	15.4496***	10.3166***	16.4591***	4.9077	7.9291	
	(3.1619)	(5.6232)	(3.1422)	(5.6717)	(3.5599)	(6.1549)	
Unemployment Rate	-1.9424	-4.1678	-2.2272	-4.6592	.3996	-.7966	.3953***
	(5.0021)	(5.2908)	(4.8840)	(5.1692)	(6.6216)	(6.7991)	(.0990)
Age, 40-59	20.2338**	17.4139**	19.7954**	16.7137*	21.2727*	19.7568*	.0929
	(8.5654)	(8.8759)	(8.3704)	(8.7135)	(11.0958)	(11.4099)	(.1853)
(Only) Basic Education	7.7732*	8.6145**	7.4315	8.3510*	10.6856*	11.1379**	.0591
	(4.5545)	(4.3457)	(4.4810)	(4.2710)	(5.6946)	(5.6102)	(.1017)
Population Density	-.0005***	-.0006***	-.0005***	-.0006***	-.0004*	-.0004*	.0000**
	(.0001)	(.0002)	(.0001)	(.0002)	(.0002)	(.0002)	(.0000)
REFORM							-.0027**
							(.0012)
Doctors Density							-.0000
							(.0000)
Pharmacists Density							.0001**
							(.0001)
GDP (per capita)							5.08e-07
							(3.47e-07)
Gini							.5402***
							(.1387)
R^2	.4248	.4153	.4584	.4472	.1345	.1324	
N	940	940	940	940	940	940	940
F-stat							115.490

Note: Robust standard errors clustered at the department level in parentheses. Each regression includes department and year fixed effects and is weighted by department population. $^{*}p < 0.1$,$^{**}p < 0.05$,$^{***}p < 0.01$.

Table E1. Opioid Consumption with Poverty Threshold at 50% (Two Stage Least Squares)