WORKING PAPERS

N° 1563

September 2024

"Economic Opportunity and Opioid Regulation: the Case of Codeine in France"

Ilaria Natali

Toulouse School of Economics

Economic Opportunity and Opioid Regulation: the Case of Codeine in France

Ilaria Natali*

September 3, 2024

Abstract

This paper empirically assesses the impact of laws restricting access to opioid painkillers and shows how local economic conditions matter for the magnitude of responses to these policies. By using a difference in differences (DiD) approach, I first estimate the causal impact of a new regulation that forbids over-the-counter (OTC) sales of Codeine-containing drugs. I then exploit a triple difference (TD) strategy to evaluate possible heterogeneous responses across French departments. Using *OpenHealth* monthly data on Codeine product sales in 2017 for the 94 departments of Metropolitan France allows me to verify the parallel trend assumption validity. I find that the new law proved effective in reducing Codeine consumption, but departments in economic disadvantage exhibit smaller decreases in consumption following its implementation. Hence, high-poverty departments are more 'regulatory-inelastic'. This shows that demand-side factors can contribute to amplifying or hindering the effect of supply-side interventions. Substitution effect analysis finds an increase in non-opioid analgesic use after the new law in wealthy departments relative to poor departments, but no significant substitution towards the black market. Results suggest that increased barriers to access should move in parallel with additional measures addressing the most deprived local communities.

JEL Codes: I11, I14, I15, I18
Keywords: Drug Regulation, Economic Opportunity, Codeine, France.

*Toulouse School of Economics (TSE), Université de Toulouse I Capitole

I would like to thank Catherine Commaille-Chapus and *OpenHealth* for providing access to their database. I gratefully acknowledge Patrick Legros, Mathias Dewatripont, Paula Gobbi, Mathieu Parenti, Glenn Magerman, Paola Conconi, Georg Kirchsteiger, Pierre Dubois, and Iris Kesternich, as well as all the participants to the ECARES and I3H seminar series and the TSE winter IO workshop for useful comments. I also thank Thomas Demuynck for financial support. This research has benefited from the Funding of the European Research Council under the European Union's Seventh Framework Program (FP7-IDEAS-ERC)/ERC Grant N. 339950, and from the financial support of Baillet-Latour Fund, the Agence Nationale de la Recherche under grant ANR-17-EURE-0010 (Investissements d'Avenir program), and the "PSPC" call for projects operated on behalf of the French government by Bpifrance as part of the "investments for the future" program (PIA) ARPEGE. All errors are mine.

1 Introduction

When essential medicines for palliative care have the potential of being abused, implementing effective health policies that help monitor access to these drugs can prevent harm and save many lives. This paper empirically assesses the impact of restricting access to opioid pain relievers and shows how local economic conditions matter for the magnitude of responses to these policies. These are important themes to be investigated because this type of analysis can guide decision-makers on which supply-side policies are effective and to what extent. Moreover, it provides evidence on which geographical areas are more inelastic to these regulations and, hence, where additional interventions and support services should be addressed.

The abuse and misuse of opioid painkillers have caused the worst drug epidemic in US history, with a death toll as large as 130 lives lost per day (Department of Health and Human Services, 2020) and a total economic burden of 78.5 billion dollars per year (National Institute on Drug Abuse, 2020).[1] Although this phenomenon has not reached the extent of an epidemic (yet), opioid analgesic use has undoubtedly risen in Europe over the last two decades (van Amsterdam and van den Brink, 2015). In France, recent increases in consumption of some opioid pain-killers have raised serious concerns. An article published in the popular French newspaper *Le Monde* in October 2018 claims that opioid addiction is now the first cause of death for an overdose in France[2] while some studies (Orriols et al., 2009 and Casati et al., 2012) provide evidence of abuse and misuse of some opioid analgesics among French patients. The French authorities have first responded by forbidding over-the-counter (OTC) sales of Codeine and, more recently, by shortening the duration of Tramadol prescriptions from 12 to 3 months (Agence National de Sécurité du Médicament et des Produits de Santé, 2020).[3] The former measure, in particular, was introduced in July 2017[4] and changed the regulatory regime for a group of Codeine products still available OTC (and available under prescription only since then). The remaining Codeine products have always been prescription-only medicines.

In the growing literature on the US opioid epidemic, a few empirical studies evaluate the impact of supply-side interventions aimed at limiting patients' access to opioid pain-killers. However, scant attention has been directed towards understanding the effect of their interaction with demand-side factors, such as local economic prosperity. Hence, the contribution of this paper is

[1] It would be the most important public health crisis if one abstracts from the novel COVID-19 pandemic. Interestingly, some observers have pointed out that the spread of the new pandemic may exacerbate the effects of the opioid epidemic due to widening social, economic and health inequalities (Haley et al., 2020).

[2] 'L'addiction aux opiacés, première cause de mort par overdose en France', *Le Monde* (15th October 2018). For additional examples from regular newspapers, the reader can refer to 'La surconsommation d'antalgiques opioïdes alarme les experts' from *Le Figaro* (9th August, 2018) and 'Crise des opioïdes: la France aussi' from *Le Monde* (17th October, 2018).

[3] Appendix Figure A1 depicts consumption trends for Codeine and Tramadol over a ten-year period. Codeine consumption rose by 45% between 2008 and 2017, while Tramadol sales increased by 22% over the same period. These are the most commonly administered opioids in France and, even though the WHO classifies them as mild opioids, the addiction risks related to their use remain serious.

[4] Arrêté du 12 juillet 2017 portant modification des exonérations à la réglementation des substances vénéneuses.

two-fold. First, I evaluate the impact of forbidding OTC sales of Codeine in France. I do this by using a difference in differences (DiD) approach that allows to compare before-after changes in consumption across the two groups of Codeine drugs (the 'newly regulated' versus the 'always regulated' ones). I find that the new law more than halved consumption for treated products. To the best of my knowledge, this type of analysis has never been performed so far for any European country, although some researchers have raised concerns regarding the availability of Codeine OTC in some European countries (Foley et al., 2015). Second, I investigate how the introduction of the law interacted with the local economic environment. I do this by exploiting a triple difference (TP) strategy, which allows me to compare the effect of the regulatory change across French departments[5] and, hence, evaluate the existence of heterogeneous treatment effects. Throughout the paper, I refer to this as the 'regulatory elasticity' of demand. I focus on the local poverty rate as a proxy for the department's economic prospect since prior research using French data has shown a positive and significant link between the department poverty rate and opioid analgesic use (Natali et al., 2023).[6] I find that departments in economic hardship are more regulatory inelastic, and the policy effect behaves as a decreasing function of the poverty rate. This is the most novel contribution of the paper and complements the literature on the US opioid crisis that usually studies the effects of demand and supply-side factors in isolation. I am not aware of any study evaluating how the imposition of a law at the national level may generate different responses across geographical areas, depending on the local economic prosperity. It is worth noticing, however, that the French context is different from the US one. Indeed, in the US, prescription opioid misuse caused the worst drug epidemic in the history of the country, and this phenomenon was mainly driven by the widespread abuse and diversion of strong opioids, such as Oxycodone and Fentanyl. In France, the abuse of opioid analgesics remains (at least so far) less common than in the US. Moreover, this paper studies consumption of a mild opioid, such as Codeine. As I will show, this has important implications in the analysis of substitution effects, and, consequently, for policy recommendations.

A comprehensive analysis of the policy under study requires, indeed, an evaluation of possible substitution effects towards alternative substances. From a policy perspective, this is important because it allows to identify and quantify the intended and adverse consequences of the regulatory change. Moreover, this permits a more accurate evaluation of the channels driving the results in the main analysis. Hence, I perform an evaluation of possible substitution effects towards non-opioid analgesics and the black market. I find that part of the demand for Codeine products

[5]Continental (or Metropolitan) France is divided into 94 districts, called 'departments'. They represent the second smallest administrative entities in which the French territory is divided, between the communes and the regions. The French territory additionally includes two departments in Corsica, plus five overseas departments (Guadeloupe, Martinique, Guyane, La Réunion, and Mayotte). For the analysis in this paper, I will focus on the 94 departments composing Metropolitan France.

[6]In the US opioid crisis literature, unemployment is often used as a proxy for economic disadvantage. However, Natali et al. (2023) do not find a significant association between the unemployment rate and opioid use in France. Since the French system provides monetary support to unemployed individuals, unemployment does not necessarily represent a good proxy of economic disruption in France and the type of despair mentioned by Case and Deaton (2017) is more likely to be a poor individual than a (temporary) unemployed one.

switches to non-opioid pain relievers after the regulatory shock and this effect is more important in wealthier that in poorer departments. I do not identify any substitution effect towards the black market, instead. This result seems reasonable, since, as mentioned, the prevalence of opioid analgesic abuse in France is lower than in the US, and the substance under analysis in this paper, Codeine, is a mild opioid which may not find close substitutes on the black market.

Finally, the health economic literature has highlighted the importance of taking into account the addictive nature of products subject to regulatory changes when evaluating their impact. This is important for policy purposes because, if consumption in a given time period is correlated to consumption a subsequent period, the policy may have a cumulative effect over time and it is possible to estimate its long-run impact. For this reason, I conclude the analysis with an evaluation of possible dynamic effects. I find that, indeed, Codeine consumption is positively correlated across time and I calculate the effect of the policy on consumption, as well as the regulatory elasticity of demand in the long-run.

The analysis in this paper is made possible by using the *OpenHealth* database that enables access to high-resolution, high-frequency retail sales data for the universe of opioid active ingredients available on the French market. The structure of the data provided by *OpenHealth* allows me to estimate the causal impact of imposing a stricter regulation on Codeine consumption and show how different French departments react differently to such a regulatory shock, depending on their economic characteristics. Indeed, the granularity of this data allows controlling for a large pool of potential confounding factors. Moreover, the availability of longitudinal data allows checking the parallel trend assumption validity, essential for identifying causal effects in DiD and TD models. For the evaluation of substitution effects, I use *OpenHealth* data on non-opioid analgesic sales, together with data on drug-related crimes, provided by the Ministry of Internal Affairs, and on emergency department (ED) visits, provided by Santé Publique France.

The rest of the paper is organized as follows. In Section 2, I offer an overview of the existing literature on the opioid epidemic, the economic determinants of health outcomes and healthcare consumption, and the difference-in-differences design. I provide additional information on the law imposing Codeine re-scheduling in Section 3 while, in Section 4, I identify a few channels through which economic opportunity might generate heterogeneous responses to a national regulatory shock. Details on the data sources and summary statistics are provided in Section 5. In Section 6, I use a Difference-in-Difference strategy to find out whether the new law caused a drop in Codeine sales and to measure its magnitude whereas, in Section 7, I exploit a Triple Difference approach that permits a comparison of the magnitude of treatment effects across two department groups (poor versus wealthy departments). The analysis of substitution effects is contained in Section 8, while the analysis of dynamic effects is contained in Section 9. In Section 10, I discuss the results, and Section 11 concludes.

2 Literature Review

2.1 The Opioid Crisis Literature

In the existing literature on the US opioid crisis, there is a large consent on the importance of identifying the driving causes of the epidemic for policy purposes. Previous research efforts on this topic can be roughly divided between those papers focusing on the demand-side determinants of opioid use and those stressing, instead, the importance of supply-side factors.

Those studies focusing on the demand-side determinants have mostly framed their analysis in terms of the so-called 'deaths of despair'. Case and Deaton (2017) coined this expression to conceptualize the idea that economic and social impairment induce individuals to use more licit and illicit substances, including pharmaceutical opioids, with adverse consequences on health and mortality. Along these lines, Hollingsworth et al. (2017) focus on the impact of macroeconomic conditions and find a positive relationship between the unemployment rate and opioid abuse. Likewise, Ghertner and Groves (2018) show that both poverty and unemployment are associated with increases in opioid prescriptions and sales, as well as opioid-related hospitalizations and deaths. Venkataramani et al. (2019) find automotive assembly plant closures to be responsible for increased opioid overdose mortality. In France, Natali et al. (2023) study the association between the local poverty rate and opioid retail sales and find a positive and significant link between the two. Nordmann et al. (2013), instead, analyze geographical variations in the prevalence of doctor-shopping by focusing on three French regions.[7] They observe that this practice is more common in the region characterized by the most unfavorable socioeconomic environment.

Other papers cast doubt on the validity of the 'deaths of despair' hypothesis and suggest that the causes of the US opioid crisis should be identified in supply-side factors. For example, Currie and Schwandt (2020) argue that the relationship between opioid-related harm and labor market opportunities is too weak to justify the magnitude of the US opioid epidemic. Similarly, Ruhm (2018) states that the epidemic's triggering factors cannot be found in eroding economic opportunity. These authors conclude that specific policies and characteristics of the US healthcare system must rather stand at the roots of the crisis and suggest that regulatory levers aimed at affecting the public health environment (such as prescription drugs monitoring programs, development of abuse-deterrent drugs, and improved education for healthcare professionals) would more effectively tackle with the crisis. Some researchers have explored these channels. For instance, Dave et al. (2019) and Buchmueller and Carey (2017) investigate the impact of participating in Prescription Drug Monitoring Programs[8] on measures of prescription opioid abuse. Both papers find that mandatory participation in these programs is significantly associated with reductions in opioid misuse. Alpert et al. (2018) study the consequences of introducing the abuse-deterrent version of OxyContin in 2010. The authors show that OxyContin's

[7] Doctor-shopping is defined as the practice of visiting multiple physicians to obtain multiple prescriptions illicitly.

[8] Prescription Drug Monitoring Programs (PDMP) record a patient's opioid prescribing history. Some states in the US imposed compulsory participation in these programs as a response to the epidemic.

reformulation caused a reduction in the rates of misuse of this drug. However, this also led to an increase in heroin deaths due to substitution effects. Schnell and Currie (2017) consider the role of physicians' education and find that physicians who attended the best-ranked medical schools prescribe significantly fewer opioids. As shown in Alpert et al. (2019), stricter regulations on prescribing rules may also make a difference. The authors show that US states where triplicate prescription forms (comparable to the French 'ordonnance securisée') are required exhibit fewer opioid prescriptions because this regulation discourages pharmaceutical companies from marketing aggressively. Finally, McMichael et al. (2020) show that (recreational and medical) cannabis access laws contribute to reducing opioid prescriptions.

To sum up, prior literature on the opioid epidemic seems to be rather polarized between supporting the validity of the 'deaths of despair' hypothesis and suggesting, instead, that regulations and characteristics of the health system are those factors that actually matter. Perhaps strikingly, none of the existing papers considers the possibility that demand and supply-side factors may interact with each other, and their effects may be intertwined. To the best of my knowledge, Finkelstein et al. (2019) is the only paper recognizing a role for demand and supply determinants and measuring the relative importance of the former versus the latter. They exploit cross-county migration to disentangle the roles of person-specific (e.g., employment status and income) and place-specific factors (e.g., the presence of policies such as prescription monitoring programs) and conclude that all the determinants highlighted by past research may play an important role. Despite its importance, this work does not identify which specific factors determine opioid use and does not spell out the effects of their interactions.

2.2 Income Effects of Health Inequalities and Healthcare Consumption

This paper is also related to a vast literature on the relationship between poverty, income, income inequality, and health outcomes. In this literature, there is a significant agreement on the existence of a positive relationship between poverty and poor health. Mackenbach et al. (2008) perform a study comparing health inequalities across 22 European countries by considering data on mortality, self-reported health, age, sex, and socioeconomic status. They show that, in each selected country, mortality rates are more prominent among the least educated and those belonging to lower occupational classes. Worse self-reported health is also more prevalent in lower socioeconomic groups in all countries. In France, Heritage (2009) studies the relationship between socioeconomic status and self-reported health. By controlling for age and gender, she shows that self-reported health is positively associated with income, education, and professional status. Benzeval and Judge (2001) offer a brief review of 16 longitudinal studies on this topic. These works use various techniques to control for reverse causality, also called, in this specific context, *health selection*, referring to the idea that poor health limits the individual's ability to work, thus exerting a negative impact on future earnings and income. Results suggest that the relationship running from poverty to health has to be considered causal. Finally, Pickett and Wilkinson (2015) offer a review of the literature on income inequality and health. They find strong evidence that poor health outcomes are more prevalent in more unequal communities and

argue that this evidence is convincing enough to conclude that the link between income inequality and health is causal.

Despite these findings, the relationship between poverty, healthcare services utilization, and drug consumption is controversial. A recent OECD study (Devaux and de Looper, 2012) examines healthcare utilization (as proxied by doctors' visits) in 19 countries in 2008-2009. By adjusting for healthcare needs, they find that, in France, individuals on a low income are less likely to visit a GP, but they consult more frequently when they do. Instead, income-related inequalities are much larger for specialist visits: the well-off are much more likely to visit a specialist and do so more frequently. France is among the most inequitable countries in this respect. Studies analyzing socioeconomic inequalities in medicine consumption also provide mixed evidence. In the Austrian context, Mayer and Österle (2014) find that wealthier individuals are more likely to self-medicate with non-prescribed medicines while the worse-off are more likely to consume prescribed medicines. They conclude that these findings align with institutional incentives since non-prescribed drugs must be fully paid out of pocket. A study on a representative sample of the Danish adult population (Nielsen et al., 2003) also finds a positive association between low income and prescription medicine use after adjusting for health status. However, they do not find an association between income and OTC drug consumption. Finally, a study comparing prescription and non-prescription medicine use in eight Central and Eastern European countries (Vogler et al., 2015) finds a positive association between income and non-prescription medicine consumption in seven of the eight studied countries and between income and prescribed medicines use in three countries.

2.3 Difference-in-Differences and Event Studies

During the last few years, a growing body of literature has focused on difference-in-differences (DiD) approaches in contexts that deviate from the standard two-countries two-dates setting. Results from most of these studies do not apply to the current paper, but are worth mentioning here. Several recent papers, for example, study the properties of the standard difference-in-differences estimator in a setting with panel data and staggered treatment adoption, and propose interpretations of this estimator as a weighted average of causal effects. Among these are the papers by Athey and imbens (2022), Goodman-Bacon (2021), Chaisemartin and d'Haultfœuille (2020), Callaway and Sant'Anna (2021). Ferman and Pinto (2019), instead, propose a new method to perform DiD estimation when there are few treated and many control groups as well as heteroskedasticity due to different group sizes, while Chaisemartin and d'Haultfœuille (2018) derive two estimands to be used in case of a fuzzy DiD design, when the treatment rate simply increases by more in the treatment than in the control group. Butts (2021) considers DiD estimation when the treatment and control groups are formed by different geographical units and, hence, spatial spillovers may occur. He proposes a methodology that allows to remove the bias in the DiD estimator due to the presence of spillovers, as well as estimate the magnitude of the spillover effect. Arkhangelsky et al. (2021) elaborate a new synthetic DiD estimator and study its properties and performance. Finally, Roth and Sant'Anna (2021) investigate whether

the parallel-trend assumption is sensitive to alternative specifications of the functional form for the outcome variable and provide conditions under which the common trend assumption holds for all strictly monotonic transformations of the dependent variable.

3 Background

The vast majority of papers studying the opioid epidemic focuses on the US. The French healthcare and regulatory system, however, is profoundly different from its US counterpart. The goal of the following subsection is summarizing the reasons and implications of the July 2017 regulatory shift, while Appendix B describes in more detail the drug scheduling and healthcare system in France.

3.1 Codeine Re-Scheduling in France

In France, medicines are classified into different lists (i.e., *Médicaménts non-listés*, *Liste 1*, *Liste 2*, and *Stupefiants*), according to the risks linked to their use and the severity of their side effects. This implies that the type of regulation applied to each medicinal product is a function of the list it belongs to and ranges from a lenient regulation for *Médicaménts non-listés* to a much stricter regulation for *Stupefiants*. For example, products classified as *Médicaménts non-listés* are available over-the-counter (OTC) and can be purchased on the Internet while products belonging to the class *Stupefiants* need a special prescription form, called 'ordonnance securisée'.

In July 2017, the French Ministry of Health decided to annex a group of Codeine products to *Liste 1*[9] so that the new regulation now bans their OTC sales and makes these pain relievers available under prescription only. The remaining Codeine products were already scheduled as *Liste 1* drugs. This decision was made via a decree signed on the 12th of the month and was the result of alarming increases in consumption and diversion of OTC Codeine products. Already in 2013, a study by Roussin et al. (2013) raised concerns regarding patients' misuse and dependence on non-prescription Codeine analgesics (notably, Codeine in combination with Paracetamol). The authors found misuse of these drugs in 6.8% and dependence in 17.8% of the surveyed patients, while 19.5% of them used non-prescription Codeine products daily in the previous six months. Moreover, the French Authority for the Safety of Medicines and Health Products (Agence National de Sécurité du Médicament et des Produit de Santé, ANSM) reported a considerable surge in purchases of OTC codeine drugs since 2013. This trend led, in 2017, to five severe intoxication cases related to Codeine, among which two deaths, and to the decision of forbidding Codeine OTC availability. Although this change in Codeine regulation was the result of a rising number of episodes of abuse and diversion, I argue that the policy shift was exogenous from the patients' point of view. Indeed, the decree was applied with immediate effect, not previously announced and the decision was exclusively made by the Ministry of Health. Figure 4 and 5 below seem to corroborate the assumption that patients could not anticipate the policy

[9] Arrêté du 12 juillet 2017 portant modification des exonérations à la réglementation des substances vénéneuses.

change since the application of the new law was simultaneous with an immediate and significant drop in consumption for OTC Codeine products.

Appendix Tables B1 and B2 provide the list of Codeine products under study, together with the pharmaceutical companies' names, the active ingredients contained in each product, the ATC classification code,[10] and the available dosages. Products in Table B1 make up the treatment group since they were subject to the regulatory change, while products in Table B2 represent the comparison group as they have always belonged to Liste 1.

4 Potential Channels and Testable Hypotheses

While it may seem intuitive that restricting access to self-medication would cause a drop in consumption, whether the regulatory elasticity of demand varies across geographical areas is an inherently empirical question whose answer is non-trivial. In light of the existing literature, I identify here a few channels through which economic opportunity might generate heterogeneous treatment effects and formulate three testable hypotheses as suggested by these channels.

First, empirical evidence in the US and Europe shows a positive link between opioid analgesic consumption and poor socioeconomic conditions, which have been explained in the framework of the so-called 'deaths of despair'. Moreover, the literature on the socioeconomic determinants of health inequalities has largely documented that the distribution of mortality and health problems is significantly skewed towards lower socioeconomic groups. As a consequence, we expect greater use of healthcare products and services among patients in disadvantaged conditions. One hypothesis is that introducing a new regulation that limits access to opioids would be less effective in departments characterized by a poor economic status than in those characterized by a prosperous economic activity. Individuals in deprived conditions would seek these drugs, although the new law makes access more difficult, and the effect of the regulatory shock would be inducing these patients to visit a doctor more frequently to obtain Codeine products.[11] Due to the addictive nature of these drugs, part of the demand in poorer departments could also be re-addressed towards the black market, while patients in wealthier departments are likely to switch to more easily accessible (OTC) pain-killers, such as Paracetamol or Ibuprofen. Therefore,

Hypothesis 1. Poorer departments are more 'regulatory inelastic'. In these departments, part of the demand switches to the black market, while wealthier patients switch to alternative OTC products.

[10] The ATC (Anatomical Therapeutic Chemical) classification is a drug classification system established by the WHO. It codes each active substance (and combination of active substances) according to their therapeutic, pharmacological and chemical properties and depending on the organ or system of the human body that they target. Further information on this is given in Appendix B.

[11] It is, indeed, not clear a priori the role of the 'opportunity cost of visiting a doctor'. On the one hand, seeing a doctor entails a loss of time that the patient may have used to work. On the other hand, however, not visiting a doctor is also costly since this entails suffering for the patient as well as a loss of productivity.

At the same time, a strand of the literature focusing on the socioeconomic determinants of prescribed and non-prescribed drugs finds that OTC medicine use is positively associated with income while the worse-off are more likely to consume prescribed drugs. If this is the case, one would expect more consumption of these drugs by the well-off before the regulatory shift and a larger drop in consumption in wealthier departments once these products become prescription-only medicines since wealthier patients would switch to alternative OTC drugs. Once again,

Hypothesis 2. Poorer departments are more 'regulatory inelastic'. Wealthier patients switch to alternative OTC products.

On the other hand, some studies suggest that, in France, individuals on a low income are less likely to consult a GP and much less likely to visit a specialist compared to wealthier patients. Furthermore, the poorest are more likely to lack complementary health insurance coverage and report larger forgone care levels. As a result, poorer departments should be more sensitive to introducing a regulation that forbids sales of Codeine OTC and requires patients to visit a doctor to obtain these medicines. One would then expect poorer departments to feature a larger drop in consumption and a larger increase in sales of alternative non-opioid analgesics following the new law.

Hypothesis 3. Poorer departments are more 'regulatory elastic'. Part of the demand in these departments switches to alternative OTC products.

5 Data and Summary Statistics

The analyses in this paper exploit several types of data: (i) data on poverty rate and population, (ii) retail sales data for Codeine products, (iii) retail sales data for non-opioid analgesics, (iv) data on drug-related crimes, (v) emergency department (ED) data. The purpose of the following subsections is describing in detail the data structure and sources and providing summary statistics.

5.1 Poverty Rate and Population

5.1.1 Data sources and methodology

Data for the department population and poverty rate in 2017 are downloaded from the Institut National de la Statistique et des études économiques (INSEE) website.

The poverty rate is defined by the Organization for Economic Co-operation and Development (OECD) as the share of individuals living below the poverty line, usually set at 60% of the national median income. The INSEE analogously defines the poverty rate. [12] The portion of individuals below the poverty line is computed based on the disposable income per consumption unit (CU), that is, the disposable income per 'adult equivalent'. This is calculated by dividing the household's disposable income by the number of consumption units composing it. All persons attached to the same tax household have, therefore, the same disposable income per CU. The number of consumption units in a household is, in turn, calculated as follows: 1 consumption unit for the first adult in the household; 0.5 CU for other people aged 14 or over; 0.3 CU for children under 14 years old. For example, a couple without children counts for 1.5 CU while a couple with two children under 14 counts for 2.1 CU. This computation allows taking into account the economies of scale generated when living together.

5.1.2 Summary Statistics

Table 1 displays detailed summary statistics for the poverty rate. On average, 14% of the department population lived at or below the poverty line in 2017. There is substantial variation in poverty across departments, going from a minimum of 9% to a maximum of 28%.[13] For the Triple Difference estimation of Section 7, departments are classified as rich or poor based on the average department poverty rate, that is, they are considered poor if their poverty rate is above the average (14.34%), they are considered rich otherwise. Figure 1 maps the 94 departments composing Metropolitan France and distinguishes between rich and poor areas according to this definition.

The Triple Difference analysis is further developed in Subsection 7.4 by focusing exclusively on 'extremely' poor and 'extremely' rich departments, defined as those departments whose poverty

[12] For the computation of the poverty rate in France, the national median income refers to the median income in Metropolitan France.

[13] This substantial variation is important because it facilitates the analysis in the TD framework.

Table 1. Summary Statistics - Poverty Rate in Detail

Percentiles		Others	
10%	11.2	Mean	14.34
25%	12.3	Std. dev.	2.97
50%	14.25	Min	9.1
75%	15.4	Max	27.9
90%	18.5	Obs.	30,926

Note: The table reports detailed summary statistics for the poverty rate. The first column shows the percentiles of the distribution. The second column shows other summary statistics. Source: INSEE

rate falls in the first and last quartile of the distribution. Hence, this analysis considers departments whose poverty rate is below 12.3% and above 15.4%. This is done for two reasons. First, to show that results are not sensitive to the choice of the average poverty rate as a threshold. Second, to investigate whether the treatment effect varies with the intensity of poverty.

5.2 Codeine-product Sales

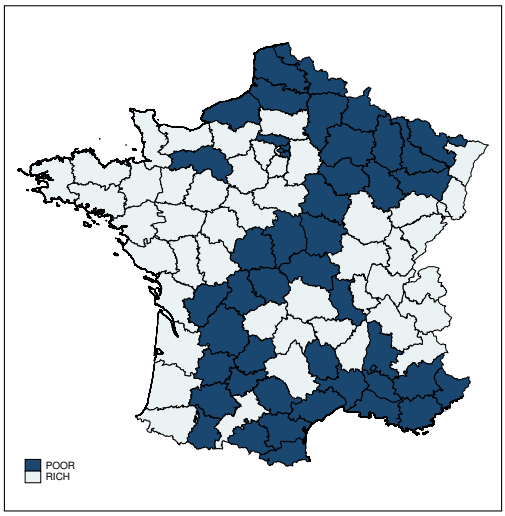
5.2.1 Data sources and methodology

Retail sales data for Codeine products are extracted from the *OpenHealth* database. This database contains information on opioid analgesic sales in France, both in terms of turnover and consumer units sold. Consumer units indicate the number of packs sold for each product while turnover is expressed in euros (RRP, including VAT). I exploit monthly data for the year 2017 by product and at the department level. Since the new law entered into force in July 2017, this allows having six pre-treatment and five post-treatment periods. These data refer to the 94 French departments composing 'Metropolitan France'.[14]

For each product, the database indicates the pharmaceutical company's name, the number of packs sold, the number of pills in each pack, the quantity of the active ingredient (in milligrams) contained in each pill, and the turnover generated by its sales. With this information, I compute

[14]The *OpenHealth* database provides data on sales by community pharmacies only (retail sales), thus neglecting hospital usage (non-retail). In addition, Corse and overseas departments are not included in the database.

Figure 1. Poor versus Rich Departments



Note: Rich and poor department classification based on the average department poverty rate. Source: INSEE.

four alternative measures of consumption and sales for each Codeine product in each department: the number of milligrams consumed per 1000 inhabitants, the number of DDDs consumed per 1000 inhabitants, the number of boxes sold per 1000 inhabitants, and the turnover, in euros, per 1000 inhabitants. These four measures of sales will represent the dependent variables in the analyses of Section 6 and 7.[15]

DDD means 'Defined Daily Dose' and is defined by the World Health Organization (WHO) as *'The assumed average maintenance dose per day for a drug used for its main indication in adults'*, that is the amount of an active ingredient that should be administered to an adult patient with average weight (i.e., 70 kilograms) daily for a drug's main indication.
Drug usage in terms of the number of DDDs is computed by exploiting the following formula:

$$DrugUsage = \frac{\#boxes * \#pills/box * mg/pill * 1000}{DDD * \#ofinhabitants}$$

The official DDDs employed to compute drug usage are provided on the WHO website.[16]

Appendix Tables B1 and B2 provide the complete list of Codeine products under study, together with the pharmaceutical companies' names, the active ingredients contained in each product, the ATC classification code, and the available dosages. For both the DiD estimation of Section 6 and the TD estimation of Section 7, the set of products listed in Table B1 make up

[15]This allows me to check the robustness of results across alternative measures of sales.

[16]Codeine is only available in combination on the French market. When the DDD for a particular Codeine combination was not available on this website, I contacted the WHO and applied the DDD that they suggested.

the treatment group since these are the products subject to the regulatory change. Instead, the set of products listed in Table B2 constitute the comparison group as they have always belonged to Liste 1. I only focus on products for which the indication is pain treatment.

5.2.2 Summary Statistics

Table 2 reports summary statistics, both at an aggregate level and for each department and product group. These figures refer to the period before the regulatory change (January 2017 - June 2017). The final dataset is at the product-department-month level. Since I have information on sales for 28 products (14 products forming the treatment group and the remaining 14 forming the comparison group) in 94 French departments and for a period of 12 months, this would yield a total of 31,584 observations for the whole sample period. However, sales for one of these products (Algicalm) first appear in June 2017, while sales for Gaosedal are missing as of November 2017. This leaves us with 30,926 observations in total and 15,322 observations for the first six months of 2017. All figures in the table are expressed in terms of sales per 1000 inhabitants.

Across products and departments, in the first half of 2017, the average monthly consumption of Codeine-containing products was equal to 1104 MGs per 1000 inhabitants, which is equivalent to around 12 DDDs. About two boxes were sold, generating an average monthly turnover of approximately 7 euros for each product in each department. Consumption for products in the comparison group is approximately three times larger than for products in the treatment group, both in poorer and in wealthier departments. More interestigly, poorer departments consume more Codeine pain-killers on average, which is true both for products in treatment and in the comparison group. This is in line with prior research in the US and in France, showing that individuals in disadvantaged economic conditions tend to consume more opioid analgesics.

5.3 Non-opioid Analgesic Sales

5.3.1 Data sources and methodology

To evaluate the existence of substitution effects towards non-opioid analgesics, I exploit retail sales data on non-opioid pain-killers provided by *OpenHealth*. The structure of the data is the same as for Codeine-product sales. For the analysis of Section 8, I use monthly data on the number of boxes sold in 2017 for each product in each department.

5.3.2 Summary Statistics

Table 3 reports summary statistics for the period preceding the regulatory shift, both at an aggregate level and for each department group. As before, the final dataset is at the product-department-month level and all figures in the table are expressed in terms of sales per 1000 inhabitants.

Across products and departments, the average monthly consumption is 4.7 boxes per 1000 inhabitants. As for Codeine-containing products, consumption is larger in poorer than in wealth-

Table 2. Summary Statistics - Codeine-product Sales (Jan 2017 - June 2017)

Variable	No. of Obs.	Mean	Std. dev.
Aggregated			
MGs	15,322	1103.7	2089.538
DDDs	15,322	11.653	22.329
No. Boxes	15,322	2.446	4.446
Turnover	15,322	7.129	12.293
Treatment Products in Poor Departments			
MGs	3,634	573.917	1016.829
DDDs	3,634	6.935	12.622
No. Boxes	3,634	1.667	3.093
Turnover	3,634	5.867	10.408
Treatment Products in Rich Departments			
MGs	3,792	542.876	962.182
DDDs	3,792	6.560	11.944
No. Boxes	3,792	1.577	2.927
Turnover	3,792	5.549	9.850
Control Products in Poor Departments			
MGs	3,864	1662.665	2719.772
DDDs	3,864	16.731	28.723
No. Boxes	3,864	3.313	5.494
Turnover	3,864	8.708	14.274
Control Products in Rich Departments			
MGs.	4,032	1572.954	2575.822
DDDs	4,032	15.828	27.203
No. Boxes	4,032	3.135	5.203
Turnover	4,032	8.238	13.519

Note: No of observations, mean and SD for each outcome variable. The first panel reports aggregate summary statistics. The last four panels display summary statistics for for each product and department group. Source: OpenHealth.

Table 3. Summary Statistics - Non-opioid Analgesic Sales (Jan 2017 - June 2017)

Variable	No. of Obs.	Mean	Std. dev.
Aggregated			
No. Boxes	92,778	4.724	18.930
Poor Departments			
No. Boxes	45,402	4.855	19.436
Rich Departments			
No. Boxes	47,376	4.597	18.431

Note: No of observations, mean and SD for the outcome variable. The first panel reports aggregate summary statistics. The last two panels display summary statistics for each department group. Source: OpenHealth.

ier departments. Figure 9 in Section 8 offers a graphical representation of consumption trends in rich and poor departments.

5.4 Drug-related Crimes

5.4.1 Data sources and methodology

To evaluate substitution effects towards the black market, I first exploit drug-related crime data. Data on the prevalence of crime in France are released by the Ministry of Internal Affairs ('Ministère de l'Intérieur') and made publicly available at `https://www.data.gouv.fr`. This data provide information on the number of crimes reported by both the police and gendarmerie. Crimes are classified into 107 different categories. I focus on three types of drug-related crimes: traffic and sale (without use) of narcotics, use and sale of narcotics, use of narcotics. I consider monthly figures at the department level in 2017.

5.4.2 Summary Statistics

Table 4 reports summary statistics for the first half of 2017, both at an aggregate level and for each department group. The final dataset is at the department-month level which yields a total of 1,128 observations (564 for the first six months). All figures in the table are expressed in terms of number of crimes per 100,000 inhabitants. During the first half of 2017, 20.4 crimes per 100,000 inhabitants were related to drug use, 2,8 to use and sale and 0.9 to traffic and sale. These are monthly averages across departments. Crimes are more prevalent in poor than in rich

departments for each type of drug-related crimes. Figure 11 in Section 8 depicts trends in the number of crimes for rich and poor departments.

Table 4. Summary Statistics - Drug-related Crimes (Jan 2017 - June 2017)

Variable	No. of Obs.	Mean	Std. dev.
Aggregated			
Drug Usage	564	20.409	10.424
Drug Sales	564	2.773	2.243
Drug Traffic	564	0.864	1.037
Poor Departments			
Drug Usage	276	21.497	10.617
Drug Sales	276	2.819	2.326
Drug Traffic	276	1.029	1.340
Rich Departments			
Drug Usage	288	19.366	10.146
Drug Sales	288	2.729	2.163
Drug Traffic	288	0.705	0.581

Note: No of observations, mean and SD for each outcome variable. The first panel reports aggregate summary statistics. The remaining two panels display summary statistics for each department group. Source: `https://www.data.gouv.fr`.

5.5 Emergency Department (ED) Visits

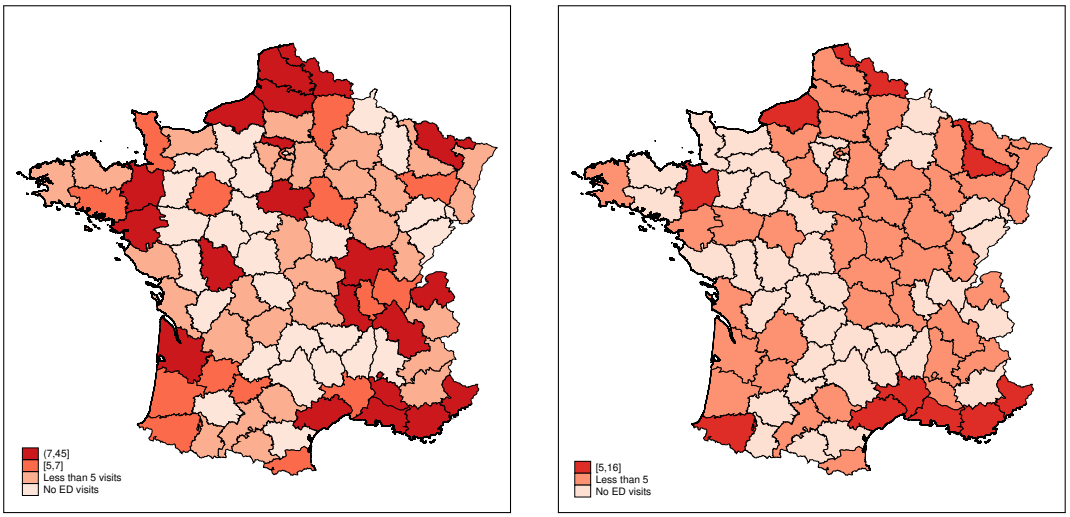
5.5.1 Data sources and methodology

The analysis of substitution effects is complemented by using emergency department (ED) data provided by Santé Publique France and collected by hospitals joining the OSCOUR network.

In France, ED data collection is based on the extraction of anonymized information from the patient's computerized medical file, created during his/her visit to the emergency room. These data are daily transmitted from the emergency service to the OSCOUR network, directly or through regional servers. The number of emergency units joining the OSCOUR network grew from 23 in 2004 to 695 in 2018,[17] thus covering 93% of all emergency visits in France. Emergency units now report 54,000 passages per day on average.

[17]There were 682 in 2017.

Figure 2. ED Visits (first semester 2017)



(a). ED visits in group T40.2 (b). ED visits in group T40.0-1-3

Note: Emergency department (ED) visits for the first semester of 2017. Sources: Santé Publique France, OSCOUR network.

To identify visits related to opioid use, I use data related to all emergency department visits for which the primary or associated diagnosis has one of the following ICD-10 codes: T40.0 (opium), T40.1 (heroin), T40.2 (other opioids, codeine or morphine), T40.3 (methadone). In particular, I use data for the group T40.2 as a proxy for Codeine-related intoxications and evaluate whether the law had a different impact on Codeine-related ED visits in poor and rich departments. Aggregated data for the groups T40.0, T40.1 and T40.3 are, instead, used for the evaluation of substitution effects towards the black market.

Unfortunately, these data are left-truncated.[18]. In order to minimize the loss of information related to this truncation, I use department-level data by semester and for the years 2016, 2017 and 2018. Notice, however, that some degree of left-truncation remains.

The two maps of Figure 2 summarize the number of ED visits related to Codeine (on the left) and to Opium, Heroine and Methadone (on the right) in each department. ED visits related to Codeine tend to be more prevalent than those related to Opium, Heroine or Methadone. Moreover, departments in the north and south-east of the country are among those with the largest prevalence of ED visits, especially as referred to Codeine. It is worth noticing that they are also among the poorest in the country.

[18]For each ICD-10 code, I observe the exact number of ED visits if this is either zero or bigger than four. When this number is between 1 and 4, included, the dataset mentions 'less than 5'.

6 The Impact of the New Law

We now turn to the econometric analysis of the impact of the law issued in July 2017 by the French Ministry of Health. I exploit a difference-in-differences (DiD) approach that permits a before-after comparison of consumption levels across two groups of Codeine pain-killers. Throughout the paper, those products experiencing the regulatory shift represent the treatment group, while those products that always belonged to Liste 1 represent the comparison group. Moreover, the first six months of 2017 represent the 'before' period, while the last six months represent the 'after' period.

6.1 Parallel Trend Assumption

The central identifying assumption for any difference-in-differences (DiD) specification is the 'parallel trend assumption'. In this context, it requires that consumption trends across the two product groups would evolve on parallel paths in the absence of the policy shock. The validity of this assumption cannot be directly verified. However, the availability of longitudinal data allows to compare differences in consumption between the two product groups in each period before the regulatory shift and test the non-existence of differential trends.[19]

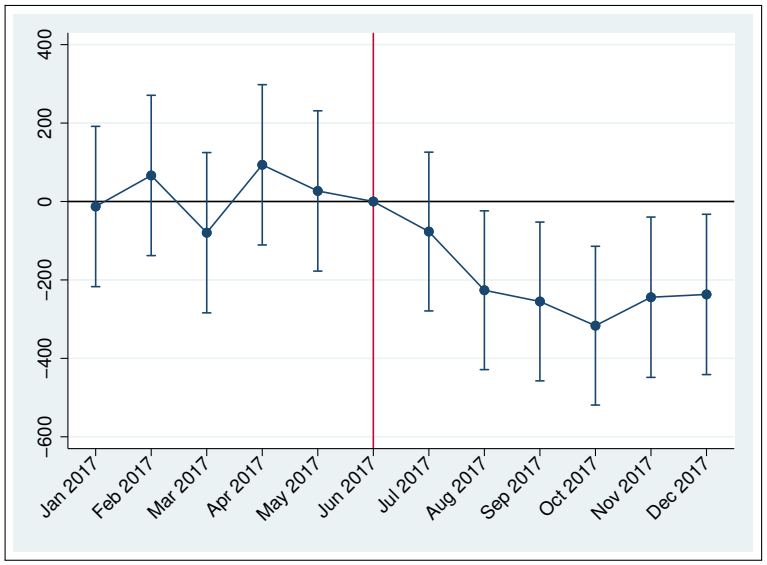
Figure 3 plots the differences in average consumption for products in the treatment and comparison group for each month in 2017.[20] Each panel refers to one of the four outcome variables. The red vertical line signals the period immediately before the policy (June 2017), which is taken as the reference period. Therefore, each blue dot is the difference in average consumption across the two product groups relative to June, while the blue vertical bars represent the 95% confidence interval. To provide a more extensive overview of consumption trends, Figure 4 additionally considers national-level monthly data between July 2015 and July 2019. Figure 5 focuses on the treatment group by considering the same period. For the last two graphs, consumption is measured in terms of DDDs per 1000 inhabitants.[21] This graphical analysis is important for two reasons. First, it suggests that the regulatory shift caused a decrease in consumption for products in the treatment group. Sales were immediately reduced by more than half at the national level, going from around 84 DDDs per 1000 inhabitants in June 2017 to 38 DDDs in August 2017. The figure for July stands in the middle since the new regulation was applied as of July 12th, 2017. Second, and most importantly, these graphs confirm that the strict exogeneity assumption holds. Figure 4 shows that consumption trends across the two groups were almost perfectly parallel before applying the new law while, in Figure 3, none of the differences-in-differences is statistically significant in the period before July 2017 but turn negative and significant starting from August 2017.

[19] See Angrist and Pischke (2009)

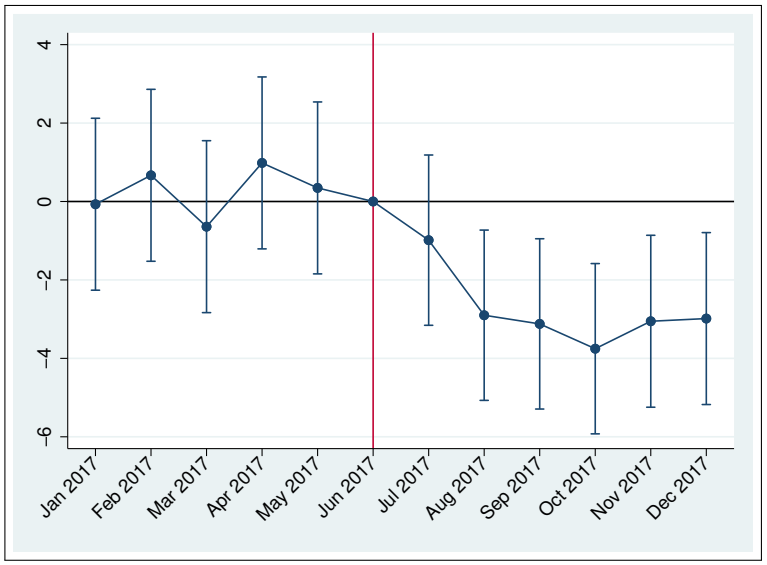
[20] These are means across products (for each product group) and across departments. Observations are weighted by the department population.

[21] Alternative measures of consumption would give similar results.

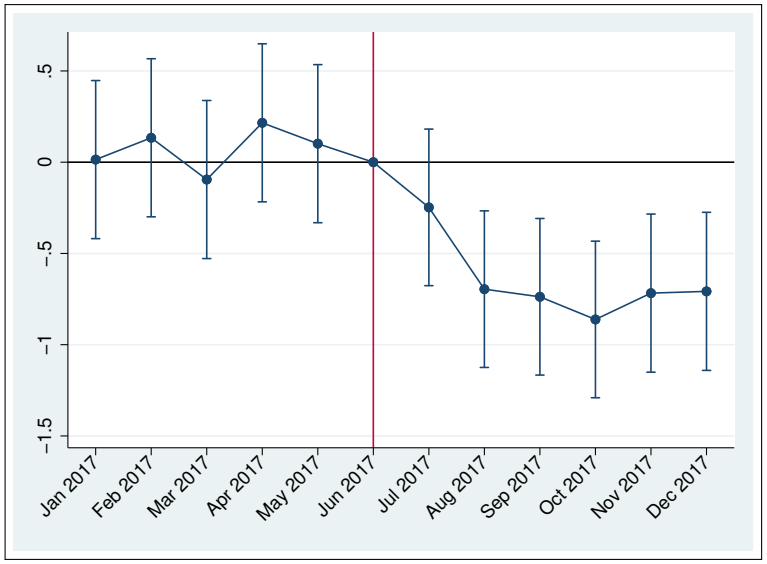
Figure 3. Differences in Average Consumption for Products in the Treatment and Control Group (Jan 2017 - Dec 2017)



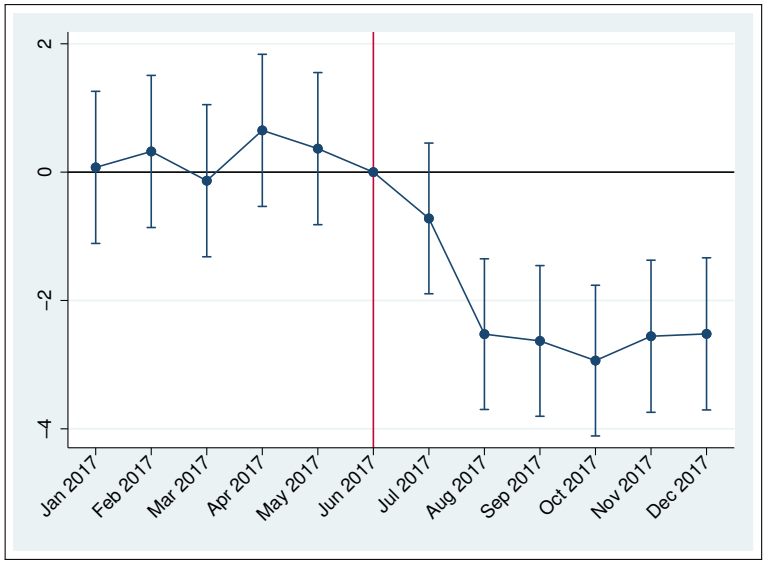
(a). Consumption Trends in *MGs*



(b). Consumption Trends in *DDDs*



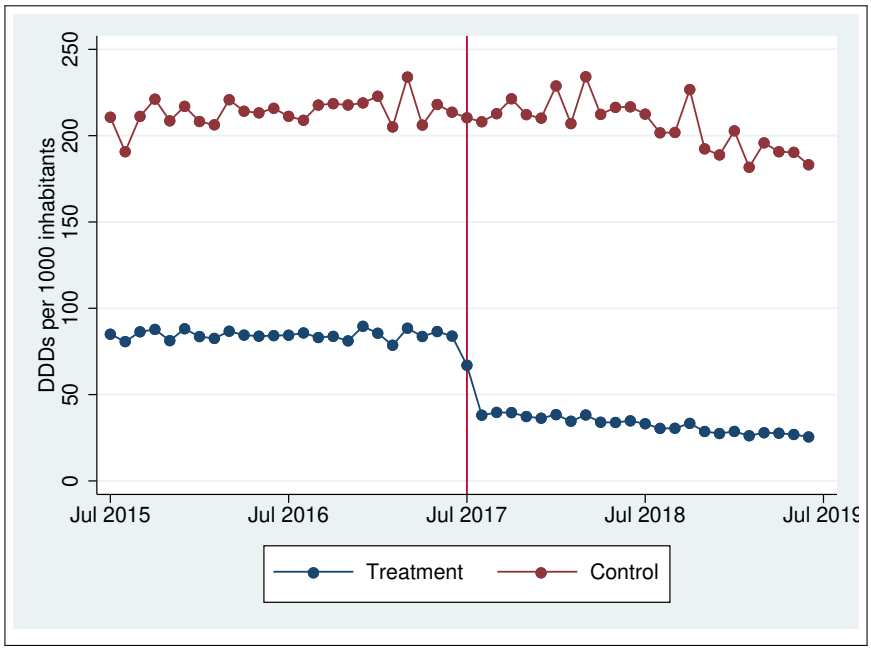
(c). Consumption Trends in *No of Boxes*



(d). Consumption Trends in *Turnover*

Note: Each panel refers to one of the four outcome variables and plots the differences in average consumption for products in the treatment and control group in each month of 2017. Observations are weighted by the department population. Sources: OpenHealth.

Figure 4. Consumption Trends in Treatment and Control Group (Jul 2015 - Jul 2019)



Note: Aggregate monthly sales for Codeine products in the treatment (in blue) and control (in red) group, July 2015 - July 2019. Sales are measured in DDDs per 1000 inhabitants. Source: OpenHealth.

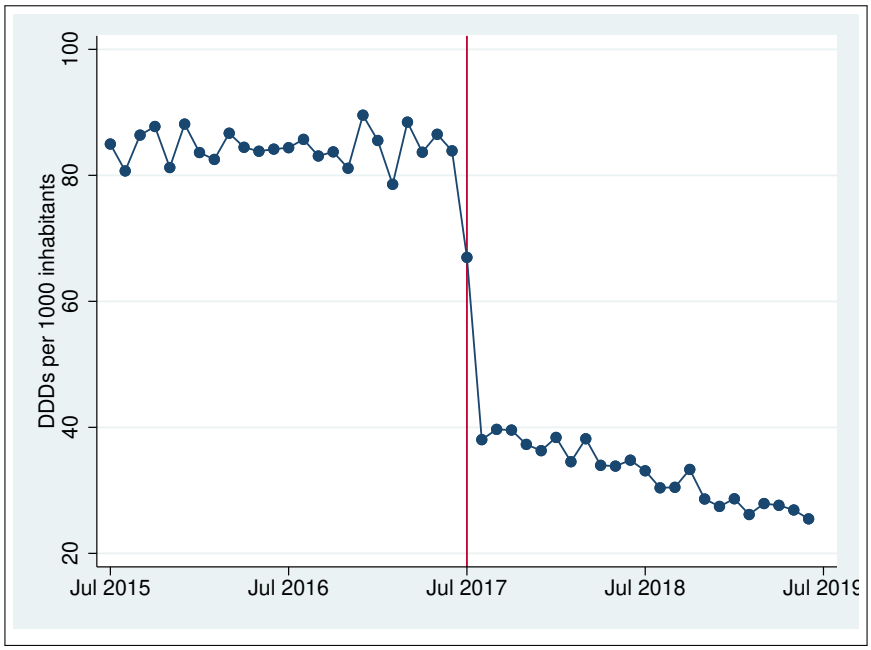
6.2 Econometric Specification

In what follows, I use regression analysis to corroborate the evidence provided by the graphical investigation in the previous subsection. The unit of analysis is the department-product combination and the econometric specification is given by:

$$Y_{pdt} = \beta_0 + \beta_1 TREAT * AFTER + \delta_d + \eta_p + \phi_t + u_{pdt}, \tag{1}$$

where Y_{pdt} is the value of the outcome variable for product p in department d and in month t. This can be consumption, in terms of MGs or DDDs per 1000 inhabitants, number of boxes sold or turnover per 1000 inhabitants. $TREAT$ is a dummy variable equal to one if the product in question belongs to the treatment group and zero, otherwise. $AFTER$ is a dummy equal to zero for the first six months of 2017 and equal to one for the remaining six months. The coefficient β_1 is the DiD estimator, which measures the causal impact of the regulatory shock. δ_d, η_p, and ϕ_t, represent, respectively, department, product and period fixed effects. Their inclusion allows to control for observed and unobserved time-invariant department and product characteristics, as well as for nation-wide shocks or unexpected events affecting opioid analgesic consumption. Note, however, that the inclusion of department fixed effects, as well as the combination of

Figure 5. Focus on Treatment Group (Jul 2015 - Jul 2019)



Note: Aggregate monthly sales for Codeine products in the treatment group, July 2015 - July 2019. Sales are measured in DDDs/1000 people. Source: OpenHealth.

department and period and/or department and product fixed effects, do not have an impact on the magnitude of the DiD estimates. This is because the policy was applied at the national level and, hence, department-specific characteristics cannot represent a source of omitted-variable bias. Finally, u_{pdt} is an idiosyncratic error term. Regressions are weighted by the department population to correct for heteroskedasticity due to different group sizes (Solon at al., 2015). Eicker-Huber-White robust standard errors are used.

6.3 Results

The first panel of Table 5 reports the estimated values for the coefficient of interest, β_1, for a baseline specification of equation (1) in which I do not include any fixed effect. In the second panel, instead, I add department, product and month fixed effects. The estimated coefficients are always negative and significant at the one percent confidence level, thus confirming that the new regulation significantly reduced sales for Codeine products in the treatment group. These estimates yield a measure of the average reduction in sales and turnover across products and departments. Hence, monthly sales decreased on average by 236 MGs per 1000 inhabitants for each product in each department. This is equivalent to a decline of about 3 DDDs per 1000 inhabitants. Approximately, 0.7 boxes less were sold and the law caused a loss in monthly turnover of around 2.5 euros every 1000 inhabitants, for each product in each department.

Table 5. The Impact of the Law - Difference-in-Differences Estimates

	(1) Consumption in MG per capita	(2) Consumption in DDD per capita	(3) No of Boxes per capita	(4) Turnover per capita
DiD Estimate without FE	-240.6067***	-3.001***	-0.720***	-2.517***
	(50.890)	(0.547)	(0.108)	(0.298)
DiD Estimate with FE	-235.854***	-2.939***	-0.705***	-2.470***
	(11.927)	(0.131)	(0.027)	(0.081)
N	30,926	30,926	30,926	30,926

Note: Robust standard errors in parenthesis. Regressions are weighted by department population. $^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$

7 Differences in Treatment Effect: Rich versus Poor

The goal of the analysis in this section is to investigate how the local economic environment interacts with the regulatory change. More precisely, I want to determine whether and how the magnitude of treatment effects varies across geographical areas depending on the department poverty rate. To this end, I exploit a triple difference (TD) approach, which allows a before-after comparison of sales across the two groups of Codeine pain-killers and across two department groups (rich versus poor). As mentioned, I distinguish poor or wealthy departments based on the average poverty rate.

7.1 Parallel Trend Assumption for Triple Difference Estimation

Gruber (1994) first introduced the triple difference approach to identify the labor-market impact of mandated maternity benefits. After its introduction, this approach became widely used. Walker (2013), for instance, uses TD to estimate the impact of new environmental laws concerning air pollution on labor market outcomes, while Bergman et al. (2016) exploit a TD framework to evaluate the impact of opening nursing-home care for the elderly to private provision on mortality in Sweden. The goal of these studies is to identify the causal effect of policies targeting a specific population group and use a TD approach to correct for the potential bias of a simple DiD estimator due, for example, to self-selection into treatment. Instead, the goal of this section is to measure the difference in magnitude between two treatment effects and determine whether this difference is statistically significant.

The parallel trend in TD requires the non-existence of differences in differential trends between two groups across geographical entities (Olden and Møen, 2020). In the context of the present paper, this means that the trend in differential consumption for products in the treatment and in the control group in poor departments should be the same as in more affluent

departments, in the absence of treatment.[22] Indeed, the poverty rate, on which the distinction of departments into two groups is based, is likely to be correlated with other socioeconomic factors affecting opioid use. If these other factors cause consumption for treated products to trend differently, relative to control products, in affluent and poor departments, the TD estimate would be biased, and the comparison across departments would not be informative. The validity of this assumption can be indirectly tested by exploring differential trends in consumption during the pre-treatment period. Figure 6 plots these differential trends for poor and wealthy departments by using monthly sale data in 2017. I first consider aggregate consumption for products in the treatment and comparison group in each department and period. I then consider the average consumption in rich versus poor departments for each product group. Hence, the blue line represents the difference in average consumption for products in the control and treatment group in poor departments, while the red line represents the same difference for departments classified as rich. The light red vertical line represents the moment in which the new law came into force.

This set of graphs has two important take-aways. First, they show that differential trends in consumption evolved reasonably parallel before introducing the new law, which confirms the validity of the parallel trend assumption. Second, they suggest that sales for products in the treatment group, relative to products in the comparison group, decreased by more in wealthier than in poorer departments, and, hence, the new regulation was more effective in the former than in the latter. Indeed, the before-after 'jump' is larger for affluent departments. Further discussion on pre-existing trends is carried out in subsection 7.3.

7.2 Econometric Specification

The following econometric specification is used to estimate the difference in treatment effects across departments. The unit of analysis is the department-product combination:

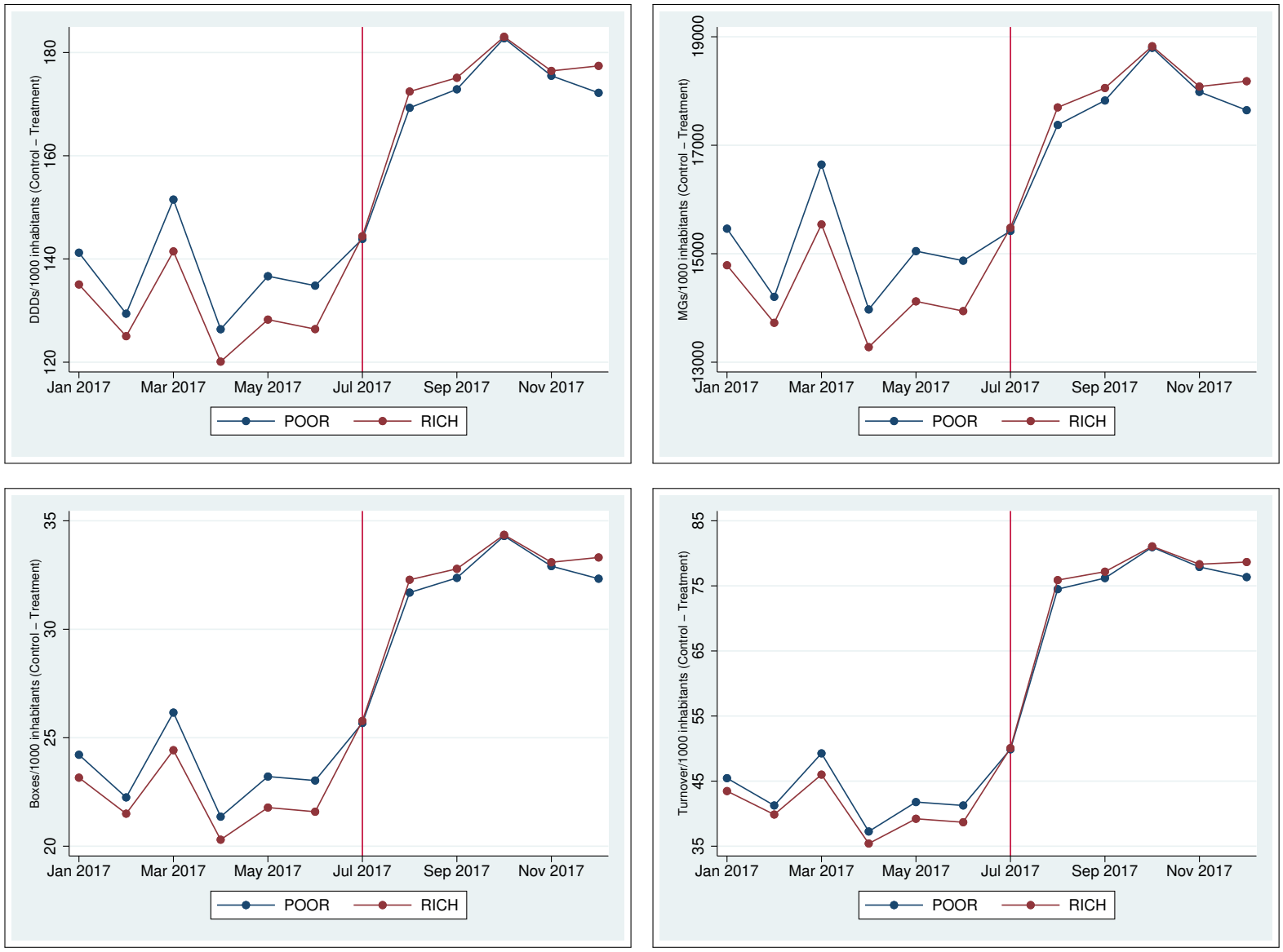
$$Y_{pdt} = \beta_0 + \beta_1(TREAT * AFTER * POOR) + \delta_d * \eta_p + \eta_p * \phi_t + \delta_d * \phi_t + u_{pdt}, \qquad (2)$$

where, as before, $TREAT$ is a dummy for the group of products that was treated by the reform and $AFTER$ allows to distinguish between the six months preceding the implementation of the new law and the six months following it. $POOR$ is a dummy to distinguish between poorer (poverty rate above the average) and wealthier (poverty rate below the average) departments: it is equal to one if the department is classified as poor; it takes on value zero otherwise.[23] The coefficient β_1 is the triple difference estimator of interest since it yields a measure of the difference in treatment effects across departments.

[22] Notice, however, that the parallel trend assumption can be relaxed through the introduction of fixed effects. In my richest specification (see subsection 7.2), I include all the possible combinations of department, product and period fixed effects.

[23] The average poverty rate is displayed in Table 1 of Subsection 5.1, together with other detailed summary statistics and a map indicating which departments are classified as poor and which are classified as rich.

Figure 6. Differential Trends in Consumption for Rich and Poor Departments (Jan 2017 - Dec 2017)



Note: Differential trends in consumption for poor (in blue) and rich (in red) departments, January 2017 - December 2017. Each panel refers to one of the four outcome variables. Observations are weighted by the department population. Sources: OpenHealth.

The specification of equation (2) includes department, δ_d, product, η_p, and period, ϕ_t, fixed effects, as well as all the possible combinations of these fixed effects. Department-by-period fixed effects, $\delta_d * \phi_t$, allow to control for observed and unobserved time-varying department characteristics affecting Codeine product consumption (or department-level shocks common to all Codeine products). For instance, previous research shows that opioid analgesic use is more common among individuals with less than college education and more widespread in rural areas. These factors are likely correlated with the level of poverty in the department and, hence, may represent a source of omitted-variable bias. Product-by-period fixed effects, $\eta_p * \phi_t$, enable to control for time-varying determinants of specific products' consumption, such as seasonality effects. They also allow to control for potential time variations in pharmaceutical companies marketing strategies and in product prices. Department-by-product fixed effects, $\delta_d * \eta_p$, are used to model any time-invariant factor affecting Codeine use. An example here may be given by the presence of peer effects. Indeed, physicians may exchange opinions about what they think is the best drug to cure a given condition. Previous research has shown that peer effects are important and there exists significant clustering in treatment. In addition, this would also control for the presence of high-frequency prescribers of specific products. Notice that the first and second-order interactions usually included in the triple difference specification are absorbed here by the fixed effects. Finally, u_{pdt} is an idiosyncratic error term. As before, regressions are weighted by the department population to correct for heteroskedasticity due to different group sizes (Solon at al., 2015) and Eicker-Huber-White robust standard errors are used.

The availability of consumption data for several periods before and after the intervention allows performing a placebo test in the spirit of Granger (1969) and, hence, to expand on the discussion concerning the validity of the identifying assumption. The idea behind the Granger test is that the consequences of a policy should appear after the implementation of such a policy and not vice versa. Thus, if an effect appears before the regulatory shock, this should cast doubts on the parallel trend assumption's validity. To implement this test, I generalize equation (2) to include leads and lags. This yields the following event-study style regression:

$$Y_{pdt} = \beta_0 + \sum_{j=-6}^{+5} \beta_1^{t+j}(TREAT * POOR * \mathbf{1}(t+j)) + \delta_d * \eta_p + \eta_p * \phi_t + \delta_d * \phi_t + u_{pdt}, \quad (3)$$

where t is the period in which the regulatory shift takes place and $\mathbf{1}(t+j)$ is a set of indicator variables, each equal to one for one of the twelve months of the year 2017. The remaining controls are defined as in equation (2). The insignificance of the coefficients β_1^{t-6} to β_1^{t-1} would support the hypothesis of parallel trends and prove that there have not been anticipatory effects.[24]

Beside checking the validity of the common trend assumption, the Granger test can also be done to obtain useful insights on the evolution of the treatment effect over time. Compared to equation (2), equation (3) allows the impact of the policy to evolve over time, instead of assuming that this effect is immediate and perpetual.

[24]Notice, however, that Codeine re-scheduling has been immediate. This consideration leads us to suppose that the presence of anticipatory effects is here unlikely.

7.3 Results

Table 6 reports the estimated values for the coefficient β_1 of equation (2). Each row considers one of the four outcome variables while each column adds a different combination of fixed effects.

The estimated coefficients are positive across the four outcome variables and across different specifications. In the most complete specification of column (4), the difference in treatment effects between poor and rich departments is significant at the one percent confidence level.

Table 6. Heterogeneous Treatment Effects - Triple Difference Estimates

Dependent Variable	(1)	(2)	(3)	(4)
Consumption in MGs per 1000 people	70.579***	70.566***	70.566***	70.267***
	(23.828)	(23.647)	(20.769)	(11.822)
Consumption in DDDs per 1000 people	0.646**	0.645**	0.645***	0.642***
	(0.261)	(0.259)	(0.220)	(0.126)
No of Boxes per 1000 people	0.111**	0.111**	0.111***	0.110***
	(0.054)	(0.054)	(0.043)	(0.025)
Turnover per 1000 people	0.208	0.208	0.208*	0.205***
	(0.161)	(0.161)	(0.116)	(0.067)
Product, department, period fixed effects	✓	✓	✓	✓
Department-by-period fixed effects		✓	✓	✓
Product-by-period fixed effects			✓	✓
Department-by-product fixed effects				✓
N	30,926	30,926	30,926	30,926

Note: Robust standard errors in parenthesis. Regressions are weighted by department population. $^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$

Whatever the outcome variable considered is, the combination of product and period fixed effects does not influence the magnitude of the estimates, but their inclusion contributes to improve the precision of the estimates. The inclusion of time-varying and invariant department-specific controls, instead, contributes to decrease the magnitude and increase the precision of the estimates. In the estimation of Section 6, the inclusion of department fixed effects does not play a role because the independent variable only varies across products and time periods and, hence, department-specific factors cannot be a source of omitted-variable bias. In equation (2), instead, the independent variable also varies across departments, depending on the poverty rate, and, hence, department-specific characteristics or shocks can pose an omitted-variable problem.

The positive sign of the estimated coefficients suggests that poorer departments react, on

Table 7. Rich versus Poor Departments - Difference-in-Difference Estimates

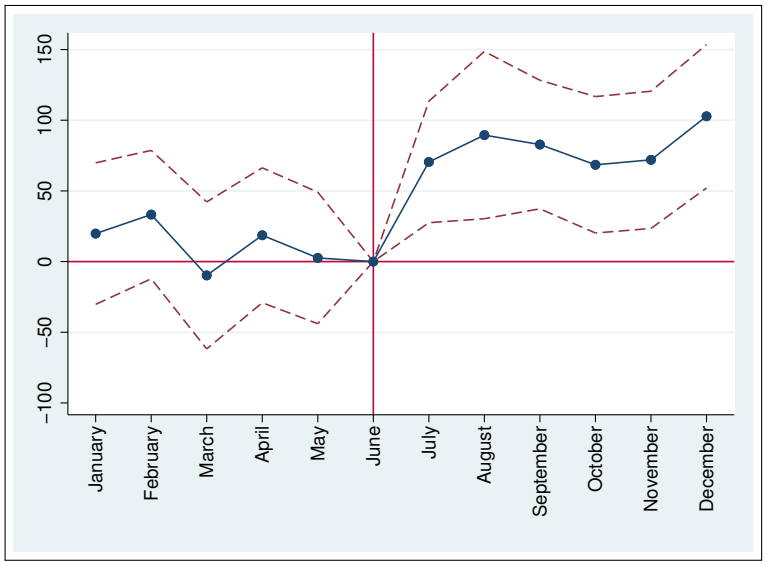
	(1) Consumption in MG per capita	(2) Consumption in DDD per capita	(3) No of Boxes per capita	(4) Turnover per capita
Rich	-268.825***	-3.240***	-0.757***	-2.566***
(Poverty below average)	(9.953)	(0.114)	(0.025)	(0.081)
N	15,792	15,792	15,792	15,792
Poor	-198.558***	-2.598***	-0.646***	-2.361***
(Poverty above average)	(13.815)	(0.157)	(0.035)	(0.111)
N	15,134	15,134	15,134	15,134

Note: Robust standard errors in parenthesis. Regressions are weighted by department population. $^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$

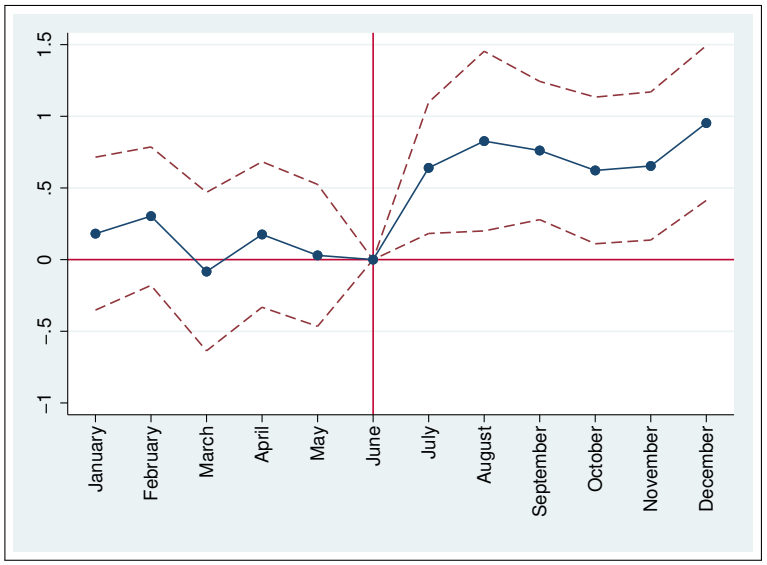
average, less than wealthier departments to the introduction of the new law: departments characterized by a disadvantaged economic status are more 'regulatory inelastic'. Following the regulatory change, monthly Codeine consumption was reduced, on average, by 70 MGs and 0.64 DDDs per 1000 inhabitants more in wealthier departments for each product in the treatment group. To make this more clear, Table 7 reports estimation of treatment effects for poor and rich departments separately. The reduction in Codeine sales is significant at one percent confidence level both in rich and in poor departments, but systematically larger in rich departments. Note also that taking the difference in treatment effects between rich and poor departments yields the same value as in the fourth column of Table 4.

Figure 7 depicts the estimation results from the event-study specification in equation (3) for each outcome variable. Each dot on the blue line represents a point estimates while the dashed red line represents the 95% confidence interval. The light red vertical line refers to the period preceding the regulatory change (June). The indicator for this period, β_1^{t-1}, is set equal to zero and serves, therefore, as a reference point. As a consequence, the coefficients associated with all the other interactions are expressed relative to this omitted period. The estimated coefficients β_1^{t-j} are not significant, thus supporting the validity of the common trend assumption. The estimated coefficients β_1^{t+j}, instead, are all positive, substantially larger in magnitude and all statistically significant in panels (a), (b) and (c). Their magnitude further suggests that the difference in treatment effects across the two department groups persisted until the end of 2017. Table C1 in Appendix C further reports point estimates for the specification in equation (3). Each cell displays estimates for each β_1^{t-j} and β_1^{t+j} coefficient and for each outcome variable. The estimate for the coefficient β_1^{t-1} is omitted since this represents the reference period.

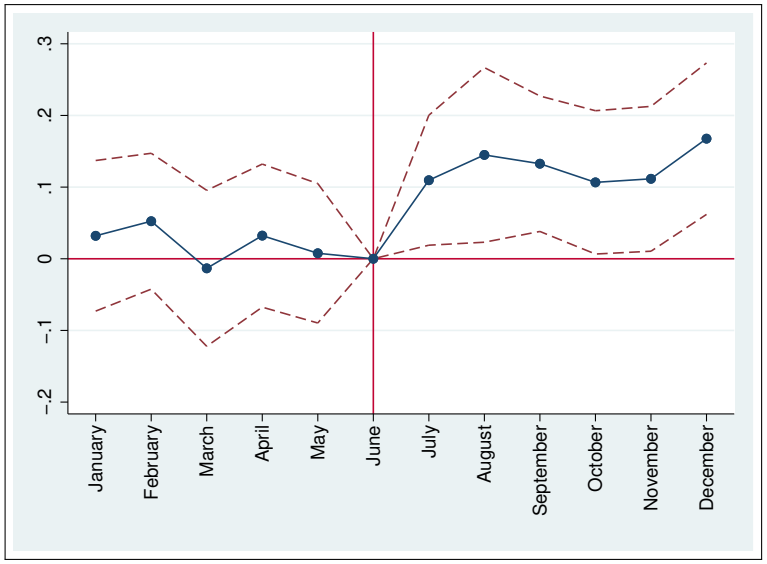
Figure 7. Granger Test - Coefficient Plots



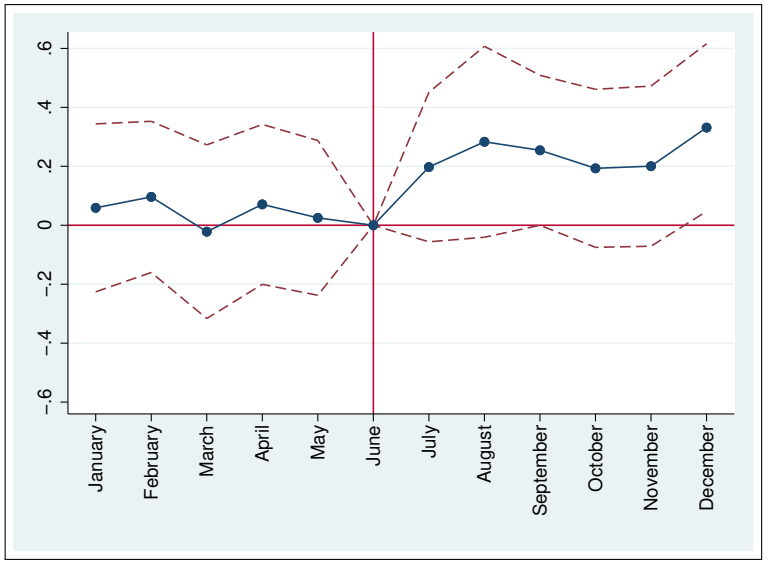
(a). Consumption Trends in *MGs*



(b). Consumption Trends in *DDDs*



(c). Consumption Trends in *No of Boxes*



(d). Consumption Trends in *Turnover*

Note: Each graph plots the point estimates from the event study (in blue) with the 95 percent confidence intervals (dashed red lines). Each panel refers to one of the four outcome variables. Sources: OpenHealth.

7.4 Treatment Effects at the Extremes

For the analysis in the previous subsection, I classify departments as rich or poor, based on the average poverty rate. This implies that, by construction, a department with a poverty rate just above the average is considered poor while a department with a poverty rate just below this threshold is considered wealthy. That is, the two departments are included into different groups even though they are close in terms of poverty levels. This may hinder the magnitude and significance of the estimates in Table 6. For this reason, in this subsection, I repeat the same analysis as above by excluding departments close to the threshold and by focusing, instead, on 'extremely' poor and 'extremely' rich departments only. In particular, I restrict attention to those departments whose poverty rate falls in the first and last quartiles of the poverty rate distribution.[25]

Table 8. Heterogeneous Treatment Effects at the Extremes - TD Estimates

Dependent Variable	(1)	(2)	(3)	(4)
Consumption in MGs per 1000 people	114.152***	114.262***	114.262***	113.555***
	(33.072)	(32.957)	(28.845)	(15.659)
Consumption in DDDs per 1000 people	1.088***	1.089***	1.089***	1.080***
	(0.362)	(0.362)	(0.306)	(0.167)
No of Boxes per 1000 people	0.199***	0.199***	0.199***	0.197***
	(0.076)	(0.075)	(0.060)	(0.033)
Turnover per 1000 people	0.436*	0.437*	0.437***	0.429***
	(0.225)	(0.226)	(0.161)	(0.089)
Product, department, period fixed effects	✓	✓	✓	✓
Department-by-period fixed effects		✓	✓	✓
Product-by-period fixed effects			✓	✓
Department-by-product fixed effects				✓
N	14,805	14,805	14,805	14,805

Note: Robust standard errors in parenthesis. Regressions are weighted by department population.
$^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$

Results are reported in Table 8. These not only largely confirm the results in the previous subsection, but also provide some further interesting insights. The Triple Difference estimates are again all positive, meaning that the treatment effect is larger in wealthier than in poorer

[25] See Table 1 for detailed summary statistics concerning the poverty rate.

departments. Compared to Table 6, however, they are now larger in magnitude and more significant. Standard errors are larger than in Table 6, due to the smaller number of observations. By comparing column (4) in Table 6 with the same column in Table 8, we observe that estimates are at least 60% larger in magnitude. By considering Table 9, we observe, once again, that the treatment effect is systematically larger in richer than in poorer departments. By comparing this table with Table 7 above, we further observe that, for each outcome variable, the treatment effect in the rich departments is systematically larger while the treatment effect for the poor departments is systematically smaller. Hence, these findings suggest that the more we move to the extremes of the poverty rate distribution, the larger the difference in treatment effects between the two department groups. In other words, the treatment effect seems to be a decreasing function of the poverty rate.

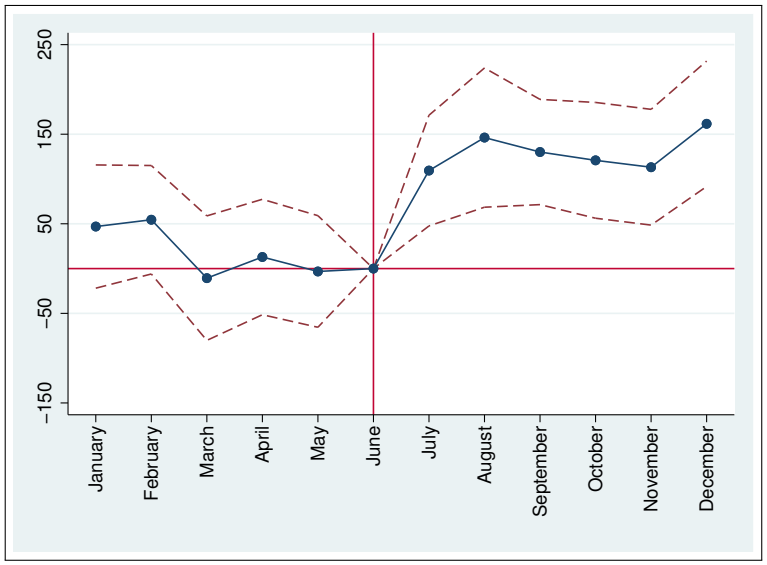
Table 9. Rich versus Poor Departments at the Extremes - DiD Estimates

	(1) Consumption in MG per capita	(2) Consumption in DDD per capita	(3) No of Boxes per capita	(4) Turnover per capita
Rich	-280.099***	-3.358***	-0.781***	-2.632***
(Poverty in fourth quartile)	(13.332)	(0.154)	(0.035)	(0.114)
N	7,238	7,238	7,238	7,238
Poor	-166.544***	-2.277***	-0.584***	-2.202***
(Poverty in first quartile)	(19.311)	(0.220)	(0.049)	(0.155)
N	7,567	7,567	7,567	7,567

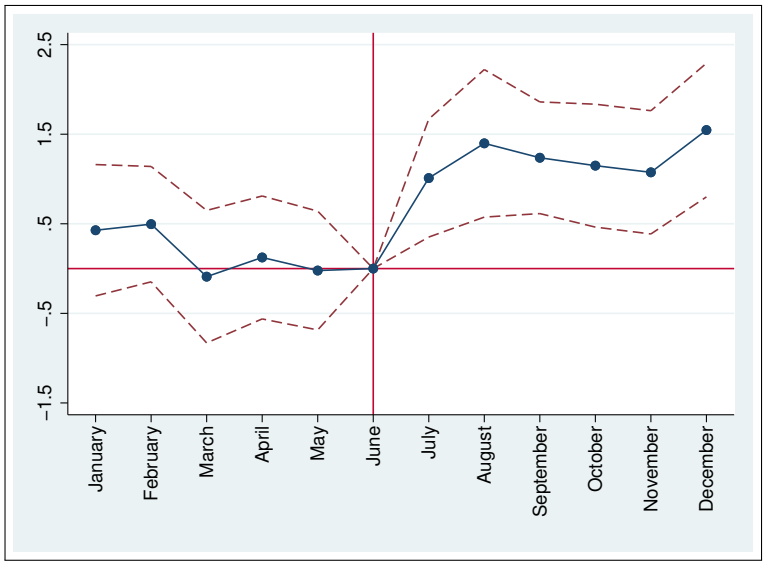
Note: Robust standard errors in parenthesis. Regressions are weighted by department population.
$^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$

Figure 8 plots coefficient estimates from equation (3) for this restricted set of departments. As before, the dots on the blue line represents the point estimates while the dashed red line represents the 95% confidence interval. The light red vertical line refers to the period preceding the regulatory shift (June), which serves as the reference point. Compared to Figure 7, the 95% confidence interval lies well above zero in the post-treatment period for each of the four outcome variables. For what concerns the turnover, while in Figure 7 some of the point estimates of the post-treatment period are not statistically significant, here most of them are significant at 5% level.

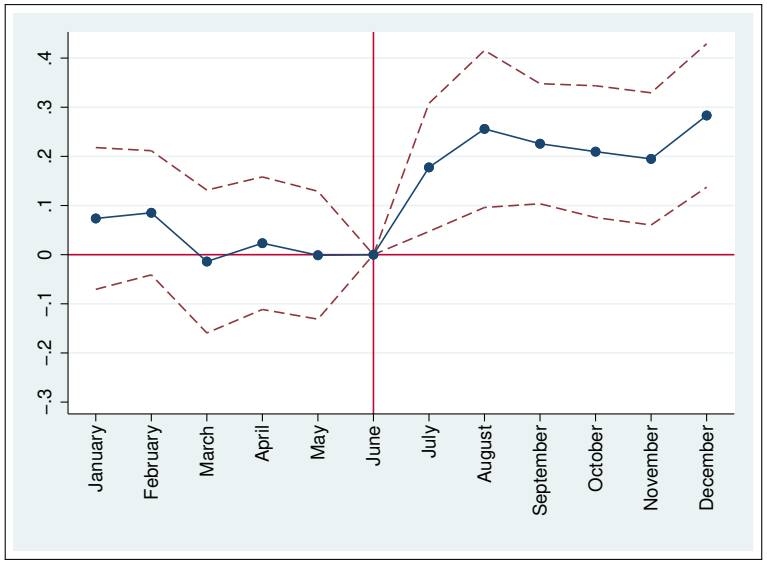
Figure 8. Granger Test - Coefficient Plots at the Extremes



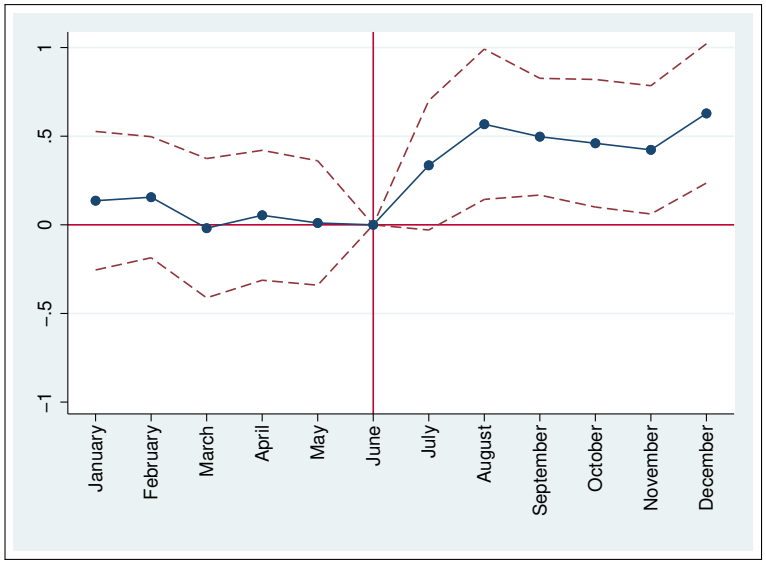
(a). Consumption Trends in *MGs*



(b). Consumption Trends in *DDDs*



(c). Consumption Trends in *No of Boxes*



(d). Consumption Trends in *Turnover*

Note: Each graph plots the point estimates from the event study (in blue) with the 95 percent confidence intervals (dashed red lines). Each panel refers to one outcome variable and considers departments in the first and last quartiles of the poverty rate distribution

7.5 Continuous Poverty Rate

Results in the previous sections suggest that the treatment effect, in absolute terms, behaves as a decreasing function of the poverty rate. Drops in consumption after the regulatory shock decrease with increasing poverty. To test this hypothesis, I perform the same analysis as in subsection 7.3, where now the dichotomous variable $POOR$ is replaced by the continuous variable $PovertyRate$. The econometric specification becomes, therefore:

$$Y_{pdt} = \beta_0 + \beta_1(TREAT * AFTER * PovertyRate) + \delta_d * \eta_p + \eta_p * \phi_t + \delta_d * \phi_t + u_{pdt}, \quad (4)$$

where each variable in equation (4), except the $PovertyRate$, is defined as before. If the treatment effect is a decreasing function of poverty, we expect the coefficient β_1 to be positive and significant. This is confirmed by the results displayed in Table 10 below.

Table 10. Continuous Poverty Rate - Triple Difference Estimates

Dependent Variable	(1)	(2)	(3)	(4)
Consumption in MGs per 1000 people	8.053**	8.073**	8.073***	8.059***
	(3.667)	(3.636)	(3.111)	(1.695)
Consumption in DDDs per 1000 people	0.073*	0.074*	0.074**	0.073***
	(0.040)	(0.040)	(0.033)	(0.018)
No of Boxes per 1000 people	0.013	0.013	0.013*	0.013***
	(0.008)	(0.008)	(0.006)	(0.003)
Turnover per 1000 people	0.023	0.023	0.023	0.023**
	(0.025)	(0.025)	(0.017)	(0.009)
Product, department, period fixed effects	✓	✓	✓	✓
Department-by-period fixed effects		✓	✓	✓
Product-by-period fixed effects			✓	✓
Department-by-product fixed effects				✓
N	30,926	30,926	30,926	30,926

Note: Robust standard errors in parenthesis. Regressions are weighted by department population. $^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$

The coefficient β_1 is positive for each of the dependent variables under study and significant at 1 or 5% confidence level in the richest specification of column (4). Consistent with results in the previous subsections, this effect is less evident for the turnover than for the remaining outcome variables.

8 Substitution Effects

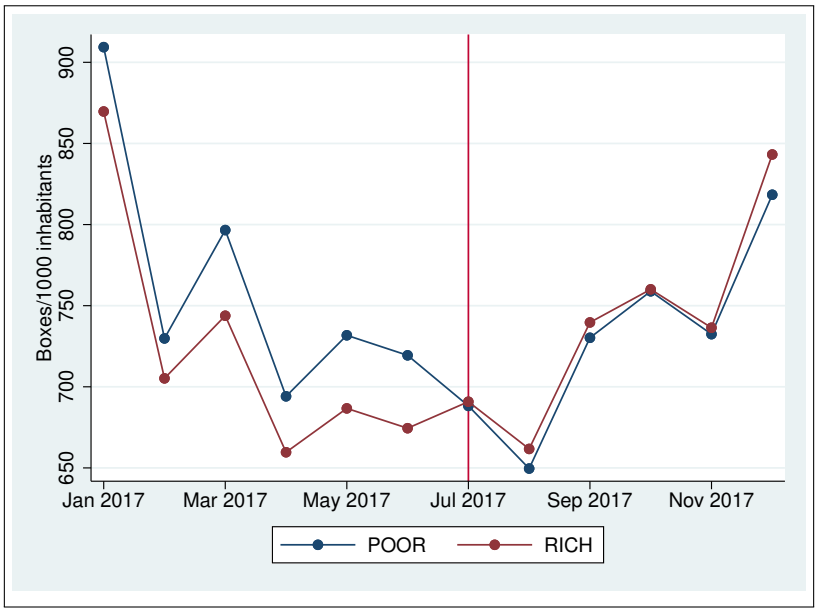
As many other policy interventions, the one under analysis here may have intended as well as unintended consequences. In the opioid crisis context, Doleac and Mukherjee (2019) find that facilitating access to Naloxone[26] increases the prevalence of risky behavior, thus raising the number of opioid-related ED visits and crimes. Alpert et al. (2018), instead, show that the introduction of the abuse-deterrent version of OxyContin led to increased heroin-related deaths. Several papers in the health economics literature underline the relevance of substitution effects across drugs. For example, Powell et al. (2018) find that individuals substitute opioids with marijuana in the presence of medical marijuana laws. The intended effect of the law under study in this paper is to reduce Codeine abuse by impeding its use for recreational purposes and inducing (at least) a part of the demand to switch to non-opioid analgesics. Unintended effects, instead, would be inducing a part of the demand to switch to the black market, thus increasing opioid-related harm and crimes, or visit a doctor more frequently to obtain Codeine. In light of this, the observed differences in the magnitude of treatment effects across departments may provide evidence both in support and against the 'deaths of despair' hypothesis. On the one hand, it is possible that individuals in poor conditions consume more opioids and continue to consume more even though the new law makes access more difficult. By contrast, patients on high income switch to less dangerous non-opioid analgesics. However, it is also possible that high-income individuals more easily switched to the black market after the regulatory change: rich people often have wider networks and face fewer financial hurdles for buying substances on the black market. A comprehensive evaluation of the health impact of the law requires, therefore, an analysis of both positive and negative substitution effects. This is the purpose of the following subsections.

8.1 Positive Substitution Effects

Positive substitution effects translate in an increase in non-opioid analgesic use after tightening Codeine regulation. To evaluate whether differences in treatment effects across departments are due to this positive substitution, I use monthly data on non-opioid analgesic sales in 2017 at the department level. Figure 9 plots the average number of boxes sold per 1000 inhabitants for poor departments in blue and for rich departments in red. The figure documents larger analgesic consumption during the winter in both rich and poor departments and a larger consumption in poor departments during the first half of the year. In addition, consumption trends for rich and poor departments look fairly parallel for the first six months. However, in July, when the new law was adopted, consumption increased in rich departments relative to poor departments. This provides a first visual evidence that the new regulation induced a positive substitution effect and that this effect was more important in rich areas.

[26]Naloxone is a drug that can reverse an overdose. Some states in the US adopted laws that facilitate access to this medicine in an attempt to contain the opioid epidemic.

Figure 9. Non-Opioid Sales in Rich and Poor Departments (Jan 2017 - Dec 2017)



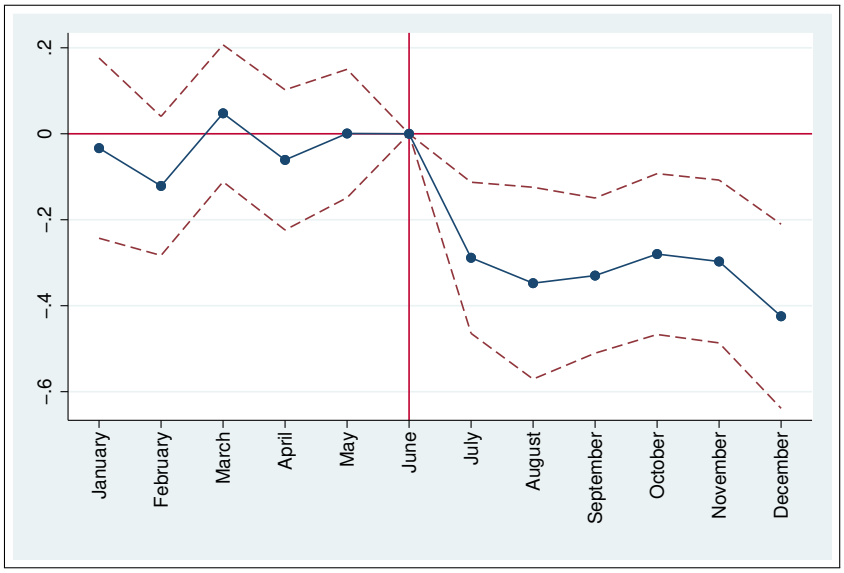
Note: Non-opioid analgesic sales in poor (in blue) and rich (in red) departments, January 2017 - December 2017. Sales are measured in boxes/1000 inhabitants. Observations are weighted by the department population. Source: OpenHealth.

To test this hypothesis, I run an event-study regression that allows a comparison of consumption across the two department groups over time. The econometric specification is:

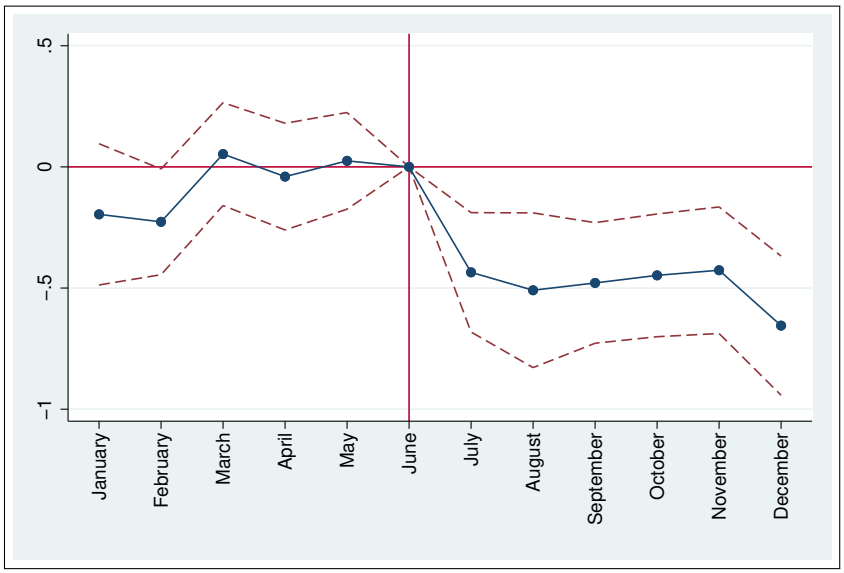
$$NonOpioids_{pdt} = \beta_0 + \sum_{j=-6}^{+5} \beta_1^{t+j}(POOR * \mathbf{1}(t+j)) + \eta_p + \delta_d + \phi_t + u_{pdt}, \tag{5}$$

where $NonOpioids_{pdt}$ is the number of boxes sold per 1000 inhabitants for each (non-opioid) product in each department and time period. $POOR$ is a dummy equal to one if the department is classified as poor and zero, otherwise. This dummy is interacted with a full set of indicator variables, each equal to one for one month of the year 2017. Each regression includes product, department and month fixed effects and is weighted by the department population. Eicker-Huber-White robust standard errors are used. Figure 10 shows the coefficient plots from regression (5) for the full set of departments (a) and for departments in the first and last quarter of the poverty rate distribution (b), where June is chosen as the reference period. These graphs confirm that consumption trends were evolving on parallel paths before the regulatory change since none of the estimated coefficients is statistically different from zero. However, non-opioid use increased in rich departments, relative to poor departments, after the law and point estimates are larger once we restrict attention to departments in the first and last quarter of the poverty rate distribution. Hence, this positive substitution effect also seems to be monotonically decreasing in poverty.

Figure 10. Non-Opioid Consumption - Event Study Results - Coefficient Plots



(a). Full set of departments.



(b). Departments at the extremes of the poverty rate distribution.

Note: Each graph plots the point estimates from the event study (in blue) with the 95 percent confidence intervals (dashed red lines). Panel (a) refers to the full set of departments. Panel (b) considers departments in the first and last quartiles of the poverty rate distribution. Sources: OpenHealth.

8.2 Negative Substitution Effects

Negative substitution effects translate here in an increase of the demand for illicit opioids after tightening Codeine regulation. Reliable data on illicit drug consumption on the French black market, though, are lacking. Hence, by following the existing literature, I evaluate the impact of the law on illicit opioid use by using the number of drug-related crimes as a proxy. As mentioned, I consider information related to traffic and sale (without use) of narcotics, use and sale of narcotics, use of narcotics.

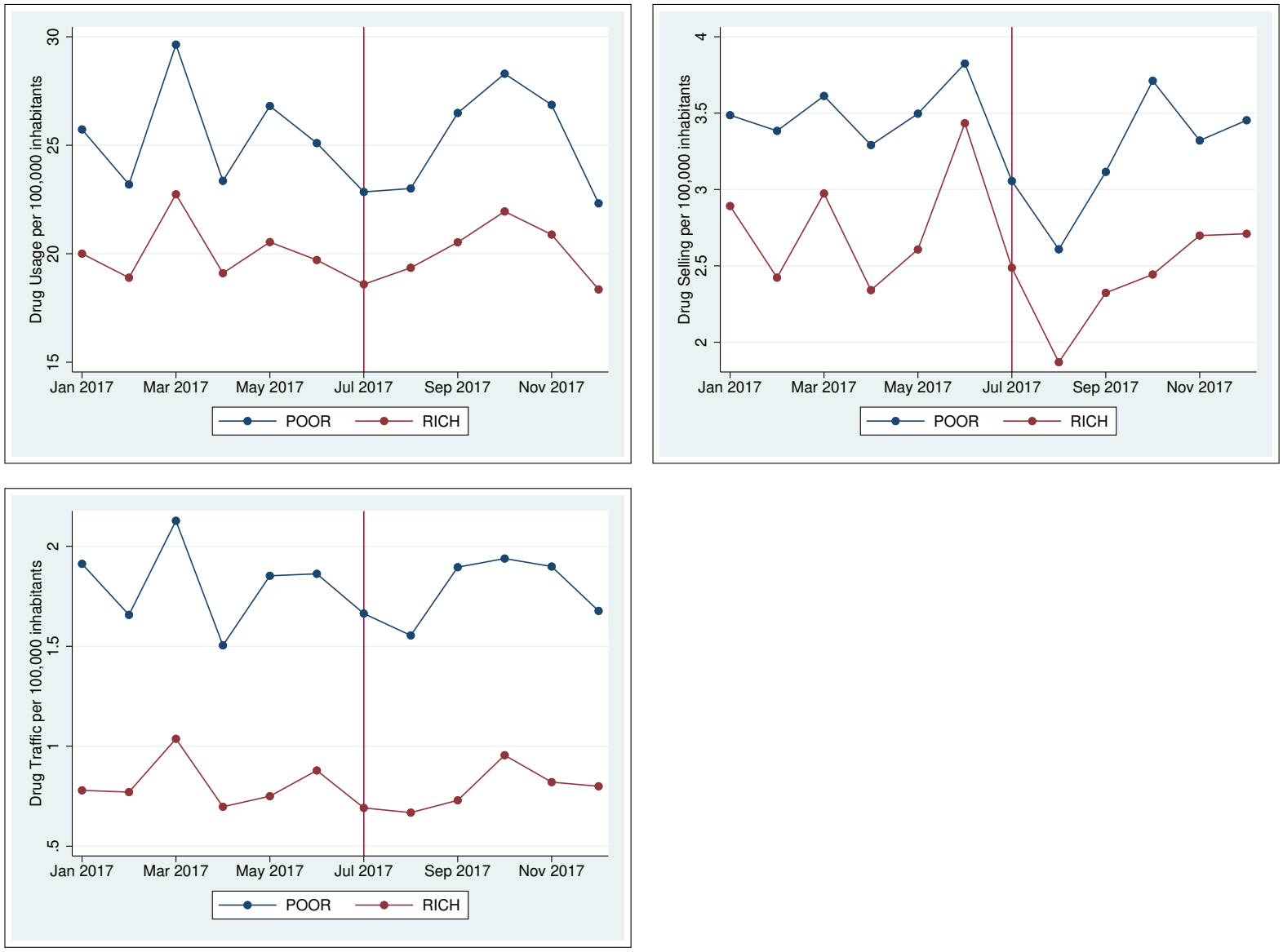
8.2.1 Crime

Figure 11 plots the average number of drug-related crimes for rich (in red) and poor (in blue) departments. Each subfigure refers to one of the outcome variables of interest. Trends for drug-related crimes in rich and poor departments look parallel, but this is true both before and after the new law. Nothing suggests that substitution effects towards the black market have been more important in rich than in poor departments (or vice versa). Once again, to formally test this hypothesis, I run the following event-study regression:

$$Crime_{dt} = \beta_0 + \sum_{j=-6}^{+6} \beta_1^{t+j}(POOR * \mathbf{1}(t+j)) + \delta_d + \phi_t + u_{dt}, \tag{6}$$

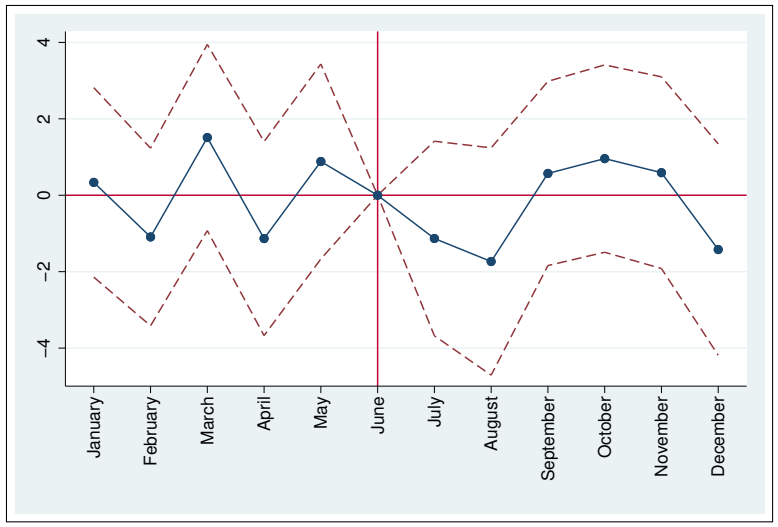
where $Crime_{dt}$ is the number of drug-related crimes per 100,000 inhabitants in each department and time period. $POOR$ is a dummy equal to one if the department is classified as poor and equal to zero, otherwise. This dummy is interacted with a full set of indicator variables, each equal to one for one month of the year 2017. Each regression includes department and month fixed effects, and is weighted by the department population. Eicker-Huber-White robust standard errors are applied. Figure 12 shows the coefficient plots from regression (6). As before, June represents the reference period. These graphs confirm that there have not been significant changes in drug-related crimes across departments since none of the estimated coefficient is statistically significant. This suggests that the observed differences in treatment effects across the two department groups are not explained by a more significant substitution effect towards the black market in rich areas.

Figure 11. Drug-related Crimes in Rich and Poor Departments (Jan 2017 - Dec 2017)

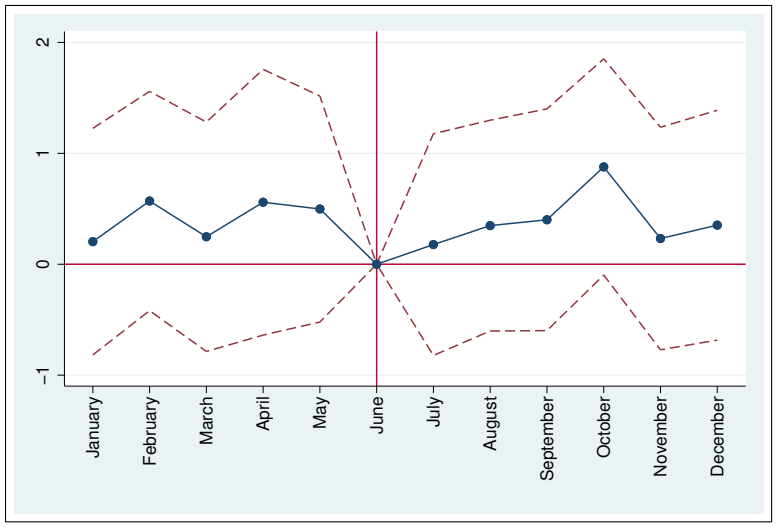


Note: Drug-related crimes in poor (in blue) and rich (in red) departments, January 2017 - December 2017. Each panel refers to one of the three outcome variables. Observations are weighted by the department population. Source: `https://www.data.gouv.fr`.

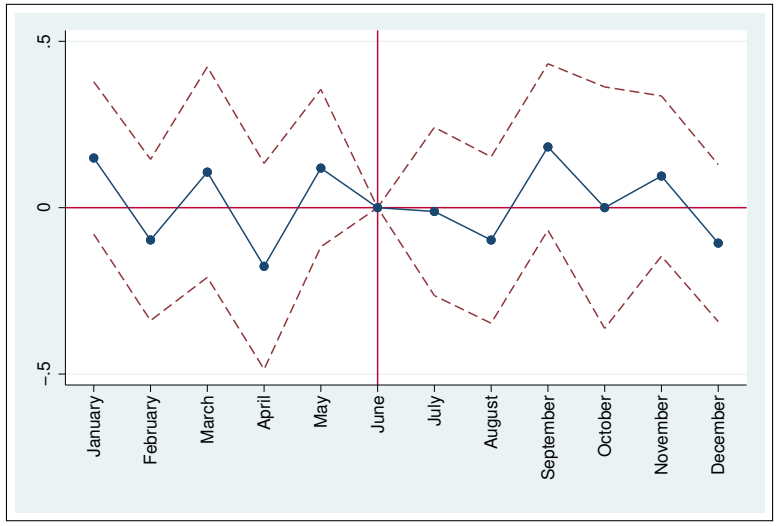
Figure 12. Drug-related Crimes - Event Study Results - Coefficient Plots



(a). Drug Usage.



(b). Drug Selling



(c). Drug Traffic

Note: Each graph plots the point estimates from the event study (in blue) with the 95 percent confidence intervals (dashed red lines). Each panel refers to one of the three outcome variable. Source: `https://www.data.gouv.fr`.

8.2.2 Emergency Department (ED) Visits

Finally, to complement the analysis of substitution effects, I use data on ED visits for the ICD-10 codes T40.2, T40.0, T40.1 and T40.3. Information for the group T40.2 is used as a proxy for Codeine-related intoxications while aggregated data for the groups T40.0, T40.1 and T40.3 are used as a proxy for illicit opioid use (hence, to evaluate substitution towards the black market). As mentioned, these data are left-truncated. When the number of visits is between 1 and 4, included, the dataset mentions 'less than 5'. For the analysis of this subsection, these observations are replaced with a number of visits equal to 4. Notice, however, that substituting for any number between 1 and 3, included, would yield similar results, with slightly larger estimates. Hence, in this sense, the approach used here can be viewed as the most conservative. I compare ED visits across poor and rich departments over time by using the following specification:

$$EDvisits_{dt} = \beta_0 + \beta_1(POOR * AFTER) + \delta_d + \phi_t + u_{dt}, \tag{7}$$

where $EDvisits_{dt}$ is the number of ED visits per 100,000 inhabitants in each department and time period. $POOR$ is a dummy equal to one if the department is classified as poor and zero, otherwise. AFTER is a dummy equal to zero for the two semester of the year 2016 and for the first semester of 2017 while it is equal to 1 for the second semester of 2017 and for the year 2018. Each regression includes department and semester fixed effects and is weighted by the department population. Eicker-Huber-White robust standard errors are applied.

Table 11. Emergency Department (ED) Visits - Difference-in-Difference Estimates

	All Departments		Extremes	
	(1) Codeine per 100,000 people	(2) Illicit opioids per 100,000 people	(3) Codeine per 100,000 people	(4) Illicit opioids per 100,000 people
Diff.-in-Diff. Estimate	0.136** (0.060)	0.050 (0.048)	0.194** (0.080)	0.070 (0.066)
Department and period fixed effects	✓	✓	✓	✓
N	564	564	270	270

Note: Robust standard errors in parenthesis. Regressions are weighted by department population.
$^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$

Results are displayed in Table 11. After the application of the law, ED visits related to Codeine increased in poor departments relative to rich departments. When restricting attention

to departments in first and last quartile of the poverty rate distribution, the magnitude of this estimate increases and remains statistically significant at 5% level. By contrast, no significant effect is found when I consider ED visits related to illicit opioids.

Despite the evident limitation of these data due to left-truncation, these results are consistent with the analyses of the previous sections. Wealthier departments feature a larger drop in Codeine-product sales after the regulatory change. A part of this demand switches to non-opioid analgesics while no significant substitution towards the black market is found. Poor departments, instead, feature a smaller drop in Codeine-product sales after the regulatory change. The share of the demand switching to non-opioid analgesics is significantly smaller than in rich departments, as these patients continue to use Codeine, even though they do not use significantly more (or more frequently) illicit opioids.

The lack of substitution effects towards the black market seems reasonable in this context. Indeed, France did not experience a proper 'opioid crisis' and the prevalence of opioid analgesic abuse and misuse is much lower than in the US. Moreover, the US opioid epidemic was mainly caused, at least in a first moment, by the widespread abuse and diversion of Oxycodone, a strong opioid for which heroin represents a close substitute. The substance under study in this paper, instead, is a mild opioid and, hence, not easily substitutable with illicit opioids available on the black market.

9 Dynamic Effects

The addictive nature of the products under study suggests a positive and significant association between consumption in a given time period and consumption one period after. This is relevant for policy purposes because it implies that the short-run and long-run effects of the policy may differ, as the policy has a cumulative impact on consumption over time. The importance of considering dynamic effects in the study of addictive products has been highlighted by prior research. Meier and Licari (1997), for instance, introduce a lagged version of the dependent variable as control to account for the dynamics of the relationship between tobacco taxes and cigarettes consumption. More recently, Pretis (2022) exploits a similar specification to study the impact of carbon taxes on emissions, where the lagged dependent variable is used to account for persistence in emissions. By following the existing literature, I use the specification in equation (8) below to evaluate the short-run and long-run effect of the policy under analysis in this paper. This specification is the same as in equation (1) of Subsection 6.2, with the exception of the additional lagged dependent variable on the right-hand side.

$$Y_{pdt} = \beta_0 + \beta_1 TREAT * AFTER + \alpha Y_{pdt-1} + \delta_d + \eta_p + \phi_t + u_{pdt}, \tag{8}$$

Table 12 reports the results. Each column refers to one of the four measures of consumption and sales. The first row reports estimates for the coefficient β_1, the DiD estimator, while the second row displays estimates for α. Since lagged consumption is now included as a control, we loose one observation for each department and product. Therefore, the total number of

observations is now equal to 28,294. The significance of the coefficient associated to lagged consumption confirms the importance of studying dynamic effects in this context. The presence of the autoregressive term means that the DiD estimate now represents the impact of the new law for the first period only. The effect for the second month is obtained by multiplying the DiD estimate by the coefficient of lagged consumption. The effect for subsequent periods is calculated in the same fashion. Hence, considering consumption in terms of MGs per 1,000 inhabitants, the impact of the policy in the second month is -79.852 x $0.870 = -69.471$, in the third month -79.852 x $(0.870)^2 = -60.440$, and so forth. The effect of the regulatory change on Codeine consumption is, therefore, increasing at a gradually decreasing rate. The long-run equilibrium effect of the policy is $\beta_1/(1-\alpha) = -614.25$. That is, in long-run (for t going to $+\infty$), the policy will induce an average decrease in consumption of 614.25 MGs per 1,000 inhabitants for each Codeine product in each department.[27]

Table 12. Dynamic Effects - Difference-in-Differences Estimates

	(1) Consumption in MG per capita	(2) Consumption in DDD per capita	(3) No of Boxes per capita	(4) Turnover per capita
DiD Estimate	-79.852***	-0.977***	-0.227***	-0.796***
	(6.797)	(0.075)	(0.016)	(0.048)
Lagged Consumption	0.870***	0.871***	0.871***	0.869***
	(0.008)	(0.008)	(0.008)	(0.007)
N	28,294	28,294	28,294	28,294

Note: Robust standard errors in parenthesis. Regressions are weighted by department population. $^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$

Analogous reasoning can be applied to evaluate the regulatory elasticity of demand in the long run. To do this, I consider the same specification as in equation (2) of subsection 7.2 by adding the lagged dependent variable as control. Results are reported in Table 13. In the long run (for t going to $+\infty$), Codeine consumption decreases, on average, by $32.433/(1-0.765) = 138$ MGs per 1,000 inhabitants more in rich departments than in poor departments.

10 Discussion

The analysis in this paper makes two important contributions. First, requiring a doctor's prescription to obtain Codeine products proves to be an effective measure for reducing legal consumption: Codeine product sales more than halved following the regulatory shift.

[27] Additional regressions show that lagged consumption on the right-hend side is significant up to three lags. Results available from the authors upon request.

Table 13. Dynamic Effects - Triple Difference Estimates

	(1) Consumption in MG per capita	(2) Consumption in DDD per capita	(3) No of Boxes per capita	(4) Turnover per capita
TD Estimate	32.433***	0.296***	0.051***	0.094**
	(7.896)	(0.084)	(0.016)	(0.045)
Lagged Consumption	0.765***	0.766***	0.766***	0.763***
	(0.014)	(0.015)	(0.014)	(0.012)
N	28,294	28,294	28,294	28,294

Note: Robust standard errors in parenthesis. Regressions are weighted by department population. $^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$

Second, departments in which the economic situation is more precarious exhibit a more 'regulatory-inelastic' demand. This is the most important novelty introduced by the paper and, hence, this result deserves further discussion.

Section 3 highlights the centralized nature of the French healthcare system. Regulations concerning medicinal products and, more broadly, the healthcare sector, are applied at the national level. There exist regional health agencies, but these play a supportive role and do not have regulatory power. Their tasks mainly consist of implementing national regulations and directives from the central government and guaranteeing the efficient allocation of healthcare resources. This facilitates the identification of causal effects in this paper since it precludes the existence of local rules or discrepancies in healthcare policies across geographical areas, which is, instead, common in the US. In addition, in the TD estimation set-up, the existence of potential discrepancies in healthcare management across areas and across time is controlled for by the department-by-period fixed effects.

As noted in Section 4, some papers find wealthy patients to consume more OTC drugs while the worse-off tend to consume more prescribed medicines. Hence, we should expect larger consumption for OTC Codeine products in richer departments before the regulatory shift and a larger drop in consumption for these products afterwards. While results in the previous sections are in line with this second prediction, they are not in line with the first. From the descriptive statistics in Section 5, we observe that poorer departments feature higher consumption for both products in the treatment and in the comparison group before the new law was applied. Moreover, in France, drug pricing is unlikely to influence the patients' choice to consume Codeine products. Most drugs in the treatment group were reimbursed even before July 2017 (when prescribed). Those who were not, and for which the price can be freely set by the pharmaceutical company, exhibit relatively low prices, which hardly constitute a barrier to access. Finally, even though discrepancies in the price and reimbursement schemes across products and across time exist, in

the TD estimation, these are controlled for by the product-by-period fixed effects.

Another strand of the literature finds poorer individuals to be less likely to visit a physician. Hence, one would expect the most deprived areas to be more sensitive to the regulatory change. However, findings in this paper contradict this prediction. The reason for this may be that, even though individuals in disadvantage are less likely to visit a physician, income inequality in the probability of seeing a GP is small. In addition, once an individual on low income engages with a GP, the former visit the later more frequently than wealthier patients. It is noteworthy here that, in France, around 90% of opioid analgesics are prescribed by GPs (Chenaf et al, 2018). The patients' insurance status is also unlikely to play a role. Although 4 million French remain uncover by health insurance (Perronnin et al., 2011), this represents less than 7% of the population.

Results in this paper seem, instead, to corroborate the 'deaths of despair' hypothesis. Poorer departments feature larger consumption of both prescribed and non-prescribed opioid analgesics before July 2017 and exhibit smaller drops in consumption after the regulatory change. This, coupled with the analysis of substitution effects, suggests that the regulatory change induced patients in poor conditions to visit a physician more frequently to obtain Codeine products. After all, pain cannot be objectively measured by a physician, and obtaining a prescribed opioid may remain a more attractive alternative than the black market.

11 Conclusion

Improving our understanding of which regulatory tools can be leveraged to limit the harmful effects of inappropriate pharmaceuticals' use is a crucial step towards enhancing pain management, opioid prescribing, and, more broadly, our healthcare systems. This paper shows that re-scheduling represents a powerful instrument in this sense and adds to a growing literature evaluating the role of supply-side interventions in the US opioid epidemic. This type of studies has the potential to enrich the portfolio of regulatory levers at the disposal of policy-makers and avoid the costly implementation of health policies that might turn out to be ineffective.

While regulation is a key factor in preventing inappropriate use, the opioid market is inhabited by a large number of stakeholders, whose behavior inevitably interacts with each other. Patients are possibly the most important stakeholders that regulations are meant to protect and prior research shows that patients' socioeconomic background matters for opioid consumption. Hence, the current tendency of the opioid literature to study the impact of regulatory and economic factors in isolation may be overlooking important aspects related to individuals' responses to national health policies. Results in the present study confirm that this is the case. Economic conditions have the potential to amplify or hinder the effect of supply-side interventions. As a result, policy-makers should carefully consider the former when evaluating the latter's impact. Increased barriers to access should move in parallel with additional pharmacovigilance and support services targeting the most deprived local communities. Information campaigns aimed at raising patients' awareness of addiction risks should be re-optimized to address the

most disadvantaged areas and individuals living in precarious conditions. The physician's role is also key here since re-scheduling requires a mandatory prescription. Doctors should be extra cautious when facing a patient with low socioeconomic status, and healthcare professional education should be intensified in underserved areas. Silhol et al. (2020) show that, in France, GPs practicing in underserved (mostly rural) areas[28] prescribe opioid analgesics more frequently. Finally, reimbursement policies may play an important role as well. Reducing reimbursement rates for opioid analgesics in order to reduce usage would obviously raise ethical issues, since this would also penalize those patients who cannot avoid using these medicines. However, a valid alternative for policy-makers would be better subsidizing non-opioid pain killers. This would provide incentives to substitute from opioid to non-opioid analgesics and this effect should be more important among individuals in economic hardship.

Last but not least, as largely documented, pharmaceutical companies represent major stakeholders in the opioid market. The imposition of barriers to Codeine consumption is likely to induce a reallocation of pharmaceutical marketing expenses across departments *and* from pharmacists to physicians since the unavailability of Codeine on the shelves renders advertising to pharmacists meaningless. Investigating how the 2017 regulatory shift has modified pharmaceutical advertising is important to understand to what extent and through which channels, policy measures can be hindered by companies' marketing efforts. Furthermore, this helps understand in which geographical areas pharmaceutical advertising can be problematic and, hence, where healthcare professionals should be more cautious about conflicts of interest emerging when interacting with companies' sales representatives.[29] This is the focus of my future research.

Understanding the interactions among multiple stakeholders in the opioid market will move us a step forward in the research of better patient-centric solutions for pain management.

[28] Underserved areas are defined as geographical locations with low GPs density.

[29] Prior research shows that pharmaceutical advertising can effectively influence physicians' prescribing behavior. Furthermore, in France, Etain et al. (2014) reports that the 85.2% of medical students do not feel prepared to face conflicts of interest arising when interacting with pharmaceutical companies.

References

[1] Alpert, A., Powell, D. and Pacula, R. L. (2018), Supply-Side Drug Policy in the Presence of Substitutes: Evidence from the Introduction of Abuse-Deterrent Opioids. *American Economic Journal: Economic Policy*. 10 (4). 1-35.

[2] Alpert, A., Evans, W., Lieber, E. and Powell, D. (2019), Origins of the Opioid Crisis and its Enduring Impacts. NBER Working Paper no. 26500. Available at `https://www.nber.org/papers/w26500`.

[3] Angrist, J. D. and Pischke, J.-S. (2009), Mostly Harmless Econometrics: An Empiricist's Companion. *Princeton University Press*.

[4] ANSM, Agence National de Sécurité du Médicament et des Produits de Santé (2020), TRAMADOL: une mesure pour limiter le mésusage en France - Point d'information. `https://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/TRAMADOL-une-mesure-pour-limiter-le-mesusage-en-France-Point-d-information`. Last access: May 2020.

[5] Arkhangelsky, D., Athey, S., Hirshberg, D. A., Imbens, G. W. and Wager, S. (2021), Synthetic Difference-in-Differences. *American Economic Review*. 111(12). 4088-4118.

[6] Athey, S. and Imbens, G. (2022), Design-Based Analysis in Difference-In-Differences Settings with Staggered Adoption. *Journal of Econometrics*. 226(1). 62-79.

[7] Benzeval, M. and Judge, K. (2001), Income and Health: the time dimension. *Social Science and Medicine*. 52. 1371-1390.

[8] Bergman, M. A., Johansson, P., Lundberg, S.and Spagnolo, G. (2016). Privatization and quality: Evidence from elderly care in Sweden. *Journal of Helath Economics*. 49. 109-119.

[9] Buchmueller, T. C. and Carey, C. (2018), The Effect of Prescription Drug Monitoring Programs on Opioid Utilization in Madicare. *American Economic Journal: Economic Policy*. 10 (1). 77-112.

[10] Butts, K. (2021), Difference-in-Differences Estimation with Spatial Spillovers, *Working Paper*. DOI: `https://doi.org/10.48550/arXiv.2105.03737`.

[11] Callaway, B. and Sant'Anna, P. H. C. (2021), Difference-in-Differences with Multiple Time Periods. *Journal of Econometrics*. 225(2). 200-230.

[12] Casati, A., Roumen, S. and Pfeiffer-Gerschel, T. (2012), Misuse of Medicines in the European Union: A Systematic Review of the Literature. *European Addiction Research*. 18. 228-245. DOI: 10.1159/000337028.

[13] Case, A. and Deaton, A. (2017), Mortality and Morbidity in the 21st Century. *Brookings Papers on Economic Activity*. Spring, 2017. 397-476.

[14] Chenaf, C., Kaboré, J.-L., Delorme, J., Pereira, B., Mulliez, A., Zenut, M., Delage, N., Ardid, D., Eschalier, A., Authier, N. (2018), Prescription opioid analgesic use in France: Trends and impact on morbidity-mortality. *European Journal of Pain*. DOI: 10.1002/ejp.1291.

[15] Currie, J. and Schwandt, H. (2020), The Opioid Epidemic Was Not Caused by Economic Distress But by Factors that Could be More Rapidly Addressed. *NBER Working Paper No. 27544*.

[16] Dave, D. M., Grecu, A. M. and Saffer, H. (2019), Mandatory Access Prescription Drug Monitoring Programs and Prescription Drug Abuse. *Journal of Policy Analysis and Management*. 38 (1). p. 181-209.

[17] de Chaisemartin, C. and d'Haultfœuille, X. (2018), Fuzzy Differences-in-Differences. *The Review of Economic Studies*. 85(2). 999-1028.

[18] de Chaisemartin, C. and d'Haultfœuille, X. (2020), Two-Way Fixed Effects Estimators with Heterogeneous Treatment Effects. *American Economic Review*. 110(9). 2964-2996.

[19] Devaux, M. and de Looper, M. (2012), Income-Related Inequalities in Health Service Utilization in 19 OECD Countries, 2008-2009. *OECD Health Working Papers, No. 59, OECD Publishing*. DOI:10.1787/5k95xd6stnxt-en.

[20] Doleac, J. L. and Mukherjee, A. (2019). The Moral Hazard of Lifesaving Innovations: Naloxone Access, Opioid Abuse, and Crime. Available at SSRN: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3135264.

[21] Etain, B., Guittet, L., Weiss, N., Gajdos, V. and Katsahian, S. (2014), Attitudes of medical students towards conflict of interest: A national survey in France. textitPLoS ONE. 9 (3). doi.org/10.1371/journal.pone.0092858.

[22] Ferman, B. and Pinto, C. (2019), Inference in Differences-in-Differences with Few Treated Groups and Heteroskedasticity. *The Review of Economics and Statistics*. 101(3). 452-467.

[23] Finkelstein, A., Gentzkow, M. and Williams, H. (2019). *What Drives Prescription Opioids Abuse? Evidence from Migration.*

[24] Foley, M., Harris, R., Rich, E., Rapca, A., Bergin, M., Norman, I. and Van Hout, M.C. (2015), The availability of over-the-counter codeine medicines across the European Union. *Public Health*. 129. 1465-1470.

[25] Ghertner, R. and Groves, L. (2018), The opioid crisis and economic opportunity: geographical and economic trends. *ASPE Research Brief*, 1-22.

[26] Goodman-Bacon, A. (2021), Difference-in-Differences with Variation in Treatment Timing. *Journal of Econometrics*. 225(2). 254-277.

[27] Gruber, J. (1994). The incidence of mandated maternity benefits. *American Economic Review*. 84 (3). 622-641.

[28] Haley, D. F., and Saitz, R. (2020), The Opioid Epidemic During the COVID-19 Pandemic, *American Medical Association.*

[29] Heritage, Z. (2009). Inequalities, social ties and health in France. *Public Health.* 123. e29-e34.

[30] HHS, Department of Health and Human Services (2020). `https://www.hhs.gov/opioids/about-the-epidemic/`. Last access: August, 2020.

[31] Hollingsworth, A., Ruhm, C. J. and Simon, K. (2017), Macroeconomic conditions and opioid abuse. *Journal of Health Economics.* 56. p. 222-233.

[32] Mackenbach, J. P., Stirbu, I., Roskam, A.-J. R., Schaap, M. M., Menvielle, G., Leinsalu, M., Kunst, A. E. (2008). Socioeconomic Inequalities in Health in 22 European Countries. *The New England Journal of Medicine.* 358 (23).

[33] Mayer, S. and Österle, A. (2014), Socioeconomic determinants of prescribed and non-prescribed medicine consumption in Austria. *European Journal of Public Health*

[34] McMchael, B. J., Van Horn, R. L., Viscusi, W. K. (2020), The impact of cannabis access laws on opioid prescribing. *Journal of Health Economics.* 69.

[35] Natali, I., Dewatripont, M., Ginsburgh, V., Goldman, M. and Legros, P. (2023, forthcoming), Prescription Opioids and Economic Hardship in France. *European Journal of Health Economics.*

[36] National Institute on Drug Abuse (2020). *Opioid Overdose Crisis.* `https://www.drugabuse.gov/drug-topics/opioids/opioid-overdose-crisis`. Last access: August, 2020.

[37] Nielsen, W. M., Hansen, E. H. and Rasmussen, N. K. (2003), Prescription and non-prescription medicine use in Denmark: association with socio-economic position. *European Journal of Clinical Pharmacology.* 59. 677-684. DOI 10.1007/s00228-003-0678-z.

[38] Nordmann, S., Pradel, V., Lapeyre-Mestre, M., Frauger, E., Pauly, V., Thirion, X., Mallaret, M., Jouanjus, E. and Micallef, J. (2013), Doctor Shopping Reveals Geographical Variations in Opioid Abuse. *Pain Physician 2013*, 16 (1), 89-100.

[39] Olden, A. and Møen, J. (2020). The Triple Difference Estimator. *NHH Dept. of Business and Management Science Discussion Paper No. 2020/1.*

[40] Orriols, L., Gaillard, J., Lapeyre-Mestre, M., Roussin, A. (2009). Evaluation of Abuse and Dependence on Drug Used for Self-Medication. A Pharmacoepidemiological Pilot Study Based on Community Pharmacies in France. *Drug Safety.* 32(10). 859-873. DOI: 10.2165/11316590-000000000-00000.

[41] Perronin, M., Aurélie, P. and Rochereau, T. (2011). Complementary Health Insurance in France: Wide-Scale Diffusion but Inequalities of Access Persist. *Institute for Research and Information in Health Economics, IRDES.* `https://www.irdes.fr/EspaceAnglais/Publications/IrdesPublications/QES161.pdf`.

[42] Pickett, K. E. and Wilkinson, R. G. (2015). Income inequality and health: A causal review. *Social Science and Medicine*. 128. p. 316-326.

[43] Powell, D., Pacula, R. L., Jacobson, M. (2018). Do medical marijuana laws reduce addictions and deaths related to pain killers?. *Journal of Health Economics*. 58. p. 29-42.

[44] Roth, J. and Sant'Anna, P. H. C. (2021), When Is Parallel Trends Sensitive to Functional Form?. *Working Paper*. DOI: `https://doi.org/10.48550/arXiv.2010.04814`.

[45] Roussin, A., Bouyssi, A., Pouché, L., Pourcel, L. and Lapeyre-Mestre, M. (2013). Misuse and Dependence on Non.Prescription Codeine Analgesics or Sedative H1 Antihistamines by Adults: A Cross-Sectional Investigation in France. PloS ONE. 8(10). DOI: 10.1371/journal.pone.0076499.

[46] Ruhm, C. J. (2018), Deaths of Despair or Drug Problems? *NBER Working Papers 24188*. National Bureau of Economic Research, https://doi.org/10.3386/w24188.

[47] Sandier, S., Polton, D., Paris, V. and Thompson, S. France in: Dixon, A. and Mossialos, E. (2002). Health Care Systems in Eight Countries: Trends and Challenges. London School of Economics and Political Science. 2002. 30-45.

[48] Schnell, M. and Currie, J. (2017). Addressing the Opioid Epidemic: Is there a Role for Physician Education?. NBER Working Paper 23645.

[49] Silhol, J., Ventelou, B. and Zaytseva, A. (2020), How French practitioners respond to declining medical density: a study on prescription practices, with an insight into opioids use. *The European Journal of Health Economics*. 21. 1391-1398.

[50] Solon, G., Haider, S. J., Wooldridge, J. M. (2015), What are we weighting for?, *Journal of Human Resources*, 50 (2), 301-316.

[51] Van Amsterdam, J. and van den Brik, W (2015), The Misuse of Prescription Opioids: A Threat for Europe?, *Current Drug Abuse Reviews*, 8, 3-14.

[52] Venkataramani, A. S., Bair, E. F., O'Brien, R. L. and Tsai, A. C. (2019), Association Between Automotive Assembly Plant Closure and Opioid Overdose Mortality in the United States. A Difference-in-Difference Analysis. *JAMA Internal Medicine*. Published online December 30, 2019, `https://doi.org/10.1001/jamainternmed.2019.5686`.

[53] Vogler, S., Österle, A. and Mayer, S. (2015), Inequalities in medicine use in Central Eastern Europe: an empirical investigation of socioeconomic determinants in eight countries. *International Journal of Equity in Health*. 14(124). DOI 10.1186/s12939-015-0261-0.

[54] Walker, W. R. (2013), The Transitional Costs of Sectoral Reallocation: Evidence from the Clean Air Act and the Workforce. *The Quarterly Journal of Economics*. 128 (4), 1787-1836.

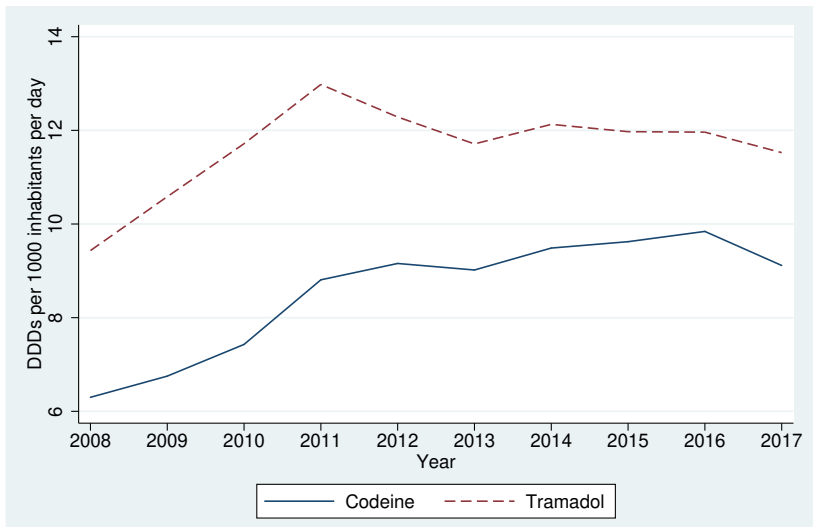
A Mild Opioid Consumption in France

This appendix describes consumption trends for Codeine and Tramadol in France over a ten-year period, from 2008 to 2017. Consumption is measured here in number of DDDs per 1000 inhabitants per day since the use of this metric permits comparison of consumption trends across different active ingredients.

Codeine and Tramadol are the most commonly used opioid analgesics in France. According to the WHO three-step ladder for treatment of chronic pain, they are classified as mild opioids even though the addiction risks related to their use remain considerable.

As mentioned, Codeine is only available in combination with other non-opioid analgesics on the French market while Tramadol can be found both alone or in combination. For Figure A1 below, consumption, in terms of DDDs, for Tramadol alone or in combination has been aggregated. The figure shows that Codeine sales have increased by 45% during the period under consideration, going from 6.3 DDDs in 2008 to 9.1 in 2017. Sales for Tramadol also rose, even though at a slower pace, going from 9.4 to 11.5 DDDs. Consumption for these two active ingredients together increased by 31% over the period.

Figure A1. Codeine and Tramadol Consumption in France



Sources: OpenHealth database; authors' calculations.

B Products and Pricing

This appendix provides a list of all products included in the treatment and control groups as well as detailed information on the French healthcare system.

B.1 Codeine Products

This list of Codeine products for the analyses in this paper has been downloaded from the ANSM (Agence National de Sécurité du Médicament et des Produit de Santé).[30]

For each product, I specify the active ingredients contained, the name of the pharmaceutical company marketing it, the ATC code and the dosages. All products have the same route of administration (oral) and indication. Specifically, each one of these product is used to treat pain of moderate intensity that can not be relieved by other analgesics such as paracetamol, ibuprofen or aspirin alone. Recall that Codeine is only available in combination on the French market. Note also that, in the last columns of Tables B1 and B2 reporting the dosages, the first quantity refers to the amount of the non-opioid analgesic used in the combination while the second quantity refers to the amount of Codeine.

The Anatomical Therapeutic Chemical (ATC) classification is a drug classification system established by the WHO and existing since 1976. It codes each active substance (and combination of active substances) according to their therapeutic, pharmacological and chemical properties and depending on the organ or system of the human body that they target. In this system, the first entry (1st level) indicates the drug's anatomical or pharmacological group, the second couple of digits (2nd level) indicates the pharmacological or therapeutic subgroup, the 3rd and 4th levels refer to the chemical, pharmacological or therapeutical subgroup and the 5th level indicates the chemical substance. In the case at hand, N means that the product acts on the nervous system; 02 refers to analgesics; A tells us that the analgesics in question contain an opioid; J is used to indicate combinations of opioids with non-opioid analgesics. Most products under examination share the same code up to the 4th level while the 5th level clearly differs, due to different non-opioid analgesics used in combination with Codeine. For instance, 06 indicates combinations of Codeine and Paracetamol whereas 08 refers to combinations of Codeine with Ibuprofen.

B.2 The National Health Insurance

The French healthcare system guarantees universal coverage through the National Health Insurance scheme. By law, all those who reside in France for at least three months must be registered with a health insurer. For French residents, a subscription to an insurance fund is automatic and based on their occupation.[31] There are three main insurance funds: Caisse Na-

[30] available at `http://dev4-afssaps-marche2017.integra.fr/S-informer/Points-d-information-Points-d-information/L-ANSM-publie-la-liste-des-medicaments-contenant-de-la-codeine-du-dextromethorphane-de-l-ethylmorphine-ou-de-la-noscapine-desormais-disponibles-uniquement-sur-ordonnance-Point-d-Information`

[31] Note that retirees, students, interns, beneficiaries of a minimum revenue allowance (e.g., recipients of the Revenu de Solidarité Active, RSA), and unemployed individuals receiving jobless benefits are also

tionale d'Assurance Maladie des Travailleurs Salariés (CNAMTS) targeting salaried employees, Mutualité Sociale Agricole (MSA) concerning those working in agriculture, and Caisse National d'Assurance Maladie des Professions Indépendentes (CANAM) for autonomous professionals. The first of these is the most common and covers over 80% of the population (Sandier et al., 2002). The national insurance system covers a considerable part of medical expenses, that is, about 70% of doctors' fees and about 80% of hospital costs. The remaining part represents out-of-pocket spending, which is paid either by the patient or through supplementary insurance. 90% of French residents own a supplementary health insurance (Sandier et al., 2002), while patients whose income is below a certain threshold are entitled to receive the Universal Complementary Health Insurance (Couverture Maladie Universelle Complémentaire, CMU-C) or the State Medical Assistance (Aide au Paiement d'une Complémentaire Santé, ACS).[32] In particular, the CMU-C provides free supplementary coverage to those individuals whose income is below 634 euros per month. The ACS, instead, covers half of the supplementary insurance cost and targets individuals whose income is below 26% of the CMU-C threshold. Despite this, Perronnin et al. (2011) observe that around 4 million people still lack supplementary health insurance. These individuals most often belong to the poorest households, feature worse self-reported health and higher levels of forgone care.

B.3 Physicians' fees and reimbursement

In France, each resident is free to select a family doctor ('médecin traitant') of his/her choice. When visiting a doctor, the patient pays an up-front fee, which is then reimbursed by the insurance. Although around 70% of GPs in France are self-employed and paid on a fee-for-service basis, physicians' fees are highly regulated. The up-front fee that general practitioners can charge is established annually at the national level through negotiations involving the three main insurance funds, the State, and physicians' associations. Since 2017, doctors' fees have been set at 25 euros per consultation. These fixed fees apply to all general practitioners, except to those that explicitly opt out. Indeed, in France, doctors can belong to one of two branches, called 'secteur 1' and 'secteur 2'. Only physicians belonging to the latter are allowed to set fees higher than those negotiated with the State.[33] However, access to 'secteur 2' was closed in 1992 to reduce primary care expenditure. Consequently, the vast majority of physicians (around 90%) now belong to 'sectuer 1'.

B.4 Pricing and reimbursement of drugs

Pharmaceutical pricing and reimbursement schemes are also highly regulated in France. As for physicians' fees, treatments and drugs are mostly reimbursed by national health insurance.

covered.

[32] Since the 1^{st} November 2019, these instruments have been replaced by the Complémentaire Santé Solidaire.

[33] The majority of these are specialists.

The procedure for a new drug to reach the market is articulated in several steps. First, the medicine must receive marketing authorization (Autorisation de Mise sur le Marché, AMM) by the European or national authorities.[34] This marketing authorization is issued for a period of five years and is renewable.[35]

Conditional on receiving an AMM, the drug manufacturer may decide whether to apply for the medicine to be reimbursed by Social Security. If the pharmaceutical company does not apply for reimbursement, the product can be directly launched onto the market, and the patient has to pay its full price, which the company can freely set. If, instead, the manufacturer requires reimbursement, the medicine is assessed by a Transparency Committee (Commission de la Transparence). Its task consists of evaluating the drug's therapeutic benefit (Service Médical Rendu, SMR), its added value relative to existing treatments (Amélioration du Service Medical Rendu, ASMR), and providing suggestions on the reimbursement rate.[36]

After this, negotiations are carried out between the drug manufacturer and an Economic Committee for Health Products (Comité Economique des Produits de Santé), composed of representatives of the Ministry of Health and the Ministry of Economy and Finance. The drug's price is the result of these negotiations[37] and depends mainly on the ASMR of the new drug.[38]

Finally, the National Healthcare Insurance Funds (Union Nationale des Caisses d'Assurance Maladie, UNCAM) establishes the reimbursement rate, which varies according to the product's medical benefit (SMR). The Health Ministry eventually decides whether to include the drug on the registry of reimbursable medicines. The duration of this inscription is five years,[39] after which the Transparency Committee must reassess the drug. Once the described procedure is concluded, the new drug can be launched onto the market.

In the French context, it is important to distinguish between two types of OTC drugs: (i) OTC products that can be bought without a prescription and, even when prescribed, are not reimbursed; (ii) OTC products for which a prescription is not compulsory, that can be bought without a prescription, but, when prescribed, are reimbursed. Tables B3 and B4 report the price and reimbursement rate for each Codeine product in the present study. This information is extracted from `http://base-donnees-publique.medicaments.gouv.fr`.[40] The control group is formed by products for which a prescription has always been compulsory during the sample period (the 'always regulated' products), and all of them, except one, are reimbursable. The treatment group includes both products that, before July 2017, were not reimbursed, even when prescribed, and products for which the prescription was not compulsory, but would be reimbursed,

[34] At the European level, the regulatory agency in charge of providing marketing authorization is the European Medicines Agency (EMA). At the national level, this is the National Agency for the Safety of Medicines and Health Products (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM).

[35] Article L. 5121-8 et L. 5121-9 du code de la santé publique.

[36] Article R. 163-5 I 2 du code de la sécurité sociale.

[37] The public price of a medicinal product includes the wholesalers and pharmacies' margins, who are also regulated at the national level. Pharmacies have a monopoly on the retail distribution of drugs.

[38] Article R. 163-16-4 du code de la sécurité sociale.

[39] Article R. 163-2 du code de la sécurité sociale.

[40] When information was missing on this website, it was complemented through an Internet search.

when prescribed. The July 2017 regulatory shift imposed a compulsory prescription for products in the treatment group but did not change their reimbursement regime.

B.5 Drugs' Scheduling

In France, drugs are classified into different lists according to the risks linked to their use. Scheduled medicines entail higher risks than non-scheduled ones. Medicines in *Liste 1* are associated with higher risks than those in *Liste 2*. *Stupefiants* stands for narcotics and are considered the most dangerous. Each list features different rules concerning the type and length of the prescription, and the possibility to market the products through the Internet or media. In more detail, *Médicaments non listés* can be obtained at the pharmacy without a prescription and can be reimbursable or not. It is possible to distinguish between *médicaments conseils*, suggested by the pharmacists to a patient asking advice, and *médicaments grand publique* that can be marketed through media and requested by the patient to the pharmacist. Notice that, even before July 2017, advertising of OTC Codeine products through media was not allowed since the French law forbids the advertisement of narcotic drugs to the general public. For both *Liste 1* and *Liste 2* drugs, it is required a simple prescription form. However, while for the latter the prescription can be renewed, for the former, the prescription is usually non-renewable and its duration cannot exceed 12 months. Finally, *Stupefiants* need a special prescription form, called 'ordonnance sécurisée'. The prescription's duration cannot exceed 28 days, but this term can vary between 7 and 28 days, depending on the active substance.

Table B1. Codeine Products in Treatment Group

Product	Active Ingredients	Company	ATC Code	Dosages
ALGISEDAL, comprimé (16)	Codeine and Paracetamol	MYLAN MEDICAL SAS (MEDAPHARMA)	N02AJ06	400mg/25mg
ALGICALM 400mg/25mg, comprimé (16)	Codeine and Paracetamol	COOPERATION PHARMACEUTIQUE FRANÇAISE	N02AJ06	400mg/25mg
CLARADOL CODEINE 500mg/20mg, comprimé (16)	Codeine and Paracetamol	BAYER SANTE FAMILIALE (TEOFARMA srl)	N02AJ06 (N02BE51)	500mg/20mg
CODOLIPRANE ADULTES 400mg/20mg, comprimé sécable (16)	Codeine and Paracetamol	SANOFI AVENTIS FRANCE	N02AJ06 (N02BE51)	400mg/20mg
COMPRALGYL 400mg/20mg, comprimé sécable (16)	Codeine and Paracetamol	GIFRER BARBEZAT	N02AJ06 (N02AA59)	400mg/20mg
GAOSEDAL CODEINE, comprimé (12)	Codeine and Paracetamol	MERCK MEDICATION FAMILIALE SAS	N02AJ06 (N02BE51)	500mg/20mg
KLIPAL CODEINE 300mg/25mg, comprimé (16)	Codeine and Paracetamol	PIERRE FABRE MEDICAMENT	N02AJ06 (N02BE51)	300mg/25mg
LINDILANE 400mg/25mg, comprimé (16)	Codeine and Paracetamol	GRUNENTHAL	N02AJ06 (N02BE51)	400mg/25mg
MIGRALGINE, gélule (12-18)	Paracetamol, Cafeine and Codeine	JOHNSON JOHNSON SANTE BEAUTE FRANCE	N02BE51 (N02AA59)	400mg/62,5mg/20mg
NOVACETOL, comprimé (24)	Acide acétylsalicylique, Paracetamol and Codeine	LABORATOIRE PHARMASTRA	N02BA51	300mg/187,5mg/ 62,5mg/10mg
PARACETAMOL CODEINE ARROW 400mg/20mg, comp. séc. (16)	Codeine and Paracetamol	ARROW GENERIQUES	N02AJ06 (N02BE51)	400mg/20mg
PRONTALGINE, comprimé 18	Paracetamol, Cafeine and Codeine	BOEHRINGER INGELHEIM FRANCE (IPSEN CONSUMER HEALTHCARE)	N02BE51	400mg/50mg/20mg
SEDASPIR, comprimé (20)	Acide acétylsalicylique, Cafeine and Codeine	LABORATOIRE BRIDE	N02BA51	500mg/50mg/20mg

Table B2. Codeine Products in Comparison Group

Product	Active Ingredient	Company	ATC Code	Dosages
ANTARENE CODEINE 200mg/30mg, comprimé pelliculé (20)	Codeine and Ibuprofen	LABORATOIRE DES REALISATIONS THERAPEUTIQUES ELERTE	N02AJ08 (N02AA59)	200mg/30mg
ANTARENE CODEINE 400mg/60mg, comprimé pelliculé (10)	Codeine and Ibuprofen	LABORATOIRE DES REALISATIONS THERAPEUTIQUES ELERTE	N02AJ08 (N02AA59)	400mg/60mg
CODOLIPRANE 500mg/30mg, comprimé (16)	Codeine and Paracetamol	SANOFI AVENTIS FRANCE	N02AJ06 (N02BE51)	500mg/30mg
CODOLIPRANE 500mg/30mg, comprimé eff. sécable (16)	Codeine and Paracetamol	SANOFI AVENTIS FRANCE	N02AJ06 (N02BE51)	500mg/30mg
DAFALGAN CODEINE, comprimé pelliculé (16)	Codeine and Paracetamol	BRISTOL MYERS SQUIBB - UPSA SAS	N02AJ06 (N02BE51)	500mg/30mg
DAFALGAN CODEINE, comprimé effervescent sécable (16)	Codeine and Paracetamol	BRISTOL MYERS SQUIBB - UPSA SAS	N02AJ06 (N02BE51)	500mg/30mg
DOLIPRANE CODEINE 400mg/20mg, comprimé sécable (16)	Codeine and Paracetamol	SANOFI AVENTIS FRANCE	N02AJ06 (N02BE51)	400mg/20mg
KLIPAL CODEINE 600mg/50mg, comprimé (12)	Codeine and Paracetamol	PIERRE FABRE MEDICAMENT	N02AJ06 (N02BE51)	600mg/50mg
PARACETAMOL CODEINE ARROW 500mg/30mg, comprimé eff. sécable (16)	Codeine and Paracetamol	ARROW GENERIQUES	N02AJ06 (N02BE51)	500mg/30mg
PARACETAMOL CODEINE BIOGARAN 500mg/30mg, comprimé eff. sécable (16)	Codeine and Paracetamol	BIOGARAN	N02AJ06 (N02BE51)	500mg/30mg
PARACETAMOL CODEINE CRISTERS 500mg/30mg, comprimé eff. sécable (16)	Codeine and Paracetamol	CRISTERS	N02AJ06 (N02BE51)	500mg/30mg
PARACETAMOL CODEINE EG 500mg/30mg, comprimé eff. sécable (16)	Codeine and Paracetamol	EG LABORATOIRE	N02AJ06 (N02BE51)	500mg/30mg
PARACETAMOL CODEINE MYLAN 500mg/30mg, comprimé eff. sécable (16)	Codeine and Paracetamol	MYLAN SAS	N02AJ06 (N02BE51)	500mg/30mg
PARACETAMOL CODEINE SANDOZ 500mg/30mg, comprimé eff. sécable (16)	Codeine and Paracetamol	SANDOZ SAS	N02AJ06 (N02BE51)	500mg/30mg

Table B3. Codeine Products in Treatment Group

Product	Price	Reimbursement
ALGISEDAL, comprimé (16)	2.74 €	65%
ALGICALM 400mg/25mg, comprimé (16)	3.63 €*	N.A.
CLARADOL CODEINE 500mg/20mg, comprimé (16)	2.74 €	65%
CODOLIPRANE ADULTES 400mg/20mg, comprimé sécable (16)	2.74 €	65%
COMPRALGYL 400mg/20mg, comprimé sécable (16)	5.62 €*	N.A.
GAOSEDAL CODEINE, comprimé (12)	6.00 €*	N.A.
KLIPAL CODEINE 300mg/25mg, comprimé (16)	2.64 €	65%
LINDILANE 400mg/25mg, comprimé (16)	2.74 €	65%
MIGRALGINE, gélule (12-18)	5.90/6.90 €*	N.A.
NOVACETOL, comprimé (24)	5.83 €*	Free price (not reimbursable)
PARACETAMOL CODEINE ARROW 400mg/20mg, comp. séc. (16)	2.53 €	65%
PRONTALGINE, comprimé (18)	7,87 €*	Free price (not reimbursable)
SEDASPIR, comprimé (20)	6.00 €*	N.A.

Source: `http://base-donnees-publique.medicaments.gouv.fr`. *N.A.* indicates that the information is not available on this website. The * indicates that the price is the average observed price from on Internet search.

Table B4. Codeine Products in Comparison Group

Product	Price	Reimbursement
ANTARENE CODEINE 200mg/30mg, comprimé pelliculé (20)	3.03 €	65%
ANTARENE CODEINE 400mg/60mg, comprimé pelliculé (10)	3.03 €	65%
CODOLIPRANE 500mg/30mg, comprimé (16)	2.74 €	65%
CODOLIPRANE 500mg/30mg, comprimé eff. sécable (16)	2.74 €	65%
DAFALGAN CODEINE, comprimé pelliculé (16)	2.74 €	65%
DAFALGAN CODEINE, comprimé effervescent sécable (16)	2.74 €	65%
DOLIPRANE CODEINE 400mg/20mg, comprimé sécable (16)	4.16 €*	N.A.
KLIPAL CODEINE 600mg/50mg, comprimé (12)	2.74 €	65%
PARACETAMOL CODEINE ARROW 500mg/30mg, comprimé eff. sécable (16)	2.74 €	65%
PARACETAMOL CODEINE BIOGARAN 500mg/30mg, comprimé eff. sécable (16)	2.74 €	65%
PARACETAMOL CODEINE CRISTERS 500mg/30mg, comprimé eff. sécable (16)	2.74 €	65%
PARACETAMOL CODEINE EG 500mg/30mg, comprimé eff. sécable (16)	2.74 €	65%
PARACETAMOL CODEINE MYLAN 500mg/30mg, comprimé eff. sécable (16)	2.74 €	65%
PARACETAMOL CODEINE SANDOZ 500mg/30mg, comprimé eff. sécable (16)	2.74 €	65%

Source: `http://base-donnees-publique.medicaments.gouv.fr`. *N.A.* indicates that the information is not available on this website. The * indicates that the price is the average observed price from on Internet search.

C Event-Study Coefficient Estimates

Table C1. Granger Test - Coefficient Estimates

	(1) Consumption in MG per capita	(2) Consumption in DDD per capita	(3) No of Boxes per capita	(4) Turnover per capita
Regulation (t-6)	19.817	0.181	0.032	0.059
	(25.533)	(0.272)	(0.054)	(0.145)
Regulation (t-5)	33.262	0.303	0.052	0.096
	(23.174)	(0.246)	(0.048)	(0.131)
Regulation (t-4)	-9.766	-0.083	-0.013	-0.022
	(26.526)	(0.282)	(0.055)	(0.150)
Regulation (t-3)	18.627	0.175	0.032	0.071
	(24.347)	(0.259)	(0.051)	(0.138)
Regulation (t-2)	2.597	0.030	0.008	0.025
	(23.743)	(0.253)	(0.050)	(0.134)
Regulation (t)	70.485***	0.640***	0.110**	0.197
	(21.927)	(0.233)	(0.046)	(0.129)
Regulation (t+1)	89.483***	0.827***	0.145**	0.283*
	(30.175)	(0.320)	(0.062)	(0.165)
Regulation (t+2)	82.812***	0.761***	0.133***	0.254**
	(23.205)	(0.246)	(0.048)	(0.130)
Regulation (t+3)	68.480***	0.622**	0.107**	0.193
	(24.613)	(0.261)	(0.051)	(0.137)
Regulation (t+4)	71.984***	0.653**	0.112**	0.200
	(24.770)	(0.263)	(0.051)	(0.139)
Regulation (t+5)	102.786***	0.953***	0.168***	0.331**
	(25.867)	(0.275)	(0.054)	(0.145)
N	30,926	30,926	30,926	30,926

Note: Robust standard errors in parenthesis. Regressions are weighted by department population.
$^{*}p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$