When Do Supply-Side Drug Policies Save Lives? Evidence from Pharmacy Methadone Restrictions

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Abstract

The literature commonly finds that supply-side drug policies are ineffective because they cause substitution to more dangerous illicit drugs. We provide evidence of a policy that sharply contradicts this. In 2008, policymakers halted shipments of highly potent methadone products to all U.S. pharmacies due to concerns about rising methadone overdose mortality rates. Rather than causing substitution to illicit drugs, we show this response caused substitution to safer methadone products and prevented roughly 1,600 overdose deaths. Findings underscore that supply-side drug policies can be an effective response to drug epidemics in a context where they reduce accidental exposures to harmful drugs.

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I. Introduction

Limiting deaths from dangerous and addictive substances, such as alcohol, opioids, sedatives, and stimulants, is a major focus of U.S. drug policy. Many policies pursue this goal by restricting or eliminating the legal supply of certain substances. A common concern in the literature is that such "supply-side drug policies" will fail to reduce harm—or even increase it—by forcing production underground and causing people to substitute to more dangerous illicitly made products. Examples of empirical studies finding this effect include studies of alcohol prohibition in the 1920s (Miron & Zwiebel, 1995), efforts to restrict methamphetamine precursor supply in the early 2000s (Dobkin et al., 2014; Dobkin & Nicosia, 2009), and recent policy responses to the U.S. opioid crisis such as reformulating the blockbuster opioid *OxyContin* to be abuse-deterrent (Alpert et al., 2018; Evans et al., 2019; Powell & Pacula, 2021).

This literature raises the question of whether the public health benefits of restricting harmful and addictive substances can ever be positive. Indeed, considering this literature, many drug policy scholars and advocates argue that there is no role for supply-side drug policies to improve public health outcomes.[1] In this article, we argue that this view is not always the correct one. To do so, we document the remarkable public health effectiveness of a supply-side policy that was implemented in response to the prescription opioid crisis in the early 2000s.

In January 2008, the U.S. Drug Enforcement Administration (DEA) and pharmaceutical manufacturers ended the distribution of methadone 40mg diskettes (methadone diskettes, hereafter) to all pharmacies nationwide. Methadone diskettes are highly potent opioids that are clinically indicated for treating opioid use disorders. Due to their potential for misuse, people using methadone diskettes for opioid use disorder treatment could only access them through highly regulated opioid use disorder treatment programs. However, starting in the early 2000s, methadone diskettes were increasingly prescribed off-label for pain due to their status as a low-cost alternative to branded opioids like *OxyContin* (GAO, 2009, p. 8). While lower-potency forms of methadone can be appropriate for pain treatment, the highly potent diskettes are not;

[1] For recent examples, see Beletsky and Davis, 2017, "Today's fentanyl crisis: Prohibition's Iron Law, revisited," *International Journal of Drug Policy*, 14: 156-159; Miron, Sollenberger, and Nicolae, 2019, "Overdosing on Regulation: How Government Caused the Opioid Epidemic," *CATO Institute*, Policy Analysis No. 864; and Drug Policy Alliance 2023 Press Release, "In Response to House Vote on Xylazine Criminalization, Hundreds of Medical Experts, Scientists, Advocates call for a Public Health Approach," available at: https://drugpolicy.org/news/in-response-to-house-vote-on-xylazine-criminalization-hundreds-of-medical-experts-scientists-advocates-call-for-a-public-health-approach/.

moreover, they place users at considerable risk of death. Thus, the increases in methadone diskette use for pain treatment were accompanied by a 606 percent increase in methadone overdose death rates from 1999 to 2007, outpacing the rise in prescription opioid death rates over the same period. Ultimately, this led the DEA and manufacturers to intervene by halting methadone diskette shipments to all pharmacies in January 2008.

We study this restriction's impacts on methadone supply and mortality, as well as on mortality from potential substitute opioids. To estimate effects on methadone supply, we use pharmacy-level data on all prescription opioid shipments (including methadone) from the Automation of Reports and Consolidated Ordering System. We calculate quantities of opioid shipments (denominated in morphine milligram equivalents [MMEs] per capita) to all pharmacies in all counties on a quarterly basis. To examine mortality effects, we use data on methadone and other drug overdose death rates from the Centers for Disease Control's restricted-use National Vital Statistics System data for the same period.

Our primary analysis studies the restriction's impacts for 2.5 years after it was implemented (i.e., through mid-2010). This is before other major supply-side opioid policy responses, such as increased enforcement (Donahoe, 2024), the introduction of abuse-deterrent *OxyContin* (Alpert et al., 2018; Evans et al., 2019), and implementation of modern prescription drug monitoring programs (Horwitz et al., 2021). We identify the causal effects of the restriction using a continuous treatment difference-in-differences design that takes advantage of county-level heterogeneity in pre-restriction methadone diskette shipments. The design is similar to empirical models used in previous studies of the effects the *OxyContin* reformulation on mortality (Alpert et al., 2018; Powell & Pacula, 2021). We also show that our results are robust to several alternative specifications, including models that include additional years of post-treatment data, non-parametric difference-in-differences models, and models that are stratified by individual and county factors that could drive heterogeneous patterns of substitution to illicit substances (age, sex, and county pre-restriction heroin death rates).

Our main finding is that the restriction caused substantial, immediate, and persistent reductions in methadone shipments and overdose deaths. Further, we find that the restriction did *not* cause increased overdose deaths involving any other potential substitute drugs, including prescription opioids or heroin. Rather, the restriction caused substitution from relatively high-risk methadone 40mg diskettes to lower risk 10mg methadone tablets. Although methadone users

could have substituted each 40mg diskette for an equivalent amount of 10mg tablets, they did not do so, resulting in significant reductions in overall methadone supply and use.

Ultimately, this policy-induced substitution to lower-risk substances was highly effective at preventing mortality. In total, we estimate the restriction prevented roughly 1,600 total overdose deaths over 2.5 years. This equates to the restriction preventing approximately one death per every 889 averted diskette prescriptions.

Our findings stand in sharp contrast to a large body of literature that concludes supply-side restrictions are ineffective at preventing mortality (Dobkin & Nicosia, 2009; Dobkin et al., 2014; Alpert et al., 2018; Evans et al., 2019; Balestra et al., 2021; Kim, 2021; Powell & Pacula, 2021). However, it is consistent with recent studies that reached different conclusions in other settings (Moore & Schnepel, 2021; Donahoe, 2024; Soliman, 2024). Findings have major policy implications for addressing drug epidemics. Economists and policymakers should not assume that substitution effects will cause supply-side restrictions to be ineffective. We add to evidence that substitution is likely following such restrictions but show that it can lead to significant public health improvements when substitute products are safer than those being restricted.[2] This highlights the importance of understanding the context in which supply-side restrictions occur to predict the behavioral responses that they will induce.

One useful comparison is with the *OxyContin* reformulation, a supply-side policy that was rendered ineffective by substitution to illicit substances (Alpert et al., 2018; Evans et al., 2019). What explains the differences in substitution patterns induced by *OxyContin* reformulation and methadone diskette discontinuation? *OxyContin* reformulation largely targeted intentional opioid misuse. Discontinuing methadone diskettes, on the other hand, targeted accidental misuse due to patients and their clinicians being unaware of the risks of using high-potency methadone for pain treatment (GAO, 2009, p. 20). While there is a clear theoretical rationale for substitution from legal to illegal substances when use is deliberate and supply is disrupted, there is not when misuse is accidental. Instead, one would expect substitution to closely related legal substances under the purview of clinicians, as we find in our analyses. We conclude that supply-side drug policies are more effective at reducing harm when exposure is accidental. Of course, more research is needed to confirm the generalizability of this conclusion.

[2] See also Bradford & Lozano-Rojas (2023) for an example of heroin sellers and users substituting to safer substances (prescription opioids) in response to a heroin shortage in Colombia.

More broadly, our study contributes to a larger literature that highlights the importance of supply-side factors in driving the U.S. opioid epidemic (Ruhm, 2019; Alpert et al., 2021; Arteaga & Barone, 2021; Cutler & Glaeser, 2021; Eichmeyer & Zhang, 2022). While factors that drive demand for opioids (e.g., psychological despair) have played important roles in the extent of the epidemic in particular segments of the population (Case & Deaton, 2017, 2020), our work suggests that supply-side factors (e.g., whether to authorize the sale of a specific substance) remain important determinants of outcomes. In particular, results reinforce that policymakers can address drug epidemics through drug control policies and not solely through addressing social problems that lead to drug use, as some have argued (Dasgupta et al., 2018).

Our paper proceeds as follows. Section II reviews background information on methadone shipments and mortality in the context of the broader opioid epidemic. Sections III, IV, and V cover data sources, our empirical strategy, and results. Section VI concludes.

II. Background on Methadone and the Opioid Epidemic

Opioid overdose death rates in the U.S. have been increasing for decades. The first wave of the epidemic is commonly dated to the mid-1990s and involved rising rates of overdose deaths from legally prescribed opioids through the early 2010s (Moore & Pacula, 2021). It is widely attributed to aggressive prescription opioid marketing tactics and inadequate oversight of opioid supply, which enabled a 400 percent rise in opioid prescribing and overdose deaths (Alpert et al., 2021; Cutler & Glaeser, 2021; Arteaga & Barone, 2021).

Methadone also emerged as a national policy issue during the first wave of the opioid epidemic. Methadone is a synthetic opioid that was developed in the 1930s in Germany. It was introduced to the U.S. in 1947 and was available in a variety of generic forms by the 1990s. As such, methadone emerged as a much cheaper alternative to branded opioids like *OxyContin* that were being heavily marketed. Cost savings were sufficiently large relative to branded opioids that commercial and Medicaid insurers encouraged or even required providers to prescribe methadone as first-line treatment for pain over other opioids (Webster et al., 2011). Clinical guidelines and reviews furthered these shifts by describing methadone as an attractive option for treating chronic pain (Chou et al., 2009; Lynch, 2005).

Between 1999 and 2007, methadone overdose death rates increased by 2 deaths per 100,000 (606 percent) (see **Figure 1**), outpacing prescription opioid overdose death rate

increases. This led the U.S. Drug Enforcement Administration (DEA) to convene a working group on methadone deaths in April 2007.[3] The group concluded that a large part of the problem stemmed from 40mg methadone diskettes being used inappropriately for pain treatment.

Three types of methadone were available during our study period: 5mg tablets, 10mg tablets, and 40mg water-soluble diskettes. The lower-potency tablets are approved by the Food and Drug Administration (FDA) for treating pain, whereas the higher-potency 40mg diskettes are approved for treating opioid use disorders (FDA, 2007). These clinical indications are important because the 40mg diskettes are extremely potent, equivalent in potency to 320 milligrams of morphine.[4] This amount is enough to cause death in people without high opioid tolerance. The DEA working group concluded that these high-potency products were increasingly being used inappropriately for pain treatment. Governmental investigations further concluded that this inappropriate use was due to the lack of awareness of these risks (GAO, 2009, p. 20).

To address this issue, at the behest of the DEA, methadone manufacturers agreed to stop shipping methadone diskettes to all pharmacies nationwide starting January 2008. Using administrative data on all U.S. opioid shipments, which we describe below in Section III, **Figure 2** shows trends in diskette shipments to pharmacies (which were subject to this restriction) and opioid treatment programs (which were not) before and after this policy was implemented. The restriction abruptly reduced methadone diskette shipments to pharmacies, with shipments falling by 14.3 million units from the end of 2007 to the beginning of 2008. Methadone diskette shipments to opioid use disorder treatment programs (which were not subject to the restriction) continued the same trend that they were on prior to the restriction. In the remainder of the paper, we study what affect this large and abrupt reduction in methadone diskette shipments had on methadone supply and mortality, as well as mortality from other potential substitute opioids.

Notably, this restriction—which was implemented in January 2008—is one of the earliest major supply-side responses to the U.S. opioid crisis. Other significant responses include increased enforcement targeting excessive opioid prescribers, pharmacies, and distributors

[3] See DEA, 2007, "Methadone Mortality Working Group." Available at: https://www.deadiversion.usdoj.gov/drug_chem_info/methadone/methadone_presentation0407_revised.pdf.

[4] Beyond its potency, there are two additional reasons methadone can pose a high risk of overdose compared to other opioids. First, unlike other opioids, the potency of methadone increases non-linearly at higher doses. As an example, taking 40mg of methadone at once is 8x more potent than taking 10mg of methadone at once despite 40mg just being 4x the amount of active ingredient. Second, another unique feature of methadone is that it remains present in a person's system for longer than people can feel its effects. This can cause a person to take more methadone even though they still have it in their system.

starting in June 2010 (Donahoe, 2024), the reformulation of *OxyContin* to be abuse deterrent in August 2010 (Alpert et al., 2018; Evans et al., 2019), and the implementation of modern must-access prescription drug monitoring programs starting around 2013 (Horwitz et al., 2021).

III. Sources of Data

We use two national data sets on prescription opioid supply and mortality. Opioid supply data comes from the DEA's transaction-level Automation of Reports and Consolidated Orders System from 2006 to 2014, released by the DEA under a court order in 2019 (SLCG Economic Consulting, 2006). These data comprehensively track the manufacture, distribution, and endpoints (typically pharmacies, opioid treatment programs, practitioner offices, or hospitals) of all prescription opioids circulating in the U.S. We use them to quantify total shipments of methadone—overall and for each dosage strength—and potential substitute opioids to pharmacies in all U.S. counties. We present data using standardized units that account for the potency of different products (denoted morphine milligram equivalents [MMEs]).

Data on overdose death rates come from restricted-use National Vital Statistics System data from the National Center for Health Statistics from 2006 to 2014 (National Center for Health Statistics, 2022). We follow coding conventions used in prior literature to identify deaths involving methadone, natural prescription opioids (e.g., *OxyContin*), heroin, synthetic opioids other than methadone (e.g., fentanyl), and any drug (opioid or otherwise).[5]

Lastly, we obtained age- and sex-specific population counts for each county and year from the Surveillance Epidemiology and End Results (SEER) program. We used the population data to denominate opioid shipments on a per capita basis and calculate age- and sex-adjusted (to the U.S. 2010 population) overdose death rates per 100,000 people for each county and period.

[5] Drug overdose deaths were identified based on the International Classification of Diseases (ICD), 10th edition underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Overdoses by category were identified by multiple-cause-of-death codes T40.1 (heroin), T40.2 (prescription opioids = natural and semisynthetic opioids), T40.3 (methadone), and T40.4 (fentanyl/tramadol = synthetic opioids other than methadone). Total opioid deaths also included code T40.6 (other/unspecified narcotics). Deaths involving more than one opioid category are counted in both. See Hedegaard, Miniño, and Warner (2020) for more details.

IV. Empirical Approach

a. Primary estimating equations

We estimate the causal effects of restricting methadone diskette shipments to pharmacies on opioid shipments and health outcomes by taking advantage of geographic variation in exposure to the restriction. **Supplementary Appendix Figure A1** displays geographic variation in treatment exposure by mapping county-level variation in 40mg diskette shipments in the fourth quarter of 2007, just preceding the intervention. We observe tremendous variation. Thirty-eight percent of counties did not receive any diskette shipments and would have been unaffected by the restriction. At the same time, some counties received many methadone diskette shipments and would have experienced sharp declines in diskette supply after the restriction. For example, counties above the 95th percentile of baseline exposure received roughly enough shipments to provide one diskette to every 10 people in the county.

Taking advantage of this extensive geographic variation in exposure to the restriction, we estimate a continuous treatment event study model,

$$Y_{c,t} = \beta_r d_c \times \theta_{r(2008Q1)} + \alpha_c + \tau_t + \epsilon_{c,t}, \quad (1)$$

where $Y_{c,t}$ denotes outcomes (opioid shipments or overdose deaths rates) for county c in quarter-year t; d_c denotes the quantity of methadone 40mg diskettes distributed to pharmacies in each county in 2007Q4 (just before the restriction); and $\theta_{r(2008Q1)}$ is a vector of indicators for each quarter relative to the restriction (2008Q1). We normalize the period just before the restriction (2007Q4) to zero. Lastly, α_c and τ_t are county and time fixed effects, and $\epsilon_{c,t}$ is an error term. The coefficients β_r give the differential change in the outcomes for areas with one MME per capita greater exposure to the restriction for each quarter relative to the restriction.

We also present the analogous pooled difference-in-differences model:

$$Y_{c,t} = \beta d_c \times Post_t + \alpha_c + \tau_t + \epsilon_{c,t}, \quad (2)$$

where $Post_t$ is an indicator for the post-restriction period (i.e., January 2008 and after). We weight all regressions by county population and cluster standard errors at the county-level. Our

main analysis focuses on the time-period from 2006Q1-2010Q2, cutting off just before other major supply-side responses to the opioid crisis that began to be implemented around mid-2010 (Alpert et al., 2018; Evans et al., 2019; Donahoe, 2024). However, we also show that we obtain similar results over longer time intervals.

b. Robustness exercises

i. Non-parametric models

Identification of equation (2) relies on the strong parallel trends assumption, that the evolution of potential outcomes for counties that experienced a given dose of exposure to the restriction (denote d) equals the realized outcomes of the counties that experienced dose d (Callaway et al., 2024). This is like the standard parallel trends assumption but imposes additional restrictions on treatment effect heterogeneity. We assess the plausibility of this assumption in two ways: (i) using event study plots to test whether outcomes were evolving similarly for counties with varying exposure to treatment prior to the restriction (a standard pre-trends test); and (ii) presenting estimates from non-parametric models that allow for heterogeneous effects with respect to dose of exposure.

For the non-parametric models, we bin counties that were treated by the restriction (i.e., had positive levels of pre-restriction diskette shipments) into 20 quantiles based on their exposure dose (denote b) and form a control group of counties that did not have any pre-restriction diskette shipments. Then, we estimate a modified version of equation (2):

$$Y_{c,t} = \sum_{b=1}^{20} \gamma_b 1(c \in b) \times Post_t + \alpha_c + \tau_t + \epsilon_{c,t}, \quad (3)$$

where $1(c \in b)$ indicates whether county $c's$ treatment exposure dose group is bin b. We construct an average causal response for counties in each bin (denote $ACR \mid b$) by dividing the treatment effect for counties in each bin by their average exposure dose:

$$\widehat{ACR} \mid b = \frac{1}{N_b} \sum_{c \in b} \frac{\hat{\gamma}_b}{d_c}. \quad (4)$$

ii. Heterogeneous treatment effects by age and heroin availability

Prior literature suggests that there is more substitution to illicit drugs following supply-side policies targeting prescription opioids for younger populations (Alpert et al., 2018), males (Alpert et al., 2018), and in areas where there is more pre-existing heroin use (indicating that heroin is more available) (Evans et al., 2019). Harmful effects of the restriction in these subgroups may be masked by average effects, which we estimate in equation (2). As such, we stratify equation (2) by these factors to assess heterogeneity in substitution responses. We estimate separate models for individuals in three different age groups (ages 18-24, 25-44, and 45-64), males and females, and counties with below vs. above median heroin overdose death rates prior to the restriction from 2006-2007. Supporting the fact that the latter is a good marker of heroin availability, the average annual heroin death rate in counties with above median heroin deaths from 2006-2007 (1.75 deaths per 100,000) was higher than the heroin death rate in the average county from 2011-2013 (1.36 deaths per 100,000), commonly dated as the heroin wave of the U.S. opioid epidemic and when prior studies found evidence of *OxyContin* reformulation causing substitution to heroin (Alpert et al., 2018; Evans et al., 2019).

iii. Other time-varying policy changes

The strong parallel trends assumption may also be violated if other policies targeting the opioid market differentially affected areas that were more exposed to the methadone diskette restriction. As noted above, we partly address this by restricting our analysis to before most substantial policy responses to the prescription opioid epidemic—e.g., *OxyContin* reformulation (Alpert et al., 2018; Evans et al., 2019), increased pill mill and pharmaceutical distributor enforcement (Donahoe, 2024), and must-access Prescription Drug Monitoring Programs (PDMPs) (Horwitz et al., 2021)—all of which took place after mid-2010. However, there were other policy changes that did occur over our study period and which may be important to account for. These include states establishing operational PDMPs (Horwitz et al., 2021) and legalizing medical marijuana (Powell et al., 2018). We examine robustness to adding state-by-time fixed effects to equation (1) to control for these and all other observable and unobservable state-level policy changes.

V. The Restriction Reduced Methadone Use and Mortality

a. Event study estimates

Figure 3 presents estimates of equation (1) for methadone shipments and overdose death rates. The figure shows estimated changes in outcomes in each quarter for counties with one MME per capita higher rate of methadone diskette shipments prior to the restriction. **Panel A** shows results for the first stage outcome: methadone diskette shipments. Intuitively, each one MME per capita of exposure to the restriction was related to one MME per capita fewer diskette shipments in the post-restriction period. Considering this, we interpret results below as the effects of "a one MME per capita reduction in diskette shipments."

Panel B shows that the restriction caused significant substitution to lower potency 10mg methadone tablets. In the same quarter as the restriction began, 10mg tablet shipments increased by 0.52 MME per capita per every one MME per capita reduction in diskette shipments (i.e., offsetting the effects of the restriction by roughly 52 percent). This increase persisted at roughly the same magnitude for the 2.5 years post-restriction. Next, **Panel C** shows results for total methadone shipments (40mg diskettes plus 5mg and 10mg tablets). Results show that substitution to other forms of methadone partially but did not fully offset the effects of the methadone diskette restriction on total methadone supply. Furthermore, reductions in total methadone supply were markedly persistent over time.

Figure 3 Panel D shows effects on methadone overdose death rates. The estimates for mortality follow a very similar pattern to the estimates for methadone shipments. In the pre-period, methadone deaths trended similarly in areas with higher exposure to the restriction as areas with lower exposure.[6] In the exact quarter of the restriction, methadone mortality fell by 0.0097 deaths per 100,000 people for every one MME per capita reduction in diskette shipments. The parallel pre-trends and sharp change in mortality strongly support a causal interpretation of the restriction's impact on mortality. The estimated declines in methadone mortality were also markedly persistent over time, evident for the entire 2.5 years post-restriction.

[6] There are a few potential explanations for pre-trends being roughly parallel for methadone mortality but not for methadone shipments (for which pre-trends were differentially increasing). The first is measurement error in exposure to the restriction (i.e., methadone diskettes being consumed in counties other than the ones they were being shipped to, causing deaths to rise in other counties). This is akin to classical measurement error in x and would bias our estimates of effects on mortality towards the null (Greene, 2000). The second possibility is that people were developing tolerance to methadone such that further increases in diskette shipments were not contributing to further increases in mortality in highly exposed areas.

Figure 4 presents estimates of equation (1) for potential substitute opioids and all drugs. **Panels A** to **C** show that the restriction did not cause any increase in overdose deaths in potential substitute opioids in the short- or long-term after the restriction. In all cases, deaths from potential substitute opioids trended similarly in areas with varying exposure before the restriction and continued trending similarly for several years after. Furthermore, confidence intervals on these estimates are extremely tight and rule out increases in mortality that approach the same order of magnitude as the reduction in methadone overdose death rates.

Figure 4 Panel D shows impacts on total drug overdose death rates (i.e., deaths from any substance, including methadone). Results mirror the estimates for methadone mortality. Trends in overall opioid mortality were similar for areas with lower and higher exposure to the methadone diskette restriction in the pre-period. In the quarters following the restriction, total overdose mortality fell significantly and persisted throughout the 2.5 years post-restriction.

In Supplementary **Appendix Figure A2**, we examine event studies over the full time-period for which we have data on both opioid shipments and deaths (from 2006Q1 to 2014Q4). Results show that reductions in methadone shipments and mortality persisted over this entire period, without any significant offsetting increases in mortality from substitute opioids. Further, reductions in methadone and total mortality grew in magnitude as time went on. While this clearly indicates that the restriction had very long-term impacts on mortality that were not offset by substitution, we interpret the estimated reductions in mortality after mid-2010 with caution as they may be related to correlated exposures to other supply-side policies that were implemented after this time or interactions with them (see section II).

In **Supplementary Appendix Figure A3**, we also examine whether there was substitution from methadone to other prescription opioids using prescription opioid shipments as an outcome instead of deaths. **Panel A** shows that areas with greater exposure to the diskette restriction experienced faster growth in other prescription opioid shipments in the pre-period. This implies that areas with methadone diskette problems were the same areas with general prescription opioid problems and is consistent with the discussion in **Section II**. The faster rate of growth continued into the post-period, leading higher exposure to the restriction to be related to increased rates of other opioid shipments in the post-period.

Because the differential increase in other opioid shipments in areas with greater exposure to the methadone diskette restriction appears to be the result of a secular trend, we also present

event study results after removing the linear pre-trend in **Panel B**. Specifically, we extrapolate the linear pre-trend from t = -3 to -1 using the approach of Freyaldenhoven and colleagues (2019). The results show that, after accounting for differential pre-period growth, the restriction did not cause any increase in other opioid shipments. Further, the 95% confidence intervals rule out increases in other opioid shipments of more than 28 percent as large as the estimated decrease in methadone diskette shipments in **Figure 3 Panel C**. Because of the presence of differential trends, we interpret these specific estimates with caution. Still, we note that, combined with our sharp null estimates of the effects of the diskette restriction on prescription opioid deaths, the overall evidence suggests that the methadone diskette restriction did not cause large amounts of substitution from methadone to other kinds of prescription opioids.

b. Pooled difference-in-differences estimates

Table 1 presents pooled estimates of equation (2) on each of the mortality outcomes over the 2.5 years after the restriction (from 2008Q1-2010Q2). The first column shows that methadone overdose death rates fell by 0.0110 (95% CI = -0.0178, -0.0042) deaths per 100,000 per each MME per capita reduction in methadone diskette shipments. The next three columns show sharp null estimates of the effects of the restriction on mortality involving prescription opioids, heroin, and other synthetic opioids. Further, the 95% confidence intervals surrounding these null estimates rule out large increases in deaths from these potential substitutes. The confidence intervals for prescription opioid deaths rule out increases 59 percent as large as the reduction in methadone deaths. The confidence intervals for heroin deaths rule out increases 9 percent as large as the reduction in methadone death rates. The last column shows that net mortality—i.e., total overdose death rates—fell by 0.094 (95% CI = -0.0186, -0.0001) deaths per 100,000 per each MME per capita reduction in methadone diskette shipments.

To provide insights about the magnitude of these estimates, we transform our results for total overdose death rates into the implied number of overdose deaths that the diskette restriction prevented over the 2.5 years post-restriction. Specifically, we use equation (1) to predict counterfactual mortality rates in all counties if they had no exposure to the restriction vs. the level of exposure that they actually experienced. We then took the difference between these two counterfactual predictions and aggregated them across counties and time periods. In total, we estimate that the restriction prevented 1,661 deaths over two years (around one death per 889

averted prescriptions).[7] Note that this is an estimate over 2.5 years and is likely conservative given that **Supplementary Appendix Figure A3** shows the restriction was related to reduced overdose death rates for several years beyond that.

c. Robustness checks

i. Robustness to violation of the strong parallel trends assumption

In addition to the standard parallel trends assumption, the strong parallel trends assumption requires that potential outcomes for counties that experienced treatment dose d are equal to the realized outcomes of counties that experienced that dose. Here, we focus on probing robustness to this additional assumption for continuous treatments.

We start by plotting estimates of equation (3) and visually inspecting whether the estimated effects of the restriction across different bins of counties (i.e., $\hat{\gamma}_b$) are linear with respect to exposure to the restriction. Results are plotted in **Appendix Figure A4**. There is a clear linear relationship between increased exposure and reduced methadone shipments (see **Panel A**). The relationship between exposure and methadone deaths appears somewhat non-linear (see **Panel B**), with small positive and/or null effects for counties with low exposure, but a linear relationship between increased exposure and reduced methadone deaths at higher levels of exposure (particularly for the two bins with the highest exposure). The relationship between exposure and impacts (or lack of impacts) and other outcomes largely appear linear (see **Panels C** to **F**), though estimates for some outcomes (prescription opioid and total drug deaths) are noisier than others (heroin and synthetic opioid deaths).

To examine the extent to which the non-linearities observed in **Appendix Figure A4** might lead us to over- or under-estimate the effects of the restriction, we present average causal response parameter estimates using equation (4) in **Appendix Table A1**. We present overall estimates and separate estimates for counties above vs. below the 90th percentile of exposure. The latter gauges the extent to which there are non-linearities in treatment effects for counties with very high exposure to treatment. Results are generally consistent with results from our continuous difference-in-differences models. Mirroring the results in **Appendix Figure A4**, there

[7] The latter estimate of the number of prescription restrictions needed to prevent one death comes from dividing the implied reduction in deaths by the number of pre-restriction methadone diskette prescriptions supplied, assuming a prescription bottle size of one-hundred diskettes. The bottle size comes from the drug's Food and Drug Administration approved label (https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/017058s019lbl.pdf).

are nonlinearities in effects on methadone overdose mortality rates, with the overall reductions in mortality being driven by a small number of highly exposed counties (those above the 90th percentile of exposure). However, we do not observe significant substitution to other substances for any group of counties with respect to exposure to the restriction. Moreover, results for effects on net mortality are negative for all exposure groups and imply even larger reductions in total overdose deaths due to the restriction (6,416 total deaths prevented vs. 1,661 in the continuous exposure model). Thus, our estimates in section V.b are, if anything, conservative relative to models that allow for heterogeneous treatment effects with respect to dose of exposure.

ii. Heterogeneous treatment effects by age and heroin availability

Next, we examine potential treatment effect heterogeneity with respect to characteristics that could drive differential patterns of substitution to other substances. Results for age and sex are presented in **Appendix Table A2**. The results show the magnitude of estimated reductions in methadone overdose mortality are larger for younger age groups (ages 15-44) than for older adults (ages 45-64) and for males than for females. We do not observe significant increases in deaths from other substitute drugs for any subgroup, though there is some (imprecise) evidence that decreases in methadone overdose deaths for the oldest age group (adults ages 45-64) may have been offset by increased prescription opioid death rates. Results for illicit opioids (heroin) are tightly estimated nulls for all subgroups, including the ones for which prior literature indicates substitution would be most likely (males and younger adults). Estimates for net overdose mortality are large and negative for those ages 15-44 and positive and close to null (albeit imprecisely estimated) for adults ages 45-64. By sex, we observe large reductions in net mortality for males and small (and imprecise) reductions for females. These differences by sex largely result from higher in reductions in methadone mortality for males, suggesting that they are due to increased exposure to the restriction (i.e., higher methadone diskette use prior to the restriction) for males than females and not differential patterns of substitution by sex.

Results stratified by pre-restriction heroin death rates are presented in **Appendix Table A3**. If anything, the impacts of the epidemic on both methadone and total drug overdose mortality were largest in areas where heroin was more commonly used prior to the restriction, and where one would expect more substitution illicit drugs based on prior literature. Though, results are somewhat imprecisely estimated, and confidence intervals overlap across the two sets

of counties. The main implication of **Table A3** is that results precisely rule out increased substitution to heroin even in counties where it would have been available.

iii. Other time-varying policy changes

Finally, we examine robustness to confounding from state policy changes by including state-by-time fixed effects. These fixed effects control for state-level policy changes (e.g., PDMP implementation) that may affect opioid death rates and could be correlated with exposure to the methadone diskette restriction. Plotted results in **Appendix Figure A5** are very similar to our main estimates: we see abrupt and significant reductions in methadone shipments and overdose deaths in areas with greater exposure to the methadone diskette restriction immediately after implementation, but we do not see corresponding increases in deaths from substitute opioids.

VI. Conclusions

In this article, we study the effects of eliminating the supply of methadone diskettes to all U.S. pharmacies in 2008 on overdose mortality. We find that this supply-side drug intervention was highly effective at reducing mortality and prevented roughly 1,600 overdose deaths. The fact that this intervention prevented so many deaths is surprising in the context of extant literature that commonly finds supply-side drug policies undermine public health by causing substitution to harmful and more dangerous illicit substances.

We identify two main reasons that harmful substitution did not take place in this setting, and which may offer important lessons for supply-side drug policies generally. First, government reporting and our findings (e.g., the lack of complete offset of 40mg diskettes with perfectly substitutable 10mg tablets) suggests there was a significant amount of methadone "overuse," with health care providers supplying more methadone (and consumers using more of it) than they intended when the high-potency diskette formulations were available. Eliminating the product was a straightforward way to correct these errors and improve public health.

Second, rather than focusing on outright prohibition of methadone, this intervention eliminated the highest-potency—and hence most dangerous—methadone product. This has the advantage of the lower-potency product being a natural close substitute, rather than an illicitly made good that might be more variable in quality and dangerous. More research would be

helpful to inform whether similar policies (e.g., potency restrictions on other prescription opioids or alcohol) have positive public health effects without inducing harmful substitution.

Overall, these findings have important implications for policy. We provide clear evidence of a supply-side intervention that successfully diminished the severity of the opioid epidemic, at a time when the epidemic was expanding considerably. The public health rationale for supply-side drug policies should not be disregarded a priori because of their potential for unintended consequences. Instead, it is important to understand the context of a given restriction and the risk of the alternative substances to which substitution is likely to occur. These results show that well-targeted supply-side policies can be highly effective tools for responding to drug epidemics.

References

Alpert, A., Evans, W. N., Lieber, E. M. J., & Powell, D. (2021). Origins of the Opioid Crisis and its Enduring Impacts*. *The Quarterly Journal of Economics*, qjab043. https://doi.org/10.1093/qje/qjab043

Alpert, A., Powell, D., & 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.

Arteaga, C., & Barone, V. (2021). A Manufactured Tragedy: The Origins and Deep Ripples of the Opioid Epidemic. *Working Paper*, 72.

Balestra, S., Liebert, H., Maestas, N., & Sherry, T. B. (2021). *Behavioral Responses to Supply-Side Drug Policy During the Opioid Epidemic* (Working Paper 29596; Working Paper Series). National Bureau of Economic Research. https://doi.org/10.3386/w29596

Bradford, W. D., & Lozano-Rojas, F. (2023). THE EFFECT OF A LARGE PRESCRIPTION OPIOID DIVERSION EVENT ON OPIOID MORTALITY IN THE US. *Available at SSRN*.

Callaway, B., Goodman-Bacon, A., & Sant'Anna, P. H. C. (2024). *Difference-in-differences with a Continuous Treatment* (Working Paper 32117). National Bureau of Economic Research. https://doi.org/10.3386/w32117

Case, A., & Deaton, A. (2017). Mortality and morbidity in the 21st century. *Brookings Papers on Economic Activity*, *2017*, 397.

Case, A., & Deaton, A. (2020). Deaths of Despair and the Future of Capitalism. In *Deaths of Despair and the Future of Capitalism*. Princeton University Press.

Chou, R., Fanciullo, G. J., Fine, P. G., Adler, J. A., Ballantyne, J. C., Davies, P., Donovan, M. I., Fishbain, D. A., Foley, K. M., Fudin, J., Gilson, A. M., Kelter, A., Mauskop, A., O'Connor, P. G., Passik, S. D., Pasternak, G. W., Portenoy, R. K., Rich, B. A., Roberts, R. G., … Miaskowski, C. (2009). Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. *The Journal of Pain*, *10*(2), 113-130.e22. https://doi.org/10.1016/j.jpain.2008.10.008

Cutler, D. M., & Glaeser, E. L. (2021). When Innovation Goes Wrong: Technological Regress and the Opioid Epidemic. *Journal of Economic Perspectives*, *35*(4), 171–196. https://doi.org/10.1257/jep.35.4.171

Dasgupta, N., Beletsky, L., & Ciccarone, D. (2018). Opioid Crisis: No Easy Fix to Its Social and Economic Determinants. *American Journal of Public Health*, *108*(2), 182–186. https://doi.org/10.2105/AJPH.2017.304187

Dobkin, C., & Nicosia, N. (2009). The War on Drugs: Methamphetamine, Public Health, and Crime. *American Economic Review*, *99*(1), 324–349. https://doi.org/10.1257/aer.99.1.324

Dobkin, C., Nicosia, N., & Weinberg, M. (2014). Are supply-side drug control efforts effective? Evaluating OTC regulations targeting methamphetamine precursors. *Journal of Public Economics*, *120*, 48–61. https://doi.org/10.1016/j.jpubeco.2014.07.011

Donahoe, J. (2024). Supplier Enforcement and the Opioid Crisis. *Working Paper*. https://static1.squarespace.com/static/632f3a2e33b0e9116c23e95a/t/660c28dda996cc5781ba1336/1712072926680/Supplier+Enforcement.pdf

Eichmeyer, S., & Zhang, J. (2022). Pathways into Opioid Dependence: Evidence from Practice Variation in Emergency Departments. *American Economic Journal: Applied Economics*, *14*(4), 271–300. https://doi.org/10.1257/app.20210048

Evans, W. N., Lieber, E. M., & Power, P. (2019). How the reformulation of OxyContin ignited the heroin epidemic. *Review of Economics and Statistics*, *101*(1), 1–15.

FDA. (2007). *NDA 17-058/S-019*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/017058s019lbl.pdf

Fingerhut, L. A., & Cox, C. S. (1998). Poisoning mortality, 1985-1995. *Public Health Reports*, *113*(3), 218.

Freyaldenhoven, S., Hansen, C., & Shapiro, J. M. (2019). Pre-event trends in the panel event-study design. *American Economic Review*, *109*(9), 3307–3338.
GAO. (2009). *Methadone-Associated Overdose Deaths: Factors Contributing to increased Deaths and Efforts to Prevent Them* (GAO-09-341). Government Accountability Office. https://www.gao.gov/assets/a287907.html
Greene, W. H. (2000). Econometric analysis 4th edition. *International Edition, New Jersey: Prentice Hall*, 201–215.
Hedegaard, H., Miniño, A. M., & Warner, M. (2020). *Drug overdose deaths in the United States, 1999-2019* (NCHS Data Brief 394). National Center for Health Statistics.
Horwitz, J. R., Davis, C., McClelland, L., Fordon, R., & Meara, E. (2021). The importance of data source in prescription drug monitoring program research. *Health Services Research*, *56*(2), 268–274.
Kim, B. (2021). Must-access prescription drug monitoring programs and the opioid overdose epidemic: The unintended consequences. *Journal of Health Economics*, *75*, 102408. https://doi.org/10.1016/j.jhealeco.2020.102408
Lynch, M. E. (2005). A Review of the Use of Methadone for the Treatment of Chronic Noncancer Pain. *Pain Research and Management*, *10*(3), 286713. https://doi.org/10.1155/2005/286713
Miron, J. A., & Zwiebel, J. (1995). The economic case against drug prohibition. *Journal of Economic Perspectives*, *9*(4), 175–192.
Moore, T. J., & Pacula, R. L. (2021). *Causes and Consequences of Illicit Drug Epidemics* (Working Paper 29528; Working Paper Series). National Bureau of Economic Research. https://doi.org/10.3386/w29528
Moore, T. J., & Schnepel, K. T. (2021). *Opioid use, health and crime: Insights from a rapid reduction in heroin supply*. National Bureau of Economic Research.
National Center for Health Statistics. (2022). *Deaths (mortality)—Multiple cause of death, states, and all counties—Detailed, 1990-2022* [Dataset]. https://www.cdc.gov/nchs/nvss/nvss-restricted-data.htm
Powell, D., & Pacula, R. L. (2021). The evolving consequences of oxycontin reformulation on drug overdoses. *American Journal of Health Economics*, *7*(1), 000–000.
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*, 29–42. https://doi.org/10.1016/j.jhealeco.2017.12.007
Ruhm, C. J. (2019). Drivers of the fatal drug epidemic. *Journal of Health Economics*, *64*, 25–42.
SLCG Economic Consulting. (2006). *Opioid Data* [Dataset]. https://www.slcg.com/opioid-data/
Soliman, A. (2024). *Disrupting Drug Markets: The Effects of Crackdowns on Rogue Opioid Suppliers*.
Webster, L. R., Cochella, S., Dasgupta, N., Fakata, K. L., Fine, P. G., Fishman, S. M., Grey, T., Johnson, E. M., Lee, L. K., Passik, S. D., Peppin, J., Porucznik, C. A., Ray, A., Schnoll, S. H., Stieg, R. L., & Wakeland, W. (2011). An Analysis of the Root Causes for Opioid-Related Overdose Deaths in the United States. *Pain Medicine*, *12*(suppl_2), S26–S35. https://doi.org/10.1111/j.1526-4637.2011.01134.x

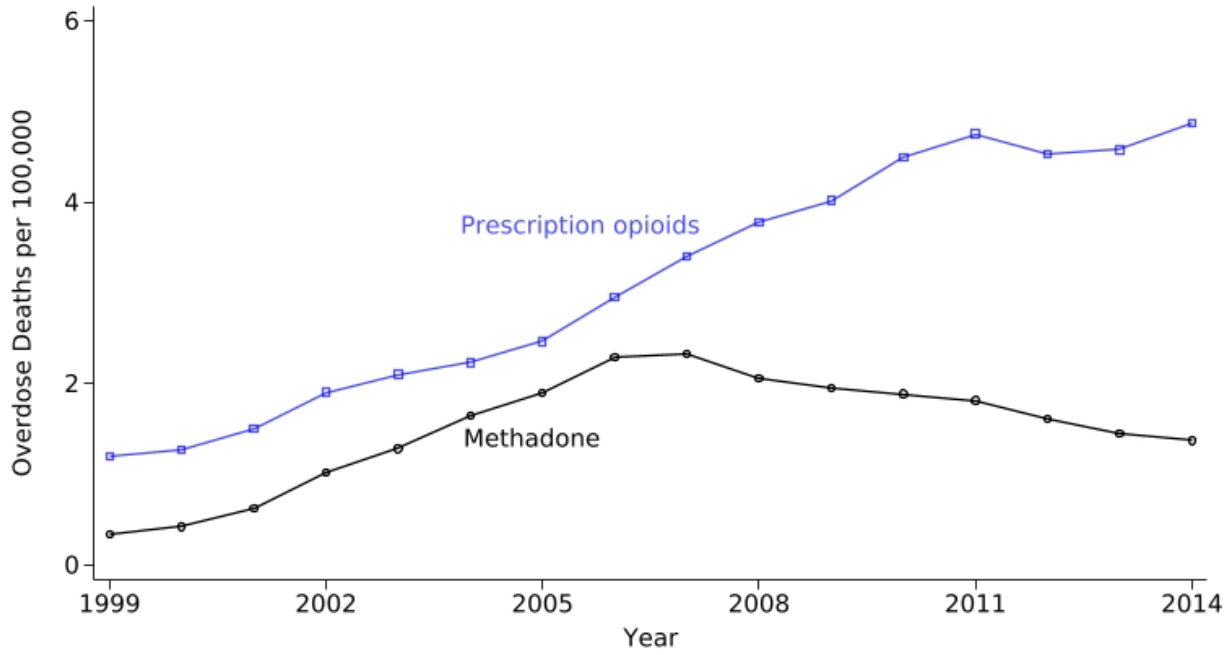
TABLES AND FIGURES

Table 1. The methadone diskette restriction caused significant reductions in overdose mortality.

	Impact of each MME per capita exposure on opioid deaths per 100,000				
	Methadone	Natural/rx	Heroin	Other synthetic	Any drug
	(1)	(2)	(3)	(4)	(5)
Exposure × post	-0.0110	0.0026	-0.0003	-0.0003	-0.0094
[95% CI]	[-0.0178, -0.0042]	[-0.0013, 0.0065]	[-0.0015, 0.0008]	[-0.0020, 0.0014]	[-0.0186, -0.0001]
County fixed effects	X	X	X	X	X
Time fixed effects	X	X	X	X	X
			Implied total overdose deaths prevented (2008Q1-2010Q2)		**1,661**
			Implied number of scripts averted to prevent one death		**889**

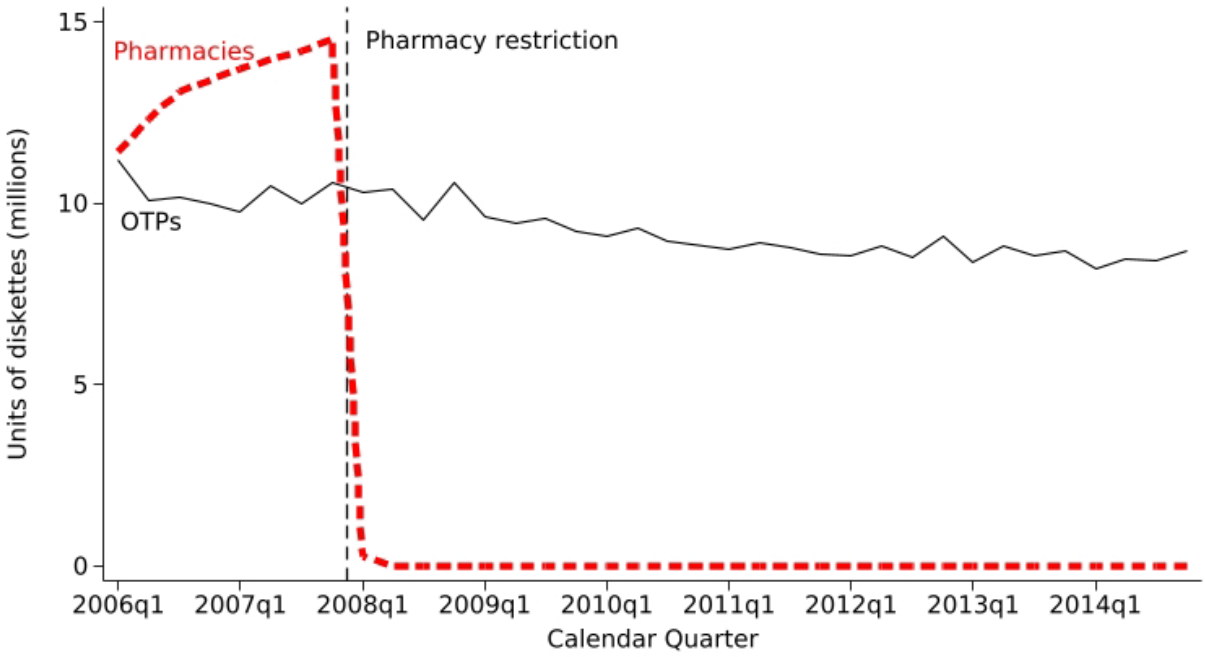
Notes. The dependent variables are county and quarterly overdose death rates per 100,000 people from various substances for all counties from 2006Q1-2010Q2. Estimates are of equation (2), weighted by county population. 95% confidence intervals that use county-clustered standard errors are reported in brackets. The estimates are interpreted as the change in death rate per each one morphine milligram equivalent (MME) per capita reduction in diskette shipments. To facilitate interpretation of these magnitudes, the bottom rows present the implied reduction in total drug overdose deaths attributable to the restriction over 2.5 years and the number of 40mg diskette prescriptions averted needed to prevent one overdose deaths (assumes 100 diskettes per script). See sections IV-V for more details.

Figure 1. Trends in U.S. methadone and prescription opioid overdose death rates, 1999-2014.



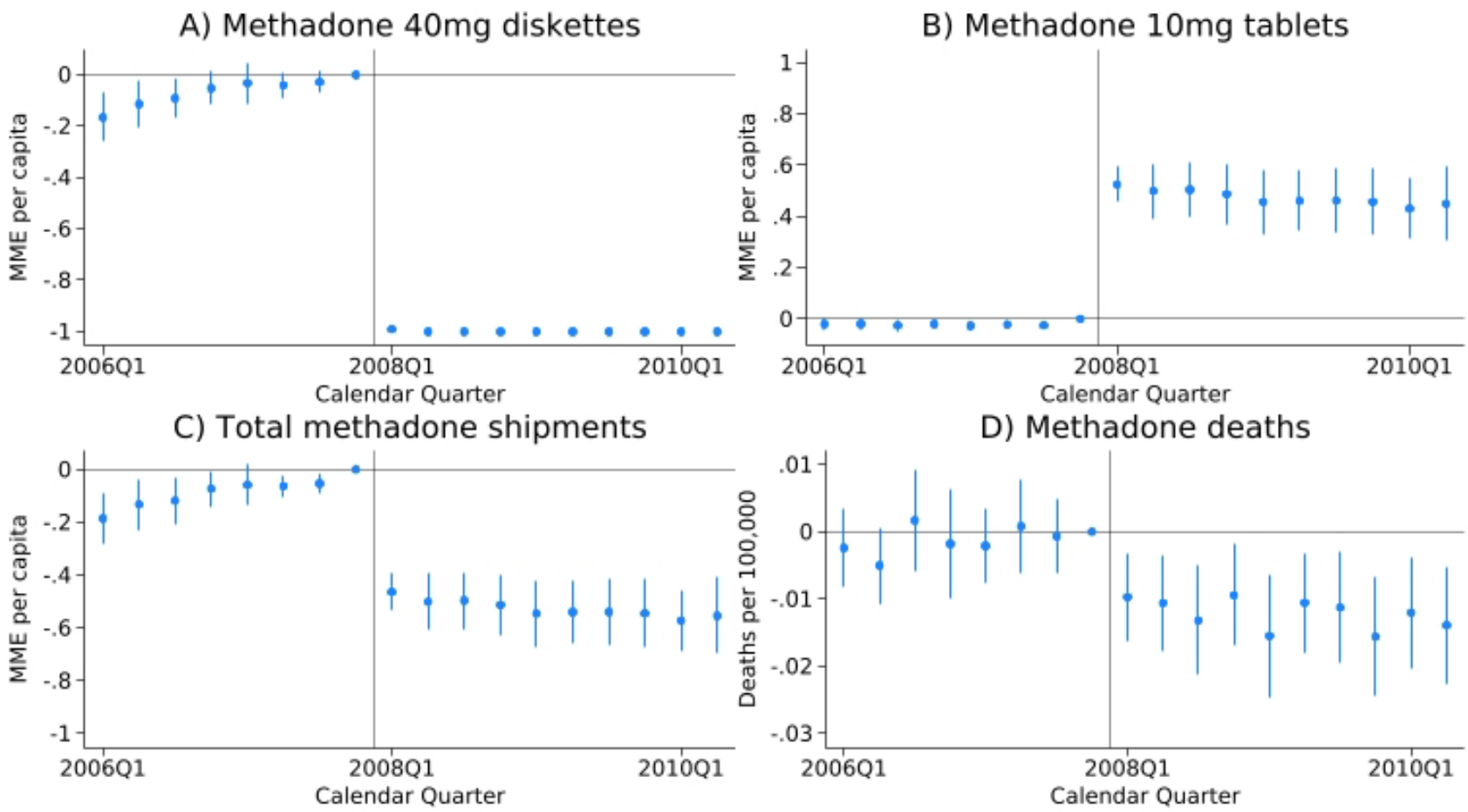
Notes. Data are from the National Vital Statistics System. See section III of the text for more details.

Figure 2. The DEA and methadone manufacturers ended methadone diskette shipments to all U.S. pharmacies in January 2008.



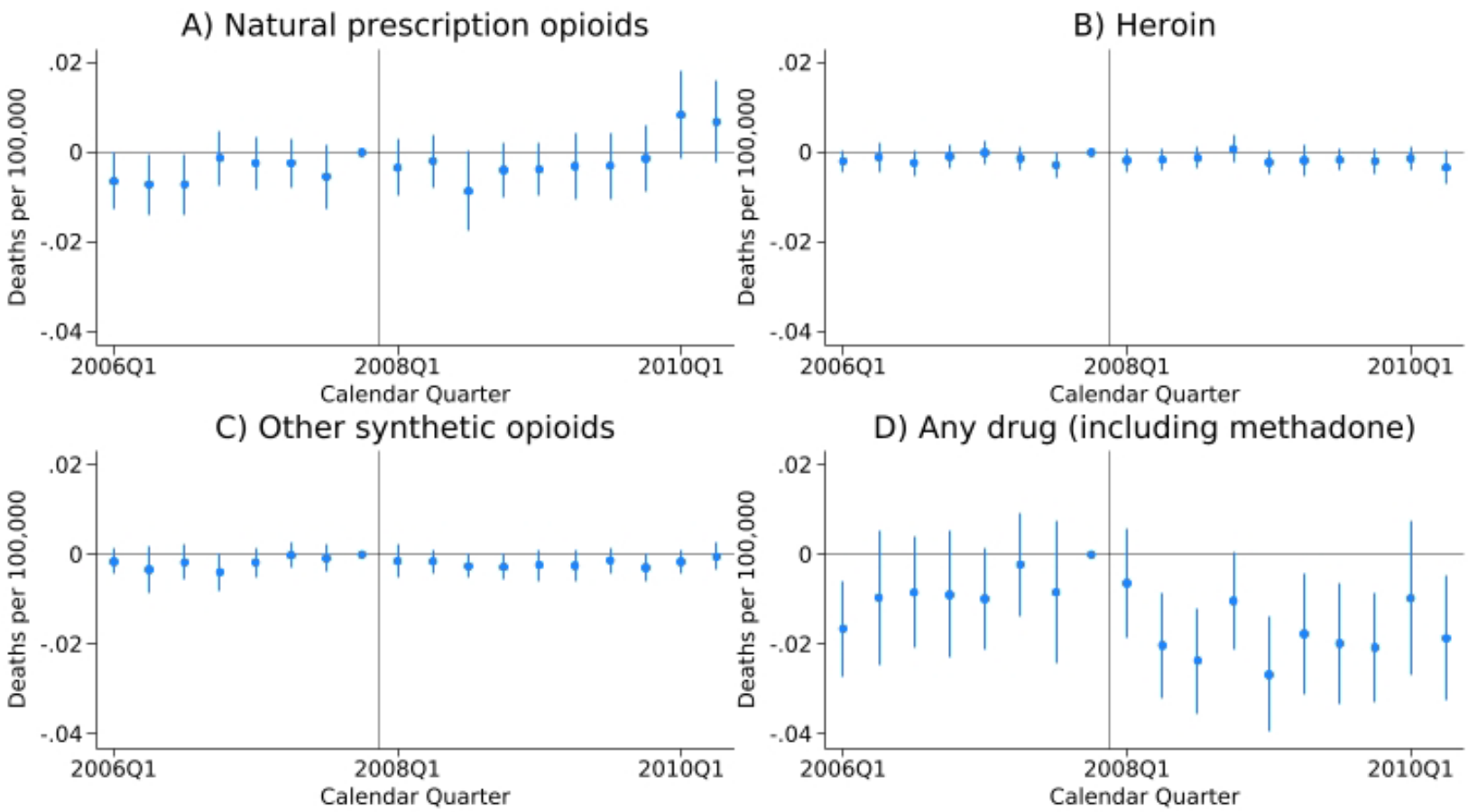
Notes. Data are from the Automation of Reports and Consolidated Orders System. OTPs = opioid treatment programs, which were not affected by the restriction. See sections II-III of the text for more details.

Figure 3. The methadone diskette restriction reduced methadone shipments and overdose death rates.



Notes. Estimates from equation (1) of the text. The vertical line divides the figure into pre- and post- restriction. See sections IV-V of the text for more details.

Figure 4. The methadone diskette restriction did not increase deaths from other opioids, resulting in net mortality reductions.



Notes. Estimates from equation (1) of the text. The vertical line divides the figure into pre- and post- restriction. See sections IV-V for more details.

SUPPLEMENTARY APPENDIX. ADDITIONAL TABLES AND FIGURES

Table A1. Parametric vs. non-parametric estimates of the diskette restriction's impacts on methadone shipments and overdose mortality.

	Continuous DiD	$\widehat{\mathbf{ACR}} \mid \mathbf{b} > \mathbf{0}$	$\widehat{\mathbf{ACR}} \mid \mathbf{b} \in [\mathbf{1}, \mathbf{18}]$	$\widehat{\mathbf{ACR}} \mid \mathbf{b} \in [\mathbf{19}, \mathbf{20}]$
	(1)	(2)	(3)	(4)
Panel A. Methadone shipments				
Pooled impacts	-0.4420	-0.2050	-0.1579	-0.3505
[95% CI]	[-0.5985, -0.2855]	[-0.2889, -0.1212]	[-0.2568, 0.0591]	[-0.5321, -0.0591]
Panel B. Methadone deaths				
Pooled impacts	-0.0110	-0.0047	0.0009	-0.0135
[95% CI]	[-0.0178, -0.0042]	[-0.0133, 0.0039]	[-0.0158, 0.0177]	[-0.0192, -0.0077]
Panel C. Prescription opioid deaths				
Pooled impacts	0.0026	-0.0016	-0.0091	0.0068
[95% CI]	[-0.0013, 0.0065]	[-0.0136, 0.0105]	[-0.0328, 0.0146]	[-0.0002, 0.0138]
Panel D. Heroin deaths				
Pooled impacts	-0.0003	0.0033	0.0066	0.0007
[95% CI]	[-0.0015, 0.0008]	[-0.0041, 0.0107]	[-0.0080, 0.0212]	[-0.0025, 0.0040]
Panel E. Other synthetic opioid deaths				
Pooled impacts	-0.0003	-0.0096	-0.0186	-0.0030
[95% CI]	[-0.0020, 0.0014]	[-0.0178, -0.0014]	[-0.0351, -0.0020]	[-0.0068, -0.0002]
Panel F. Total overdose deaths				
Pooled impacts	-0.0094	-0.0388	-0.0722	-0.0153
[95% CI]	[-0.0186, -0.0001]	[-0.0646, -0.0130]	[-0.1230, -0.0213]	[-0.0299, -0.0007]
Implied total deaths prevented	***1,661***	***6,416***	***5,354***	***1,062***

Notes. Model (1) presents pooled estimates from equation (2) and 95% confidence intervals. Models (2) to (4) presents estimates from equations (3)-(4), separately for all counties (2), counties between the 1st and 90th percentile of exposure to treatment (3), and counties above the 90th percentile of exposure (4). See sections IV-V of the text for more details.

Table A2. Stratified estimates of the diskette restriction's impacts on mortality by age and sex.

	By age group			By sex	
	15-24	**25-44**	**45-64**	**Male**	**Female**
	(1)	(2)	(3)	(4)	(5)
Panel A. Methadone deaths					
Exposure × post	-0.0153	-0.0158	-0.0063	-0.0212	-0.0075
[95% CI]	[-0.0241, -0.0066]	[-0.0273, -0.0042]	[-0.0105, -0.0022]	[-0.0337, -0.0087]	[-0.0122, -0.0029]
Panel B. Prescription opioid deaths					
Exposure × post	0.0011	0.0026	0.0042	0.0031	0.0017
[95% CI]	[-0.0019, 0.0041]	[-0.0037, 0.0088]	[-0.0007, 0.0091]	[-0.0015, 0.0076]	[-0.0018, 0.0051]
Panel C. Heroin deaths					
Exposure × post	-0.0014	0.0002	-0.0003	0.0009	0.0003
[95% CI]	[-0.0030, 0.0001]	[-0.0020, 0.0023]	[-0.0015, 0.0009]	[-0.0032, 0.0050]	[-0.0010, 0.0016]
Panel D. Other synthetic opioid deaths					
Exposure × post	-0.0006	-0.0007	0.0008	0.0018	-0.0003
[95% CI]	[-0.0022, 0.0009]	[-0.0037, 0.0023]	[-0.0013, 0.0029]	[-0.0015, 0.0050]	[-0.0015, 0.0010]
Panel E. Total drug deaths					
Exposure × post	-0.0244	-0.0161	0.0021	-0.0257	-0.0056
[95% CI]	[-0.0331, -0.0158]	[-0.0366, 0.0044]	[-0.0115, 0.0157]	[-0.0375, -0.0140]	[-0.0129, 0.0016]

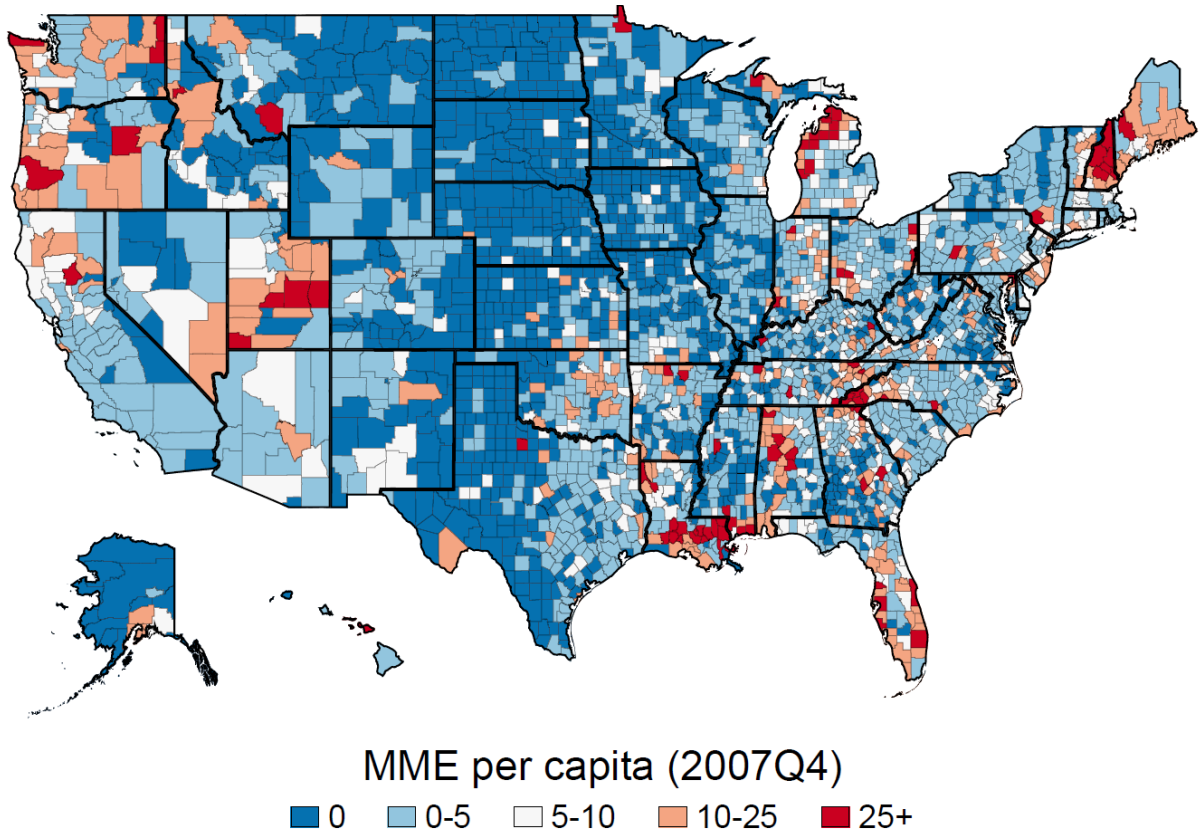
Notes. Presents pooled estimates from equation (2) and 95% confidence intervals for individuals in different age groups and males vs. females. See sections IV-V of the text for more details.

Table A3. Stratified estimates of the diskette restriction's impacts on mortality by county pre-restriction (2006-2007) heroin overdose death rates.

	Low heroin	High heroin
	(1)	(2)
Panel A. Methadone deaths		
Exposure × post	-0.0088	-0.0146
[95% CI]	[-0.0165, -0.0012]	[-0.0241, -0.0050]
Panel B. Prescription opioid deaths		
Exposure × post	0.0001	0.0068
[95% CI]	[-0.0029, 0.0031]	[-0.0020, 0.0157]
Panel C. Heroin deaths		
Exposure × post	0.0001	-0.0009
[95% CI]	[-0.0007, 0.0009]	[-0.0038, 0.0020]
Panel D. Other synthetic opioid deaths		
Exposure × post	-0.0002	-0.0005
[95% CI]	[-0.0028, 0.0025]	[-0.0018, 0.0008]
Panel E. Total drug deaths		
Exposure × post	-0.0046	-0.0172
[95% CI]	[-0.0152, 0.0059]	[-0.0310, -0.0035]
Average annual heroin death rate (2006-07)	0.12	1.75

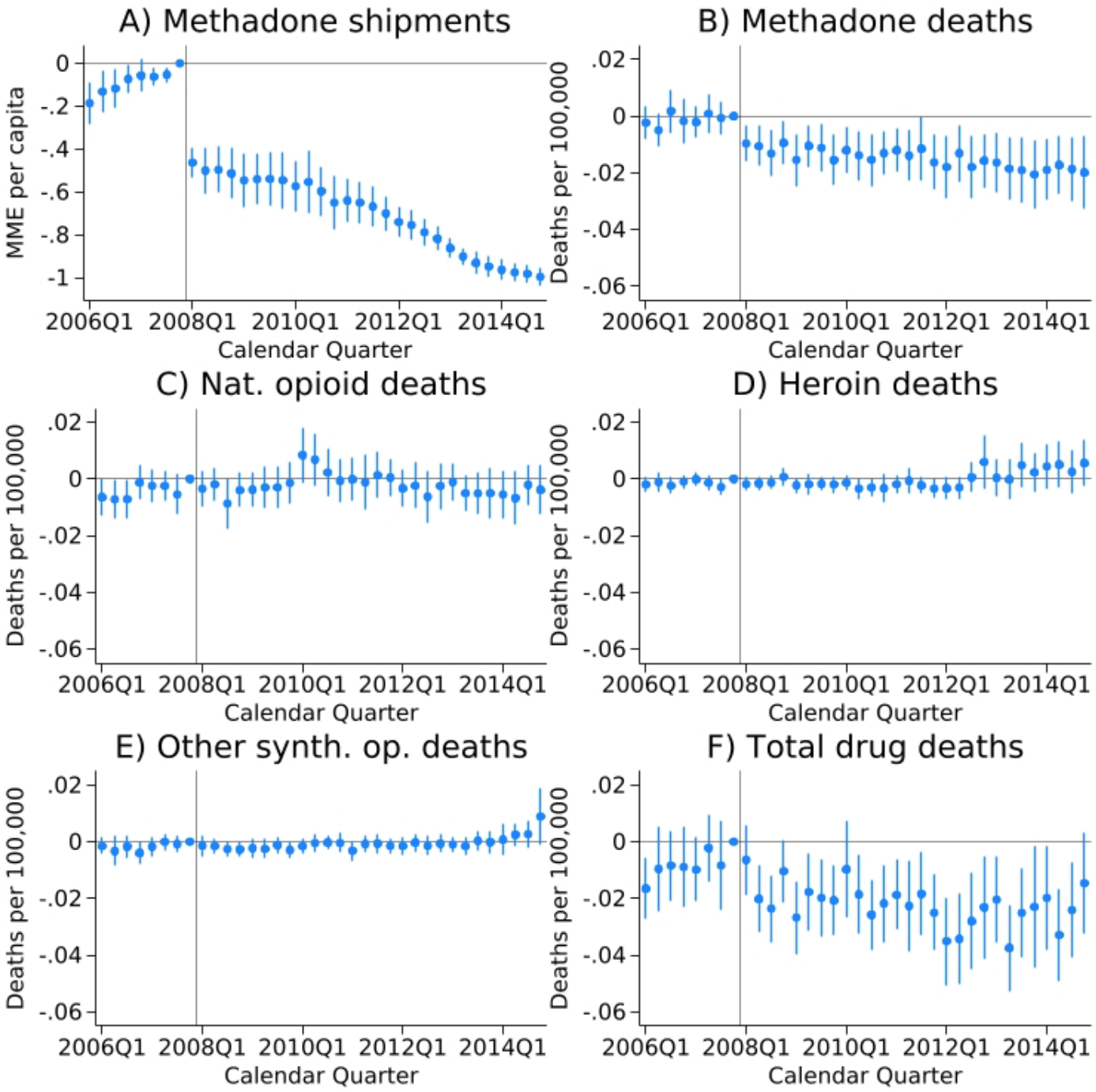
Notes. Presents pooled estimates from equation (2) and 95% confidence intervals for counties, stratified by whether the county had a below or above median 2006-2007 heroin overdose death rate. See sections IV-V of the text for more details.

Figure A1. Geographic variation in county-level exposure to the restriction of methadone 40mg diskettes.



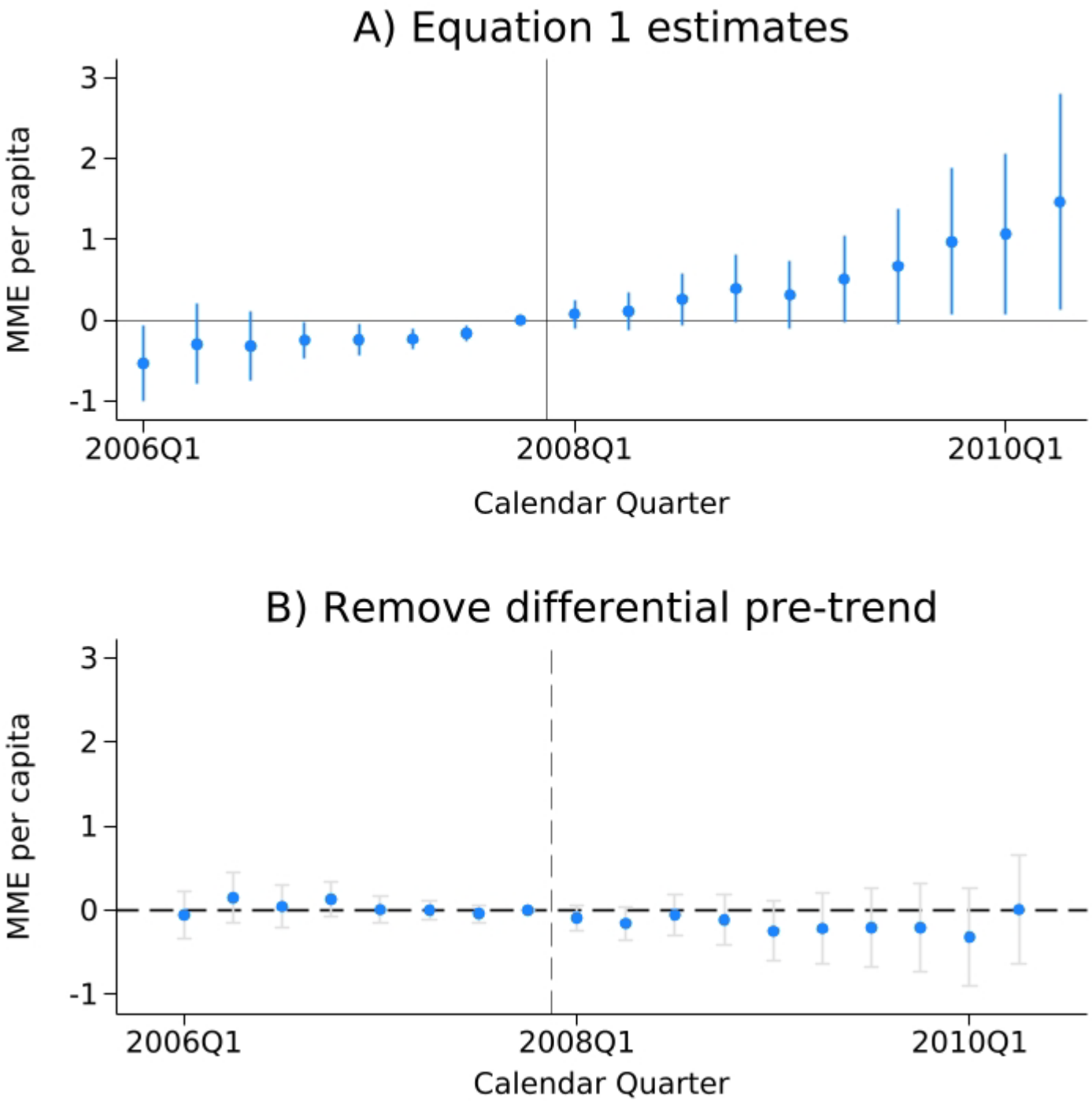
Notes. Data are from the Automation of Reports and Consolidated Orders System. The figure shows total shipments of methadone 40mg diskettes to pharmacies in each county (in terms of morphine milligram equivalents [MMEs] per capita) in the calendar quarter just prior to diskettes being restricted (2007Q4). See sections III-IV of the text for more details.

Figure A2. The diskette restriction caused persistent reductions in methadone shipments and overdose deaths.



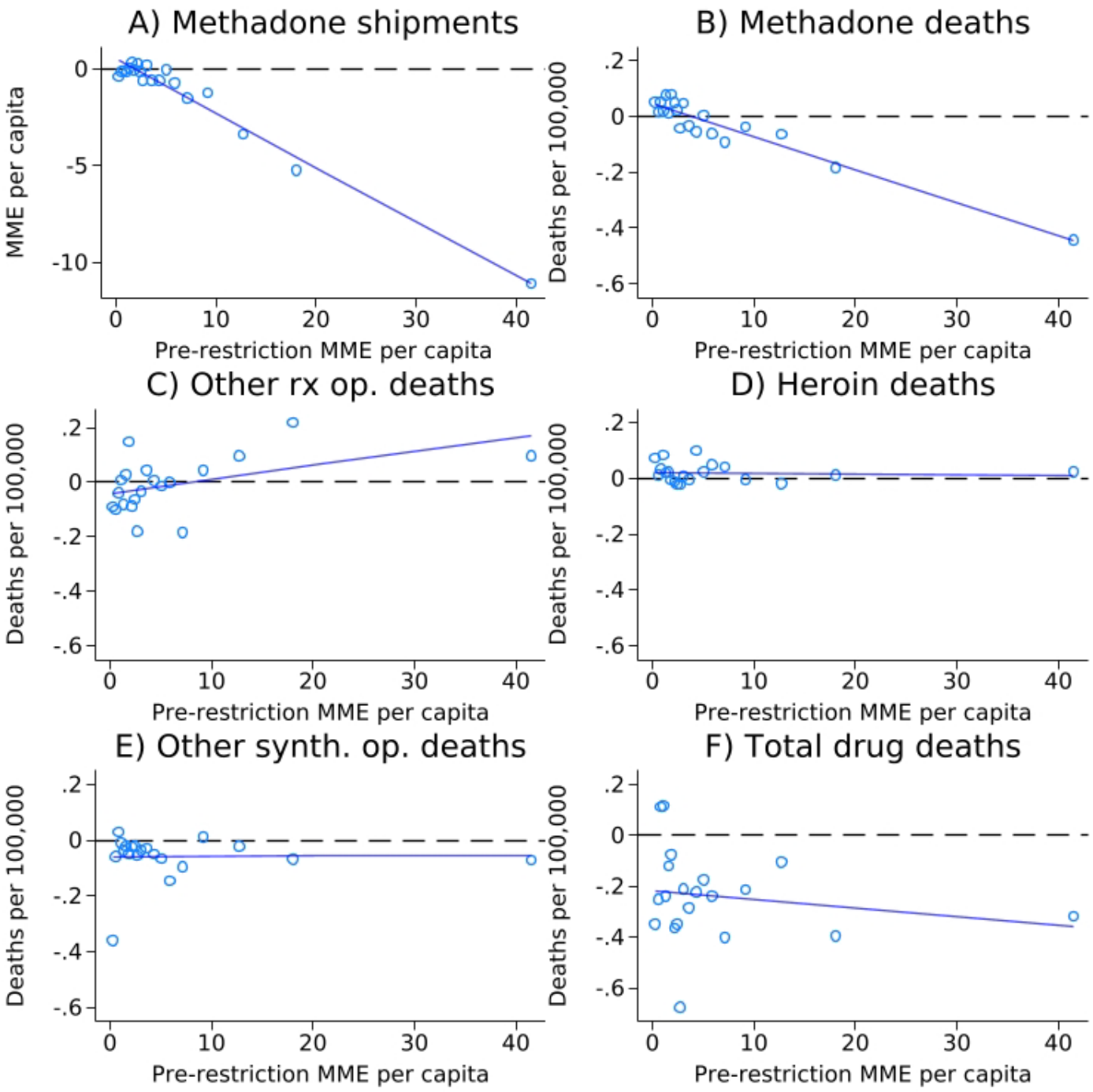
Notes. Estimates from equation (1) of the text. See sections IV-V of the text for more details.

Figure A3. The restriction did not alter counties' trajectories of non-methadone prescription opioid shipments.



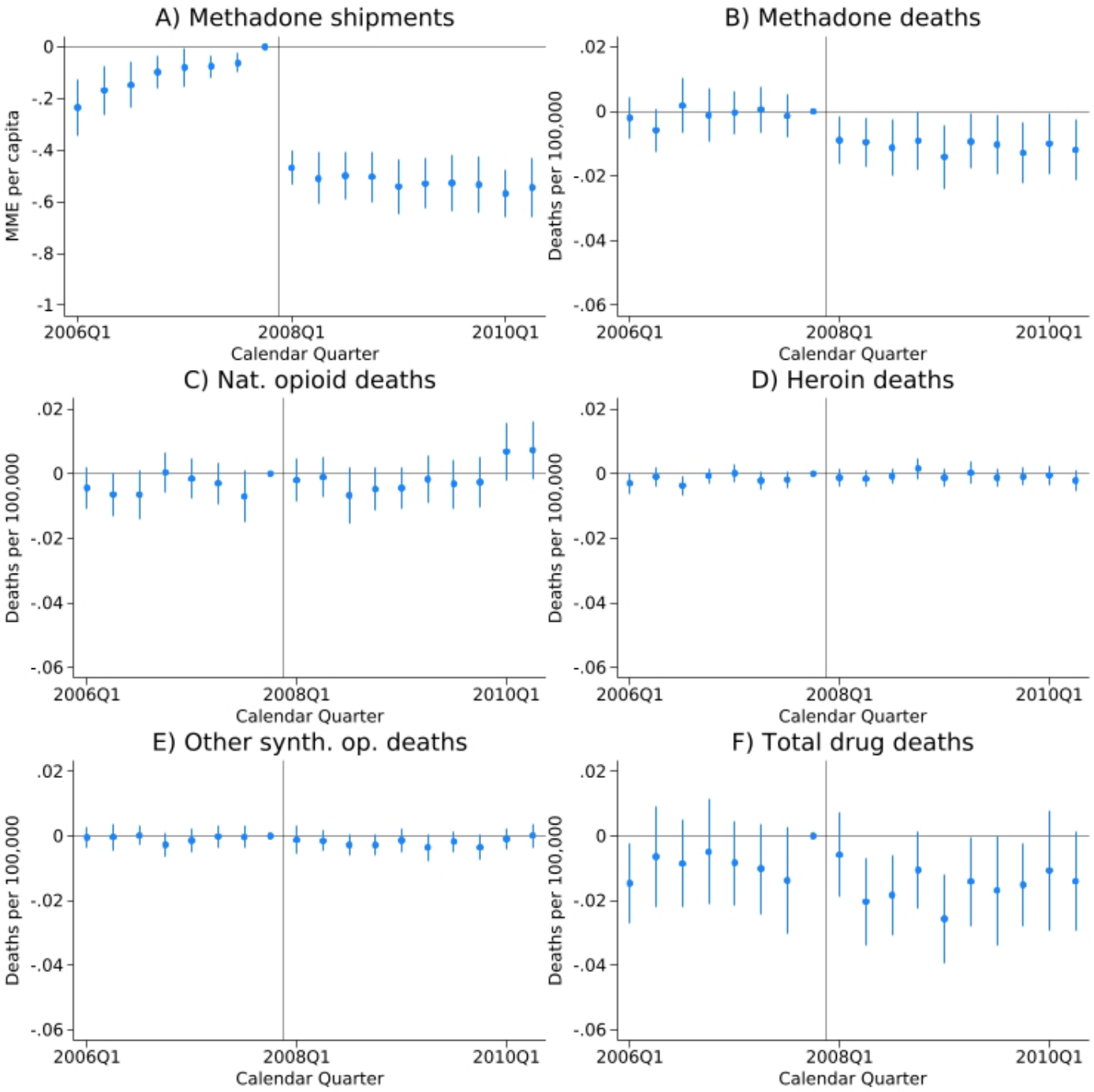
Notes. Data are from the Automation of Reports and Consolidated Orders System. The dependent variable is non-methadone opioid shipments, denominated in MME per capita. Non-methadone opioids included codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, morphine, opium, oxycodone, oxymorphone, and tapentadol. Panel A presents estimates of equation (1). Panel B presents estimates after removing a differential linear pre-trend, based on an extrapolation of the linear pre-trend from 2007Q2 to 2007Q4 (Freyaldenhoven et al., 2019). See sections IV-V of the text for more details.

Figure A4. The relationship between exposure to the restriction and outcomes is approximately linear.



Notes. The figure presents estimates of equation (3) for 20 bins of counties on the y-axis. The average exposure dose in each county is on the x-axis. The figure overlays a best fitting regression line. See sections IV-V of the text for more details.

Figure A5. Robustness of main event study results to controlling for state-by-time fixed effects.



Notes. Estimates from equation (1) of the text with the addition of state-by-time fixed effects to control for the effects of state policy changes (e.g., implementation of Prescription Drug Monitoring Programs). See sections IV-V of the text for more details.