Drivers of the Fatal Drug Epidemic

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Abstract

This study examines the contributions of the medium-run evolution of local economies and of changes in the "drug environment' in explaining county-level changes in drug and related mortality rates from 1999-2015. A primary finding is that drug mortality rates did increase more in counties experiencing relative economic decline than in those with more robust growth, but that the relationship is weak and mostly accounted by confounding factors. In the preferred estimates, less than one-tenth of the rise in drug and opioid-involved fatality rates is explained and the contribution is even smaller, quite possibly zero, when allowing for plausible selection on unobservables. Conversely, the risk of drug deaths varies systematically over time across population subgroups in ways that are consistent with an important role for the public health environment related to the availability and cost of drugs. In particular, the relative risk and share of drug mortality increased rapidly for males and younger adults, compared to their counterparts, when the primary driver of the fatal drug epidemic transitioned from prescription to illicit opioids. These results suggest that efforts to improve local economies, while desirable for other reasons, are not likely to yield significant reductions in overdose mortality, but with greater potential for interventions directly addressing the drug environment.

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The United States is in the midst of a fatal drug epidemic. The number of Americans dying from overdoses rose from 16,849 to 63,632 between 1999 and 2016 (Hedegaard, Warner, and Miniño 2017). Drug mortality is the leading cause of injury deaths in the United States, exceeding the number of motor vehicle fatalities since 2009 (Paulozzi 2012). The rapid growth in fatal overdoses originally involved prescription opioids like OxyContin, often in combination with other drugs (Jones, Mack, and Paulozzi 2013; Paulozzi, Mack, and Hockenberry 2014). However, the 19,413 and 15,469 fatalities during 2016 reported on death certificates to involve synthetic opioids (mostly fentanyl) and heroin substantially exceeded the 14,487 deaths due to opioid analgesics (Hedegaard, Warner, and Miniño 2017). Poisoning deaths, over 90 percent of which are now due to drugs, are by far the most important factor explaining the increases in mortality rates observed since 1999 initially among 45-54 year old non-Hispanic whites in influential research by Anne Case and Angus Deaton (2015) and subsequently among a broader age range of mid-life whites (Kochanek, Arias, and Bastian 2016; Kolata and Cohen 2016; Squires and Blumenthal 2016; Ruhm 2018).

This analysis investigates whether the fatal drug epidemic is primarily driven by underlying demand-side or supply-side factors.[1] Specifically, on the demand-side, I examine to what extent the county-level evolution of economic conditions is related to corresponding growth in drug mortality rates. With regards to supply, evidence is provided on the alternative hypothesis that changes in the drug environment are a main cause of rising overdose deaths. Since direct measurement of these environmental factors is difficult, the strategy below exploits the dramatic changes in sources of drug-related deaths occurring over the sample period. Specifically, increases in fatal overdoses during the first decade of the 21st century primarily

[1] The terms "supply-side" and "demand-side" must be interpreted cautiously since with addictive products, such as opioids, prior supply-driven increases in consumption will raise contemporaneous demand and vice versa.

involved opioid analgesic medications, whereas later growth has mainly been due to illicit opioids such as heroin and fentanyl.

The analysis reveals four main results. First, counties suffering relative or absolute economic decline did experience larger increases in drug and related mortality rates than those with more robust economic performance. This pattern shows up using most of the economic proxies examined, in part because they are reasonably highly correlated with each other. Second, the estimated impact of the economy is dramatically attenuated – by three-quarters or more – when adding controls for county-level characteristics, suggesting that the observed correlations are largely spurious. Third, in the preferred specifications, changes in economic conditions explain less than one-tenth of the observed increase in drug deaths occurring from 1999-2015. In sensitivity tests, a slightly larger share may sometimes be accounted for and, even using the multiple proxy methods, modest attenuation bias could persist. However, a small amount of remaining omitted variables bias would be sufficient to completely eliminate the contributions of economic factors, making it quite plausible that they play no role at all. Fourth, the temporal patterns of drug deaths across sex and age groups suggest that changes in the drug environment are an important determinant of rising overdose mortality. Of particular relevance, the explosive growth in illicit opioid death rates after 2010 was accompanied a rising share of drug deaths among males and relatively young adults. These results suggest a predominant role for the public environment surrounding drugs in causing the fatal overdose epidemic. While they do not completely eliminate a possible contribution of demand-side mechanisms, they strongly suggest the efficacy of policies aimed at addressing availability, cost and risky use of drugs.

1. Background

Economists and other social scientists have examined how a variety of specific factors or policies are related to opioid use or drug fatalities including: medical marijuana (Bachhuber et al. 2014; Chu 2015; A. C. Bradford and Bradford 2016; A. C. Bradford et al. 2018; Wen and Hockenberry 2018; Powell, Pacula, and Jacobson 2018), abuse-deterrent drug formulations (Alpert, Powell, and Pacula 2018; Evans, Lieber, and Power 2018), naloxone availability (Rees et al. 2017; Doleac and Mukherjee 2018), substance abuse treatment (Swensen 2015; Borgschulte, Corredor-Waldron, and Marshall 2018), advertising (D. M. Anderson 2010), physician market structure (W. D. Bradford 2017), and state prescription opioid policies (Dowell et al. 2016; Meinhofer 2016; Buchmueller and Carey 2018; Dave, Grecu, and Saffer 2017). However, the observed effects explain, at most, only a small portion of the total change in overdose deaths.[2] This study examines the broader question of the sources of the extremely large (278 percent from 1999-2016) overall rise in drug deaths. The investigation also implements methods of measuring the combined effects of multiple proxies for economic conditions, accounting for the incomplete reporting of drug involvement on death certificates, and testing sensitivity of the findings to the presence of uncontrolled confounding factors.

The rise in fatal drug overdoses could be part of a broader phenomenon of growing "deaths of despair" which "respond more to prolonged economic conditions than to short-term fluctuations, and especially social dysfunctions … that come with prolonged economic distress" (Deaton 2017, p.3). Others have asserted potential roles for rising income inequality, international trade, stagnant wages, increased unemployment or general social and economic decline (Stiglitz 2015; Meara and Skinner 2015; Pierce and Schott 2016). These hypotheses

[2] For example, Dowell et al. (2016) find that implementing a combination of two state policies designed to reduce access to prescription opioids (pain clinic laws and mandated provider review of information in prescription drug monitoring programs) would reduce drug overdose deaths by around 12 percent.

suggest that demand-side factors are fundamental drivers of the increases in deaths. In addition to drug mortality, Case and Deaton (2015, 2017) emphasize the importance of fatalities due to suicides and alcoholic liver disease (hereafter "alcohol").[3] For this reason, combined mortality rates from drugs, suicides and alcohol (DSA) are also often examined below.

At first glance, the particularly large growth in overdose mortality in Appalachia and the rust-belt seems consistent with the demand-driven increases in drug problems. However, other areas not with robust economies have also experienced strong upsurges in overdose fatalities. For instance, New Hampshire and Massachusetts had the first and fourth highest state opioid death rates in 2014 (Ruhm 2017b), despite healthy economic performance. It may also be difficult to reconcile demand-related mechanisms with dramatically larger increases in drug death rates experienced by whites than blacks, despite the generally greater economic insecurity faced by minorities and an absence of similar mortality growth among midlife adults in other developed countries also encountering economic difficulties.

An alternative is that changes in supply-side factors related to the availability and use of risky drugs are of particular importance. Under such an explanation, whites might have been more affected than nonwhites because they have been more widely prescribed opioids (K. O. Anderson, Green, and Payne 2009; Burgess et al. 2014; Singhal, Tien, and Hsia 2016) and deaths may have grown more in the United States than in other countries because of the large U.S. share of prescription opioid consumption.[4] Similarly, drug fatality rates could have increased more

[3] Dowell et al. (2017) confirm that mortality rates from these sources have trended upward, albeit by fairly small amounts.

[4] Case and Deaton (2017) show that there has been little change in DSA mortality since 2000 for 50-54 year olds in France, Germany, Sweden, the United Kingdom, Canada and Australia. In 2007, by one estimate, the United States contained 4.6 percent of the world's population but constituted 80 percent of global opioid and 99 percent of global hydrocodone consumption (Manchikanti et al. 2010).

rapidly in rural than urban areas because of differences in education, age or race/ethnicity.[5] If so, the measured effect of changes in macroeconomic conditions should decline or disappear once county population characteristics are controlled for.

This study first examines the ability of medium-run changes in economic conditions – related to labor market outcomes, household wealth and international trade shocks – to explain the rapid rise in fatal overdoses. These are distinguished from prior literature examining how *transitory* economic fluctuations affect various types of drug problems (Arkes 2007; Ruhm 2015; Carpenter, McClellan, and Rees 2017; Martin Bassols and Vall Castelló 2016; Hollingsworth, Ruhm, and Simon 2017; Betz and Jones 2017).[6] The working assumption is that economic conditions *cause* changes in drug problems. However, there is also evidence of reverse causation – whereby rising opioid use negatively affects labor markets (Krueger 2017; Harris et al. 2017; Aliprantis and Schweitzer 2018). To the extent this occurs, the empirical findings may *overstate* the role of economic conditions in contributing to the fatal drug epidemic.[7]

Evidence is next provided on the alternative hypothesis that changes in the drug environment are an important cause of rising overdose deaths. Directly measuring such supply-side factors is difficult and the strategy used here is to exploit the dramatic changes in sources of drug-related deaths occurring over the sample period. Specifically, growth in fatal overdoses

[5] For instance, less educated individuals are likely to be particularly vulnerable to a more dangerous drug environment due to being less knowledge about the risks (Cutler and Lleras-Muney 2010) or having less to lose from them (Becker and Murphy 1988).

[6] These analyses indicate that drug problems increase during temporary downturns. For example, Hollingsworth, et al. (2017) find that a one percentage point increase in annual county unemployment rate predicts a 3.6% increase in the opioid death rate and a 7.0% rise in opioid-related emergency department visits. However, it is unclear how the effects of temporary fluctuations in economic conditions are related to the longer-term changes focused upon here, or what share of short-term variations in drug death rates are accounted for by them.

[7] On the other hand, Currie et al. (2018) find evidence that opioids may be associated with small increases in the employment-to-population ratios of women (but not men).

during the first decade of the 21st century primarily involved opioid analgesic, whereas later increases (since around 2010) were mainly due to illicit opioids such as heroin and fentanyl.

The timing of these patterns probably reflects supply-related changes in the drug environment. The number of opioid prescriptions dispensed more than doubled between 1996, when OxyContin first became available on the U.S. market, and 2010 (Pezalla et al. 2017), in large part because of aggressive marketing efforts by pharmaceutical manufacturers as well as recommendations for aggressive therapeutic opioid use to treat "pain as the 5th vital sign" (Quinones 2015; Presidents Commission 2017; Baker 2017). From 2010 through 2016, the number of opioid prescriptions written declined by 13% as increasing attention to the growth in opioid-related deaths led to aggressive actions to reduce consumption involving (among others): increased monitoring of drug; closure of "pill mills" and pain clinic regulation; revision of prescriber guidelines; and physician education (Dowell, Haegerich, and Chou 2016; Meinhofer 2016; Pezalla et al. 2017).[8] Also, the release of an abuse-deterrent formulation of OxyContin in 2010 reduced demand but almost certainly fueled some substitution to heroin which had been become increasingly available at high levels of purity and low cost, in part due to the expansion of Mexican imports into the eastern United States, and with illicit fentanyl emerging as a major risk in 2013 (Drug Enforcement Administration 2016; Jones, Lurie, et al. 2016; Evans, Lieber, and Power 2018; Alpert, Powell, and Pacula 2018).

Prior research provides mixed evidence on how the evolution of economic conditions is related to drug deaths and other mortality. Pierce and Schott (2016) find that import competition is positively related to county-level suicide and accidental poisoning mortality rates, with

[8] However, the intensive marketing efforts by drug manufacturers continued during this period (Committee on Homeland Security and Governmental Affairs. 2018).

especially strong effects for middle-aged whites.[9] Charles et al. (2018) show that declines in manufacturing employment are linked to high rates of opioid use and deaths, while a cross-sectional analysis by Monnat (2018) indicates that rates of economic or family distress and dependence on mining, are positively associated with county drug mortality rates. Finally, O'Brien and Venkataramani (2017) finds that low levels of economic mobility predicted larger increases in overall county mortality rates of 45-54 year old Non-Hispanic whites, for three-year periods centered around 2000 and 2012, but with no effect obtained for per capita incomes, poverty and unemployment rates or Gini coefficients. On the other hand, Case and Deaton (2017) indicate that national trends in median household incomes and all-cause mortality rates are poorly aligned (although with some indication of an inverse association for middle-aged non-Hispanic whites) and tentatively conclude that the data do not support income-based explanations of the mortality patterns. However, they note the limitations of such national comparisons and do not consider economic conditions other than household incomes. Generally, these studies control for a limit set of economic measures and do not fully account for the potential effects of confounding factors.

There has been even less investigation of the role of the drug environment using credible identification strategies, probably because of the difficulty in measuring its components well. Evidence has been provided of strong positive correlations between the national opioid

[9] Their primary analysis does not control for alternative economic indicators and there could be measurement issues since the analysis period spans the changeover from the ICD-9 to ICD-10 coding systems. The main specifications include an interaction between the post-trade shock period and 1990 median household incomes but will not capture the effects of changing income levels or of other potentially important economic factors. Increasing import competition predicts growth in unemployment rates and declines in incomes, employment and labor force participation rates but these are not simultaneously included in models that directly controlling for trade shocks. Since their analysis ends in 2013, they do not capture the effects of economic conditions on drug deaths during the period where illicit opioids have become dominant. The increase in accidental poisoning deaths explained by international trade exposure is also small compared to the total growth observed over the analysis period.

prescribing behavior and fatal overdoses (Paulozzi 2012; Dart et al. 2015) but this association could potential reflect demand-side or confounding factors.

2. Methods

2.1 Examining the Role of Economic Conditions

I first investigate the extent to which sustained deterioration in economic conditions are a driver of increases in fatal overdoses by performing a county-level analysis where the outcomes are changes in drug or DSA mortality rates occurring between 1999 and 2015 and the key explanatory variables are changes in five measures of economic conditions over the same or similar periods.

Denote mortality rates per 100,000 in county k at time t by M_{kt}. Let $t = [0,1]$ indicate an early and later period (usually 1999 and 2015) with mortality determined according to:

$$M_{kt} = \boldsymbol{E}_{kt}\boldsymbol{b} + \boldsymbol{X}_{kt}\boldsymbol{c_t} \quad (1)$$

where $\boldsymbol{E}_{kt}$ represents one or more proxies for economic conditions and $\boldsymbol{X}_{kt}$ is a vector of supplementary explanatory variables. The coefficients on the supplementary regressors can change over time, reflecting potential shifts in determinants of mortality that differentially affect population subgroups, while the effect of economic conditions is assumed to be time-invariant.

The change in mortality rates between the two periods can be written as:

$$\Delta M_k = M_{k1} - M_{k0} = \Delta\boldsymbol{E}_k\boldsymbol{b} + \boldsymbol{X}_{k0}\Delta\boldsymbol{c} + \Delta X_k c_1, \quad (2)$$

where $\Delta E_k = E_{k1} - E_{k0}$, $\Delta X_k = X_{k1} - X_{k0}$, and $\Delta\boldsymbol{c} = c_1 - c_0$. The regression analog to (2) is:

$$\Delta M_k = \Delta\boldsymbol{E}_k\beta + \boldsymbol{X}_{k0}\gamma_1 + \Delta\boldsymbol{X}_k\gamma_2 + \varepsilon_k, \quad (3)$$

where ε_k is the error term.[10]

[10] It is unclear conceptually how to examine the effects of changes in economic conditions in a framework where these effects are time-varying. Empirically, such a model would be estimated as: $\Delta M_k = \boldsymbol{E_0}\boldsymbol{\alpha} + \Delta\boldsymbol{E}_k\beta + \boldsymbol{X}_{k0}\gamma_1 + \Delta\boldsymbol{X}_k\gamma_2 + \varepsilon_k$. I discuss below the results of this model when examining changes in total drug mortality rates.

The coefficients of interest, $\hat{\beta}$, show estimated economic effects on mortality growth. A requirement for unbiased estimates is that the supplementary covariates must adequately control for influences on mortality trends that are spuriously correlated with $\Delta\boldsymbol{E}$ such that cov($\Delta E_k, \varepsilon_k$) = 0. However, the estimates will be attenuated if the supplementary controls include variables that are caused by changes in economic conditions. This is not a problem for the predetermined variables, $\boldsymbol{X}_0$, but could be an issue for $\Delta\boldsymbol{X}$. For example, individuals, particularly young ones, often migrate to areas with better economic conditions (Greenwood 1997), implying that changes in age-specific population shares are likely to be affected by economic performance. Similarly, localities hit by international trade shocks experience reductions in the supply of marriageable men and increases in the fraction of children born to unwed mothers (D. Autor, Dorn, and Hanson 2017).

For this reason, I also estimate an alternative version of equation (3) using "instrumented" values of $\Delta\boldsymbol{X}$, denoted as $\Delta\boldsymbol{X^I}$, that are constructed by calculating changes between initial year county level values of $\boldsymbol{X}$ and *census division* changes occurring between the starting and ending analysis years, as detailed in Appendix A. The operational assumption is that economic conditions may causally affect the supplementary covariates within but not across census divisions.[11]

Models controlling for $\Delta\boldsymbol{X^I}$ largely avoid the problem of endogeneity bias but at the cost of less fully accounting for potential confounding factors. Therefore, I present results for

[11] For the migration example, this implies that individuals might systematically move to counties with better economic conditions within a census region but not outside it. This procedure will not address potential biases from differential migration rates between counties as a function of drug use or dependency. The direction of any resulting bias is uncertain, but movement is typically from areas with weaker to stronger economies, with healthy individuals being more mobile that those who are less healthy (Blanchard et al. 1992; Halliday 2007). If mobility based on drug use follows a similar pattern, the estimates here will overstate the effects of economic conditions since persons with low overdose mortality risk will have relatively high rates of migration to counties with strong economies.

specifications that alternatively control for $\Delta \boldsymbol{X}$ and $\Delta \boldsymbol{X^I}$. Empirically, the estimated economic effects are generally attenuated more when including $\Delta \boldsymbol{X}$ rather than $\Delta \boldsymbol{X^I}$.

Observations are generally weighted by 2015 county populations, to avoid attributing undue influence to the treatment effects observed in small counties.[12] However, weighting can reduce efficiency under some circumstances (Wooldridge 1999; Solon, Haider, and Wooldridge 2015) so sensitivity of the results to use of unweighted estimates is explored. Most models examine how changes in mortality rates from 1999-2015 are related to the evolution of economic conditions over approximately the same period. However, I also allow economic conditions operate with a delay, by controlling for lagged rather than contemporaneous changes in these variables over approximately the 1990-2000 period, and I examine results for subperiods.

The explanatory variables, $\Delta \boldsymbol{E}, \boldsymbol{X_0}, \Delta \boldsymbol{X}$ and $\Delta \boldsymbol{X^I}$, are standardized to have a mean of zero and a standard deviation of one (by subtracting the mean and dividing by the standard deviation), so the regression coefficients show estimated "effect sizes" of a one standard deviation change in the regressor and the intercept term indicates the average change in the dependent variable.

The econometric results from equation (3) are used to estimate how changes in economic conditions affect trends in fatal overdoses and the predicted impacts are then compared to the actual change over the period. In a model with only a single proxy for economic conditions, this is measured as:

$$\% \text{ of } \Delta \text{M Explained} = \frac{\hat{\beta}}{\sigma_{\text{M}}} \times 100\% \tag{4}$$

[12] For example, in 2015, the smallest 50 percent of counties contained just 5.8 percent of the U.S. population.

where $\hat{\beta}$ is the regression coefficient on $\Delta\boldsymbol{E}$ and σ_M is the standard deviation of ΔM. Since $\Delta\boldsymbol{E}$ has been standardized, $\frac{\hat{\beta}}{\sigma_M}$ shows the standard deviation change in mortality rates predicted from a one standard deviation growth in $\Delta\boldsymbol{E}$.[13]

2.2 Multiple Proxy Estimates

Implementing the strategy just described faces challenges. There is not a clear conceptual framework determining what aspects of the economy are likely to be the most important determinants of growth in drug mortality, nor exactly what is meant by changes in economic conditions. This is addressed by including proxies for multiple, potentially overlapping, aspects of the economy including: labor market conditions, income, poverty rates and home prices (an important component of household wealth), and international trade exposure.

Since no single economic indicator completely captures the effects of interest, I implement the method developed by Lubotsky and Wittenberg (2006) for simultaneously including multiple proxies in the model and then including a weighted sum of the coefficients to minimize attenuation bias.[14] An important advantage of this framework is that the covariances between the error terms of the proxies are unrestricted and, specifically, are allowed to be non-zero.[15] Details of the Lubotsky and Wittenberg (LW) procedure are provided in Appendix A.

Bootstrapped standard errors (with 1000 replications) are calculated for the multiple proxy (MP) estimates. In other cases, robust standard errors, clustered at the commuter zone level, are displayed on the tables.[16]

[13] For example, if a one standard deviation increase in $\Delta\boldsymbol{E}$ predicts a one-half standard deviation increase in ΔM ($\hat{\beta} = 0.5\sigma_M$), 50 percent of the mortality growth is estimated to be accounted for by changing economic conditions.
[14] Since, the coefficients on the individual proxies may sometimes also be of interest (e.g. if economic conditions cannot be well summarized by a single latent variable) these results are also presented for the primary specifications.
[15] Instrumental variables estimates and factor or principal component analyses require zero covariances.
[16] Clustering is at the commuter zone since this is the level of the observations on the import exposure variable.

2.3 Incomplete Specification of Drug Categories Involved in Overdose Deaths

Identifying the drug involved in fatal overdoses is complicated because no specific drug category is identified on the death certificates on around one-fifth of drug fatalities, leading to a substantial understatement of mortality rates involving specific types of drugs.[17] Corrected mortality rates were obtained using information from death certificate reports where at least one specific drug category was identified to impute drug involvement for cases where none was identified, using a procedure previously implemented by Ruhm (Ruhm 2017b).

Year-specific probit specifications were first estimated for the sample of fatal overdoses with at least one drug mentioned. The dependent variables in these models were equal to one if opioid analgesics or illicit opioids, respectively, were mentioned and zero if not. Dichotomous explanatory variables included: sex, race (white, black, other nonwhite), Hispanic origin, marital status (currently married at the time of death versus not), education categories (high school dropout, high school graduate, some college, college graduate), age categories (≤20, 21-30, 31-40, 41-50, 51-60, 61-70, >70), day-of-the-week of death indicators, location of death (hospital inpatient, hospital outpatient/ED, dead on arrival at hospital/ED, home, other) and census region. Predicted probabilities of opioid analgesic or illicit opioid involvement were next imputed, using the probit estimates, for deaths without mention of a specified drug category. Robustness of the results to the use of uncorrected mortality rates was also examined.

2.4 Selection on Unobservables

A condition for obtaining unbiased estimates of the economic measures of key interest, $\hat{\beta}$ in equation (3), is that cov($\Delta E_k, \varepsilon_k$) = 0 or, equivalently, that the supplementary covariates $\boldsymbol{X}_0$ and $\Delta\boldsymbol{X}$ account for all relevant confounding factors. However, if there are omitted variables that

[17] This was the case for 21.9 percent of overdose fatalities in 1999 and 17.2 percent in 2015. For these fatalities, the death certificate lists only an unspecified category of drugs (ICD T-Code 50.9).

affect mortality rates and are correlated with ΔE, $\text{cov}(\Delta E_k, \varepsilon_k) \neq 0$) and $\hat{\beta}$ will be biased. This is referred to below as selection on unobservables and examined using methods developed by Oster (2016) that extend on those introduced by Altonji, Elder and Taber (2005).

Oster (2016) shows that the true treatment effect is approximated by:

$$\beta^* \approx \tilde{\beta} - \delta(\beta^o - \tilde{\beta}) \left(\frac{R_{max} - \tilde{R}}{\tilde{R} - R^o}\right) \quad (5)$$

where: β^o and R^o are the coefficient on E and R-squared from a "short" regression that excludes controls for $\boldsymbol{X_0}$ and $\Delta\boldsymbol{X}$; $\tilde{\beta}$ and $\tilde{R}$ are the corresponding coefficient and R-squared from the "long" equation that includes the supplementary covariates; R_{max} is the R-squared from a hypothetical regression with an additional vector of covariates, $\boldsymbol{W}$, that are orthogonal to $\boldsymbol{X_0}$ and $\Delta\boldsymbol{X}$ and capture all remaining determinants of mortality rates; δ measures the relative importance of selection of observables and unobservables.[18] $\beta^o, \tilde{\beta}, R^o$ and $\tilde{R}$ are obtained by estimating the "long" and "short" regressions; values for δ and R_{max} must be assumed.

Manipulation of equation (5) also allows the relative importance of selection on unobservables that would eliminate the estimated treatment effect to be computed as:

$$\delta^* \approx \left(\frac{\tilde{\beta}}{(\beta^o - \tilde{\beta})}\right)\left(\frac{\tilde{R} - R^o}{R_{max} - \tilde{R}}\right) \quad (6)$$

and the R_{max} that would do so to be approximated by:

$$R^*_{max} \approx \tilde{R} + \left(\frac{\tilde{\beta}}{\delta(\beta^o - \tilde{\beta})}\right)(\tilde{R} - R^o). \quad (7)$$

2.5 Changes in the Drug Environment

[18] R_{max} will be less than one if the dependent variable is measured with error (e.g. due to misclassification of the cause of death or drugs involved in fatal overdoses). Defining σ_{XE} as the covariance between $\boldsymbol{X}$ and $\Delta\boldsymbol{E}$, σ_{WE} as the covariance between $\boldsymbol{W}$ and $\Delta\boldsymbol{E}$, and with σ_X^2 and σ_W^2 being the variances in $\boldsymbol{X}$ and $\boldsymbol{W}$, $\delta = \frac{\sigma_{WE}/\sigma_W^2}{\sigma_{XE}/\sigma_X^2}$. The magnitude of the difference between β^* and $\tilde{\beta}$ is therefore increasing in δ, $\beta^o - \tilde{\beta}$, $R_{max} - \tilde{R}$, and $R^o - \tilde{R}$.

To examine the hypothesis that changes in the drug environment are a key source of the rise in fatal overdoses, I estimate a series of county-level panel data models examining whether changes in the group-specific composition of opioid analgesic or illicit opioids death rates correspond, in expected ways, to breaks or reversals in overall drug-specific mortality. Define M_{gkt} as the specified drug mortality rate per 100,000 (adjusted for incomplete reporting on death certificates) for group g in county k at time t.

The first set of estimates indicate the share of fatalities accounted for by group g in county k at time t, S_{gkt}, according to:

$$S_{gkt} = \boldsymbol{X_{kt}\beta} + \boldsymbol{F_k}\kappa + \boldsymbol{T_t}\boldsymbol{\tau} + \boldsymbol{\omega_{gkt}}, \tag{8}$$

for $\boldsymbol{X_{kt}}$ a set of time-varying county characteristics,[19] $\boldsymbol{F_k}$ is a vector of county fixed-effects accounting for all time-invariant determinants, $\boldsymbol{T_t}$ is a vector of year dummy variables and $\boldsymbol{\omega_{gkt}}$ is the error term.

The time coefficients, $\hat{\boldsymbol{\tau}}$, show the year-specific share of drug deaths accounted for by the population group but do not unambiguously indicate effects of the drug environment. Consider the decomposition $\boldsymbol{T_t} = \boldsymbol{D_t} + \boldsymbol{Y_t}$, where $\boldsymbol{D_t}$ refers to the (unobserved) drug environment and $\boldsymbol{Y_t}$ to other time-varying determinants of mortality (e.g. national economic conditions or changes in medical technologies). $\hat{\boldsymbol{\tau}}$ combines both effects. However, when the drug environment changes abruptly, it is likely to be the primarily determinant of contemporaneous changes in $\hat{\boldsymbol{\tau}}$, unless other factors change at precisely the same time and in the same direction. To address this latter

[19] $\boldsymbol{X_{kt}}$ always includes the population share of group g. For example, with two population groups, denoted by $g = [0,1]$, and λ_{1kt} the county-population share of group 1 in year t, $S_{1kt} = \frac{\lambda_{1kt}M_{1kt}}{\lambda_{1kt}M_{1kt}+(1-\lambda_{1kt})M_{0kt}}$, so S_{1kt} will depend in part on λ_{1kt}. In these models, the three economic indicators with annual data available (unemployment rates, poverty rates and median incomes) are also controlled for to insure that the results are not being driven by differential effects of economic factors on mortality shares.

possibility, I conducted supplementary analyses for additional drug categories that experienced different breaks in mortality trends than those for opioid analgesics or illicit opioids.

Statistical significance of the trend breaks can be more formally examined through spline specifications of:

(9) $$S_{gkt} = \boldsymbol{X_{kt}\beta} + \boldsymbol{F_k}\kappa + Trend_t\varphi + POST_t\pi + \boldsymbol{\omega_{gkt}}.$$

$Trend_t$ is a linear trend ranging from 0-16 for 1999-2015 and $POST$ is a trend spline equal to 0 in all initial sample years and increasing by one unit annually after a specified time period. For instance, the growth in drug deaths was dominated by opioid analgesics from 1999 to around 2010 but by illicit opioids thereafter. This is represented by setting $POST$ to 0 for all years up to 2010 and from 1-5, respectively, in 2011-2015. $\hat{\varphi}$ then shows the drug death share trend from 1999-2010, with $\hat{\varphi} + \hat{\pi}$ indicating the corresponding trend from 2011-2015. The statistical significance of $\hat{\pi}$ tests the hypothesis that the mortality share changed starting around 2010.

I directly examine how drug-specific mortality rates change over time for a treatment group (e.g. males) relative to a reference group (e.g. females) using the regression model:

(10) $$M_{gkt} = \boldsymbol{F_k}\kappa + \boldsymbol{T_t\tau} + (\boldsymbol{T_t} \times G_g)\boldsymbol{\theta} + \zeta_{gkt},$$

where G is a treatment group dummy variable equal to 0 (1) for a reference (treatment) group and with ζ_{gkt} being the regression disturbance. In (10), observations for each county and year are included for at least two population groups, with controls incorporated for county fixed-effects, general time effects and treatment group-time interactions. $\widehat{\boldsymbol{\theta}}$ shows the treatment versus reference group differences in time effects. Controls for time-varying county characteristics ($\boldsymbol{X_{kt}}$) affect the estimated reference group time effects ($\hat{\boldsymbol{\tau}}$) but not the treatment group differentials ($\widehat{\boldsymbol{\theta}}$) of primary interest, and so that are optional in the model.

Corresponding trend-spline models take the form:

(11) $$M_{gkt} = \boldsymbol{F_k}\kappa + \boldsymbol{T_t}\boldsymbol{\tau} + Trend_{gt}\varphi + POST_{gt}\pi + \zeta_{gkt},$$

where $Trend_{gt}$ is a treatment group linear time trend (ranging from 0-16 for the treatment group and always equal to 0 for the reference group) and $POST$ is an additional treatment group-specific trend spline, defined as above. $\hat{\boldsymbol{\tau}}$ shows reference group time effects, $\hat{\varphi}$ indicates the initial mortality rate trend differential for the treatment group relative to the reference group, and $\hat{\varphi} + \hat{\pi}$ shows the corresponding difference in later periods.

All variables for this portion of the analysis are defined at the county-level and so robust standard errors are clustered by county.

3. **Data and Variables**

3.1 Dependent Variables

The outcomes examined are mortality rates due to drug poisonings, drug/suicide/alcoholic liver disease deaths (DSA) and drug deaths involving prescription or illicit opioids. Primary data come from the *Multiple Cause of Death (MCOD)* files (Centers for Disease Control and Prevention 2017) which provide information from death certificates on a single underlying cause of death (UCD), up to 20 additional causes, and demographic variables. Data are utilized on cause of death, using four-digit *International Classification of Diseases, Tenth Revision* (ICD-10) codes, county of residence, age, race/ethnicity, gender, education, year, and weekday of death. Special permission was obtained to use the county information, which is not provided on the public use files.

The analysis covers the universe of DSA fatalities to US residents from 1999-2015 (foreign residents dying in the US were excluded). The study begins in 1999 because ICD-9 codes, used earlier, are not fully comparable to ICD-10 categories (R. N. Anderson et al. 2001).

UCD codes are used to classify the reason for death. Drug poisonings include ICD-10 codes: X40-X44, X60-X64, X85, Y10-Y14 or Y352. DSA deaths include these plus nondrug suicides (X65-X84, Y87.0, *U03) and alcohol deaths (ICD-10 code K70). I examined sensitivity of the results to excluding intentional drug deaths (codes X60-X64) from the definition of overdoses and expanding DSA deaths to include a broader definition of alcohol-related mortality.[20]

For fatal overdoses, the death certificates list, as ICD-10 "T-codes", one or more drug categories involved as immediate or contributory causes of death. The main drug categories are opioid analgesics and illicit opioids, which include both heroin and synthetic opioids, defined by ICD-10 T-codes 40.2, 40.1 and 40.4 respectively. Synthetic opioids include several types of drugs, the most important being fentanyl. Fentanyl has legal uses but recent increases in deaths are largely driven by non-prescription consumption (Rudd et al. 2016). Although around half of fatal overdoses involve the use of more than one drug category (Ruhm 2016, 2017a), the analysis below does not examine drug combinations.

Death counts are converted into county mortality rates per 100,000 using population data from the National Cancer Institute's *Surveillance Epidemiology and End Results (SEER)* program (https://seer.cancer.gov/popdata/). The SEER data are designed to supply more accurate population estimates for intercensal years than standard census projections, and adjust for population shifts in 2005, resulting from Hurricanes Katrina and Rita.

In addition to total death rates, mortality rates are separately calculated for males and females, non-Hispanic whites (hereafter "whites") and nonwhites or Hispanics (hereafter

[20] Specifically, I follow Case and Deaton (2015, 2017) by incorporating non-alcohol and unspecified sources of chronic hepatitis (ICD-10 code K73) and cirrhosis of the liver (ICD-10 code K74) in the alcohol category. This definition is almost certainly too broad since most of the added deaths will not involve alcohol. In addition to heavy alcohol use, cirrhosis frequently results from hepatitis C (often due to injection drug use) and nonalcoholic fatty liver disease and steatohepatitis (National Institute of Diabetes and Digestive and Kidney Diseases 2018). Less than half of cirrhosis deaths in 2013 were alcohol-related (Yoon and Chen 2016).

"nonwhites"), education groups (high school graduate or less, some college but not graduated, college graduate or more among persons aged 25 and above), and for 20-59 year olds, as well as for other age groups in some analyses.[21]

3.2 Economic Indicators

Five county-level proxies for changes in economic conditions are included: unemployment and poverty rates, median household incomes and home prices, and exposure to imports. These are designed to capture multiple aspects of the economy across the domains of labor market conditions, income, wealth and international trade.

Data from the Bureau of Labor Statistics *Local Area Unemployment Statistics Database* (www.bls.gov/lau/) are used to calculate three-year averages of unemployment rates, ending in the year specified (e.g. 1997-1999 for the 1999 analysis year). Unemployment rates are averaged to smooth short-term fluctuations or measurement error, which will be particularly severe for smaller counties.[22] Information on three-year averages in poverty rates and median household incomes (ending in the year specified) are obtained from the Bureau of the Census *Small Area Income and Poverty Estimates* (www.census.gov/did/www/saipe/). Data on median home prices in 2000 are from the US Census; later data are 5-year averages from the American Community Survey (*ACS*) for the periods 2005-2009, 2007-2011 or 2011-2015, obtained from various issues of the Area Resource File/Area Health Resource File (*ARF)*, http://www.arf.hrsa.gov, and from

[21] Several challenges are encountered when calculating education-specific mortality rates. First, education is sometimes reported in years rather than specific thresholds. In these cases, ≤12, 13–15 and ≥16 years are classified as high school graduate or less, some college and college graduate. Second, schooling status is missing on around 5 percent death certificates for overdoses (e.g. 7.2% in 1999 and 4.7% in 2015). Education-specific mortality rates are computed by assuming that the county-specific distribution of educational attainment is the same for the missing and non-missing cases. Third, since the *SEER* data does not provide education-specific population estimates, these are calculated by multiplying total or group-specific population by the county education group share, with the latter obtained from 2000 Census and a five-year averages from the 2011-2015 American Community Surveys, as provided in the USDA Economic Research Service (*ERS*) County Level Data Sets, www.ers.usda.gov/data-products/county-level-data-sets/county-level-data-sets-download-data/.

[22] In some models, employment-to-population ratios are controlled for instead of unemployment rates.

American FactFinder (https://factfinder.census.gov/faces/nav/jsf/pages/index.xhtml). Median household incomes and home prices are converted to $2015 using the All-Items Consumer Price Index (www.bls.gov/cpi/). The last economic proxy reflects changes in exposure to Chinese import competition between 1999 and 2011, using a measure constructed by Acemoglu, et al. (2015), that builds upon earlier work by Autor, et al. (2013).[23]

In some specifications, lagged rather than contemporaneous changes in economic conditions are controlled for, covering the period from approximately 1990-2000, rather than 1999-2015. These specifications differ slightly based on the available data. Specifically, for the starting period (approximately 1990), unemployment rates are averaged for 1990-1992; median incomes and poverty rates a averages of 1989 and 1993 values; and the instrumented import competition variable is from 1990-2000, obtained from Autor, et al. (2013).

3.3 Additional Covariates

Most models include supplementary covariates to capture the effects of potential confounding variables. Unless otherwise noted, these were available for each analysis year. The *SEER* data were used to calculate county population shares of: females, Hispanics, black non-Hispanics, other nonwhite non-Hispanics, seven age categories (15-24, 25-34, 35-44, 45-54, 55-64, 65-74, ≥75 years old); county percentages of persons ≥25 years old with some college or who were college graduates were also included, using previously described information from the *ACS*.[24] The percentage of households headed by females in 2000 and 2010, and of foreign-born

[23] Differences in measured trade exposure occur because of variations in local industry employment structure in 1970. They use an instrumental variables procedure to account for the potential endogeneity of US trade exposure; the instruments are growth of Chinese imports to eight other developed countries. Their trade exposure measure is calculated at the commuter zone rather than the county level. For this analysis, all counties within a commuter zone are assumed to have the commuter zone level of import exposure, using a crosswalk of 1990 commuter zones to counties. The import exposure and crosswalk files were obtained from: www.ddorn.net/data.htm.

[24] Thus, in the regressions, the excluded (reference) categories are population shares of males, whites, <15 year olds and the non-college educated.

persons in the county in 2000, 2006-2010 and 2011-2015 were obtained from the *ARF*. Information on the number of hospital beds and active non-federal physicians per 1,000 population were from the same source and proxied the county's health infrastructure.[25]

The *ERS* County level data sets also provide 2013 county "rural-urban" continuum codes: metropolitan with population ≥1,000,000, 250,000 - 999,999 and <250,000 (three classifications); urban with population ≥20,000 and 2,500 – 20,000 and adjacent to or not adjacent to a metropolitan area (four classifications); rural with population <2,500 adjacent to or not adjacent to a metropolitan area (two classifications). Dummy variables for eight of these classifications are included in the regression models, with the largest metropolitan areas as the excluded reference group.

Finally, two measures of the state-level legal environment related to drug use are incorporated. The first indicates whether the state has a prescription drug monitoring program (*PDMP*) that requires reporting to it by drug dispensers. The second controls for whether the state has legalized marijuana use for medical or recreational purposes. Data for both variables come from the *Prescription Drug Abuse Policy System* (www.pdaps.org). They are included because there is evidence that each may influence drug use and abuse (Bachhuber et al. 2014; A. C. Bradford and Bradford 2016; Buchmueller and Carey 2018).

Appendix Table A.1 provides summary statistics on the dependent variables, economic proxies, and additional covariates measured in (approximately) 1999 and 2015, with observations weighted by 2015 county populations. The analysis sample consists of 3,098 counties with consistent boundaries over time period and data available for all of the economic

[25] The number of hospital beds was not available for 2011 and 2015. The former were calculated by averaging values for 2010 and 2012; the latter by using the 2014 number of beds.

proxies.[26] The table shows actual values; however, as mentioned, the independent variables are standardized in the regressions. Also, changes in median household incomes and home prices, are reverse-coded (opposite signed) in the econometric models, so that positive coefficients always indicate that worsening economic conditions are associated with higher mortality growth.

3.3 Analysis of Changes in the Drug Environment

The variables included when examining changes in the drug environment are somewhat different. Instead of a having a single observation per county (e.g. showing mortality rate changes from 1999-2015), this investigation includes use panel data with 17 observations per county (one for each year from 1999-2015). This allows county fixed-effects to be included, controlling for all time-invariant county characteristics and reducing the need for supplementary covariates. Some variables controlled for in the analysis of medium-term changes in economic conditions are inappropriate to include here because there is no time-variation (e.g. import penetration shares) or since annual values would need to be extrapolated or interpolated from a small number of years (e.g. home price changes and share foreign-born or in female-headed households), introducing measurement error which is particularly problematic in fixed-effect models. The results were generally not sensitive to the remaining choice of covariates.

Separate estimates are frequently provided by sex and for 20-39 year olds ("younger" adults) compared to 40-59 year olds ("older" adults). The use of two age groupings is convenient for examining changes in age-related patterns of drug mortality; these groups contain an equal number of years and constitute a large share of total drug mortality (e.g. 85% in 2015).

4. **Descriptive Patterns**

[26] Three counties were dropped because information on education shares was missing; 24 and 2, respectively, were excluded because of missing information on import exposure and home prices.

Figure 1 displays changes from 1999-2015 in total drug death rates, non-drug suicides and alcohol mortality, as well as opioid analgesic and illicit opioid involved drug fatality rates. Overall drug mortality rates rose steadily, from 6.0 to 16.3 per 100,000 from 1999-2015, a 170 percent increase. Nondrug suicide death rates started out considerably higher (9.3 per 100,000 in 1999) but grew more slowly, by 30%, reaching 12.1 per 100,000 in 2015.[27] Alcohol deaths also increased relatively gradually (from 4.3 to 6.5 per 100,000). Conversely, opioid analgesic and illicit opioid death rates rose extremely rapidly: from 1.3 and 1.2 per 100,000 in 1999 to 4.8 and 7.4 per 100,000 in 2015, but with quite different patterns. All of the growth in opioid analgesic mortality occurred from 1999-2011, whereas illicit opioid death rates initially rose modestly, reaching 2.1 per 100,000 in 2006, and considerably more rapidly thereafter, particularly from 2010-2015 where the mortality rate exploded from 2.6 to 7.4 per 100,000.

Figure 2 shows corresponding patterns of drug mortality for subgroups stratified by sex and age. Drug death rates were higher for males than females. While opioid analgesic deaths grew at similar rates for both sexes, illicit opioid fatalities increased much more rapidly for men after 2010. Overall drug mortality rates rose at fairly common rates for 20-39 and 40-59 year olds, although at somewhat higher absolute levels for the latter group, and with much slower growth for >60 year olds. However, the patterns again differed across types of drugs, with the increases in illicit opioid death rates skewed towards 20-39 year olds, especially after 2010, while those involving opioid analgesics particularly affected 40-59 year olds. These patterns raise initial doubts about the possibility that a single set of economic determinants can explain these differential trends in mortality rates.[28]

[27] Intentional drug deaths rose 42% over the period, from 1.2 to 1.6 per 100,000, with the result that all suicides (drug and nondrug) grew by 31%.

[28] Whites and less educated individuals experienced faster growth in drug deaths than their counterparts (Appendix Figure A.1). Trends in non-DSA mortality rates were fairly similar to those for all drug deaths but with larger

5. Changes in Economic Conditions: Econometric Results

I next present econometric results examining the extent to which medium-run changes in county economic conditions predict corresponding changes in DSA mortality rates. The first specifications show models controlling for economic conditions but without supplementary covariates. Potential confounding factors are next included. A series of robustness checks are then conducted, estimates are provided for population subgroups and investigation is provided of the effects of remaining selection on unobservables.

5.1 Models without Supplementary Covariates

Table 1 shows regression coefficients on the economic proxies where the dependent variables are growth from 1999-2015 in mortality rates due to all drugs, opioid analgesics and illicit opioids and all DSA fatalities. These models do not control for potential confounding factors. Changes in median household incomes and home prices are reverse-coded so that positive coefficients always imply that worse economic performance is associated with faster mortality increases. The regressors are standardized so that coefficients show estimated effects of a one-standard deviation change in the explanatory variable. The top panel table displays results where the economic measures have been included separately, with every cell representing results of a different regression. In the second panel, the five economic proxies are included simultaneously and each column presents findings from a single regression. P-Values refer to the null hypothesis that the coefficients on the macroeconomic variables jointly equal zero. The third panel shows the multiple proxy (MP) estimate from the model with the five economic proxies, as well as the percent of the total mortality change explained by economic conditions.

overall gender, race and education differentials and a much higher concentration among older individuals, including those ≥60 (Appendix Figure A.2).

When controlled for separately, the economic proxy coefficients are positive for all outcomes and, except for import exposure, highly significant (top panel). For example, a one-standard deviation decrease in county median household incomes ($2,817 in 2015 dollars) is associated with a 2.07 per 100,000 faster growth in overdose mortality and a 0.68 per 100,000 increase in the opioid analgesic drug death rate. Since the standard deviations for these two outcomes are 10.37 and 3.58 per 100,000, a one standard deviation income reduction predicts around a 20 percent increase in mortality rates from these sources. The uniformly positive coefficients indicate that counties experiencing relative economic deterioration had higher than average growth rates of fatal overdoses.

Including the five economic proxies simultaneously virtually always substantially attenuates the estimated effects of individual economic proxies (see the middle panel of Table 1). For instance, the coefficient on median household income is reduced 90 percent for overall drug mortality and switches sign for illicit opioid deaths and opioid analgesic death rates. This attenuation is expected because the economic variables are reasonably highly correlated with each other, except for import exposure which is barely associated with the other four measures (see Appendix Table A.2). The R-squared is also uniformly low, ranging between 0.051 and 0.082, providing a further indication of the limited explanatory power of changes in economic conditions. With that said, the p-values from the test that the coefficients for the five economic proxies are jointly equal to zero always indicate that worsening economic conditions predict higher growth in mortality rates.[29]

[29] I also estimated models that controlled for county level Gini coefficients in 2000 and changes from 2000-2010 as an additional proxy, to capture potential effects of economic inequality not accounted for by the combination of median incomes and poverty rates. Growth in inequality generally predicted *slower* growth in mortality rates, although often by statistically insignificant amounts. Gini coefficients in 2000 were also negatively related to mortality rate increases and the predicted effects were usually statistically significant.

The third panel of Table 1 shows multiple proxy estimates, as well as the estimated percentage of the growth in mortality rates accounted for by the latent measure of economic conditions. The MP estimate exceeds the coefficients for any single economic measure (in either the top or middle panel of the table) by at least 15 percent – and generally much more – indicating the importance of correcting for attenuation bias. Dividing the MP estimate by the standard deviation of the dependent variable suggests that changes in economic conditions are associated with 33 percent of the rise in drug mortality rates, 26 percent of that for all DSA death rates and 26 to 28 percent of those involving opioid analgesics and illicit opioids. However, these estimates are likely to be serious biased by omitted confounding factors, an issue addressed next.

5.2 Models With Additional Covariates

The models just described control exclusively for one or more of the economic proxies and so do not account for potential correlations with county characteristics. Table 2 begins to remedy this by summarizing estimates from models where the dependent variable is the change in drug mortality rates and various sets of controls are included. Column (a) repeats the results from Table 1, with the five economic variables included simultaneously but nothing else. Column (b) adds to this the set of 1999 county characteristics ($\boldsymbol{X_{1999}}$) and changes in these characteristics from 1999-2015 ($\Delta\boldsymbol{X}$); column (c) includes instrumented rather than actual changes in the supplementary covariates ($\Delta\boldsymbol{X^I}$).

Controlling for $\boldsymbol{X_{1999}}$ and $\Delta\boldsymbol{X}$ reduces the multiple proxy estimate by 85% (from 2.95 to 0.43). Using instrumented changes instead (column c), the MP estimate is attenuated by 73% (to 0.79). The suggests that most of the observed relationship between changes in mortality rates and economic conditions reflects confounding factors. The evolution of local economies is estimated to explain 5 percent of the rise in drug mortality in model (b) and 9 percent in column (c),

compared to 33 percent in specification (a). The MP estimates are statistically significant in model (c), but not model (b).[30] The most important confounding county characteristics are sex and race/ethnicity differences and the share foreign-born. Together, these account for 67% of the total attenuation in the MP estimate in the model controlling for $\boldsymbol{X_{1999}}$ and $\Delta\boldsymbol{X}$, and 87% when including $\boldsymbol{X_{1999}}$ and $\Delta\boldsymbol{X^I}$ (see Appendix Table A.4). Age structure of the county also plays a role but the remaining supplementary covariates (urban-rural status, share of female-headed households, medical infrastructure and the two drug policy variables) are much less important.

The starting and ending analysis years (1999 and 2015) were determined by data availability. To insure that the results are not overly sensitive to this choice, I estimated models for alternative starting dates ranging from 1999 through 2003 and ending periods varying from 2011 through 2015. These results, summarized in Table A.5, indicate moderate sensitivity to the choice of starting years –economic conditions have somewhat more explanatory power in when beginning the analysis later – but not ending periods and do not change the basic conclusion that changes in economic conditions explain little of the increases in drug death rates.

The first panel of Table 3 repeats the MP estimate and percentage change in drug death rates accounted for by economic factors, as well as displaying the P-values for the joint hypothesis of no effect of the five individual macroeconomic proxies. The next three panels show corresponding estimates for opioid analgesic, illicit opioid and all DSA. Comparing results for models (b) and (c) to (a) indicates that at least 73 percent of the original correlation between economic conditions and various types of drug mortality growth is due to confounding factors,

[30] I estimated drug mortality models with controls additional controls included for 1999 levels of the economic proxies. These findings, summarized in Table A.3, indicate slightly higher explanatory power of changes in economic conditions, 9% and 10% of the total change in models controlling for $\Delta\boldsymbol{X}$ and $\Delta\boldsymbol{X^I}$, that were offset by the 1999 levels being responsible for -3% and -9% of the growth. In the same table, I show results with employment-population ratios rather than unemployment rates used as an economic proxy. When this is done, economic conditions are estimated to account for 6% to 12% of the change in drug deaths.

with more than 100 percent accounted for in some models with the additional controls. The estimated change in mortality rates accounted for by the economic variables ranges from 5 to 7 percent for opioid analgesics, -2 to 5 percent for illicit opioids, and -3 to 3 percent of all DSA deaths. The null hypothesis of no macroeconomic effect is never rejected in specifications controlling for $\boldsymbol{X_{1999}}$ and $\Delta\boldsymbol{X}$, or for illicit opioids or DSA mortality when including $\boldsymbol{X_{1999}}$ and $\Delta\boldsymbol{X^I}$. These findings indicate that the macroeconomy accounts for no more than one-tenth of the rise in mortality rates and generally considerably less.[31]

5.3 Additional Robustness Checks

I tested the robustness of the results to a variety of changes in specifications, estimation methods and samples including using: unweighted data, reported rather than corrected opioid analgesic and illicit opioid death rates, changes in the economic conditions over an earlier period (approximately 1990-2000) rather than from 1999-2015, and estimates for sub-periods where growth in the specified category of opioid mortality was highest (1999-2011 for opioid analgesics and 2006-2015 for illicit opioids). I also estimated a series of instrumental variables (IV) models where each economic proxy was instrumented by the other four. Finally, I changed the outcome variable definitions by limiting drug deaths to those classified as accidental or of undetermined intent and employing a broader definition of alcohol-related suicide in the calculation of all DSA deaths. Results of these robustness tests, detailed in Appendix B, confirm of the conclusion that economic conditions explain little of the rise in mortality rates.

5.4 Subsamples

I examined whether the results differed for subsamples stratified by demographic characteristics and type of county. Table A.7 summarizes the results for sex, race/ethnicity,

[31] Coefficients on the individual macroeconomic proxies are displayed in Table A.6.

education and selected age groups. Economic conditions explain somewhat more of the rise in drug and DSA mortality rates for whites (particularly those aged 20-59) and females than for their nonwhite or male counterparts but in no case was more than 17% of the change in death rates accounted for and the fraction was below 10% in the large majority of cases.

Table A.8 provides results separately for counties in metropolitan statistical areas (MSAs), those that are urban but not in MSAs and rural counties. Although much attention has been paid to the plight of rural areas, the estimates provide no indication that the evolution of economic conditions is more relevant in these locations. To the contrary, the explanatory power of the combined economic proxies is highest for metropolitan counties although, even for these, they never accounts for more than 15 percent of the change. For rural counties, the percent of the change in drug mortality rates explained ranges between 0 and 3 percent.

5.5 Selection on Unobservables

The preceding analysis treats the supplemental covariates ($\boldsymbol{X}$ and $\Delta\boldsymbol{X}$ or $\Delta\boldsymbol{X^I}$) as being sufficiently comprehensive, such that cov(E_k, ε_k) = 0. This is a fairly strong assumption. Methods developed by Oster (2016) are next implemented to examine how the results change with remaining selection on unobservables. As discussed, the key parameters are β^o, $\tilde{\beta}$, R^o and $\tilde{R}$ – the multiple proxy coefficients and R-squared from "short" and "long" regressions of equation (3) – as well as δ and R_{max}, for which values must be assumed. For many applications, Altonji et al., (2005) and Oster (2016) recommend setting δ=1, implying that selection on observables and unobservables are equally important. However, here it seems likely that the key important aspects of the selection process will have been accounted for. I therefore provide results assuming that δ = 0.5, where that observables account for two-thirds of all selection. Choosing a higher δ value would further reduce the magnitude of the estimated treatment effect.

For the base model, I set $R_{max} = 0.75$, which allows for considerable measurement error in the dependent variable. These values are somewhat arbitrary and so I also present estimates of δ^* at which the estimated treatment effect would be zero with ($R_{max} = 0.75$), and the R^*_{max} value yielding a zero-treatment effect with (δ = 0.5). The findings are summarized in Table 4. Column (a) shows the prior MP estimates. Columns (b) and (c) display the selection-corrected estimated effect and percentage of the total mortality rate change explained with δ = 0.5 and $R_{max} = 0.75$. The last two columns show δ^* and R^*_{max}.

The striking result is that even small amounts of remaining selection on unobservables is sufficient to eliminate any role for economic conditions as an explanation for rising mortality rates. For instance, with δ = 0.5 and $R_{max} = 0.75$, β^* is less than zero in all 10 specifications and, in most cases, δ^* > 0.3 or $R^*_{max} > 0.5$ would be sufficient to eliminate the effect. Thus, it is quite plausible that medium-term changes in county-level economic conditions are completely unrelated to the growth in drug or DSA mortality rates from 1999-2015.

6. **Changes in the Drug Environment**

I next examine whether changes in the drug environment, rather than in economic conditions, are a cause of rising drug mortality rates. The identifying feature of this analysis is that the nature of the fatal drug epidemic changed sharply over time: being driven by opioid analgesics from 1999 through around 2010 and then with these replaced by explosive growth in fatalities involving illicit opioids. If economic or social factors are of primary importance, it is not obvious why such a change would have affected *who* would die of fatal overdoses, only *which drugs* would be involved. By contrast, if population sub-groups are at differential risk, changes in the drug environment should alter the composition of drug mortality. Particularly

important in this regard is that males and young adults are far more likely than their counterparts to use and abuse illicit drugs but with much smaller differences (and sometimes in the reverse direction) for legal pain relievers or sedatives (Substance Abuse and Mental Health Services Administration 2017).[32] Thus, while it is ambiguous which groups should have experienced the largest mortality rate growth in the initial stages of the fatal drug epidemic, which largely involved opioid analgesics, men and younger adults are expected to constitute a higher share of drug deaths in the later years, when illicit opioids dominated.

6.1 Overdose Death Rates as Proxies of the Drug Environment

Differential trends in overall opioid analgesic and illicit opioid mortality rates (and deaths from other drugs in the supplementary analysis) are used to proxy changes in the drug environment. One justification for this is that while drug quantities reflect the interaction of supply and demand, it seems implausible that the underlying components of the latter (e.g. health problems causing pain) will exhibit sudden dramatic changes. Conversely, supply-side factors could alter markedly and abruptly as technologies evolve, for instance, following the introduction of OxyContin in 1996. However, the connection between supply and death rates is imperfect since mortality rates partially depend on fatality risk per use which varies with factors such as changes in drug purity and the availability of risk mitigating technologies such as naloxone. For these reasons, I first provide evidence that mortality rates supply useful information on the drug environment.

A close relationship between opioid analgesic prescribing patterns and deaths at the national level has previously been demonstrated (Paulozzi LJ, Jones C, Mack K 2011). I used data from the Automation of Reports and Consolidated Orders System (ARCOS) to confirm that

[32] There are several likely reasons for this. For instance, males are more likely to undertake a variety of risky behaviors than females and younger individuals may have greater access to illegal drug markets than older adults.

these patterns also hold at the county-level and after adjusting for incomplete reporting of drug involvement on death certificates. ARCOS provides information on flows of controlled substances from manufacturers to retail distributors. Quarterly data were obtained at the 3-digit zip-code level from 2000-2015 and converted to county annual total per capita grams of morphine milligram equivalents (MME) from seven major opioids.[33] County-level opioid analgesic death rates were then regressed on MME grams per capita in models that included county-fixed effects.[34] The MME coefficient was .0055498, with a county-clustered robust standard error of .0002402. MME per capita rose from 134.7 in 2000 to 711.1 in 2011, and fell modestly thereafter. Based on these results, the increase in per capita MME predicted a 3.17 (95% confidence interval: 2.93-3.47) per 100,000 rise in prescription opioid death rates from 2000-2011, compared to an actual increase of 3.70 per 100,000. This suggests that higher opioid analgesic prescriptions could explain around 85% of the rise in associated deaths.

Similar data are unavailable for illicit opioids but there is good reason to believe that overdose fatalities provide a reasonable estimate of supply-side factors related to these drugs. For example, past year use of heroin among persons ≥12 exhibited no trend from 2002-2007, rose modestly from 2007-2010 and more rapidly thereafter (Substance Abuse and Mental Health Services Administration 2017), mimicking almost exactly the pattern of heroin death rates (Appendix Table C.1). Similarly, seizures of heroin by law enforcement agencies did not show a consistent trend prior to 2010 but increased sharply starting in that year (Office of National Drug Control Policy 2017). Fentanyl reports to the National Forensic Laboratory Information System

[33] The ARCOS data are less complete prior to 2000 so the analysis starts in that year rather than 1999. See www.deadiversion.usdoj.gov/arcos/index.html for further information on ARCOS. The seven opioids are: Oxycodone, Meperidine (Pethidine), Hydromorphone, Hydrocodone, Morphine, Fentanyl and Methadone. MME conversion factors were obtained from: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-Aug-2017.pdf.

[34] The regression contains 50,105 observations (weighted by 2015 populations) from 3,140 counties.

increased modestly from 2001 through 2012 but rapidly beginning in 2013 (Drug Enforcment Administration 2017), again mirroring the pattern of deaths.

6.2 Distribution of Drug Deaths

Opioid analgesic death rates rose rapidly from 1999-2010 and remained relatively stable thereafter, whereas illicit opioid mortality rates changed little from 1999-2005, increased modestly from 2006-2010 before exploding after 2010 (see Figure 1). Fatality rates involving other drugs changed over the period but not enough to affect the dominance of these trends. This is illustrated in Figure 3, which displays shares of total drug deaths involving opioid analgesics and illicit opioids, and differences between the two. The fraction of opioid analgesic overdose fatalities increased from 21% to 39% from 1999-2010 and then declined to 30% in 2015. Conversely, the share involving illicit opioids fell from 20% to 16% from 1999-2005, returned to slightly above its 1999 level by 2010 and then rose dramatically to 45% in 2015.

Since younger adults and men are relatively heavy users of illicit drugs, the drug environment hypothesis suggests that their share of overall overdose deaths should have risen after 2010. The predictions are less clear for 1999-2010, although relatively rapid growth in opioid analgesic deaths for persons in their 40s and 50s, documented in Figure 2, suggest that this group's share of drug fatalities may have increased during this period.

Figure 4 confirms these expectations. It shows estimated year coefficients from regressions of equation (8), of the group's share of county-level drug deaths on vectors of year and county effects, population share and the three measures of county economic conditions for which annual data are available (unemployment rates, poverty percentages and median household incomes).[35] The male percentage of drug deaths declined by around 5 points from

[35] The estimates are not sensitive to the choice of supplementary regressors with available annual data once county and year fixed-effects are included.

1999-2010 and then recovered by approximately 3 points between 2010 and 2015. Since sex-specific shares sum to one, the pattern is exactly reversed for females. This is not the case for 20-39 and 40-59 year olds, since some overdose deaths involve younger or older persons. Nevertheless, the fraction of fatal overdoses involving 20-39 year olds (especially males) declined rapidly between 1999 and 2009 or 2010, and increased substantially thereafter, with the reverse pattern for 40-59 year olds overall and 40-59 year old women.[36]

Table 5 formally tests for trend breaks, showing results of equation (9), where $TREND$ indicates the initial annual change in group shares of the specified drug deaths, $POST$ introduces a spline with a knot at 2010, and the intercept shows the group share in 1999. The results indicate a clear break in the trend after 2010 for all groups except 40-59 year old males.

The age-related difference is particularly dramatic: 20-39 year olds accounted for 41% of drug deaths in 1999; this share fell an estimated 0.49 percentage points per year through 2010 and then rose by 0.86 (1.35 - 0.49) points annually thereafter. The predicted proportion of deaths involving 40-59 year olds increased by 0.34 percentage points per year initially and declined by 1.25 points per annum after 2010. The male share of drug deaths decreased by an estimated 0.34 percentage points per year through 2010 and increased by 0.15 points annually thereafter. Coefficients for females are the opposite of those for males and so are not shown on the table. Younger (20-39 year old) females show similar but weaker patterns to those for younger males, suggesting stronger age than gender effects on the composition of drug use. The share of drug deaths accounted for 40-59 year old males declines throughout the analysis period, although faster towards the end of it.

6.3 Sex- and Age-Differentials in Drug-Specific Mortality Rates

[36] No clear trends were found for 20-39 year old females or 40-59 year old males, which is unsurprising given the potentially offsetting effects of age and sex on legal versus illicit drug use (see Appendix Figure A.3).

Finally, I examined whether sex- and age-specific opioid analgesic and illicit opioid mortality rates (and those due to other narcotics in supplementary analyses) varied over time in ways consistent with changes in the drug environment. The strongest prediction is that illicit opioid mortality rates of males and younger adults will rise rapidly after around 2010, relative to their counterparts, since these groups are the expected to be the heaviest users of these drugs.

Figure 5 shows regression-adjusted differences in mortality rate changes for males, relative to females, obtained by estimating equation (10). Figure 6 supplies corresponding information for 20-39 year olds compared to 40-59 year olds. Solid lines show treatment group differential year effects; dotted lines display 95 percent confidence intervals. Vertical lines indicate years with breaks or reversals in mortality trends (2011 for opioid analgesic mortality rates and 2005 and 2010 for illicit opioids). Of interest is whether the treatment (versus reference) group differentials change substantially around these years.

The patterns in figures 5 and 6 align closely with predictions of the drug environment hypothesis. Most importantly, the relative illicit opioid deaths of males and 20-39 year olds began to rise rapidly around 2010 or 2011, coinciding with explosive growth in overall drug fatality rates from this source.[37] Opioid analgesic death rates rise faster for males than females early in the analysis period but decline in relative terms after 2010. This suggests that there was some substitution by males out of opioid analgesics and into illicit opioids, but this is dwarfed by the large overall rise in male illicit opioid death rates. There was no evidence of a trend break in opioid analgesic fatality rates for 20-39 year olds relative to those for persons aged 40-59.

Statistical significance of these patterns was confirmed from estimates of equation (11), where treatment versus reference group trend spline models were estimated with knots in 2011

[37] There is also some indication of modest increases after 2005, particularly for males, consistent with the initial (much slower) growth in illicit opioid deaths.

for opioid analgesics and 2010 for illicit opioids. Illicit opioid death rates initially rose marginally faster for males and young adults year olds than for their counterparts – by 0.03 per 100,000 annually in both cases (see Table 6). However, after 2010 or 2011, the annual mortality growth was much higher for the treatment groups – by 0.91 and 0.87 per 100,000 for males and 20-39 year olds. The differences were less dramatic for opioid analgesic fatality rates, with relative trend reductions for the males and young adults late in the analysis period. But these were much smaller than the corresponding increases for illicit opioid deaths, providing further evidence that the composition of overdose deaths changed along with the drug environment.

Appendix C details a supplementary investigation where illicit opioid death rates were decomposed into those involving heroin versus synthetic opioids and with additional analysis of deaths involving cocaine and methadone. This is useful because these drug categories exhibit substantially different time patterns, reducing the possibility that the changes in sex-specific and age-specific drug death rates observed above result from confounding factors that happen to have changed around 2010 or 2011. Specifically, heroin death rates were fairly constant from 1999-2006, rose modestly from 2006-2010 and quickly from 2010-2015. Synthetic opioid mortality grw slowly from 1999-2013 and then by more than 250% from 2013-2015. Cocaine deaths rates rose substantially from 1999-2006, declined to 1999 levels by 2009 and increased again after 2012. Methadone fatality rates rose dramatically from 1999-2007 and then declined.

Results of this supplementary analysis provide further evidence that the composition of overdose deaths followed changes in the drug environment. Male heroin death rate differentials (relative to females) were virtually constant from 1999-2006, increased starting in 2007, with accelerated growth after 2010. There was essentially no sex difference in synthetic opioid death rates through 2013 but with much more rapid male growth starting in 2014. Male cocaine and

methadone death rates rose (relative to those for women) from 1999 through 2006 or 2007, then declined, with a subsequent resurgence in relative male cocaine mortality starting in 2013. There were no age-related differences in heroin-involved mortality rates from 1999-2006, but faster growth for 20-39 (relative to 40-59) year olds after 2007 and especially after 2010. Synthetic opioid rates grew slightly more for 40-59 than 20-39 year olds from 1999-2013 but with dramatically faster increases for the younger age group after 2013. Cocaine deaths became increasingly concentrated among 40-59 year olds from 1999-2006 and were mostly flat subsequently. Age differentials in methadone fatality rates were noisey but generally trending upwards prior to 2007 and then falling.[38]

7. **Discussion**

Counties experiencing economic decline from 1999-2015 had larger increases in drug, suicide and alcohol mortality than those with more robust economic growth. However, the relationship was fairly weak and mostly due to county characteristics spuriously associated with the changes in economic conditions. Empirically, the most important of these were differences in the percent of female, nonwhite and foreign-born county residents. After controlling for confounding factors, less than one-tenth of the increase in drug mortality rates was explained by economic factors and even less of all DSA deaths. Even modest amounts of omitted variables bias would be sufficient to completely eliminate any remaining associations.

Conversely, the data provide support for the hypothesis that changes in the drug environment played a key role. During the first decade of the 21st century, rising drug mortality

[38] As a placebo test, I also examined breaks in trend for non-DSA deaths. The male (vs. female) trend differential increased slightly after 2010 while that for 20-39 (versus 40-59) year olds became slightly less negative. However, both changes were tiny compared to the overall treatment vs. control group differences.

was largely driven by opioid analgesics, with more recent growth being mostly due heroin and fentanyl. This shift was accompanied by a change in the composition of overdose deaths, particularly during the period of rapidly increase in illicit opioid mortality which has been concentrated among males and younger adults. Such findings are consistent with population subgroups facing differential risks that depend on specific aspects of the public health environment related to drugs.

Changes in economic conditions from 1999-2015 (or from 1990-2000) do not address the full array of potential social or economic influences of drug mortality and it is possible that demand factors not controlled for in this analysis could play some role.[39] However, it is difficult to see how explanations attributing overdose fatalities to the effects of self-medication for feelings of hopelessness (from whatever source) would predict dramatic demographic group changes in the relative risk of drug deaths over short time periods.[40] Therefore, these results suggest that improvements in the economic and social conditions of disadvantaged groups, while desirable for other reasons, are unlikely to be the most effective means of addressing the fatal drug epidemic.[41]

Put differently, the findings can be viewed as providing information on whether the fatal overdose epidemic reflects broader consequences of changes in social and economic conditions or if there is something distinctive about the dangers of drugs themselves. This is important for both analytical approaches and policy. For instance, most specifications estimated here combine intentional drug deaths with other overdose fatalities. This is appropriate if the drug epidemic has

[39] For instance, economic inequality is included only to the extent it is captured by median incomes and poverty rates. Social mobility could also be important (Chetty et al. 2014; O'Brien, Venkataramani, and Tsai 2017).
[40] On the other hand, social interactions could magnify the effects on population groups at high risk of abusing the drug categories experiencing increased supply (Glaeser, Sacerdote, and Scheinkman 1996).
[41] Demand-side factors might play a more important role for other mortality outcomes, such as the relatively slow reductions in heart disease mortality experienced by US midlife non-Hispanic whites since 1990.

unique causes. However, if all such deaths represent a form of suicide, it may be more correct to group them with non-drug suicides, or to focus on broader categories of deaths. As an empirical matter, the findings were not sensitive to these choices. Changes in economic conditions account for essentially identical (small) shares of the growth in drug death rates, however defined, and an even lesser fraction of DSA mortality. From a policy perspective, these results indicate that the most immediate benefits will probably be obtained from interventions focusing directly on the drug environment.

Some progress has been made in addressing the harms from opioid analgesics. These efforts include: establishment of drug monitoring programs; restrictions on pain clinics and online pharmacies; development of abuse-deterrent drug formulations; promulgation of opioid prescription guidelines; and proposals for mandatory provider education (Alexander, Frattaroli, and Gielen 2015; Meinhofer 2016; Jones, Lurie, et al. 2016; Meara et al. 2016; Dowell, Haegerich, and Chou 2016; FDA 2016; Madras 2017).

Expanded treatment options should almost certainly play a larger future role given the effectiveness of medication-based approaches utilizing methadone, buprenorphine and naltrexone (Schwartz et al. 2013; Woody et al. 2014; Mattick et al. 2008). Among the small proportion of addicts currently receive treatment, medication-based approaches are limited and often use insufficient dosages (Substance Abuse and Mental Health Services 2011; Volkow et al. 2014; D'Aunno et al. 2014). Naloxone administration saves lives and efforts are underway to raise its availability to first-responders and caregivers (Compton and Throckmorton 2013; Coffin and Sullivan 2013; Jones, Lurie, and Compton 2016; Rees et al. 2017), although the benefits may be offset by increased drug consumption due to a reduction in risk per episode (Doleac and Mukherjee 2018). Primary prevention of risky drug use is critical but we know less about how to

achieve this. Ongoing physician education efforts are important, particularly in light of evidence that graduates of highly ranked medical schools prescribe fewer opioids than their counterparts (Schnell and Currie 2018). Community-based prevention strategies have shown promising results (Hawkins et al. 2008; Albert et al. 2011) and efforts to staunch the supply of illicit fentanyl and its analogs are undoubtedly necessary. However, there are questions whether an "all-of-the-above" approach, such as the proposed by the President's Commission on Combating Drug Addiction and the Opioid Crisis (2017), is best or whether it would be more efficacious to prioritize a smaller set of key initiatives.

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Table 1: Estimated Effect of Economic Conditions on Changes in Various Death Rates, 1999-2015

Economic Proxy	All Drugs	Opioid Analgesics	Illicit Opioids	DSA
Measures Included Separately				
Δ in Poverty Rate	2.205*** (0.560)	0.798*** (0.242)	1.334*** (0.446)	2.320*** (0.752)
Δ in Median Household Income	2.068*** (0.546)	0.679*** (0.254)	1.136** (0.496)	2.515*** (0.773)
Δ in Median Home Price	2.289*** (0.649)	0.908** (0.354)	1.158* (0.627)	2.840*** (0.680)
Δ in Unemployment Rate	1.370*** (0.464)	0.295** (0.131)	1.069*** (0.253)	1.144 (0.765)
Δ in Import Exposure	0.572 (0.414)	0.398** (0.182)	0.168 (0.328)	0.570 (0.511)
Measures Included Together				
Δ in Poverty Rate	1.102** (0.515)	0.519** (0.259)	0.782* (0.403)	0.793 (0.599)
Δ in Median Household Income	0.206 (0.671)	-0.097 (0.329)	-0.043 (0.543)	0.751 (0.951)
Δ in Median Home Price	1.465* (0.805)	0.710* (0.409)	0.626 (0.668)	1.959** (0.883)
Δ in Unemployment Rate	0.307 (0.452)	-0.143 (0.213)	0.536 (0.365)	-0.146 (0.669)
Δ in Import Exposure	0.212 (0.392)	0.269 (0.177)	-0.065 (0.343)	0.214 (0.470)
R^2	0.082	0.059	0.051	0.060
P-Value	<0.001	<0.001	<0.001	<0.001
Multiple Proxy Estimate	2.949*** (0.798)	1.164*** (0.239)	1.710*** (0.428)	3.256 (2.395)
% of Total Δ Explained	32.5%	27.6%	25.6%	26.3%
Dep. Var. Mean [SD]	10.37 [9.06]	3.58 [4.22]	6.27 [6.67]	15.39 [12.38]

Note: Each cell in top panel shows results of a different regression where the dependent variable is the specified drug death rate per 100,000 and only a single measure of economic conditions is included in the model (n=3,098). All five measures of economic conditions are controlled for simultaneously in the second panel. Changes in median household incomes and home prices are "reverse coded" (i.e. the signs are switched from positive to negative and vice versa) so that, for all measures, positive coefficients indicate that worsening economic conditions correlate with higher mortality rates. Observations are weighted by 2015 county populations. Regressors are standardized to have a mean of zero and a standard deviation of one, so that coefficient shows "effect sizes" of a one standard deviation change in

the independent variable. Change in unemployment and poverty rates refer to three-year averages of annual rates for the periods ending in 2015 versus 1999. Changes in median household incomes ($2015) are from 1999 to 2015. Changes in import exposure are from 1999 to 2011. Drug poisoning deaths refer to ICD underlying cause of death codes X40-X44, X60-X64, X85, Y10-Y14 or Y352. Opioid Analgesic and illicit opioids refer to ICD-10 codes T40.2 and T40.1 or T40.4 respectively. DSA indicates deaths from drug poisoning, nondrug suicides or alcoholic liver disease. Nondrug suicides refer to ICD-10 codes X65-X84, Y87.0 and *U03, and alcohol to ICD-10 code K70. Deaths involving opioid analgesics or illicit opioids are adjusted for non-reporting of the drugs involved in overdose deaths using the methods described in the text. Multiple proxy estimates refer to the model with all economic proxies are simultaneously included and are estimated using the methods discussed in the text. Bootstrapped standard errors (1000 repetitions) are shown in parentheses for the multiple proxy estimates and robust standard errors with clustering at the commuter zone level are displayed in all other cases. The percentage of total change explained is calculated by dividing the multiple proxy estimate by the standard deviation of the dependent variable. P-Value refers to the null hypothesis that the five economic measures are jointly equal to zero. *** p<0.01, ** p<0.05, * p<0.1

Table 2: Estimated Effect of Economic Conditions on 1999-2015 Change in Total Drug Death Rate, with Various Sets of Controls

Economic Conditions Proxy	(a)	(b)	(c)
Δ in Poverty Rate	1.102**	0.638	0.736**
	(0.515)	(0.397)	(0.361)
Δ in Median Household Income	0.206	-0.604	0.171
	(0.671)	(0.434)	(0.393)
Δ in Median Home Price	1.465*	0.337	0.115
	(0.805)	(0.441)	(0.350)
Δ in Unemployment Rate	0.307	0.160	-0.185
	(0.452)	(0.257)	(0.312)
Δ in Import Exposure	0.212	-0.283	-0.302
	(0.392)	(0.237)	(0.262)
R^2	0.082	0.431	0.441
P-Value	<0.001	0.496	0.003
Multiple Proxy Estimate	2.949***	0.431	0.792*
	(0.798)	(0.488)	(0.436)
% of Total Δ Explained	32.5%	4.8%	8.7%
Additional Controls	None	$\mathbf{X}_{1999}$, $\Delta\mathbf{X}$	$\mathbf{X}_{1999}$, $\Delta\mathbf{X}^{I}$

Note: See note on Table 1. Each column in table shows results of a different model where the dependent variable is the change in the total drug death rate per 100,000 from 1999-2015. $\mathbf{X}_{1999}$ refers to controls for county population shares of: females, Hispanics, black non-Hispanics, other nonwhite non-Hispanics, age categories (15-24, 25-34, 35-44, 45-54, 55-64, 65-74, ≥75 years old), and person with some college or college graduates (among those ≥25 years old), % female headed households and foreign-born. Also included are controls for 8 urban-rural categories (metropolitan with population 250,000-999,999; metropolitan with population <250,000; urban with population ≥20,000 adjacent to a metropolitan area or not adjacent to a metropolitan area, urban with population 2,500-19,999 adjacent or not adjacent to metropolitan areas, and rural with population <2,500 and adjacent or not adjacent to metropolitan areas), active non-federal physicians and total hospital beds per 1,000 and whether the state legal medical/recreational marijuana and prescription drug monitoring program (two variables). These were measured in the 1999, except urban-rural location is from 2013, % female-headed households and % foreign-born are from 2000. $\Delta\mathbf{X}$ refers to changes in these supplementary covariates between 1999 and 2015 except in the later year % female-headed households are from 2010 and % foreign-born are the average from 2011-2015. $\Delta\mathbf{X}^{I}$ refers to instrumented changes in these supplementary covariates calculated by adjusting 1999 values by the census division changes in these variables from 1999-2015 (see the text for additional details). *** p<0.01, ** p<0.05, * p<0.1

Table 3: Estimated Effect of Economic Conditions on 1999-2015 Changes in Various Death Rates

	(a)	(b)	(c)
<u>All Drugs</u>			
P-Value	<0.001	0.496	0.003
Multiple Proxy Estimate	2.949*** (0.798)	0.431 (0.488)	0.792* (0.436)
% of Total Δ Explained	32.5%	4.8%	8.7%
<u>Opioid Analgesics</u>			
P-Value	0.001	0.695	0.037
Multiple Proxy Estimate	1.164*** (0.239)	0.197 (0.185)	0.306* (0.170)
% of Total Δ Explained	27.6%	4.7%	7.3%
<u>Illicit Opioids</u>			
P-Value	<0.001	0.373	0.289
Multiple Proxy Estimate	1.710*** (0.428)	0.305 (0.407)	-0.101 (0.310)
% of Total Δ Explained	25.6%	4.6%	-1.5%
<u>DSA</u>			
P-Value	<0.001	0.604	0.106
Multiple Proxy Estimate	3.256 (2.395)	-0.343 (0.583)	0.351 (0.987)
% of Total Δ Explained	26.3%	-2.8%	2.8%
Additional Controls	None	$\mathbf{X}_{1999}$, $\Delta\mathbf{X}$	$\mathbf{X}_{1999}$, $\Delta\mathbf{X}^{I}$

Note: See notes on Tables 1 and 2. *** p<0.01, ** p<0.05, * p<0.1

Table 4: Estimated of Effects of Economic Conditions on Changes in Drug Death Rates, 1999-2015, Accounting for Selection on Unobservables

Type of Drug/Additional Covariates	Unadjusted Estimate	Adjusted Estimates			
		δ=0.5, R_{max}=0.75		δ^*	R^*_{max}
		β^*	% of Δ Explained		
	(a)	(b)	(c)	(d)	(e)
All Drugs					
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}$	0.431	-0.720	-7.9%	0.187	0.551
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}^{\mathbf{I}}$	0.792	-0.135	-1.5%	0.427	0.705
Opioid Analgesics					
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}$	0.197	-0.551	-13.1%	0.132	0.441
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}^{\mathbf{I}}$	0.306	-0.210	-5.0%	0.297	0.597
Illicit Opioids					
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}$	0.305	-0.148	-2.2%	0.336	0.660
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}^{\mathbf{I}}$	-0.101	-0.519	-7.8%	<0.00	$< \tilde{R}$
DSA					
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}$	-0.343	-2.159	-17.4%	<0.00	$< \tilde{R}$
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}^{\mathbf{I}}$	0.351	-1.164	-9.4%	0.116	0.479

Note: See notes on Tables 1 through 3. Column (a) shows multiple proxy estimates without correction for selection on unobservables (from Table 3). Columns (b) and (c) show the selection-adjusted treatment effect and% of the change in mortality rates explained, assuming that δ=0.5 and R_{max}=0.75. Column (d) shows the value of δ that would give a zero estimated treatment effect, with R_{max}=0.75, and column (e) shows the R_{max} value that would do so, with δ=0.5. $R_{max} < \tilde{R}$ implies that the hypothetical R-squared that would eliminate the treatment effect is less than the observed R-squared from the model that includes supplementary covariates. See text for further details.

Table 5: Regression-Adjusted Share of Drug Deaths Involving Specified Population Group, 1999-2015

Regressor	Males	20-39 Year Olds	Males: 20-39 Years Old	40-59 Year Olds	Females: 40-59 Years Old	Females: 20-39 Years Old	Males: 40-59 Years Old
	(a)	(b)	(c)	(d)	(e)	(f)	(g)
Trend	-0.34***	-0.49***	-0.36***	0.34***	0.49***	-0.13***	-0.15***
	(0.06)	(0.07)	(0.06)	(0.07)	(0.05)	(0.04)	(0.06)
Post	0.49***	1.35***	0.96***	-1.59***	-1.11***	0.36***	-0.47***
	(0.13)	(0.14)	(0.12)	(0.24)	(0.15)	(0.07)	(0.15)
Intercept	64.72***	40.83***	28.34***	49.20***	17.59***	12.43***	31.60***
	(0.36)	(0.48)	(0.39)	(0.39)	(0.31)	(0.24)	(0.32)

Note: Table shows predicted trends in percentages of drug poisoning deaths occurring among the specified group from a panel of 1999-2015 county-level data. The “Trend” coefficient shows the annual time trend, in percentage point terms, compared to 1999. “Post” shows deviations from the general trend for the period after 2010. Intercept shows the estimated group-specific mean value of the dependent variable in 1999. Estimates are obtained from county-level regressions also control for county fixed-effects and the group population share. Sample contains 36,207 county-year observations, for 3,062 counties with a positive number of drug deaths in the specified year. Observations are weighted by 2015 county populations. Robust standard errors, clustered at the county level, are shown in parentheses. *** p<0.01, ** p<0.05, * p<0.1

Table 6: Sex and Age-Specific Differences in Opioid Analgesic and Illicit Opioid Mortality Rate Trends

Regressor	Sex-Specific (Reference Group: Females)		Age-Specific (Reference Group: 40-49 Year Olds)	
	Opioid Analgesics	Illicit Opioids	Opioid Analgesics	Illicit Opioids
Trend	0.05***	0.03***	-0.15***	0.03***
	(0.01)	(0.01)	(0.02)	(0.01)
Post	-0.24***	0.88***	-0.11**	0.84***
	(0.03)	(0.05)	(0.05)	(0.06)
Group Main Effect	0.92***	1.13***	-0.92***	-0.66***
	(0.11)	(0.10)	(0.15)	(0.12)

Note: See note on Table 5. Table shows differences in intercepts and time trends for males compared to females and 20-39 versus 40-49 year olds. The “Trend” coefficient shows the general difference in time trends between the treatment and reference groups. “Post” show deviations from the general trend for periods after a change in the overall trend effect. Specifically, “Post” refers periods to starting in 2011 for opioid analgesics and 2010 for illicit opioids. Regressions also control for county fixed-effects and year dummy variables. Sample contains 106,426 group-year observations from 3,132 counties. Observations are weighted by 2015 county populations. Robust standard errors, clustered at the county level, are shown in parentheses. *** p<0.01, ** p<0.05, * p<0.1

Figure 1: Drug, Nondrug Suicide and Alcohol (DSA) Mortality Rates

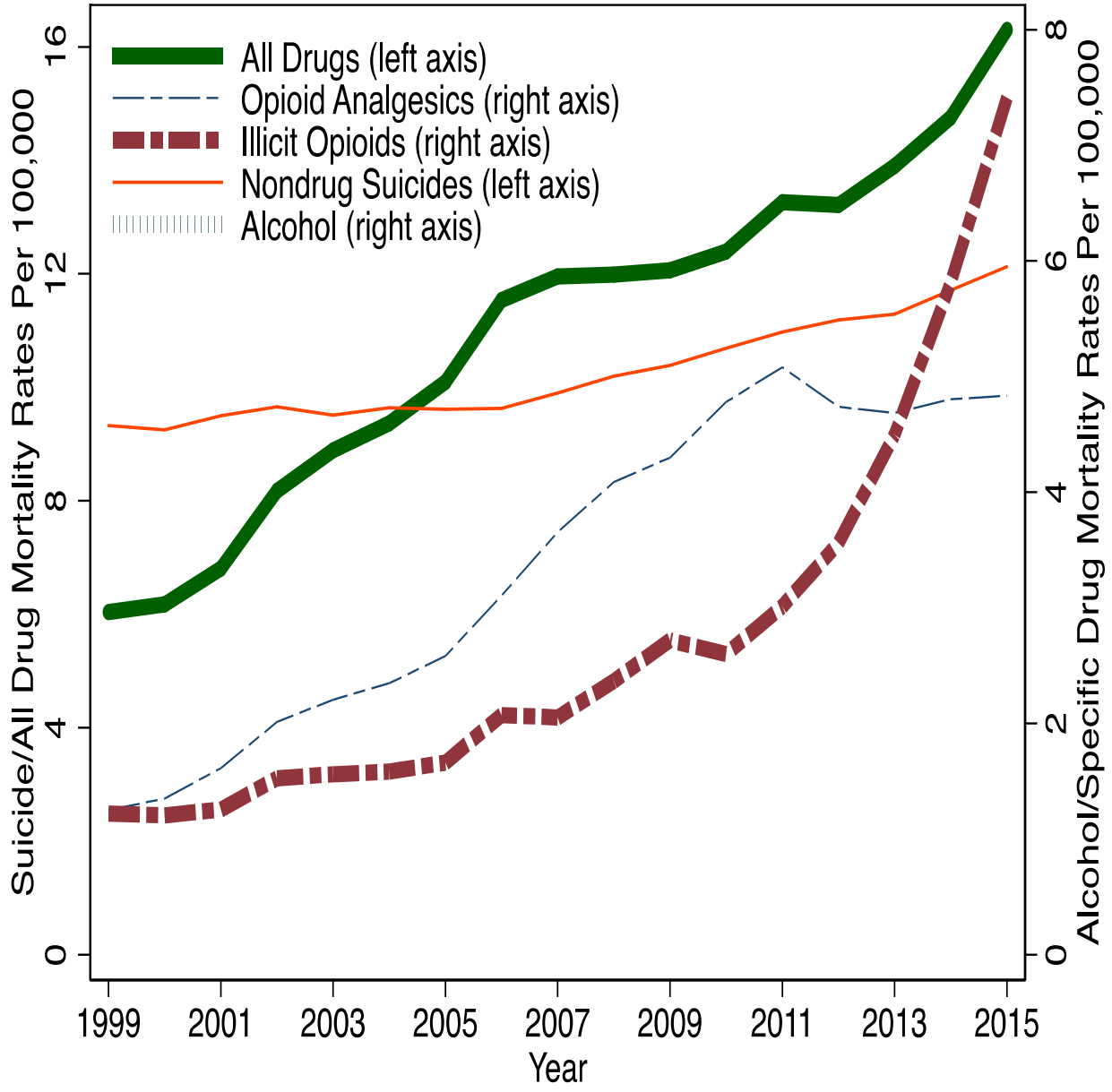


Figure 2: Drug Mortality Rates (per 100,000) by Sex and Age

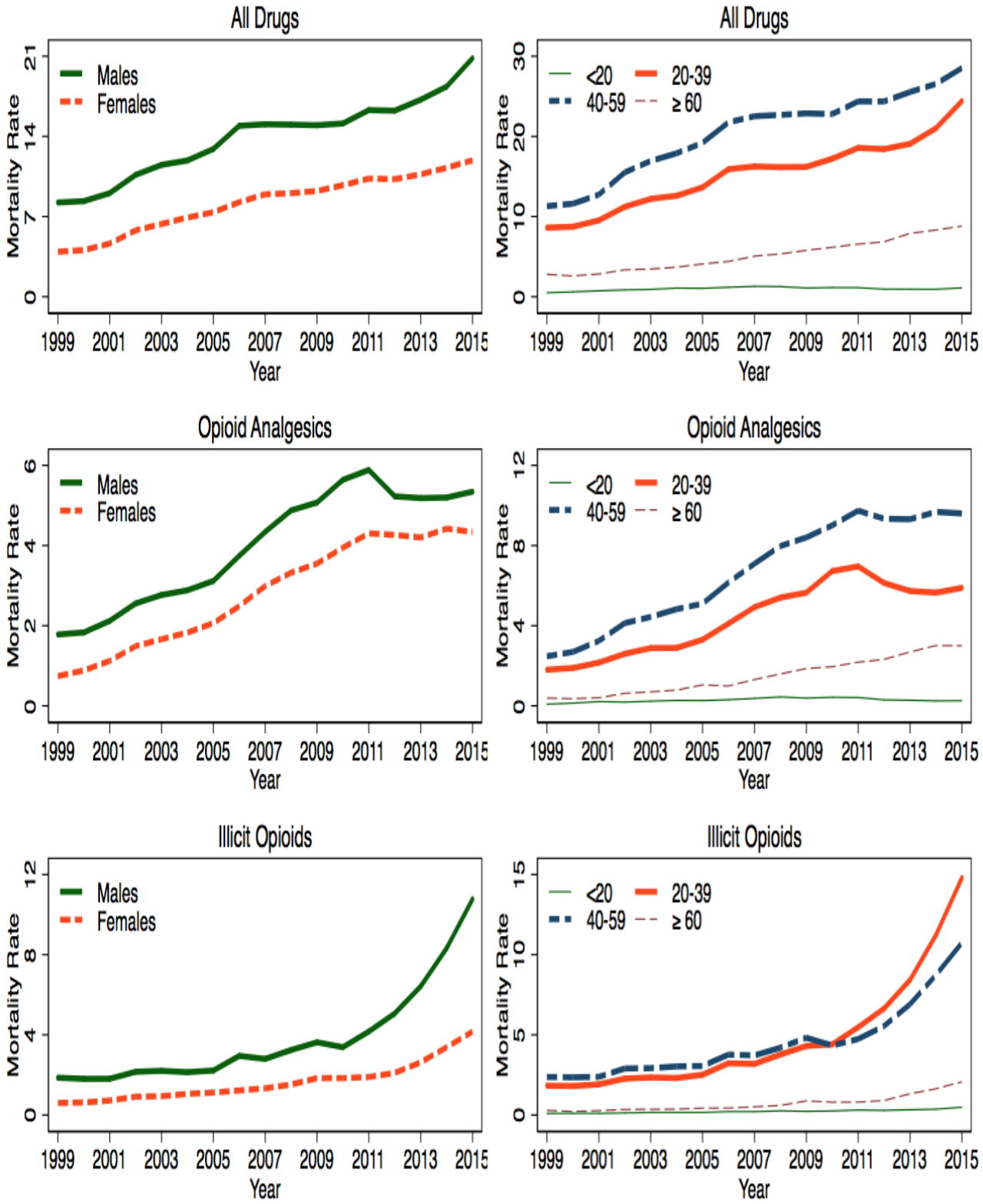


Figure 3: Percent of Drug Deaths Involving Opioid Analgesics and Illicit Opioids, 1999-2015

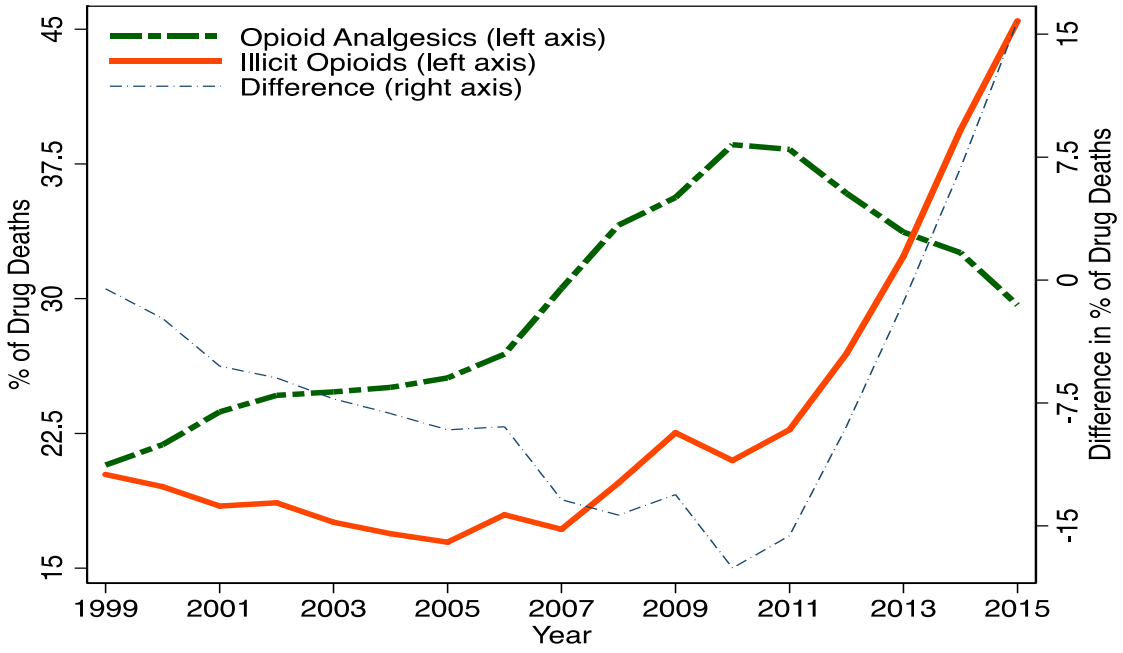
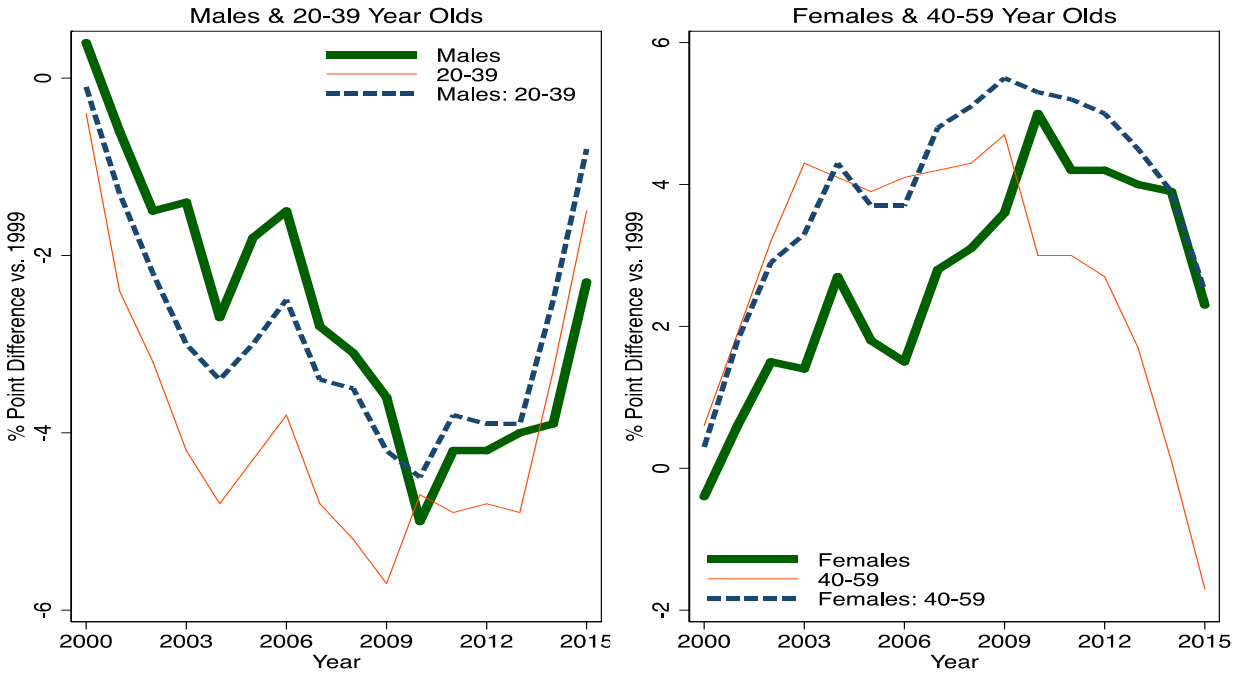
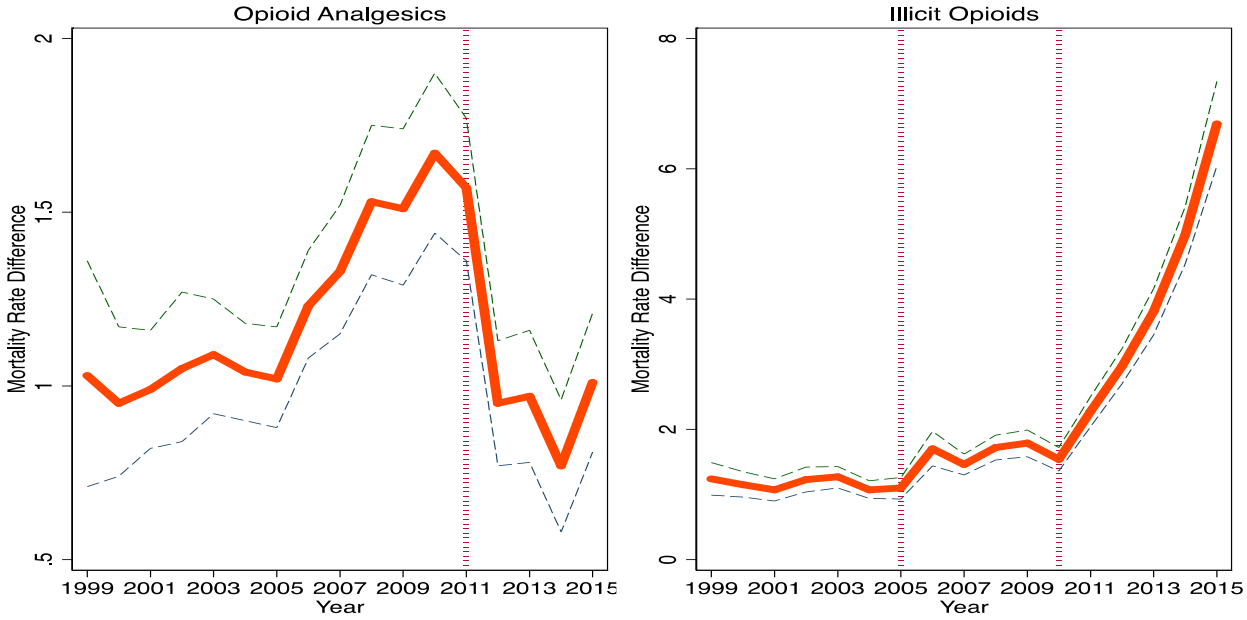


Figure 4: Regression-Adjusted Changes Since 1999 in Share of Drug Poisoning Deaths



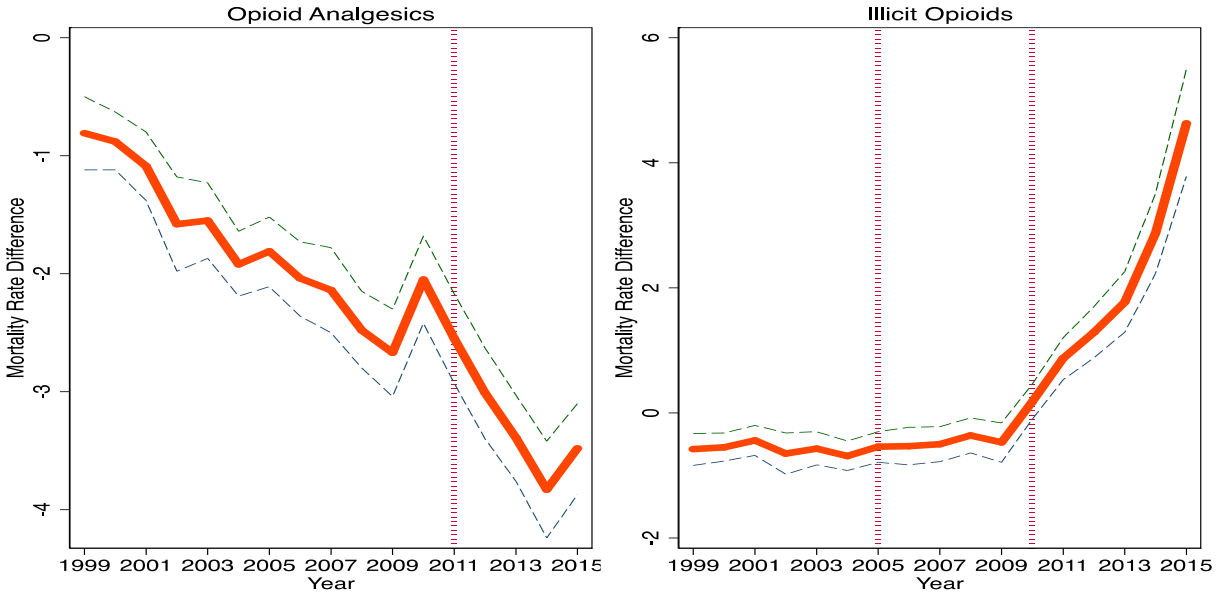
Note: Figure shows coefficients on year dummy variables from county-level regressions that also control for county fixed-effects, the group population share, as well as the county unemployment and poverty rates, and median household incomes. Data are weighted by 2015 county populations.

Figure 5: Sex Differences in Opioid Analgesic and Illicit Opioid Mortality Rates (Males vs. Females)



Note: Figure show difference in predicted mortality rates for males in the given year versus those for females from models with sex-specific mortality rates regressed against sex main effects, county fixed-effects, year dummy variables and year-by-sex interactions. Dashed lines show 95 percent confidence intervals. Vertical lines show years with a break or reversal in the drug-specific mortality rate trend.

Figure 6: Age Differences in Opioid Analgesic and Illicit Opioid Mortality Rates (20-39 vs. 40-59 year olds)



Note: Figure show difference in predicted mortality rates for 20-39 year old in the given year versus those for 40-59 year olds from models with age-specific mortality rates regressed against age main effects, county fixed-effects, year dummy variables and year-by-age interactions. Dashed lines show 95 percent confidence intervals. Vertical lines show years where with a break or reversal in the drug-specific mortality rate trend.

Appendix A: Further Description of Methods and Additional Tables

Additional Details on Methods

Instrumented Values of County Characteristics.

"Instrumented" values of $\Delta \boldsymbol{X}$, denoted as $\Delta \boldsymbol{X^I}$, are constructed by calculating changes between initial year county level values of $\boldsymbol{X}$ and *census division* changes occurring between the starting and ending analysis years. For continuous variables, these are calculated as:

(A.1) $$\Delta X_k^I = X_{k0} \times \frac{X_{d1} - X_{d0}}{X_{d0}}$$

where X_{dt} refers to the value of the supplemental covariate in census division d containing county k. The vector of covariates also includes binary variables indicating whether states have specific policies in place. In all cases, once implemented, these policies remained in effect through the end of the sample period. Therefore, for these variables. ΔX_k^I was set to zero for counties with the policies in place at time 0 (i.e. $X_{k0} = 1$). Where $X_{k0} = 0$, the instrumented change was calculated as the expected change in census division values for persons in counties without the policy at time 0:

(A.2) $$\Delta X_k^I|_{X_{k0}=0} = (X_{d1} - X_{d0})|_{X_{d0}=0}.$$

Multiple Proxy Estimates

In the Lubotsky and Wittenberg (LW) approach, E_k^* is a latent variable for economic conditions that affects changes in mortality rates according to:

(A.3) $$\Delta M_k = \beta \Delta E_k^* + \boldsymbol{X}_{k0}\gamma_1 + \Delta \boldsymbol{X}_k \gamma_2 + \varepsilon_k.$$

We do not observe E_k^* but instead have multiple proxies, E_{kj}, where the additional subscript indicates the j^{th} proxy, which are related to the latent variable according to:

(A.4) $$\Delta E_{kj} = \rho_j \Delta E_{kj}^* + \mu_{kj}.$$

The key assumptions are that ΔE_k^* is uncorrelated with ε_k and that all of the μ_{kj} are uncorrelated with ΔE_k^* and ε_k. The second assumption implies that the proxy variables operate only through their effect on ΔE_k^* and do not independently affect ΔM_k. An important advantage of this framework is that the covariances between the error terms of the economic proxies (μ_{kj}) are unrestricted and, specifically, are allowed to be non-zero.[42]

Equations (A.3) and (A.4) cannot be directly estimated, since E^* is unobserved, but LW show that attenuation bias can be minimized by simultaneously including all of the economic proxies in the model in the regression model:

(A.5) $$\Delta M_k = \sum_{j=1}^{m} \beta_j \, \Delta E_{jk} + \boldsymbol{X}_{k0}\gamma_1 + \Delta \boldsymbol{X}_k \gamma_2 + \varepsilon_k,$$

(where $m = 5$ in this application) and then calculating the weighted sum of the proxy coefficients as:

(A.6) $$\hat{\beta} = \sum_{j=1}^{m} \frac{cov(\Delta M, \Delta E_j)}{cov(\Delta M, \Delta E_1)} \hat{\beta}_j,$$

where ΔE_1 is the proxy chosen as the base. I use as $\Delta E_1$the proxy with the largest regression coefficient ($\hat{\beta}_j$) in a model that includes all of the economic measures but without supplementary covariates. LW show that $\hat{\beta}$, calculated in this manner, has the same scale as ΔE_1. Since the explanatory variables are all standardized, $\hat{\beta}$ can also be interpreted indicating effect sizes for changes in the latent variable ΔE^*. However, to the extent that the vector of proxy variables does not fully account for all aspects of ΔE^*, some attenuation bias may remain.

[42] Models with a single economic proxy will suffer from attenuation bias. Suppressing the supplementary covariates and with the simplifying normalization that $\rho_1 = 1$, the OLS estimator of $\Delta M_k = \beta_1 \Delta E_k + \varepsilon_k$ converges to $\hat{\beta}_1 = \beta \frac{var(E^*)}{var(E^*)+var(\mu_1)}$, which is biased towards zero for positive $var(\mu_1)$.

Additional Tables

Table A.1: Summary Statistics for Variables Used in Main Analysis

Variable	Mean	Std. Dev
Outcomes: Δ in Drug Death Rates per 100,000 (2015 vs. 1999)		
All Drugs	10.37	9.06
Opioid Analgesics	3.58	4.22
Illicit Opioids	6.27	6.67
Drug, Suicide, Alcohol (DSA)	15.39	12.38
Nondrug DSA	5.02	7.35
Nondrug Suicide	2.76	5.67
Alcohol	2.26	4.21
Economic Proxies (Δ 2015 vs. 1999)		
Poverty Rate (3-year average)	2.93	2.47
Median Household Income (3-year average, 2015$	-2,817	5,586
Median Home Price, 2015$: %Δ (2011-2015 average vs. 2000)	17.85	22.31
Unemployment Rate (3-year average)	1.77	1.04
Instrumented Import Share of Employment (2011 vs. 1999)	1.57	2.03

Additional Covariates (1999 & 2015)	*1999*		*Δ: 1999-2015*	
Population Shares	Mean	SD	Mean	SD
Females	0.509	0.012	0.001	0.006
Hispanics	0.123	0.148	0.049	0.034
Non-Hispanic Blacks	0.121	0.128	0.010	0.027
Other Race (Non-Hispanics)	0.045	0.054	0.021	0.020
15-24 Year Olds	0.139	0.029	0.002	0.013
24-34 Year Olds	0.145	0.023	0.008	0.015
34-44 Year Olds	0.162	0.014	0.036	0.013
44-54 Year Olds	0.131	0.012	0.004	0.011
54-64 Year Olds	0.085	0.013	0.043	0.011
64-74 Year Olds	0.065	0.019	0.020	0.011
≥ 75 Year Olds	0.058	0.019	0.005	0.009
Some College (≥25 years old)	0.275	0.048	0.019	0.033
College Graduate (≥25 years old)	0.242	0.095	0.063	0.028
Female-headed Household (2000, 2010)	0.179	0.059	0.019	0.012
Foreign born (2000, 2011-2015)	0.109	0.102	0.021	0.020
Medical/Policy Variables (2015)				
Active Nonfederal MD's per 1000	2.514	1.903	0.247	0.720
Hospital beds per 1000: 2015	3.603	2.713	-0.708	1.616
Marijuana Legal in State for Medical/Recreational Uses	0.160	0.367	0.305	0.460
State Prescription Drug Monitoring Program	0.195	0.396	0.724	0.447
Urban-Rural Status Share (2013)				
Metropolitan Area: Population 250,000 – 999,999	0.210	0.408		
Metropolitan Area: Population <250,000	0.092	0.289		
Urban Area: Population ≥20,000, adjacent to metro	0.043	0.203		
Urban Area: Population ≥20,000, not adjacent to metro	0.015	0.122		
Urban Area: Population 2,500-19,999, adjacent to metro	0.047	0.211		
Urban Area: Population 2,500-19,999, not adjacent to metro	0.026	0.158		
Rural Area: Population <2,500, adjacent to metro	0.007	0.082		
Rural Area: Population <2,500, not adjacent to metro	0.008	0.089		

Note: Variables are measured at the county level and weighted by 2015 county populations. Independent variables are standardized to have a mean of 0 and a standard deviation of 1 in the econometric analysis. Death rates involving opioid analgesics, heroin and synthetic opioids are adjusted for incomplete reporting on death certificates. Entries in parentheses indicate if variable dates are different from 1999 or 2015. Prescription drug monitoring programs (PDMP) are those with requirement that dispensers must report data to PDMP. For poverty, unemployment rates and household incomes, the variables are three-year averages ending in the year specified.

Table A.2: Correlations Between Economic Proxies

	Poverty	Income	Home Prices	Unemployment	Imports
Poverty	1.000				
Income	-0.702	1.000			
Home Prices	-0.530	0.641	1.000		
Unemployment	0.487	-0.436	-0.284	1.000	
Imports	0.154	-0.074	-0.098	0.101	1.000

Note: Table shows correlations between economic proxies with observations weighted by 2015 county populations. Proxy names are abbreviated (e.g. “Unemployment” refers to the change in the unemployment rate).

Table A.3: Estimated Effect of Economic Conditions on 1999-2015 Change in Total Drug Death Rate, with Additional Economic Controls

Economic Proxy/% Explained	(a)	(b)	(c)	(d)	(e)	(f)	(g)
Proxies for $\Delta \boldsymbol{E}$							
Multiple Proxy Estimate	2.949*** (0.798)	0.431 (0.488)	0.792* (0.436)	0.798 (0.558)	0.891** (0.389)		
% of Total Δ Explained	32.5%	4.8%	8.7%	8.8%	9.8%		
Proxies for $\boldsymbol{E_0}$							
Multiple Proxy Estimate				-0.289 (16.237)	-0.778 (7.020)		
% of Total Δ Explained				-3.2%	-8.6%		
EP Ratios as one Proxy for $\boldsymbol{E_0}$							
Multiple Proxy Estimate						0.521 (0.481)	1.117** (0.485)
% of Total Δ Explained						5.6%	12.3%
Additional Controls	None	$\mathbf{X}_{1999}$, $\Delta\mathbf{X}$	$\mathbf{X}_{1999}$, $\Delta\mathbf{X}^{\mathbf{I}}$	$\mathbf{X}_{1999}$, $\Delta\mathbf{X}$	$\mathbf{X}_{1999}$, $\Delta\mathbf{X}^{\mathbf{I}}$	$\mathbf{X}_{1999}$, $\Delta\mathbf{X}$	$\mathbf{X}_{1999}$, $\Delta\mathbf{X}^{\mathbf{I}}$

Note: See note on Tables 1 and 2. Estimates in columns (a) through (c) repeat those in Table 2. Those in columns (d) and (e) add controls for 1999 *levels* of the economic proxies. Estimates in column (f) and (g) use employment-to-population ratios, rather than unemployment rates, as an economic proxy, with all other economic variables remaining unchanged.

Table A.4: Estimated Effect of Economic Conditions on 1999-2015 Changes in Drug Death Rates, Various Sets of Supplementary Variables

Model	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(i)	(j)	(k)
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}$											
Multiple Proxy Estimate	2.949*** (0.798)	2.114*** (0.517)	1.285** (0.561)	2.982*** (0.872)	0.983** (0.452)	2.795*** (0.770)	2.697*** (0.788)	2.651*** (0.808)	1.256** (0.542)	0.866* (0.477)	0.431 (0.488)
% of Total Δ Explained	32.5%	23.3%	14.2%	32.9%	10.8%	30.8%	29.8%	29.3%	13.9%	9.6%	4.8%
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}^{I}$											
Multiple Proxy Estimate	2.949*** (0.798)	1.808*** (0.493)	1.216*** (0.440)	2.444*** (0.780)	0.966** (0.438)	2.885*** (0.841)	2.697*** (0.788)	2.363*** (0.691)	1.066** (0.431)	0.614 (0.399)	0.792* (0.436)
% of Total Δ Explained	32.5%	20.0%	13.4%	27.0%	10.7%	31.8%	29.8%	26.1%	11.8%	6.8%	8.7%
Additional Controls	None	A	B	C	D	E	F	G	B,D	A,B,D	All

Note: See note on Table 2. Table shows multiple proxy estimates for effect of economic conditions on 1999-2015 change in total drug mortality rates. Each cell shows results of a different regression. All models control for the five economic proxies. The top panel also controls for 1999 levels and changes between 1999 and 2015 in the specified additional controls. Middle panel uses instrumented, rather than actual, changes in controls. Additional controls abbreviations are as follows. A: age shares; B: sex and race/ethnicity shares; C: education shares; D: share foreign-born; E: share female-headed households; F: urban-rural county designations; G: medical infrastructure and state drug policies. *** p<0.01, ** p<0.05, * p<0.1

Table A.5: Estimated Effect of Economic Conditions on Changes in Drug Death Rates Over Various Time Periods

Model	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(i)	(j)
Time Period	**1999-2015**		**2000-2015**		**2001-2015**		**2002-2015**		**2003-2015**	
Multiple Proxy Estimate	0.431	0.792*	0.381	0.534	1.585	0.932	1.206	0.831	1.882*	1.452
	(0.488)	(0.436)	(0.488)	(0.395)	(2.439)	(1.269)	(1.521)	(0.895)	(1.003)	(1.038)
Dependent Var. Mean [SD]	10.37 [9.06]		10.24 [8.63]		9.62 [8.47]		8.21 [8.48]		7.47 [8.35]	
% of Total Δ Explained	4.8%	8.7%	14.4%	6.2%	18.7%	11.0%	14.3%	9.8%	22.5%	17.4%
Time Period	**1999-2011**		**1999-2012**		**1999-2013**		**1999-2014**		**1999-2015**	
Multiple Proxy Estimate	0.413	0.769**	0.360	0.654**	0.386	0.634**	0.248	0.688**	0.431	0.792*
	(0.375)	(0.369)	(0.302)	(0.306)	(0.342)	(0.309)	(0.360)	(0.326)	(0.488)	(0.436)
Dependent Var. Mean [SD]	7.25 [7.45]		7.20 [7.07]		7.91 [7.22]		8.78 [7.92]		10.36 [9.06]	
% of Total Δ Explained	5.6%	10.3%	5.1%	9.2%	5.3%	8.8%	3.2%	8.7%	4.8%	8.7%
Additional Controls	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{\mathbf{I}}$	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{\mathbf{I}}$	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{\mathbf{I}}$	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{\mathbf{I}}$	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{\mathbf{I}}$

Note: See note on Tables 1 through 3. The economic conditions controlled for are the same as those above but cover the time period specified for changes in unemployment rates, median household incomes and poverty rates. All models include initial year supplementary covariates as well as changes in either actual or instrumented values over the specified time period, with the following exceptions: home price changes always refer to the average for 2011-2015 versus 2000 and changes in the shares of female-headed households always refer to 2010 versus 2010 and those of foreign-born households refer to the average for 2011-2015 versus. 2000. *** p<0.01, ** p<0.05, * p<0.1

Table A.6: Estimated Effect of Economic Conditions on 1999-2015 Changes in Various Death Rates

Economic Conditions Proxy	All Drugs		Opioid Analgesics		Illicit Opioids		DSA	
Δ in Poverty Rate	0.638	0.736**	0.229	0.291*	0.629**	0.526**	0.610	0.267
	(0.397)	(0.361)	(0.176)	(0.167)	(0.309)	(0.257)	(0.461)	(0.416)
Δ in Median Household Income	-0.604	0.171	-0.123	-0.058	-0.821*	-0.325	-0.523	0.890**
	(0.434)	(0.393)	(0.184)	(0.167)	(0.466)	(0.270)	(0.476)	(0.430)
Δ in Median Home Price	0.337	0.115	0.091	0.227	0.468	-0.010	-0.313	-0.483
	(0.441)	(0.350)	(0.202)	(0.193)	(0.399)	(0.261)	(0.482)	(0.413)
Δ in Unemployment Rate	0.160	-0.185	-0.069	-0.250*	-0.008	-0.394	0.022	-0.332
	(0.257)	(0.312)	(0.151)	(0.147)	(0.212)	(0.249)	(0.320)	(0.398)
Δ in Import Exposure	-0.283	-0.302	0.094	-0.055	-0.203	-0.204	-0.371	-0.190
	(0.237)	(0.262)	(0.129)	(0.140)	(0.182)	(0.163)	(0.300)	(0.328)
R^2	0.431	0.441	0.259	0.310	0.476	0.529	0.404	0.398
P-Value	0.496	0.003	0.695	0.037	0.373	0.289	0.604	0.106
Other Controls	Δ**X**	Δ$\mathbf{X}^{I}$	Δ**X**	Δ$\mathbf{X}^{I}$	Δ**X**	Δ$\mathbf{X}^{I}$	Δ**X**	Δ$\mathbf{X}^{I}$

Note: See notes on Tables 1 and 2. Each column in table shows results of a different model where the dependent variable is the change in the specified death rate per 100,000 from 1999-2015, with the five economic proxies simultaneously controlled for. All models include 1999 supplementary covariates as well as changes in either actual or instrumented values from 1999-2015. P-Value refers to the null hypothesis that the five economic proxies are jointly equal to zero. *** p<0.01, ** p<0.05, * p<0.1

Table A.7: Estimated Effect of Economic Conditions on 1999-2015 Changes in Various Death Rates for Population Subgroups

Group	All Drugs		Opioid Analgesics		Illicit Opioids		DSA	
	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
All	4.8%	8.7%*	4.7%	7.3%*	4.6%	-1.5%	-2.8%	2.8%
Males	0.3%	8.6%*	3.5%	6.8%	-0.6%	-3.6%	-5.2%	2.2%
Females	9.6%**	6.6%**	4.4%	5.5%	16.0%**	4.1%	2.5%	3.8%
Whites	7.2%	17.1%***	8.4%*	17.3%***	3.3%	3.4%	4.8%	17.2%***
Nonwhite/Hispanics	1.7%	6.1%	0.2%	2.6%	0.5%	1.1%	6.1%	10.9%
20-59 Years Old	3.2%	8.5%**	3.0%	7.4%**	4.4%	-0.5%	-3.1%	3.1%
Whites: Aged 20-59	7.7%	18.3%***	7.1%	17.4%***	4.1%	6.0%	3.4%	14.8%**
Whites: Aged 45-54	3.4%	11.4%*	6.3%	13.0%**	2.6%	3.3%	1.6%	7.9%
≤ High School	4.2%	2.9%	6.0%	3.8%	2.0%	-6.3%	0.9%	-0.1%
Some College	5.3%	4.4%**	6.0%	1.8%	3.4%	0.1%	-1.2%	-0.5%
College Graduate	3.0%	6.7%	0.3%	4.5%	1.6%	2.6%	0.1%	6.5%
Other Controls	$\Delta \mathbf{X}$	$\Delta \mathbf{X}^{\mathbf{I}}$	$\Delta \mathbf{X}$	$\Delta \mathbf{X}^{\mathbf{I}}$	$\Delta \mathbf{X}$	$\Delta \mathbf{X}^{\mathbf{I}}$	$\Delta \mathbf{X}$	$\Delta \mathbf{X}^{\mathbf{I}}$

Note: See notes on Tables 1 through 3. Entries show the estimated percentage of the change in the specified mortality rate explained by changes in economic conditions, based on the multiple proxy estimates. All models include 1999 supplementary covariates as well as changes in either actual or instrumented values from 1999-2015. Statistical significance is based on bootstrapped standard errors. *** p<0.01, ** p<0.05, * p<0.1

Table A.8: Estimated Effect of Economic Conditions on 1999-2015 Changes in Various Death Rates, By Type of County

	All Drugs		Opioid Analgesics		Illicit Opioids		DSA	
	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
Metropolitan Counties								
Multiple Proxy Estimate	0.541	1.207**	0.376	0.517**	0.353	0.007	-0.448	0.699
	(0.646)	(0.544)	(0.234)	(0.212)	(0.675)	(0.644)	(0.701)	(0.607)
Dependent Var. Mean [SD]	10.08 [8.51]		3.34 [3.57]		6.44 [6.68]		14.62 [10.82]	
% of Total Δ Explained	6.4%	14.2%	10.5%	14.5%	5.3%	0.1%	-4.1%	6.5%
Urban Counties								
Multiple Proxy Estimate	0.393	-0.018	0.176	0.509	0.676	-0.345	-0.131	0.358
	(1.125)	(1.145)	(0.469)	(0.466)	(0.656)	(0.573)	(152.907)	(128.934)
Dependent Var. Mean [SD]	12.35 [10.55]		4.86 [5.89]		5.70 [6.44]		20.13 [15.91]	
% of Total Δ Explained	3.7%	-0.2%	3.0%	8.6%	10.5%	-3.5%	-0.8%	2.3%
Rural Counties								
Multiple Proxy Estimate	0.091	0.061	0.167	0.271	0.107	0.200	-0.464	-0.179
	(16.535)	(18.130)	(1.229)	(1.056)	(0.450)	(0.411)	(1,103.710)	(782.132)
Dependent Var. Mean [SD]	11.31 [14.18]		5.37 [8.58]		4.10 [6.73]		19.20 [24.08]	
% of Total Δ Explained	0.6%	0.4%	1.9%	3.2%	1.6%	3.0%	1.9%	0.7%
Additional Controls (ΔX's)	Δ**X**	Δ$\mathbf{X}^{\mathbf{I}}$	Δ**X**	Δ$\mathbf{X}^{\mathbf{I}}$	Δ**X**	Δ$\mathbf{X}^{\mathbf{I}}$	Δ**X**	Δ$\mathbf{X}^{\mathbf{I}}$

Note: See notes on Tables 1 through 3. All models include 1999 supplementary covariates as well as changes in either actual or instrumented values from 1999-2015. Sample in top panel consists of metropolitan counties (n=1153). Second panel shows estimates for urban counties with ≥20,000 population or population 2,500-19,999 and adjacent to metropolitan counties (n=895). Third panel shows estimates for counties with <2,500 population or population 2,500-19,999 and not adjacent to metropolitan counties (n=1,050). *** p<0.01, ** p<0.05, * p<0.1

Figure A.1: Drug Mortality Rates by Race/Ethnicity and Education

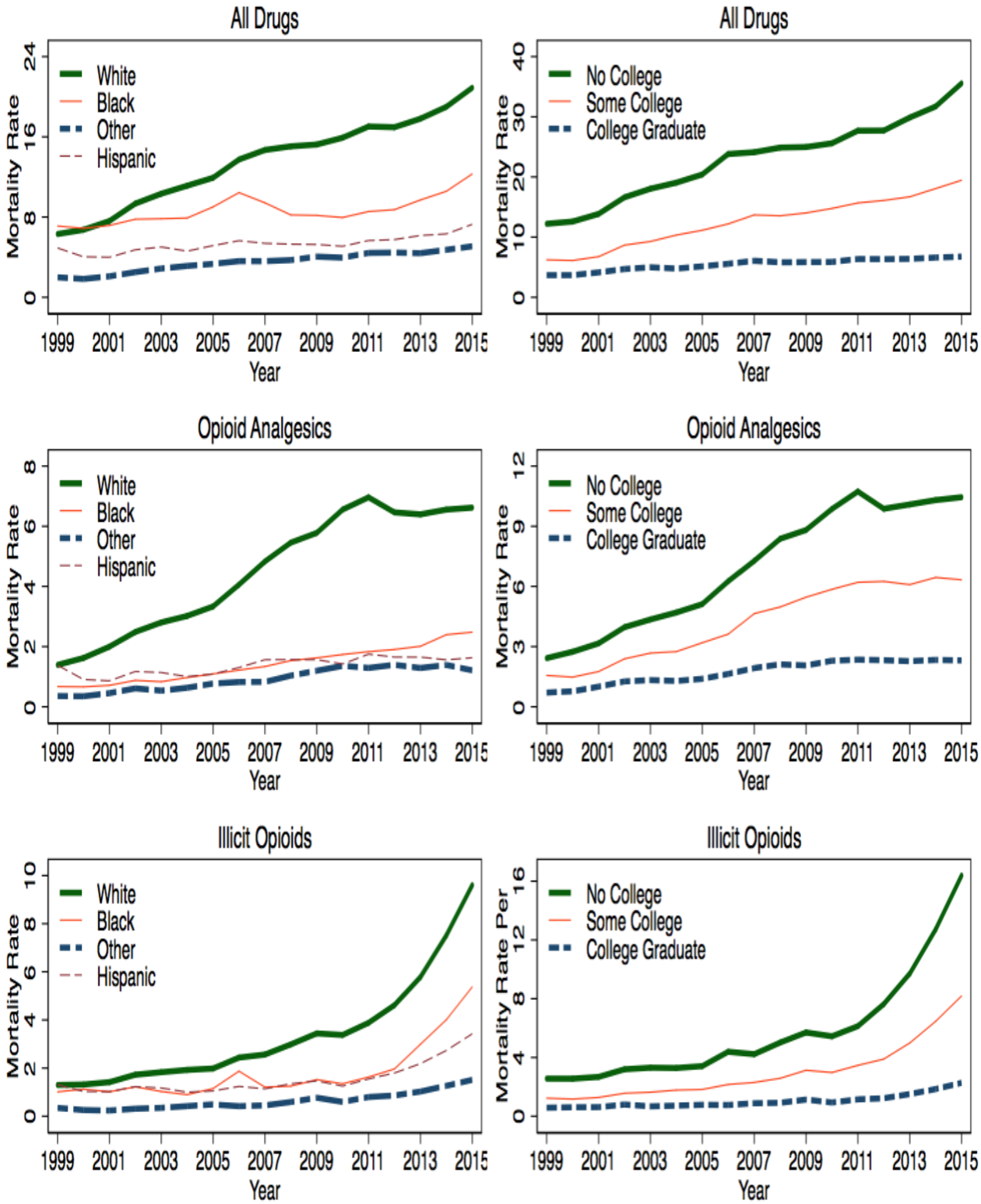


Figure A.2: Nondrug DSA Mortality Rates for Population Subgroups

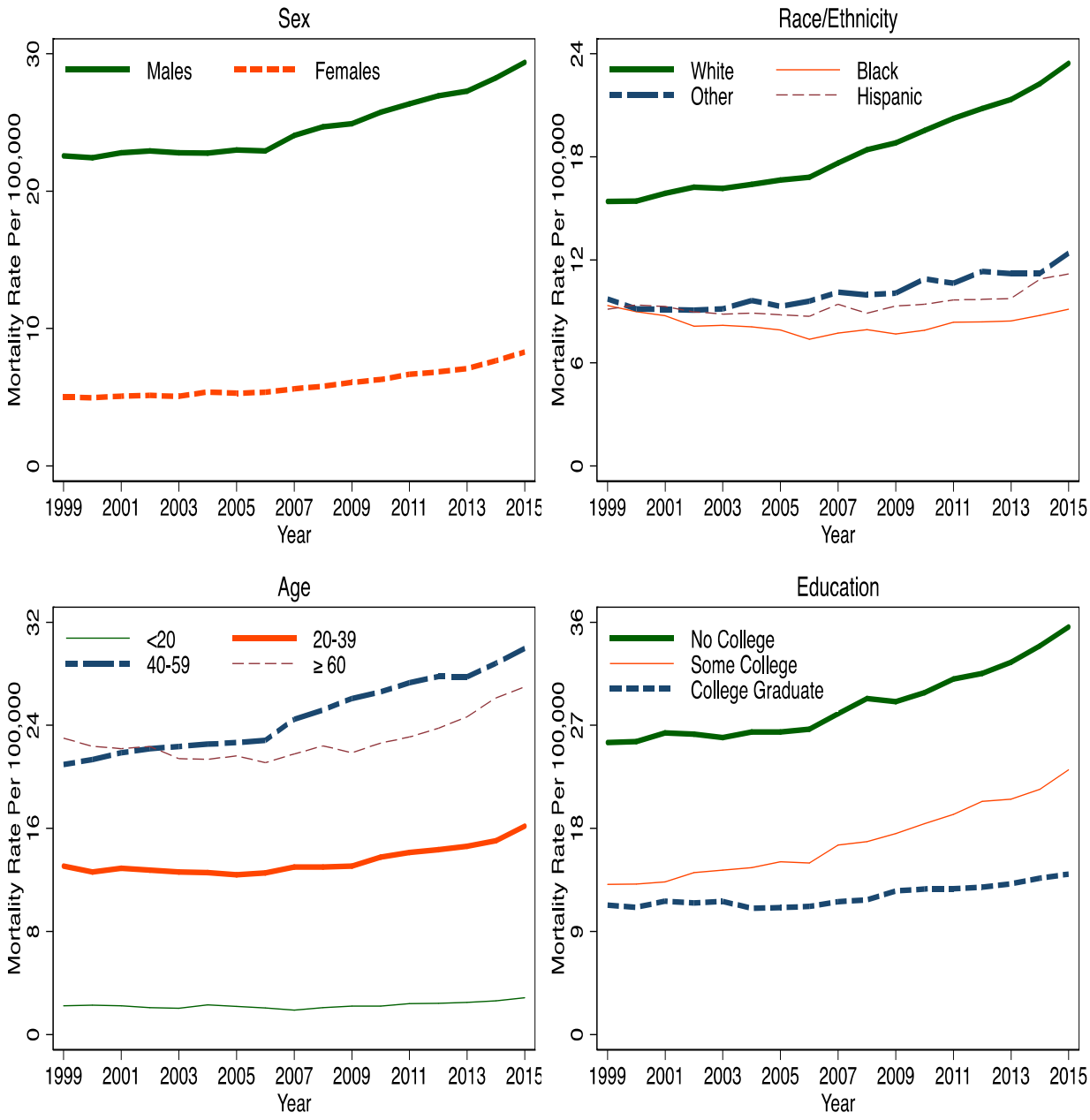
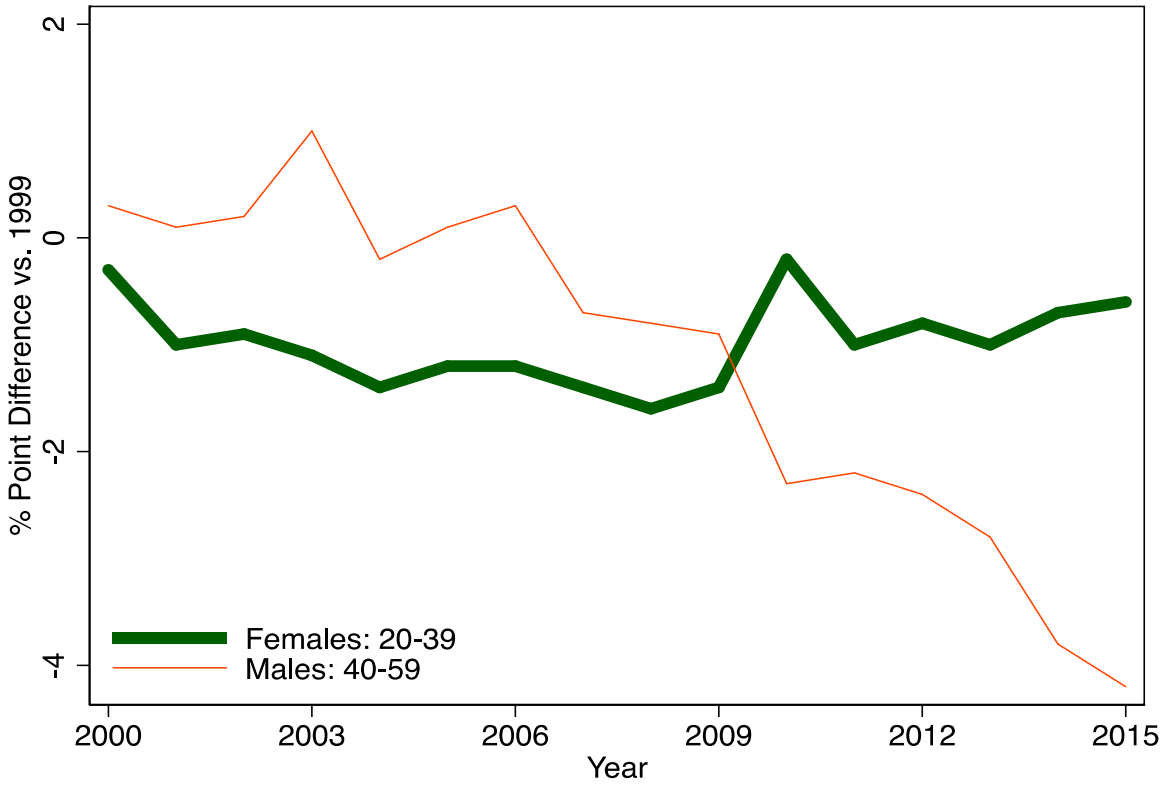


Figure A.3: Regression-Adjusted Changes Since 1999 in Share of Drug Poisoning Deaths For Additional Groups, 2000-2015



Note: See note on Figure 4.

Appendix B: Additional Robustness and Sensitivity Checks

I tested the robustness of the results to changes in specifications, estimation methods and samples. Appendix Table B.1 shows the results of models where observations are unweighted, (second panel), using reported rather than corrected opioid analgesic and illicit opioid death rates (third panel), and with changes in the economic proxies measured over an earlier period (approximately 1990-2000) rather than from 1999-2015 (fourth panel). Using unweighted data, the percentage of changes in mortality rates explained by economic conditions are occasionally higher than with weighting but there is no clear pattern and they never account for more than one-tenth of the total change.[43] The explanatory power of economic conditions is generally of similar magnitude when using reported rather than corrected opioid mortality rates. The percentage of mortality rate changes explained is always less when controlling for 1990-2000 rather than 1999-2015 changes in economic conditions, is generally insignificant and often negative. These results confirm the overall conclusion that economic conditions explain little of the rise in mortality rates.

Next, I estimated a series of instrumental variables (IV) models where each economic proxy was instrumented by the other four. As discussed, IV estimates can eliminate attenuation bias but require the strong assumption that error terms of the five proxies and the latent variable are uncorrelated. Results of these models, with $\boldsymbol{X_{1999}}$ and $\Delta\boldsymbol{X}$ included, are summarized in Appendix Table B.2. Appendix Table B.3 shows results controlling for $\Delta\boldsymbol{X^I}$ rather than $\Delta\boldsymbol{X}$.

[43] Standard deviations on the dependent variables are substantially larger in the unweighted data, but this does not appear to drive the results as the MP estimates also show no clear patterns of differences between the weighted and unweighted estimates. Unweighted dependent variable means are also generally larger than the weighted means, indicating higher mortality growth in smaller counties. However, the pattern is reversed for illicit opioids.

Estimation is by generalized method of moments (GMM), to provide efficient estimates with heteroskedastic errors.

The IV and multiple proxy estimates (repeated on the bottom panel of the tables) are usually of roughly similar magnitude, although the IV results are sometimes somewhat greater when instrumented rather than actual changes in the covariates are included. For instance, for drug mortality, the IV estimates for the poverty, household income, home price and unemployment proxies in Appendix Table B.2 range between zero and 0.85, implying that 0 to 9 percent of the change from 1999-2015 is explained, versus the MP estimate of 5 percent. The IV estimates for these four proxies indicate that the increase in opioid analgesic and illicit opioid rates explained by economic conditions are similar to those obtained using the multiple proxy approach, with most of the predicted effects being statistically insignificant. The IV coefficients on these economic measures are negative for all DSA deaths, except for a small and statistically insignificant positive estimate for median household incomes.

The one exception is for import exposure, where the IV coefficients are often quite large, although not statistically significant, in Appendix Table B.2. However, as mentioned, this proxy is barely correlated with the other economic variables (see Table A.2) and so is likely to suffer from a "weak instruments" problem (Bound, Jaeger, and Baker 1995; Staiger and Stock 1997).[44] The bottom-line is that both the MP and IV estimates indicate that changing economic conditions explain only a small portion of county-differences in the growth of drug fatalities rates.

Appendix Table B.4 provides estimates for sub-periods where growth in the specified category of opioid mortality was highest: 1999-2011 for opioid analgesics and 2006-2015 for illicit opioids. This is done because of the possibility that including periods with little change in

[44] As evidence of this, the F-statistic on the first-stage instruments is 72.5, 129.0, 23.6 & 33.0 for poverty, incomes, home prices & unemployment but just 5.4 for import exposure.

mortality rates may introduce noise into the estimates. However, doing so comes at considerable cost, both because the changes in economic conditions cover a shorter period and since data restrictions imply that the dates over which they are measured may not be ideal. For example, home price information in the *American Community Survey* is averaged over a five-year period (e.g. 2011-2015) to obtain sufficient sample sizes. When examining changes in opioid analgesic mortality from 1999-2011, median home prices averaged from 2007-2011 are compared to those in 2000. For illicit opioid fatality rates changes from 2006-2015, median home prices averaged from 2011-2015 are compared to averages from 2005-2009. These poorly captures the dates over which mortality growth is measured.[45] Also, import exposure continues to be measured from 1999-2011 in all models. In any case, Appendix Table B.4 shows that economic conditions explain a similar portion (2 to 6 percent) of the increase in opioid analgesic fatality rates from 1999-2011 as from 1999-2015, with a modestly larger fraction (4 to 5 percent) of the growth in illicit opioid mortality rates accounted for using the shorter 2006-2015 period. None of these estimates are significant at the 5% level.

Finally, I estimated models using modifications of the dependent variables. Since drug and nondrug suicides may have similar causes, drug mortality here was restricted to cases classified as of either accidental of undetermined intent, with intentional drug deaths (ICD-10 codes X60-X64) grouped with other sources of suicides. Case and Deaton (2015, 2017) use a wider definition of alcohol related deaths than that employed above. I followed them by including, in addition to deaths due to alcoholic liver disease (ICD-10 code K70), those due to chronic hepatitis unrelated to drugs or alcohol (ICD-10 code K73) and cirrhosis of the liver

[45] The table note provides additional detail on differences in the variables included for sub-periods. Other home price series do not provide sufficient information of this analysis. For example, Zillow Research (https://www.zillow.com/research/) provides county-level home value data but only for some (generally large) counties.

unrelated to alcohol but including unspecified sources (ICD-10 code K74). DSA deaths were then modified to include this broad definition of alcohol mortality.

The second panel of Appendix Table B.5 shows results with these modified dependent variables, with findings using the main outcomes provided in the top panel. The increase in mortality rates explained by economic conditions is essentially the same in either case.

Table B.1: Estimated Effect of Economic Conditions on 1999-2015 Changes in Various Death Rates, Robustness Checks

	All Drugs		Opioid Analgesics		Illicit Opioids		DSA	
	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
Primary Model								
Multiple Proxy Estimate	0.431	0.792*	0.197	0.306*	0.305	-0.101	-0.343	0.351
	(0.488)	(0.436)	(0.185)	(0.170)	(0.407)	(0.310)	(0.583)	(0.987)
Dependent Var. Mean [SD]	10.37 [9.06]		3.58 [4.22]		6.27 [6.67]		15.39 [12.38]	
% of Total Δ Explained	4.8%	8.7%	4.7%	7.3%	4.6%	-1.5%	-2.8%	2.8%
Unweighted								
Multiple Proxy Estimate	1.208***	0.503	0.344*	0.301*	0.740**	-0.004	1.240	-0.073
	(0.423)	(0.378)	(0.182)	(0.176)	(0.323)	(0.274)	(0.940)	(0.863)
Dependent Var. Mean [SD]	10.87 [13.08]		4.42 [7.05]		4.85 [7.42]		18.20 [23.93]	
% of Total Δ Explained	9.2%	3.8%	4.9%	4.3%	10.0%	-0.1%	5.2%	-0.3%
Unadjusted Mortality Rates								
Multiple Proxy Estimate			0.217	0.330*	0.198	-0.270		
			(0.187)	(0.183)	(1.496)	(0.706)		
Dependent Var. Mean [SD]				2.99 [4.09]	5.29 [6.41]			
% of Total Δ Explained			5.3%	8.1%	3.1%	-4.2%		
1990-2000 Changes in Economic Conditions								
Multiple Proxy Estimate	-0.923	0.214	-0.018	0.041	-1.130***	-0.316	-0.143	0.433
	(133.044)	(89.005)	(0.411)	(0.335)	(0.283)	(0.368)	(0.970)	(0.954)
% of Total Δ Explained	-10.9%	2.4%	-0.4%	1.0%	-16.9%	-4.7%	-1.2%	3.5%
Additional Controls (ΔX's)	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{\mathbf{I}}$	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{\mathbf{I}}$	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{\mathbf{I}}$	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{\mathbf{I}}$

Note: See notes on Tables 1 through 3. All models include 1999 supplementary covariates as well as changes in either actual or instrumented values from 1999-2015. Top panel repeats results from Table 2. Second panel shows estimates without weighting the data. Third panel show results for changes in reported (rather than adjusted) opioid analgesic, heroin and synthetic opioid mortality rates. Lower panel shows results when controlling for lagged changes in economic proxies, from approximately 1990-2000, rather than 1999-2015. *** p<0.01, ** p<0.05, * p<0.1

Table B.2: GMM (IV) Estimates of Effects of Economic Conditions on Changes in Drug Death Rates, 1999-2015

Economic Proxy	All Drugs	Opioid Analgesics	Illicit Opioids	DSA
Δ in Poverty Rate	-0.038 (0.559)	0.186 (0.303)	-0.414 (0.494)	-0.659 (0.698)
Δ in Median Household Income	0.853 (0.625)	0.281 (0.292)	0.287 (0.538)	0.200 (0.694)
Δ in Median Home Price	0.232 (0.666)	0.320 (0.354)	-0.276 (0.679)	-0.378 (0.791)
Δ in Unemployment Rate	0.358 (0.966)	0.489 (0.473)	-0.009 (0.795)	-0.009 (1.156)
Δ in Import Exposure	2.263 (2.067)	0.709 (0.817)	1.149 (1.479)	1.790 (2.282)
Multiple Proxy Estimate	0.431 (0.488)	0.197 (0.185)	0.305 (0.407)	-0.343 (0.583)

Note: See notes on Tables 1 through 3. Each cell in the top panel of the table shows results of a different estimate where the specific measure of changes in economic conditions is instrumented by the other four proxies. The bottom panel repeats the corresponding multiple proxy estimates from Table 2. All specifications also control for the 1999 set of supplementary characteristics and changes from 1999-2015. Robust standard errors with clustering at the commuter zone level are shown in parentheses for the GMM estimates and bootstrapped standard errors (1000 replications) for the multiple proxy estimates. *** p<0.01, ** p<0.05, * p<0.1

Table B.3: GMM (IV) Estimates of Effects of Economic Conditions on Changes in Various Death Rates, 1999-2015, with Instrumented Changes in Supplementary Covariates Controlled For

Economic Proxy	All Drugs	Opioid Analgesics	Illicit Opioids	DSA
Δ in Poverty Rate	0.940***	0.330**	-0.264	0.761*
	(0.282)	(0.147)	(0.275)	(0.389)
Δ in Median Household Income	1.039***	0.388**	0.050	0.414
	(0.321)	(0.169)	(0.263)	(0.449)
Δ in Median Home Price	1.387***	0.534***	-0.066	1.235**
	(0.492)	(0.190)	(0.314)	(0.582)
Δ in Unemployment Rate	1.789***	0.478**	-0.012	1.391**
	(0.485)	(0.229)	(0.366)	(0.674)
Δ in Import Exposure	3.123**	1.249***	-0.100	2.180
	(1.232)	(0.467)	(0.725)	(1.342)
Multiple Proxy Estimate	0.792*	0.306*	-0.101	0.351
	(0.436)	(0.170)	(0.310)	(0.987)

Note: See note on Table B.2. All specifications also control for the 1999 set of supplementary characteristics and instrumented changes in them from 1999-2015. *** p<0.01, ** p<0.05, * p<0.1

Table B.4: Multiple Proxy Estimates of Effect of Economic Conditions on Changes in Various Types of Drug Death Rates For Selected Time Periods

	Opioid Analgesics		Illicit Opioids	
	(1a)	(1b)	(2a)	(2b)
<u>1999-2015</u>				
Multiple Proxy Estimate	0.197	0.306*	0.305	-0.101
	(0.185)	(0.170)	(0.407)	(0.310)
Dependent Var. Mean [SD]	3.58 [4.22]		6.27 [6.67]	
% of Δ Explained	4.7%	7.3%	4.6%	-1.5%
<u>1999-2011</u>				
Multiple Proxy Estimate	0.105	0.266		
	(0.223)	(0.232)		
Dependent Var. Mean [SD]	3.81 [4.76]			
% of Δ Explained	2.2%	5.6%		
<u>2006-2015</u>				
Multiple Proxy Estimate			0.326	0.248
			(0.398)	(0.451)
Dependent Var. Mean [SD]			5.42 [6.15]	
% of Δ Explained			5.3%	4.0%
Additional Controls	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{I}$	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{I}$

Note: See notes on Tables 1 through 3. Table shows multiple proxy estimates for models with additional controls for the start year (1999 or 2006), as well as changes in either actual or instrumented values from the starting to ending years. When 2011 is the final year, the ending period for measuring changes in home prices is 2007-2011 and 2011 covariates include the average share foreign born in 2006-2010. When 2006 is the first analysis year, initial year home prices are averaged from 2005=2009. *** p<0.01, ** p<0.05, * p<0.1

Table B.5: Estimated Effect of Economic Conditions on 1999-2015 Changes in Various Death Rates, Robustness Checks

Primary Mortality Outcomes	All Drugs		DSA	
	(a)	(b)	(a)	(b)
Multiple Proxy Estimate	0.431 (0.488)	0.792* (0.436)	-0.343 (0.583)	0.351 (0.987)
Dependent Var. Mean [SD]	10.37 [9.06]		15.39 [12.38]	
% of Total Δ Explained	4.8%	8.7%	-2.8%	2.8%
Alternative Mortality Outcomes	**Drugs: Non-Suicides Only**		**DSA (broad definition)**	
	(a)	(b)	(a)	(b)
Multiple Proxy Estimate	0.399 (0.450)	0.792** (0.378)	-0.335 (0.510)	0.441 (0.484)
Dependent Var. Mean [SD]	9.89 [8.76]		16.36 [13.51]	
% of Total Δ Explained	4.6%	9.0%	-2.5%	3.3%
Additional Controls (ΔX's)	Δ**X**	Δ$\mathbf{X}^{I}$	Δ**X**	Δ$\mathbf{X}^{I}$

Note: See notes on Tables 1 through 3. All models include 1999 supplementary covariates as well as changes in either actual or instrumented values from 1999-2015. Top panel uses the main variable definitions. The second panel makes the following changes: 1) intentional drug deaths (ICD-10 Codes: X60-X64) are removed from drug deaths and included in suicide mortality; 2) the category of alcohol-related deaths is broadened to include ICD-10 codes K73 and K74 (as well as K70); 3) DSA deaths include the broader definition of alcohol deaths. *** p<0.01, ** p<0.05s, * p<0.1

Appendix C: Estimates of Drug Environment Effects Using Additional Drug Mortality Rates

I conducted of additional analyses treatment vs. reference group time-patterns of drug mortality rates by analyzing several additional categories of narcotics fatalities. Specifically, illicit opioids were decomposed into heroin and synthetic opioids (ICD-10 T-codes 40.1 and 40.4), with supplemental estimates for methadone (T-code 40.3) and cocaine (T-code 40.5) deahs. Each of these drug categories exhibited sharp breaks or reversals in mortality trends during the analysis period.

Figure C.1 shows national patterns of mortality rates for these types of narcotics (as well as for opioid analgesics included in the main analysis). Opioid analgesic deaths grew rapidly from 1999-2011 but were flat thereafter. By contrast, heroin deaths changed little from 1999-2006, rose modestly from 2006-2010 and then quickly (by 276 percent) from 2010-2015. Synthetic opioids increased throughout the period but started from a low level, 0.4 per 100,000 in 1999 and grew slowly, to 1.3 per 100,000 in 2013, before exploding to 3.5 per 100,000 by 2015. Cocaine deaths rates grew quickly, from 1.7 to 3.2 per 100,000 from 1999-2006, declined to 1999 levels by 2009 and increased again after 2012. Methadone fatality rates rose dramatically, from 0.4 to 2.5 per 100,000, between 1999 and 2007, and then fell steadily.[46]

To check the consistency of these patterns for the county-level analysis that follows, I examined the year coefficients from models where county-level mortality rates were regressed

[46] Sources of the drop in cocaine deaths after 2006 are not fully understood but may reflect combinations of price increases and quantity reductions, "aging out" of the US cocaine user population and greater demand outside the United States (Kilmer and Midgette 2017). The decline in methadone deaths after 2007 probably resulted from successful guidance and efforts by the Federal Drug Administration to decrease its use as treatment for pain (Jones, Baldwin, et al. 2016). I also examined deaths involving psychotropic medications, sedatives and non-specified narcotics but did not use them because each exhibited fairly steady trends over the analysis period, without sharp breaks or reversals.

on county fixed-effects, general time effects and the supplementary time-varying regressors The patterns, shown in Figure C.2, are virtually identical to those in Figure C.1.

I next obtained regression-adjusted differences in the mortality rate changes across population groups stratified by sex and age by estimating equation (10) for models with males and 20-39 year olds (females and 40-59 year olds) as the treatment (reference) groups. The results are summarized in Figure C.3 and C.4, with solid lines indicating coefficients on the year dummy variables, dotted lines showing 95 percent confidence intervals and vertical lines showing years with breaks or reversals in mortality trends (e.g. 2006 and 2010 for heroin deaths). Of interest is whether the treatment versus control group differentials change substantially at the time of the trend breaks or reversals.

The sex-differentials align closely with the drug environment hypothesis. Male heroin death rate differentials (relative to those for women) were virtually constant from 1999-2006, began to increase in 2007 and with accelerated growth after 2010. Synthetic opioid differentials were virtually nonexistent through 2013 but with much more rapid growth in male death rates from this source starting in 2014. Gender differences in death rates also closely tracked overall mortality risk for cocaine and methadone – rising in relative terms for males when overall rates were growing (from 1999-2006 for cocaine and 1999-2007 for methadone) and then falling, with a subsequent increase in male cocaine deaths accompanying the post-2012 rise in total cocaine fatalities.

One potential concern is that these patterns might simply reflect overall higher mortality rates for males. However, this cannot be a complete explanation since synthetic opioid mortality rates were essentially the same for males and females throughout most of the 1999-2012 period

and gender differences in initial (1999) rates were small relative to the subsequent increases for heroin and methadone.

Figure C.4 shows corresponding patterns with 20-39 year olds as the treatment group, compared to 40-59 year olds. The results again indicate differential risks that are related to the drug environment. There were no age differences in heroin-involved mortality rates from 1999-2006, but relative rates for 20-39 year olds increased slowly from 2007-2010 and more quickly thereafter. Synthetic opioid differentials were flat prior to 2013 (with lower rates for 20-39 then 40-59 year olds) but with dramatic relative growth for younger adults after 2013. Cocaine deaths became increasingly concentrated among 40-59 year olds during the 1999-2006 period of rising overall rates and then were mostly flat thereafter. Age differentials in methadone fatality rates were nosier but generally trending upwards prior to 2007, when overall death rates were growing, and then down subsequently.

To more formally evaluate whether breaks or reversals in mortality rates differentially affected sex and age groups, Table C.1 summarizes the results from estimating equation (11). The coefficients on $POST$ are of key interest, since they show treatment group changes in the relative trend differentials following a break or reversal in the overall mortality trend. These results confirm that changes in the overall drug environment differentially affect the treatment groups in the ways hypothesized.

Heroin deaths rose by fairly at fairly similar rates for men and young adults versus their counterparts through 2010 (when overall growth rates were relatively flat) but much faster thereafter. Similarly, there was fairly common trend increases in synthetic opioid fatality rates prior to 2013 but much greater subsequent rises for males and young adults than for females and older persons (and with particularly slow relative growth for 40-59 year old women). Cocaine

death rates grew more for males and 40-59 year olds than for their counterparts from 1999-2006 but more slowly thereafter, following the decline in total cocaine death rates. For methadone, the increased trend growth was concentrated among males and older adults through 2007 but with the pattern reversed subsequently.

Additional supporting evidence is provided in Table C.2, which allows for separate trend changes for heroin and after 2006 and then following 2010 and for cocaine where decreasing overall death rates after 2006 were reversed beginning in 2011.[47] Growth in heroin death rates was fairly homogenous prior to 2006, began to rise faster for men and younger adults in 2007, and with a further increase after 2010. Cocaine mortality rates grew for males and 40-59 year olds from 1999-2006, fell for these groups starting in 2007 and then again began to increase for males (but not 40-59 year olds) after 2012. These patterns of sex and age heterogeneity in predicted effects are consistent with differential responsiveness to changes in risks related to the drug environment.

[47] Deaths for heroin and cocaine exhibit two trend breaks. For instance, heroin death rates were flat from 1999-2006, increased modestly from 2006-2010 and sharply from 2010-2015. In these cases, I also estimated models of:

$$M_{gkt} = \boldsymbol{X}'_{kt}\alpha + \boldsymbol{F_k}\kappa + \boldsymbol{T_t}\tau + Trend_{gt}\varphi + POST_{gt}\pi + POST2_{gt}\sigma + \zeta_{gkt},$$

where treatment vs. control group time trend differences were $\hat{\varphi}$, $\hat{\varphi} + \hat{\pi}$ and $\hat{\varphi} + \hat{\pi} + \hat{\sigma}$ in the early, intermediate and later time periods.

Table C.1: Sex and Age-Specific Differences in Various Narcotic Mortality Rate Trends

Regressor	Heroin	Synthetic Opioids	Cocaine	Methadone
Sex-Specific (Reference Group: Females)				
Male	1.01***	0.06***	1.66***	0.13***
	(0.10)	(0.02)	(0.11)	(0.03)
Trend	0.05***	0.00	0.13***	0.17***
	(0.01)	(0.00)	(0.01)	(0.01)
Post	0.65***	1.19***	-0.24***	-0.31***
	(0.04)	(0.10)	(0.02)	(0.02)
Age-Specific (Reference Group: 40-59 Year Olds)				
Young	-0.43***	-0.35***	-0.19*	-0.38***
	(0.11)	(0.03)	(0.11)	(0.04)
Trend	0.10***	-0.03***	-0.19***	0.04**
	(0.01)	(0.00)	(0.02)	(0.01)
Post	0.54***	1.26***	0.20***	-0.07***
	(0.05)	(0.11)	(0.03)	(0.03)

Note: See note on Table 6. Table shows differences in intercepts and time trends for males compared to females and 20-39 versus 40-49 year olds. The “Trend” coefficient shows the general difference in time trends between the treatment and reference groups. “Post” show deviations from the general trend for periods after a change in the overall trend effect. Specifically, “Post” refers to periods starting after 2010, 2013, 2006 and 2007 for heroin, synthetic opioids, cocaine and methadone. Regressions also control for group main effects, county fixed-effects and year dummy variables. Sample contains 106,426 group-year observations from 3,132 counties. Observations are weighted by 2015 county populations. Robust standard errors, clustered at the county level, are shown in parentheses. *** p<0.01, ** p<0.05, * p<0.1

Table C.2: Additional Sex and Age-Specific Differences in Heroin and Cocaine Mortality Trends

	Sex-Specific		Age-Specific	
Regressor	Heroin	Cocaine	Heroin	Cocaine
Trend	0.01	0.17***	0.03***	-0.17***
	(0.01)	(0.01)	(0.01)	(0.02)
Post	0.10***	-0.42***	0.19***	0.13***
	(0.02)	(0.02)	(0.03)	(0.04)
Post2	0.56***	0.53***	0.36***	0.21***
	(0.05)	(0.03)	(0.06)	(0.06)

Note: See notes on Tables 6 and C.1. Specification is the same as in table C.1, except for the inclusion of a second post-treatment period showing further changes in changes in trend slope effects. “Post” indicates differential trends after 2006 for heroin and cocaine, with “Post2” indicating additional trend breaks after 2010 and 2012. References groups are females and 40-59 year olds in the sex-specific and age-specific models. *** p<0.01, ** p<0.05, * p<0.1

Figure C.1: Selected Drug Mortality Rates, 1999-2015

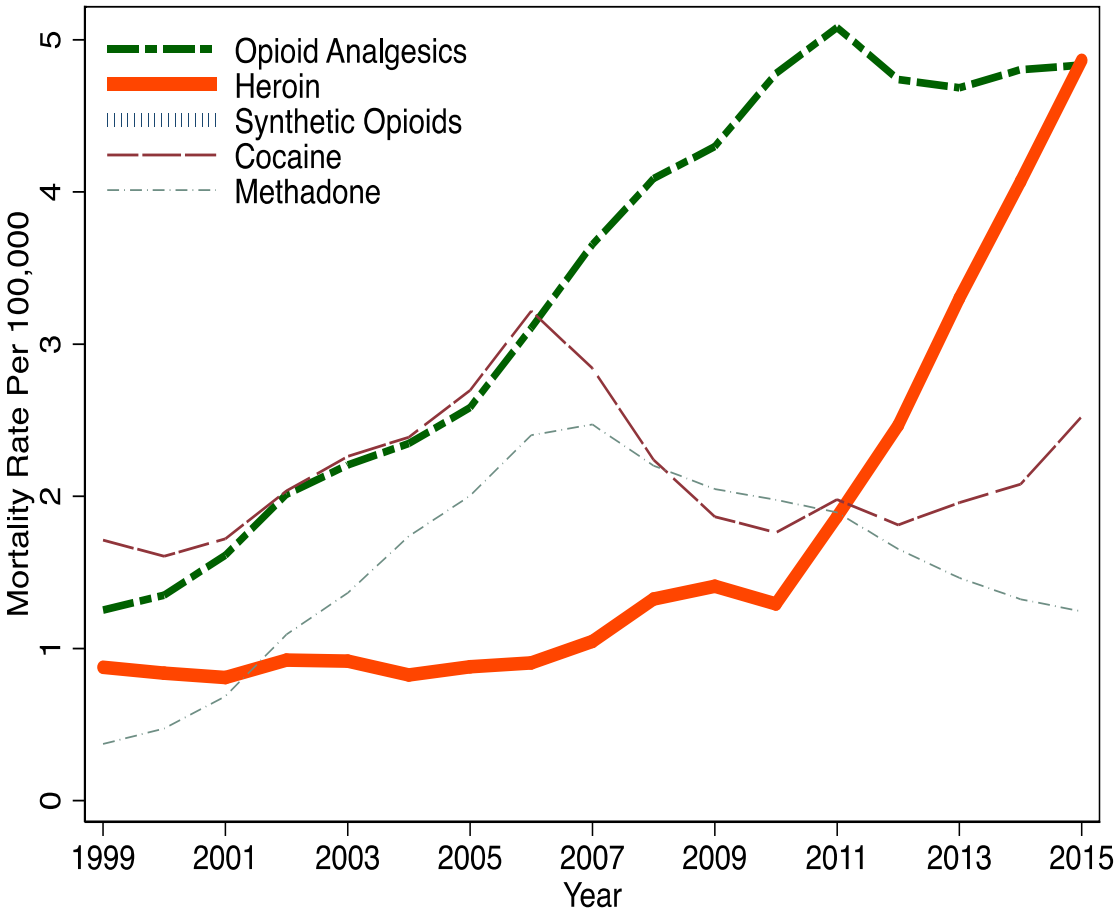
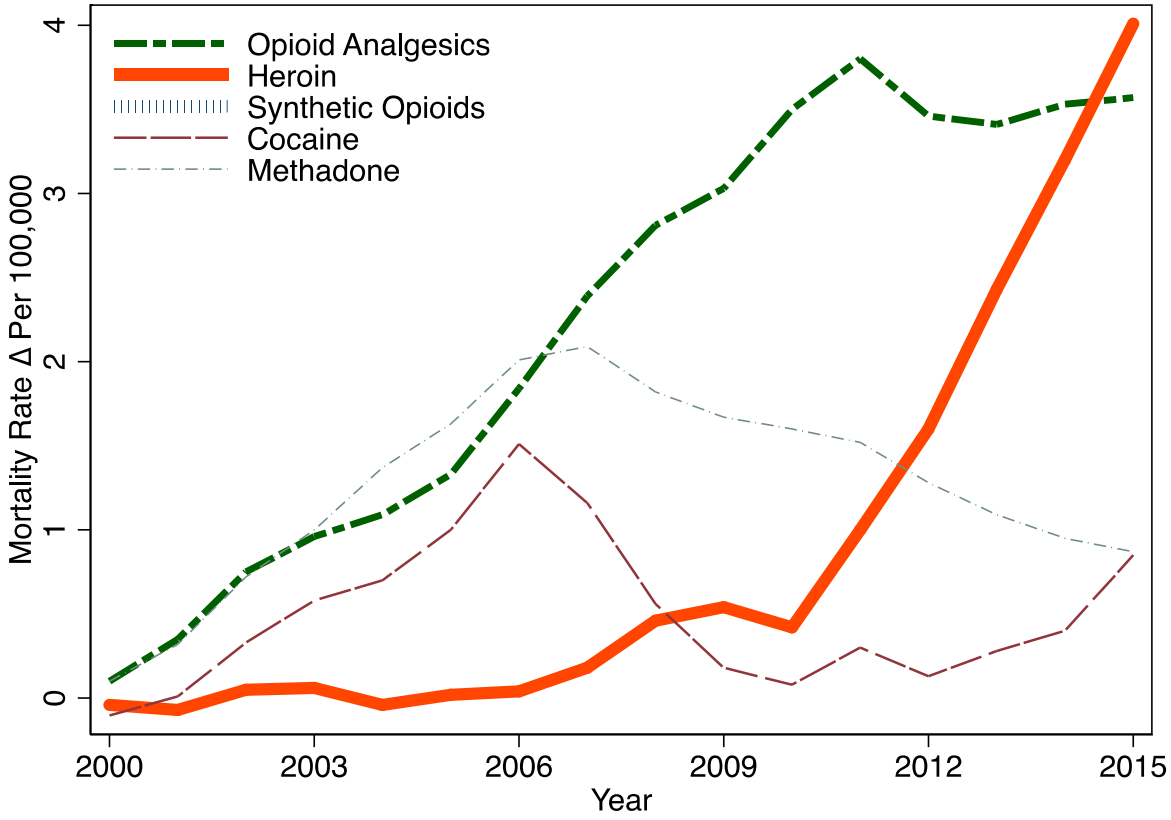
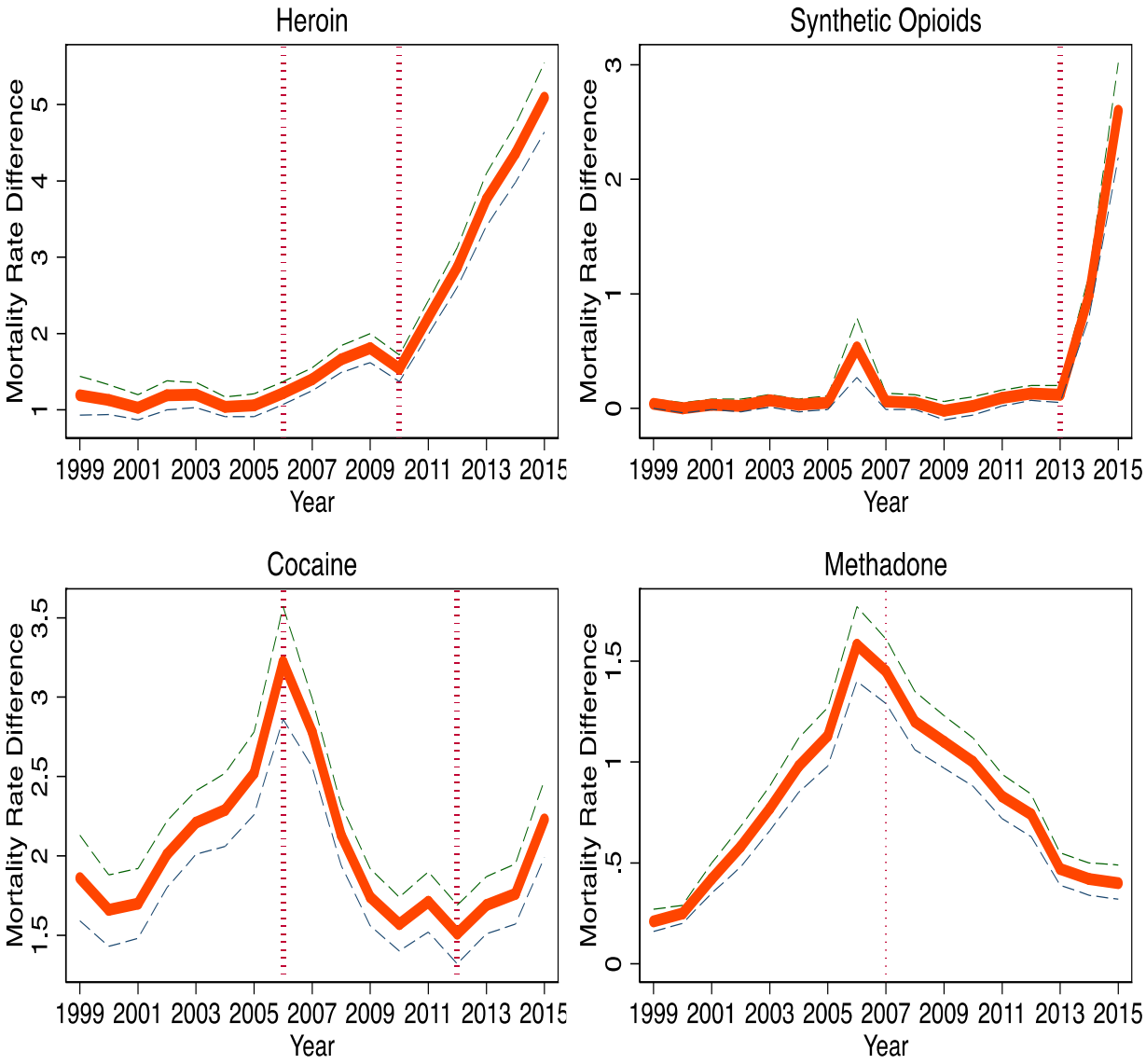


Figure C.2: Regression-Adjusted Drug Mortality Rate Changes Since 1999



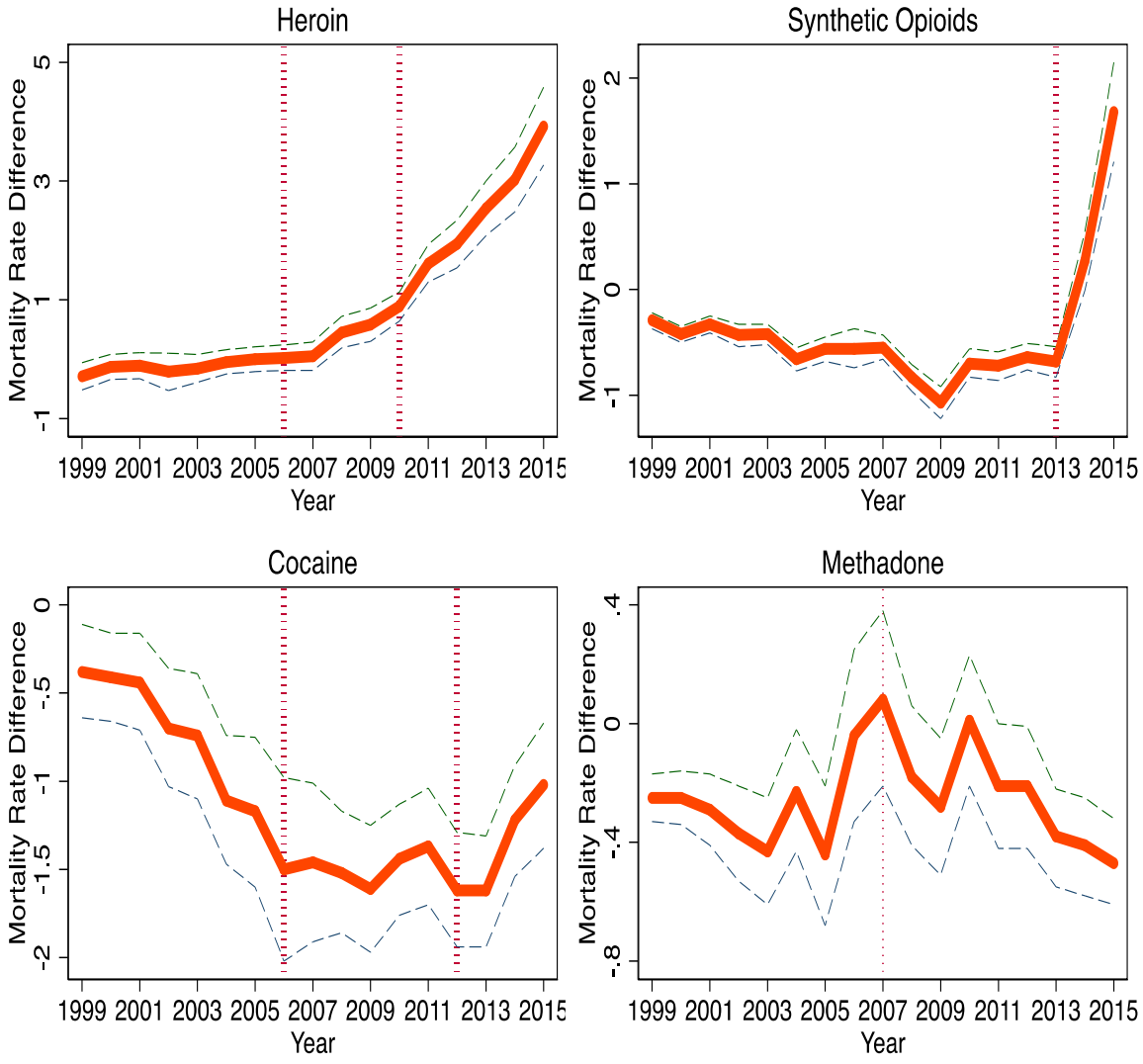
Note: Figure shows year coefficients from panel models where the dependent variables are county mortality rates per 100,000 and with 1999 as the excluded reference year. In addition to year dummy variables, the models also control for county fixed-effects. Observations are weighted by 2015 county populations.

Figure C.3: Regression-Adjusted Differences in Mortality Rates by Sex (Males vs. Females)



Note: Figures show difference in predicted mortality rates for males in the given year versus those for females from models with sex-specific mortality rates regressed against county fixed-effects, year dummy variables and year-by-sex interactions and main effects. Dashed lines show 95 percent confidence intervals. Vertical lines show years with a break or reversal in the drug-specific mortality rate trend.

Figure C.4: Regression-Adjusted Differences in Mortality Rates by Age (20-39 vs. 40-59 year olds)



Note: Figures show difference in predicted mortality rates for 20-39 year old in the given year versus those for 40-59 year olds from models with age-specific mortality rates regressed against county fixed-effects, year dummy variables and year-by-age interactions and main effects. Dashed lines show 95 percent confidence intervals. Vertical lines show years with a break or reversal in the drug-specific mortality rate trend.