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DEATHS OF DESPAIR OR DRUG PROBLEMS?

Christopher J. Ruhm

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ABSTRACT

The United States is in the midst of a fatal drug epidemic. This study uses data from the Multiple Cause of Death Files to examine the extent to which increases in county-level drug mortality rates from 1999-2015 are due to "deaths of despair", measured here by deterioration in medium-run economic conditions, or if they instead are more likely to reflect changes in the "drug environment" in ways that present differential risks to population subgroups. A primary finding is that counties experiencing relative economic decline did experience higher growth in drug mortality than those with more robust growth, but the relationship is weak and mostly explained by confounding factors. In the preferred estimates, changes in economic conditions account for less than one-tenth of the rise in drug and opioid-involved mortality rates. The contribution of economic factors is even less when accounting for plausible selection on unobservables, with even a small amount of remaining confounding factors being sufficient to entirely eliminate the relationship. These results suggest that the "deaths of despair" framing, while provocative, is unlikely to explain the main sources of the fatal drug epidemic and that efforts to improve economic conditions in distressed locations, while desirable for other reasons, are not likely to yield significant reductions in drug mortality. 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. Put succinctly, the fatal overdose epidemic is likely to primarily reflect drug problems rather than deaths of despair.

Christopher J. Ruhm
Frank Batten School of
Leadership and Public Policy
University of Virginia
235 McCormick Rd.
P.O. Box 400893
Charlottesville, VA 22904-4893
and NBER
ruhm@virginia.edu

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1. Introduction

The United States is in the midst of a fatal drug epidemic. The number of Americans dying from drugs rose from 16,849 to 63,632 between 1999 and 2016 (Hedegaard, Warner, and Miniño 2017). Drug overdoses are 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 drug mortality 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 with available data reported to involve synthetic opioids (mostly fentanyl) and heroin substantially exceeded the 14,487 fatalities involving 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 declines in life expectancy observed since 1999 initially among 45-54 year old non-Hispanic whites in 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). Case and Deaton attribute this rising mortality to "deaths of despair" (Case and Deaton 2017; Deaton 2017) which they view as a form of suicide that "respond(s) more to prolonged economic conditions than to short-term fluctuations, and especially social dysfunctions … that come with prolonged economic distress" (Deaton 2017, p. 3).[1] In their view, it is the social and economic environment rather than opioids (and presumably drugs more generally) that are the fundamental causes of increased deaths.

At first glance, the particularly large rise in drug mortality in Appalachia and the rust-belt seems consistent with the deaths of despair hypothesis. However, other areas not associated with

[1] 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).

declining economies have also experienced strong upsurges in overdose fatality rates,[2] and it is difficult to reconcile this mechanism with important patterns of life expectancy and mortality. For instance, why has the increase in drug mortality been dramatically larger for whites than non-whites, even though the latter group has faced greater economic insecurity and worse economic conditions? And why aren't similar increases being observed among midlife adults in other developed countries that have also faced difficult economic times?[3]

One alternative is that it is changes in the availability and use of risky drugs that are of particular importance – in short that the drug environment rather than economy is the key driver in rising drug fatalities. 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 in the United States might have increased more than in other countries because the large majority of opioid consumption has occurred in the U.S.[4] Similarly, drug fatality rates might have increased most rapidly in rural areas with relatively low average education levels if less educated individuals are particularly vulnerable to a more dangerous drug environment because they lack knowledge about the risks (Cutler and Lleras-Muney 2010) or have less to lose from them (Becker and Murphy 1988). If so, the measured effect of changes in macroeconomic conditions should decline or disappear once county population characteristics are controlled for.

This study sheds light on the relative contribution of these two mechanisms – deaths of despair versus deaths from the drug environment – to the rapid rise in fatal overdoses. The first

[2] For instance, New Hampshire had the highest state opioid fatality rate in 2014 and Massachusetts had the fourth highest rate (Ruhm 2017b).
[3] Case and Deaton (2017) present evidence showing that there has been little change in drug, alcohol and suicide mortality since the turn of the century for 50-54 year olds in France, Germany, Sweden, the United Kingdom, Canada and Australia.
[4] In 2007 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).

part of the analysis estimates the extent to which deteriorating economic conditions explain the growth in overdose deaths. In addition to drug mortality, Case and Deaton (2015) also emphasize the importance of deaths due to suicide and alcoholic liver disease (hereafter referred to as "alcohol").[5] With this in mind, this investigation also includes deaths from drugs, nondrug suicides and alcohol (DSA) as a group and, separately, those from nondrug suicides (hereafter often referred to simply as suicides) and alcohol.

To operationalize the examination of "deaths of despair", I focus on medium-run changes in a variety of economic factors including dimensions related to labor market outcomes, household wealth and international trade shocks. This is distinguished from prior literature examining how *transitory* economic fluctuations have affected various types of drug use or abuse (Arkes 2007; Ruhm 2015; Carpenter, McClellan, and Rees 2017; Martin Bassols and Vall Castelló 2016; Hollingsworth, Ruhm, and Simon 2017). The working assumption is that economic conditions *cause* changes in drug use and problems. However, there is some evidence of reverse causation – whereby rising opioid use has had negative effects on labor markets (Krueger 2017). To the extent this occurs, the analysis below may *overstate* the role of economic conditions as a contributor to the fatal drug epidemic.

As a second step, evidence is provided on the alternative hypothesis that changes in the drug environment are a main cause of rising overdose deaths. Since directly measuring the role of such environmental factors is difficult, the strategy used below is the exploit the dramatic changes in the sources of drug-related deaths that occurred over the sample period. Specifically, growth in fatal overdoses early in the sample period was dominated by a rise in deaths involving opioid analgesic medications, while later increases (since around 2010) have primarily involved

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

illicit opioids such as heroin and fentanyl. If economic conditions are the primary driver of fatal drug epidemic, there would be no reason to expect these shifts in the drug composition to affect the distribution of the demographic groups killed by overdoses. Instead, individuals self-medicating for their "despair" would simply switch to the newly more available types of drugs. Conversely, if the drug environment is the key driver, we anticipate changes in the composition of overdose fatalities, with groups at higher risk of abusing prescription opioids having the largest increases in drug death rates early in the analysis period whereas those most vulnerable to abuse of illicit opioids experiencing the greatest growth in mortality towards the end of it.

Economists and other social scientists have previously examined how specific factors or policies are related to opioid use or drug fatalities including the roles of: medical marijuana (Powell, Pacula, and Jacobson 2015; Chu 2015; A. C. Bradford and Bradford 2016; Ozluk 2017), abuse-deterrent drug formulations (Alpert, Powell, and Pacula 2017; Evans, Lieber, and Power 2017), Naloxone availability (Rees et al. 2017; Doleac and Mukherjee 2017), Medicare Part D (Powell, Pacula, and Taylor 2015), the availability of substance abuse treatment (Swensen 2015), advertising (D. M. Anderson 2010), physician market structure (W. D. Bradford 2017), and state policies influencing the availability of prescription opioids (Dowell et al. 2016; Meinhofer 2016; Buchmueller and Carey 2018; Dave, Grecu, and Saffer 2017). However, any observed effects explain, at most, only a small portion of the overall change in overdose deaths.[6] This study is attempting to examine the broader question of the sources of extremely large (211 percent from 1999-2015) overall rise in drug deaths. The analysis also implements methods of measuring the combined effects of multiple proxies for economic conditions, accounting for the incomplete

[6] 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.

reporting of drug involvement on death certificates, and testing the sensitivity of the findings to the presence of uncontrolled for confounding factors.

The investigation reveals four main findings. First, counties suffering relative or absolute decline did have larger increases in drug and total DSA mortality rates than those with better economic performance. This pattern shows up using most of the economic proxies examined below, in part because they are generally reasonably highly correlated with each other. Second, the estimated impact of the economy is dramatically attenuated – by over 70 percent for drug fatalities and 90 percent or more for all DSA deaths – when adding controls for county-level characteristics, implying that the observed correlations are likely to be 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 and even less of the growth in opioid analgesic or illicit opioid-involved mortality. In sensitivity tests, a slightly larger share of the increase in drug deaths may be explained by economic factors for some groups and, even using the multiple proxy (MP) methods, it is possible that there is modest remaining attenuation bias. On the other hand, even small amounts of selection on unobservables would be sufficient to completely eliminate the contributions of economic factors, making it quite plausible that "deaths of despair' play no role at all. Fourth, the patterns of drug deaths across sex and age subgroups suggests that changes in the drug environment may be an important determinant of rising drug mortality. Of particular relevance, the explosive growth in illicit opioid death rates after 2010 was accompanied a rising share of drug deaths being accounted for by males and relatively young adults, as well as a faster growth in fatalities involving these drugs for them relative to females and older adults. Overall, the results raise doubts about the hypothesis that

economic decline is a primary cause of rising overdose mortality and instead suggest an important role for the drug environment.

2. **Methods**

2.1 Basic Framework for Examining the Deaths of Despair Hypothesis

I examine the extent to which sustained deterioration in economic conditions is a driver of the increase in fatal overdoses by performing a county-level analysis where the outcomes are changes in various types of drug and DSA mortality rates and the key explanatory variables are five measures for economic conditions. In all cases, the dependent variables and economic proxies represent "long-changes", covering substantial periods of time. In the primary model, changes in county level fatal overdose rates cover the period 1999-2015, with subperiods sometimes examined. The economic proxies examine changes over the same or similar periods, although the end period for the indicator of import competition is 2011, due to data limitations.

Consider a model where mortality rates per 100,000 in county k at time t are M_{kt}. Let $t = [0,1]$ denote 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 determinants of mortality. 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.[7]

The coefficients of interest, $\hat{\beta}$, show estimated economic effects on mortality growth. A requirement for unbiased estimates is cov($\Delta E_k, \varepsilon_k$) = 0, implying that the supplementary covariates must adequately control for influences on mortality trends that are spuriously correlated with $\Delta \boldsymbol{E}$. However, the estimates will be attenuated if the vector of supplementary covariates contains 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 influenced by economic conditions.[8]

For this reason, I also estimate an alternative version of equation (3) using "instrumented" values of $\Delta \boldsymbol{X}$, denoted hereafter 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. For continuous variables, these are calculated as:

$$\Delta X_k^I = X_{k0} \times \frac{X_{d1} - X_{d0}}{X_{d0}} \quad (4)$$

[7] It is unclear conceptually how to examine the effects of changes over time 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 briefly discuss below the results of estimating this model when examining changes in total drug mortality rates.

[8] Similarly, Autor, Dorn and Hanson (2017) show that 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.

where X_{dt} refers to the value of the supplemental covariate in census division d containing county k. The operational assumption here is that economic conditions may causally affect the supplementary covariates within but not across census divisions.[9]

The vector of covariates also includes binary variables indicating whether states have specific policies in place (as described below). 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 this was not the case (i.e. 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:

$$\Delta X_k^I|_{X_{k0}=0} = (X_{d1} - X_{d0})|_{X_{d0}=0}. \quad (5)$$

As mentioned, estimates using actual values of $\Delta \boldsymbol{X}$ may suffer from endogeneity bias. Models controlling for $\Delta \boldsymbol{X^I}$ largely avoid this problem but at the cost of less fully accounting for potential confounding factors. Therefore, I present results for 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 $\Delta \boldsymbol{X^I}$.

In the most specifications, observations are weighted by 2015 county populations, to avoid attributing undue influence to the treatment effects observed in small counties.[10] However, since weighting can reduce efficiency under some circumstances (Wooldridge 1999; Solon, Haider, and Wooldridge 2015), sensitivity of the results to use of unweighted estimates is explored. Also, 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

[9] For the migration example, this would imply that individuals might systematically move to counties with better economic conditions within a census region but not outside it.
[10] For example, in 2015, the smallest 50 percent of counties contained just 5.8 percent of the U.S. population.

estimate specifications where economic conditions operate with a delay, by controlling for lagged, rather than contemporaneous, changes in these variables over approximately the 1990-2000 period.

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 that 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 general empirical strategy is to use the econometric results from equation (3) to estimate how changes in economic conditions affect trends in fatal overdoses and then to compare these predicted impacts to the total change over the period. In a model with only a single proxy for economic conditions, this is measured as:

(6) $$\% \text{ of } \Delta \text{M Explained} = \frac{\hat{\beta}}{\sigma_{\text{M}}} \times 100\%$$

where $\hat{\beta}$ is the regression coefficient on $\Delta \boldsymbol{E}$, from (3), and σ_M is the standard deviation of the change in mortality rates. Since $\Delta \boldsymbol{E}$ has been standardized, $\frac{\hat{\beta}}{\sigma_M}$ shows the standard deviation change in mortality rates expected to result from a one standard deviation increase in the economic proxy. For example, if a one standard deviation increase in $\Delta \boldsymbol{E}$ predicts a one-half standard deviation increase in ΔM (i.e. if $\hat{\beta} = 0.5\sigma_M$), 50 percent of the mortality growth is estimated to be accounted for by changing economic conditions.

2.2 Multiple Proxy Estimates

Implementing the strategy just described faces multiple challenges. There is not a clear conceptual framework determining what aspects of the economy are likely to be 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, the level and distribution of income, housing prices which are an important component of household wealth, and international trade exposure.

Since no single economic indicator completely captures the effects of interest, estimates from a lone measure will suffer from attenuation bias. The primary strategy to address this is to 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.

In this approach, E_k^* is a latent variable for economic conditions that affects changes in mortality rates according to:

$$\Delta M_k = \beta \Delta E_k^* + \boldsymbol{X}_{k0}\gamma_1 + \Delta \boldsymbol{X}_k \gamma_2 + \varepsilon_k. \quad (7)$$

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:

$$\Delta E_{kj} = \rho_j \Delta E_{kj}^* + \mu_{kj}. \quad (8)$$

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.[11]

[11] Alternative approaches including instrumental variables estimates and factor or principal component analyses require zero covariances. 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 $var(\mu_1)$.

Equations (7) and (8) cannot be directly estimated, since E^* is unobserved, but Lubotsky and Wittenberg (LW) show that attenuation bias can be minimized by simultaneously including all of the economic proxies in the model in the regression model:

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

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

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

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.[12] 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.

As an alternative, I address the issue of attenuation bias through a series of instrumental variables (IV) models, estimated by generalized methods of moments (GMM) to increase efficiency with heteroskedastic errors, where each of the economic proxies is instrumented by the other four. These are not the primary estimates for two reasons. First, the IV procedure assumes that the error terms, μ_{kj}, for the individual proxies in equation (8), are uncorrelated with each other. This is unlikely and implies that the IV estimates could be biased either upwards or downwards. Second, the estimates may vary sharply depending on which of the economic proxies is instrumented for.

[12] For these estimates, I "reverse code" the standardized changes in median household incomes and home prices (by switching the sign on the variables) so that positive coefficients on all of the economic proxies indicate that deteriorating economic conditions raise the growth rate of drug deaths.

Robust standard errors, clustered at the commuter zone level, are displayed on the tables.[13] All analyses was conducted using STATA Statistical Software: Release 15 (StataCorp 2017).

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 drug categories.[14] 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 models were first estimated for the sample of fatal overdoses with at least one drug specified on the death certificate. 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

[13] Clustering is at the commuter zone this is the level of the observations on the import exposure variable, as discussed below.
[14] 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).

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 affect mortality rates and are correlated with ΔE, 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).

Some additional notation is useful for describing the method. Define β^o and R^o as the coefficient on E and the R-squared from a "short" regression of equation (3), 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. Let R_{max} be the R-squared that would be obtained from a hypothetical regression that includes 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. R_{max} will be less than one if the dependent variable is measured with error.[15] Finally, δ measures the relative importance of selection of observables and unobservables: δ=1 implies the two are equally important; δ<1 indicates that selection on observables is more important.[16]

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

$$\beta^* \approx \tilde{\beta} - \delta(\beta^o - \tilde{\beta})\left(\frac{R_{max}-\tilde{R}}{\tilde{R}-R^o}\right). \quad (11)$$

[15] For instance, this will occur if there is misclassification in the cause of death or drugs involved in fatal overdoses.
[16] Specifically, defining σ_{XE} as the covariance between $\boldsymbol{X}$ and $\Delta\boldsymbol{E}$ and 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 $R^o - \tilde{R}$. Verbally, the difference between β^* and $\tilde{\beta}$ increases as selection on unobservables becomes more important, the difference between the observed R-squared (from the long regression) and maximum hypothetical model R-squared increases, the change in estimated treatment effects between the long and short regression models grows, and the change in R-squared between the short and long models falls. $\beta^o, \tilde{\beta}, R^o$ and $\tilde{R}$ are obtained by estimating the "long" and "short" regressions; values for δ and R_{max} must be assumed.

Manipulation of equation (11) also allows the relative importance of selection on unobservables that would eliminate the estimated treatment effect to be computed as:

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

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

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

2.5 Changes in the Drug Environment

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 mortality trends involving these drugs. 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.

A first set of estimates will examine the share of fatality rates accounted for by group g in county k at time t, S_{gkt}, according to:

(14) $$S_{gkt} = \boldsymbol{X_{kt}\beta} + \boldsymbol{F_k}\kappa + \boldsymbol{T_t}\boldsymbol{\tau} + \boldsymbol{\omega_{gkt}},$$

for $\boldsymbol{X_{kt}}$ a set of time-varying county characteristics that always includes the population share of group g,[17] $\boldsymbol{F_k}$ a vector of county fixed-effects accounting for all time-invariant determinants, $\boldsymbol{T_t}$ a vector of year dummy variables and $\boldsymbol{\omega_{gkt}}$ an error term.

The time coefficients, $\hat{\boldsymbol{\tau}}$, indicate secular changes in the share of drug deaths accounted for by the population group. However, they do not unambiguously indicate effects of the drug environment. Consider the decomposition $\boldsymbol{T_t} = \boldsymbol{D_t} + \boldsymbol{Y_t}$, where $\boldsymbol{D_t}$ indicates the (unobserved) drug environment and $\boldsymbol{Y_t}$ other time-varying determinants of mortality such as national economic conditions or changes in medical technologies. $\hat{\boldsymbol{\tau}}$ combines both effects. However, when there are abrupt breaks or reversals in the drug environment, these are likely to be the dominant determinant of changes in the time coefficients, so that the pattern of $\hat{\boldsymbol{\tau}}$ will be informative. An exception is if other factors change at precisely the same time and way as $\boldsymbol{D_t}$. To address this possibility, I conducted supplementary analyses for additional drug categories that experienced different breaks in mortality trends than those for opioid analgesics or illicit opioids.

A more formal analysis of whether trend breaks are statistically significant will be obtained by estimating spline specifications of:

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

where $Trend_t$ is a linear trend ranging from 0 in 1999 to 16 in 2015 and $POST$ is an additional trend spline equal to 0 in all initial sample years and then increasing by one unit per year after a specified time period. For instance, the growth in drug deaths is shown below to be dominated by opioid analgesics from 1999 to around 2010 but by illicit opioids thereafter. This is represented in (15) by setting $POST$ to 0 for all years up to 2010 and then increasing it from 1 to 5,

[17] 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}.

respectively, in 2011 through 2015. $\hat{\varphi}$ then shows the trend in the share of drug deaths accounted for by group g from 1999-2010, with $\hat{\varphi} + \hat{\pi}$ indicating the corresponding trend from 2011-2015. The statistical significance of $\hat{\pi}$ provides a direct test of the hypothesis that the group's mortality share changed starting around 2010.

I also 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). The basic regression model is:

$$M_{gkt} = \boldsymbol{F_k}\kappa + \boldsymbol{T_t}\boldsymbol{\tau} + (\boldsymbol{T_t} \times G_g)\boldsymbol{\theta} + \zeta_{gkt}, \tag{16}$$

where G is a treatment group dummy variable equal to zero for a reference group and one for a treatment group, and with ζ_{gkt} a regression disturbance. In (16), the sample includes observations for two (or more) population groups for each county and year, and controls are incorporated for county fixed-effects, general time effects and treatment group-time interactions. The coefficients of key interest, $\widehat{\boldsymbol{\theta}}$, show differences in the pattern of time effects for the treatment group relative to the reference group. Including time-varying county characteristics ($\boldsymbol{X_{kt}}$) will affect the estimated reference group time effects ($\hat{\boldsymbol{\tau}}$) but not the treatment group differentials ($\widehat{\boldsymbol{\theta}}$) focused on here and so that they are optional in the model.

Corresponding trend-spline models take the form:

$$M_{gkt} = \boldsymbol{F_k}\kappa + \boldsymbol{T_t}\boldsymbol{\tau} + Trend_{gt}\varphi + POST_{gt}\pi + \zeta_{gkt}, \tag{17}$$

where $Trend_{gt}$ is a treatment group linear time trend ranging from 0 in 1999 to 16 in 2015 for the "treatment" group and equal to 0 in all years for the reference group. $POST$ is an additional treatment group-specific trend set to 0 initially and then incremented by one unit per year for treatment group after a specified time period. $\hat{\boldsymbol{\tau}}$ 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 differential in later periods. This model will be run

separately for opioid analgesics and illicit opioids and, in supplementary estimates, for heroin, synthetic opioid, cocaine and methadone deaths, all of which have different timing of breaks or reversals in mortality trends.[18]

All variables for this portion of the analysis are defined at the county-level and so robust standard errors are clustered by county (rather than commuter zone).

3. **Data and Variables**

3.1 Dependent Variables

The outcomes examined in the analysis of "deaths of despair" are mortality rates due to drug poisonings, nondrug suicides and alcoholic liver disease (DSA deaths), as well as overdose deaths involving prescription and illicit opioids. Primary data come from death certificates provided on the *Multiple Cause of Death (MCOD)* files (Centers for Disease Control and Prevention 2017). Each certificate contains a single underlying cause of death, up to 20 additional causes, and demographic data. Information is 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. Permission was also obtained to use restricted geographic information on county of residence. The Institutional Review Board for the Social and Behavioral Sciences at the University of Virginia reviewed this project and determined that it did not involve the use of human subjects.

The analysis covers the universe of DSA fatalities to US residents between 1999 and 2015 (foreign residents dying in the US were excluded). The study begins in 1999 because ICD-

[18] 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.

9 codes, used earlier, are not fully comparable to ICD-10 categories (R. N. Anderson et al. 2001). Underlying cause of death (UCD) codes are used to classify the reason for death. Drug poisonings are defined as fatalities with ICD-10 codes: X40-X44, X60-X64, X85, Y10-Y14 or Y352. Nondrug suicides include ICD-10 codes X65-X84, Y87.0 and *U03; alcohol deaths refer to ICD-10 code K70.

For fatal overdoses, the death certificate lists one or more drug categories involved as immediate or contributory causes of death. These were included separately in the *MCOD* files as ICD-10 "T-codes" and are referred to below as drug involvement. The drug categories examined in the main analysis 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 (www.icd10data.com/ICD10CM/Codes/S00-T88). Synthetic opioids include several types of drugs, the most important being fentanyl. Fentanyl has legal uses but recent increases in deaths from this source 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 "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.[19]

3.2 Economic Indicators

Five county-level proxies for changes in economic conditions are included in the analysis of deaths of despair: 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. 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. These data are obtained from various issues of the Area Resource File/Area Health Resource File (*ARF)*, http://www.arf.hrsa.gov, and from *American FactFinder*

[19] 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 were 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/.

(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).[20]

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 differed slightly based on the available data. Specifically, for the starting (approximately 1990) period, unemployment rates are averaged for 1990-1992 and median incomes and poverty rates were averages of 1989 and 1993 values, and the instrumented import competition variable is from 1990-2000 using data from Autor, et al. (2013).

3.3 Additional Covariates

Most models control for additional covariates designed to capture the potential effects of confounding variables. Unless otherwise noted, each of these were available for each year during the analysis period. 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 was also included, using previously described

[20] 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.

information from the *ACS.*[21] The percentage of household headed by females in 2000 and 2010, and of foreign-born 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 provided from the same source and included to proxy the county's health infrastructure.[22]

The USDA ERS county level data sets, described above, also contain information on the 2013 "rural-urban" continuum code of the county, containing the following nine categories: metropolitan with population ≥1,000,000, 250,000 - 999,999 and <250,000 (three classifications); urban area with population ≥20,000 and 2,500 – 20,000 and adjacent to or not adjacent to a metropolitan area (four classifications); rural area with population <2,500 adjacent to or not adjacent to a metropolitan area (two classifications). In the regression models, dummy variables for eight of the classifications are included, 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).

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

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

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 boundaries that are consistent over the time period and with data available for all of the economic proxies.[23] The table shows actual values; however, as mentioned, the independent variables are standardized in the regressions. Also, while the table shows actual changes in median household incomes and home prices, these are reverse-coded (opposite signed) in the econometric models, so that positive coefficients always indicate that worsening economic conditions are associated with higher growth in mortality.

3.3 Analysis of Changes in the Drug Environment

The variables included when examining changes in the drug environment differ somewhat from those for analyzing the role of economic conditions. In this case, instead of a having a single observation per county (showing mortality rate changes from 1999-2015), this portion of the investigation includes panel data with 17 observations (one each for 1999-2015) per county. This allows county fixed-effects to be included, controlling for all time-invariant county characteristics and reducing somewhat the need for supplementary covariates. Several variables included in the analysis of medium-term changes in economic conditions are also inappropriate to here because there is no time-variation in the data (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

[23] 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.

results were generally not sensitive to the exact choice of the remaining covariates and the specific ones included in the primary models are described below. 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**

Before turning to the econometric estimates, I provide descriptive information on patterns of drug mortality over the 1999-2015 period. Figure 1 illustrates the changes in total drug death rates, suicide and alcohol mortality, as well as opioid analgesic and illicit opioid involved drug mortality rates. The overall drug fatality rate rose steadily, from 6.0 to 16.3 per 100,000 from 1999 to 2015, a 170 percent increase. Nondrug suicide death rates started out considerably higher (9.3 per 100,000 in 1999) but rose more slowly, reaching 12.1 per 100,000 in 2015. Alcohol deaths also increased relatively gradually (from 4.3 to 6.5 per 100,000). Conversely, opioid analgesic and illicit opioid death rates grew 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 rise 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 then considerably more rapidly thereafter, particularly from 2010 to 2015, where the mortality rate exploded from 2.6 to 7.4 per 100,000.

Figures 2 and 3 show corresponding patterns of drug and nondrug DSA mortality for subgroups stratified by sex, race/ethnicity, age and education. In both cases, death rates were always higher for males than females and for those without a college degree than for the college

educated. Whites had higher death rates and faster mortality growth from both sources towards the end of the sample period but drug mortality rates were similar for whites and blacks (but higher than for Hispanics or other nonwhites) in 1999, whereas nondrug DSA mortality rates were already higher for whites than nonwhites in that year. The age relationships were somewhat more complicated. Drug mortality rates rose at fairly similar rates for 20-39 and 40-59 year olds, and were somewhat higher for the latter group, which much smaller growth for >60 year olds. Conversely, alcohol/suicide deaths were much higher for 40-59 and >65 year olds than for younger persons in all years, with the sharpest trend increase for 40-59 year olds.

Figure 4 shows that illicit opioid death rates exploded for males after 2010, while growing much more slowly for females and that the particularly rapid rise in opioid analgesic (illicit opioid) death rates for whites, relative to nonwhites, occurred between 1999 and 2011 (after 2006). Increases in illicit opioid death rates were skewed towards relatively young adults (20-39 year olds), while those involving opioid analgesics fatalities particularly affected 40-59 year olds.

Appendix Figures A.1 through A.4 detail additional results for drug and nondrug DSA mortality for sex, race/ethnicity, age and education subsamples. In addition to the findings already described, they show larger sex differentials for nondrug than drug deaths and faster mortality rate growth for whites than nonwhites for all types of DSA deaths. As discussed, illicit opioid deaths skew younger than those due to opioid analgesics, particularly in the later years. Rates of nondrug suicides are fairly similar for age groups older than 20, although with the fastest growth over time for 40-59 year olds, while alcohol mortality is heavily concentrated among persons ≥40 and again among 40-59 year olds. These patterns raise initial doubts about

the possibility that a single set of economic determinants can explain these differential patterns of mortality rate increase.

5. Changes in Economic Conditions: Econometric Results

I next present econometric results examining the extent to which medium-run changes in county economic conditions predicted corresponding changes in DSA mortality rates. The first set of specifications shows models controlling for the proxies for economic conditions, but without supplementary covariates. Additional covariates, a series of robustness checks are 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 for the economic proxies where the dependent variables are growth from 1999-2015 in mortality rates due to all drugs, opioid analgesic and illicit opioid involved deaths, all DSA and suicide/alcohol fatalities.[24] These models do not include controls for potential confounding factors. As mentioned, changes in median household incomes and home prices were reverse-coded so that positive coefficients always imply that worse economic performance is associated with faster increases in mortality. Also, all regressors were standardized so that coefficients show estimated effects of a one-standard deviation change in the explanatory variable. The top panel table shows results where the economic measures have been included separately, with every cell representing the results of a different regression. In the second panel, the five economic proxies have been included simultaneously, and each column

[24] Appendix Table B.1 summarizes separate estimates for nondrug suicide and alcohol deaths for many of the models discussed below. The estimated effects of economic conditions are small in all cases.

presents/ findings from a single regression. 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.

When controlled for separately, the economic proxy coefficients are positive for all types of drug mortality 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-involved drug death rate. Since the standard deviations for these two outcomes are 10.37 and 3.58 per 100,000, these estimates suggest that 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. Conversely, the estimated effects are smaller and, except for median home prices, statistically insignificant for suicide/alcohol deaths, indicating that economic factors play little role. Also, for this reason, the coefficient estimates are smaller in relative terms for all DSA deaths than for drug mortality.

Including the five economic proxies simultaneously substantially attenuates the estimated effects of individual economic proxies in virtually all cases (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 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 0.011 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.[25]

The third panel of Table 1 shows multiple proxy estimates, obtained using the Lubotsky/Wittenberg procedure, 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, but just 15% of the change in suicide/alcohol fatality rates. 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 models where the dependent variable is the change in drug mortality rates from 1999-2015 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.

[25] I also estimated models that controlled for county level Gini coefficients in 2000 or changes from 2000-2010 as an additional proxy for economic conditions, 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.

Column (b) adds to this the set of 1999 county characteristics ($\boldsymbol{X_{1999}}$) and changes in these characteristics from 1999-2015 ($\Delta\boldsymbol{X}$), while 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% (2.95 to 0.43), while instead using the instrumented changes, based on census division trends, attenuates it by 73% (to 0.79). The implies that most of the observed relationship between changes in mortality rates and economic conditions reflects confounding factors. In model (b), "deaths of despair" are estimated to explain 5 percent of the rise in drug mortality, and 9 percent in column (c), compared to 33 percent in specification (a). The MP estimates do remain statistically significant, suggesting that changes in economic factors may continue to play some role but explain less than 10% of the rise in drug death rates.[26] The most important confounding county characteristics are sex and race/ethnicity differences, as well as the shares of female-headed households and foreign born persons. Together, these are sufficient to account for all of the attenuation in the MP estimate in the model controlling for $\boldsymbol{X_{1999}}$ and $\Delta\boldsymbol{X}$, and 87% of that when including covariates for $\boldsymbol{X_{1999}}$ and $\Delta\boldsymbol{X^I}$ (see Appendix Table A.3 for details). The age structure of the county also plays some role but the remaining supplementary covariates, particularly urban-rural status, the medical infrastructure variables and the two drug policies are much less important.

The first panel of Table 3 repeats the MP estimate and percentage change in drug death rates accounted for by economic factors. The next four panels show corresponding estimates for opioid analgesic, illicit opioid, all DSA and nondrug DSA mortality rates. Comparing results for models (b) and (c) to (a) indicates that at least 73 percent of the original correlation between

[26] I estimated drug mortality models with controls additional controls included for 1999 levels of the economic proxies. These findings, summarized in Table B.2, indicate slightly higher explanatory power of changes in economic conditions – 9% and 10% of the total mortality change in models with controls for ΔX and ΔX^I – that were offset by the 1999 levels being responsible for -3% and -9% of the change.

economic conditions and various types of drug mortality growth is due to confounding factors, with more than 100 percent accounted for in some models, and even greater attenuation for the nondrug DSA deaths. The estimated change in mortality rates accounted for by worsening economic conditions ranges from 5 to 7 percent for opioid analgesics, -2 to 5 percent for illicit opioids, and with no effect or a negative impact for non-drug suicide/alcohol deaths. These findings indicate that "deaths of despair" never account for more than one-tenth of the rise in mortality and generally considerably less.

5.3 Robustness Checks

I tested the robustness of the results to several changes in specifications, estimation methods and samples. Table 4 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.[27] The explanatory power of economic conditions is generally of similar magnitude when using reported rather than corrected opioid mortality rates, with considerable sensitivity to the choice of specification for illicit opioids. Finally, the percentage of mortality rate changes explained is always less when controlling for 1990-2000 rather than 1999-

[27] Standard deviations on the dependent variables are usually 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 deaths involving illicit opioids.

2015 changes in economic conditions, and are often negative. Overall, these results confirm the overall conclusion that economic conditions explain little of the rise in mortality rates.

Next, I addressed examined the results from 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 Table 5. Appendix Table A.4 shows results after controlling for $\Delta \boldsymbol{X^I}$ rather than $\Delta \boldsymbol{X}$. Estimation is by generalized method of moments (GMM), to provide efficient estimates with heteroskedastic errors.

Generally, the IV and multiple proxy estimates (repeated on the bottom panel of the table) are of roughly similar magnitude, although the IV results are sometimes somewhat greater when instrumented rather than actual changes in the covariates are controlled for. For instance, for drug mortality, the IV estimates for the poverty, household income, home price and unemployment proxies in Table 5 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 imply that the increase in opioid analgesic and illicit opioid rates explained by economic conditions is similar to that 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 estimates for growth in suicide/alcohol mortality growth are always negative.

The one exception is for import exposure, where the IV coefficients are often quite large (although not statistically significant in Table 5). However, as mentioned, this explanatory

variable is barely correlated with the other economic proxies (see Table A.2) and so is likely to suffer from a "weak instruments" problem (Bound, Jaeger, and Baker 1995; Staiger and Stock 1997).[28] 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 A.5 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 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.[29] Also, import exposure continues to be measured from 1999-2011 in all models. In any case, Table A.5 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 explained for the shorter 2006-2015 period.

[28] 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.

[29] 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 larger) counties.

5.4 Subsamples

Table 6 shows the multiple proxy estimates, associated standard errors and percent of the change in mortality explained for population sub-groups stratified by sex, race/ethnicity and education, with additional results for 20-59 year olds and non-Hispanic whites aged 20-59 and 45-54. Growth in drug mortality rates, of all types examined, increased relatively more for whites, 20-59 year olds, whites aged 45-54 and 20-59 and those without a college education than for their counterparts (see Appendix Table A.6). Declining economic conditions were often (although not always) also associated with the largest *absolute* increases in fatality rates for these groups and explained a greater percentage share of the mortality rate change for some of them (e.g. whites) but not others (e.g. the non-college educated). For example, overall drug mortality rates grew by 13.9 per 100,000 for whites versus 4.8 per 100,000 for nonwhites from 1999-2015. The multiple proxy estimates differed by a similar proportion (0.8 to 1.8 per 100,000 for whites versus 0.2 to 0.8 per 100,000 for nonwhites) and economic conditions explained an even larger share of the change for whites (7 to 17 percent versus 2 to 6 percent). However, this was not always the case. For instance, drug mortality grew faster for men than women, and the absolute size of the economic effect is generally larger for them, but the share of the mortality growth explained is usually similar or smaller.

Table 7 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 deaths of despair argument is more relevant to these locations. To the contrary, the explanatory power of changing economic conditions is almost highest for metropolitan counties although, even for these, it

never accounts for more than 15 percent of the change in mortality. 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 analysis to this point treats the vector of supplemental covariates (**$\boldsymbol{X}$** and ΔX or ΔX^I**)** as being sufficiently comprehensive to account for all relevant omitted variables, such that cov(E_k, ε_k) = 0. This is a fairly strong assumption. The methods developed by Oster (2016) are next implemented to examine how the results change if there is 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 the "short" and "long" regression of equation (1), 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 equal importance of selection on observables and unobservables. However, in this analysis it seems likely that the most important aspects of the selection process will have been accounted for. I therefore provide results assuming that δ = 0.5, implying that selection on observables is twice as important as that on unobservables. Choosing a higher δ value would further reduce the magnitude of the estimated treatment effect. For the base model, I also 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^*, the relative importance of unobservables versus observables, at which the estimated treatment effect would be zero (with $R_{max} = 0.75$), as well as for R^*_{max} value that would give a zero-treatment effect (with δ = 0.5). The findings are summarized in Table 8. Column (a) shows the MP estimate without accounting for selection on unobservables. Columns (b) and (c) display the

section-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 from Table 8 is that even small amounts of remaining selection on unobservables are sufficient to eliminate any estimated 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 an $R_{max} > 0.5$ would be sufficient to eliminate the effect. Thus, it seems quite likely that medium-term changes in county-level economic conditions are completely unrelated to growth in drug or non-drug DSA mortality rates.

6. **Changes in the Drug Environment**

I next examine whether changes in the drug environment, rather than in economic conditions, are the 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 the start of the analysis period through around 2010 and then with these flattening but replaced by explosive growth in fatalities involving illicit opioids. If economic (or social) factors are of primary importance, this change would not have affected *who* would die of fatal overdoses only *which drugs* would cause the fatalities. 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 data from the 2016 National Survey on Drug Use and Health indicates that males and young adults are much more likely than their counterparts to use and abuse illicit drugs, with much smaller differences (sometimes in the reverse direction) for legal pain relievers or sedatives (Substance Abuse and Mental Health

Services Administration 2017). These patterns imply that 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 reflected increases in opioid analgesic mortality), the drug environment hypothesis provides a strong prediction that males and young adults should constitute a higher share of all drug deaths and experience particularly rapid growth in mortality rates in more recent years (as illicit opioids have become the dominant cause of rising drug fatalities).

6.1 Overall Overdose Death Rates as Proxies of the Drug Environment

Differential trends in overall opioid analgesic and illicit opioid mortality rates (and other drugs in the supplementary analysis) are used to proxy changes in the drug environment. These are imperfect measures. Deaths depend on the quantity of drugs consumed and the fatality risk from a given use. The latter depends in part on drug purity (or lack thereof) and the availability of risk mitigating technologies (e.g. naloxone). The former reflects the interaction of supply and demand for the drugs. However, extremely large consumption increases over short periods of time will almost certainly primarily reflect supply-side factors, since it seems implausible the underlying components of demand (e.g. health problems causing pain) will exhibit sudden dramatic changes. Conversely, supply-side factors change dramatically and abruptly as technologies evolve, for instance, following the introduction of OxyContin in 1996.

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 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 zip-code level from 2000-2015 and converted to annual total per capita grams of morphine milligram equivalents (MME) in the county for seven major opioids.[30] County-level opioid analgesic death rates per 100,000 were then regressed on grams of MME per capita in models that also included county-fixed effects.[31] 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 consumption data are unavailable for illicit opioids but there is again good reason to believe that overdose deaths provide a reasonable estimate of environmental 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 fatal heroin overdoses (see Appendix Table C.1). Fentanyl reports to the National Forensic Laboratory Information System 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

[30] The ARCOS data are less complete prior to 2000 so the analysis starts in that year rather than in 1999. See www.deadiversion.usdoj.gov/arcos/index.html for further information on the ARCOS data. The seven opioids are: Oxycodone, Meperidine (Pethidine), Hydromorphone, Hydrocodone, Morphine, Fentanyl and Methadone. They were converted to MMEs using conversion factors obtained from: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-Aug-2017.pdf.
[31] The regressions contain 50,105 observations from 3,140 counties. Observations were weighted by 2015 county populations.

Opioid analgesic death rates rose rapidly from 1999-2010 and remained relatively stable thereafter, whereas illicit opioid mortality rates changed little from 1999-2005, then began to rise modestly before exploding after 2010 (see Figure 1). Fatality rates involving other drugs also changed over the period but not enough to affect the dominance of these trends. This is illustrated in Figure 5, 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 in 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 also rise after 2010. The predictions are less clear for the 1999-2010 period, although fairly rapid growth in opioid analgesic deaths for persons in their 40s and 50s, documented in Figure 4, suggests that their share of drug fatalities may be rising during this time-span.

Figure 6 confirms these patterns. It shows estimated year coefficients from regressions of equation (14), of the group's share of county-level drug deaths on vectors of year and county dummy variables, population share and the three measures of county economic conditions for which annual data are available (unemployment rates, poverty percentages and median household incomes).[32] The male share of drug deaths declined around 5 percentage points from 1999-2010 and then recovered by approximately 3 percentage 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.

[32] After including county fixed-effects, the estimates were not sensitive to the inclusion of other supplementary regressors with available annual data.

Nevertheless, as anticipated, the share of fatal overdoses involving 20-39 year olds (especially males) declined rapidly from 1999 to 2009 or 2010, and then increased substantially thereafter while the pattern was reversed for 40-59 year olds overall and 40-59 year old women.[33]

Table 9 provides more formal tests of breaks in trend by showing the results of equation (15) estimated where $TREND$ indicates the initial annual change in group shares of the specified type of drug deaths, $POST$ introduces a spline into the trend with a knot at 2010, and the intercept shows the average group share of drug deaths in 1999. The table shows that there is a break in the initial trend for all groups, except 40-59 year old males after 2010.

The age-related difference is particularly dramatic. For example, 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 (when opioid analgesics were the driver of the fatal drug epidemic) and then rose by 0.86 (1.35 - 0.49) points annually thereafter (when illicit opioids came to dominate the growth in overdose fatalities). The predicted proportion of deaths involving 40-59 year olds increased by 0.34 percentage points per year initially and then declined by 1.25 points per annum after 2010. The male share of drug deaths declined 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 that 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

[33] No clear pattern of trends was predicted or found for 20-39 year old females or 40-59 year old males, given the potentially offsetting effects of age and sex on legal versus illicit drug use (see Appendix Figure B.1).

Finally, I directly examined whether sex- and age-specific opioid analgesic and illicit opioid mortality rates (and those due to other narcotics in the supplementary analysis) varied over time in ways consistent with changes in the drug environment. To reiterate, the strongest prediction is that illicit opioid mortality rates of males and younger adults will rise rapidly late in the sample period, since these groups are the heaviest users of these drugs, which dominated growth in the fatal overdose epidemic after 2010.

Figure 7 shows the regression-adjusted differences in the mortality rate changes for males, relative to females. Figure 8 supplies corresponding information for 20-39 year olds relative to 40-59 year olds. These are obtained from estimates of equation (16). Solid lines show the treatment group differential year effects and dotted lines indicate 95 percent confidence intervals. Vertical lines show 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 7 and 8 align closely with predictions of the drug environment hypothesis. Most importantly, illicit opioid deaths involving males and 20-39 year olds, compared to their counterparts, begin to rise rapidly around 2010 or 2011, which coincides with the timing of the explosive growth in overall fatality rates from this source. There is also some indication of modest increases after 2005, particularly for males, consistent with the initial (much slower) growth in illicit opioid deaths. Male opioid analgesic death rates rise relative to those for 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 total rise in male illicit opioid death rates. There was no evidence of a trend break in relative rates of opioid analgesic fatality rates for 20-39 year olds relative to those aged 40-59.

These statistical significance of these patterns was confirmed from estimates of equation (17), where treatment versus reference group trend spline models were estimated knots in 2011 for opioid analgesics and 2010 for illicit opioids. Illicit opioid death rates initially grew marginally faster for males and young adults year olds than for their counterparts – by 0.03 per 100,000 annually in both cases. However, towards the end of the sample period, the treatment group relative mortality rates rose dramatically faster – by 0.91 per 100,000 yearly for males and 0.87 per 100,000 for 20-39 year olds. The differences were less dramatic for opioid analgesic deaths, with some relative trend reductions for the males and young adults late in the analysis period. However, these were much smaller than the increases for illicit opioid deaths providing further evidence that the composition of overdose deaths changed.

Appendix C details the results of supplementary investigation of additional drug types: illicit opioid death rates were decomposed into heroin and synthetic opioid (primarily fentanyl) rates and with additional analysis of cocaine and methadone involved drug deaths. Each of these categories exhibited different trends. Heroin death rates changed little from 1999-2006, rose modestly from 2006-2010 and quickly from 2010-2015. Synthetic opioid mortality increased slowly from 1999-2013 and then grew 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 increased rose dramatically from 1999-2007 and then declined.

Results of the 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, began to increase in 2007 and 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. Cocaine and

Methadone differentials rose for men from 1999 through 2006 or 2007 and then fell, with a subsequent increase for male cocaine deaths starting in 2013. There were no age-related differences in heroin-involved mortality rates from 1999-2006, but rates for 20-39 year olds, relative to 40-59 year olds, increased slowly from 2007-2010 and more quickly thereafter. Age differentials in synthetic opioid death rates were constant prior to 2013, but with dramatic growth for young adults thereafter. 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 nosier but generally trending upwards prior to 2007 and then falling.

7. **Discussion**

Counties experiencing economic decline from 1999-2015 had experienced larger increases in drug, suicide or alcohol mortality than those with more robust economic growth. However, the relationship was fairly weak and mostly due to county characteristics spuriously correlated with changes in economic conditions. After controlling for these confounding factors, less than one-tenth of the increase in drug mortality rates was explained by changes in economic factors and none of those due to nondrug suicides or alcoholic liver disease. Moreover, even modest amounts of selection on unobservables would be sufficient to completely eliminate any remaining association.

These results suggest that the “deaths of despair” framing, while provocative, probably do not explain the main sources of the fatal drug epidemic and imply that efforts to improve economic conditions in distressed locations, while desirable for other reasons, are unlikely to yield significant reductions in drug mortality. Such results probably should not be surprising since drug fatalities increased substantially – including a rapid acceleration of illicit opioid

deaths – after the end of the Great Recession (i.e. subsequent to 2009), when economic performance considerably improved.

Conversely, the data provide more support for the hypothesis that changes in the drug environment have played a key role. During the first decade of the 21st century, rising drug mortality was largely driven by increases in opioid analgesic mortality, but with more recent growth has largely being due to deaths involving heroin and fentanyl. This shift was accompanied by a change in the composition of deaths, particularly during the period of rapid growth in illicit opioid mortality, which has been concentrated among males and younger adults. These findings are consistent with the idea that population subgroups face differential risks that depend on specific aspects of the public health environment related to drugs.

Efforts to address the fatal drug epidemic will therefore probably have the largest impact if focused on such environmental factors, including primary prevention and treatment of drug problems once they emerge. To date, considerable 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 2015; 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 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 at 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 2017). 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 recent evidence that graduates of highly ranked medical schools or in specialties receiving specific training prescribe fewer opioids than their counterparts (Schnell and Currie 2017). 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 certainly important. 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	Suicide/Alcohol
Measures Included Separately					
Δ in Poverty Rate	2.205*** (0.560)	0.798*** (0.242)	1.334*** (0.446)	2.320*** (0.752)	0.115 (0.306)
Δ in Median Household Income	2.068*** (0.546)	0.679*** (0.254)	1.136** (0.496)	2.515*** (0.773)	0.447 (0.351)
Δ in Median Home Price	2.289*** (0.649)	0.908** (0.354)	1.158* (0.627)	2.840*** (0.680)	0.551** (0.255)
Δ in Unemployment Rate	1.370*** (0.464)	0.295** (0.131)	1.069*** (0.253)	1.144 (0.765)	-0.226 (0.356)
Δ in Import Exposure	0.572 (0.414)	0.398** (0.182)	0.168 (0.328)	0.570 (0.511)	-0.002 (0.196)
Measures Included Together					
Δ in Poverty Rate	1.102** (0.515)	0.519** (0.259)	0.782* (0.403)	0.793 (0.599)	-0.309 (0.228)
Δ in Median Household Income	0.206 (0.671)	-0.097 (0.329)	-0.043 (0.543)	0.751 (0.951)	0.545 (0.386)
Δ in Median Home Price	1.465* (0.805)	0.710* (0.409)	0.626 (0.668)	1.959** (0.883)	0.494* (0.255)
Δ in Unemployment Rate	0.307 (0.452)	-0.143 (0.213)	0.536 (0.365)	-0.146 (0.669)	-0.453 (0.301)
Δ in Import Exposure	0.212 (0.392)	0.269 (0.177)	-0.065 (0.343)	0.214 (0.470)	0.002 (0.183)
R^2	0.082	0.059	0.051	0.060	0.011
P-Value	<0.001	<0.001	<0.001	<0.001	0.019
Multiple Proxy Estimate	2.949*** (0.641)	1.164*** (0.349)	1.710*** (0.552)	3.256*** (0.747)	1.057*** (0.297)
% of Total Δ Explained	32.5%	27.6%	25.6%	26.3%	14.4%
Dep. Var. Mean [SD]	10.37 [9.06]	3.58 [4.22]	6.27 [6.67]	15.39 [12.38]	5.02 [7.35]

Note: In the top panel, each cell 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). In the second panel, all five measures of economic conditions are controlled for simultaneously. 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 are correlated 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 cases where the ICD underlying cause of death code is X40-X44, X60-X64, X85, Y10-Y14 or Y352. Opioid Analgesic and illicit opioids refer to deaths involving ICD-10 codes T40.2 and T40.1 or T40.4 respectively. DSA indicates deaths from drug poisoning, nondrug suicides or alcoholic liver disease (alcohol) and nondrug to deaths from 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 simultaneously included and are estimated using the methods discussed in the text. Robust standard errors clustered at the commuter zone level are in parentheses. 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***
	(0.641)	(0.218)	(0.205)
% 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. The sample mean change in the weighted drug poisoning rate is 10.34 per 100,000 and the standard deviation is 9.06 per 100,000. $\mathbf{X}_{1999}$ 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 2000, 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 changes in these variables, from 1999-2015, occurring at the census division level (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>			
Multiple Proxy Estimate	2.949*** (0.641)	0.431** (0.218)	0.792*** (0.205)
% of Total Δ Explained	32.5%	4.8%	8.7%
<u>Opioid Analgesics</u>			
Multiple Proxy Estimate	1.164*** (0.349)	0.197 (0.136)	0.306*** (0.105)
% of Total Δ Explained	27.6%	4.7%	7.3%
<u>Illicit Opioids</u>			
Multiple Proxy Estimate	1.710*** (0.552)	0.305** (0.154)	-0.101** (0.042)
% of Total Δ Explained	25.6%	4.6%	-1.5%
<u>DSA</u>			
Multiple Proxy Estimate	3.256*** (0.747)	-0.343* (0.183)	0.351*** (0.125)
% of Total Δ Explained	26.3%	-2.8%	2.8%
<u>Suicide/Alcohol</u>			
Multiple Proxy Estimate	1.057*** (0.297)	-0.533*** (0.135)	-0.053*** (0.015)
% of Total Δ Explained	14.4%	-7.3%	-0.7%
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 Effect of Economic Conditions on 1999-2015 Changes in Various Death Rates, Robustness Checks

	All Drugs		Opioid Analgesics		Illicit Opioids		DSA		Suicide/Alcohol	
	(a)	(b)	(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***	-0.533***	-0.053***
	(0.218)	(0.205)	(0.136)	(0.105)	(0.154)	(0.042)	(0.183)	(0.125)	(0.135)	(0.015)
Dependent Var. Mean [SD]	10.37 [9.06]		3.58 [4.22]		6.27 [6.67]		15.39 [12.38]		5.02 [7.35]	
% of Total Δ Explained	4.8%	8.7%	4.7%	7.3%	4.6%	-1.5%	-2.8%	2.8%	-7.3%	-0.7%
Unweighted										
Multiple Proxy Estimate	1.208***	0.503***	0.344***	0.301***	0.740***	-0.004***	1.240***	-0.073***	0.852***	0.224***
	(0.304)	(0.167)	(0.119)	(0.096)	(0.177)	(0.001)	(0.306)	(0.025)	(0.251)	(0.079)
Dependent Var. Mean [SD]	10.87 [13.08]		4.42 [7.05]		4.85 [7.42]		18.20 [23.93]		7.33 [19.88]	
% of Total Δ Explained	9.2%	3.8%	4.9%	4.3%	10.0%	-0.1%	5.2%	-0.3%	4.3%	1.1%
Unadjusted Mortality Rates										
Multiple Proxy Estimate			0.217*	0.330***	0.198*	-0.270***				
			(0.131)	(0.104)	(0.103)	(0.086)				
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***	0.044	-0.042**
	(0.227)	(0.058)	(0.009)	(0.032)	(0.252)	(0.096)	(0.038)	(0.132)	(0.032)	(0.019)
% of Total Δ Explained	-10.9%	2.4%	-0.4%	1.0%	-16.9%	-4.7%	-1.2%	3.5%	0.6%	-0.6%
Additional Controls (ΔX's)	Δ**X**	Δ**X**^{I}	Δ**X**	Δ**X**^{I}	Δ**X**	Δ**X**^{I}	Δ**X**	Δ**X**^{I}	Δ**X**	Δ**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 repeats the results shown in Table 2. The second panel shows estimates from corresponding models 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 changes. *** p<0.01, ** p<0.05, * p<0.1

Table 5: GMM (IV) Estimates of Effects of Economic Conditions on Changes in Drug Death Rates, 1999-2015

Economic Proxy	All Drugs	Opioid Analgesics	Illicit Opioids	All DSA	Suicide/Alcohol
GMM Estimates					
Δ in Poverty Rate	-0.038 (0.559)	0.186 (0.303)	-0.414 (0.494)	-0.659 (0.698)	-0.697** (0.333)
Δ in Median Household Income	0.853 (0.625)	0.281 (0.292)	0.287 (0.538)	0.200 (0.694)	-0.797** (0.344)
Δ in Median Home Price	0.232 (0.666)	0.320 (0.354)	-0.276 (0.679)	-0.378 (0.791)	-0.615 (0.391)
Δ in Unemployment Rate	0.358 (0.966)	0.489 (0.473)	-0.009 (0.795)	-0.009 (1.156)	-0.730 (0.610)
Δ in Import Exposure	2.263 (2.067)	0.709 (0.817)	1.149 (1.479)	1.790 (2.282)	-0.757 (1.181)
Multiple Proxy Estimate	0.431** (0.218)	0.197 (0.136)	0.305** (0.154)	-0.343* (0.183)	-0.533*** (0.135)

Note: See notes on Tables 1 through 3. Each cell in the top panel of the table shows results of a different generalized method of moments estimate where the specific proxy 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. *** p<0.01, ** p<0.05, * p<0.1

Table 6: Estimated Effect of Economic Conditions on 1999-2015 Changes in Various Death Rates for Population Subgroups

Group	All Drugs		Opioid Analgesics		Illicit Opioids		DSA		Suicide/Alcohol	
	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
All	0.431**	0.792***	0.197	0.306***	0.305**	-0.101**	-0.343*	0.351***	-0.533***	-0.053***
	(0.218)	(0.205)	(0.136)	(0.105)	(0.154)	(0.042)	(0.183)	(0.125)	(0.135)	(0.015)
	4.8%	**8.7%**	**4.7%**	**7.3%**	**4.6%**	**-1.5%**	**-2.8%**	**2.8%**	**-7.3%**	**-0.7%**
Males	0.043**	1.088***	0.191*	0.375***	-0.064***	-0.366***	-0.971***	0.419***	-0.964***	0.002***
	(0.018)	(0.313)	(0.102)	(0.124)	(0.025)	(0.111)	(0.362)	(0.160)	(0.283)	(0.001)
	0.3%	**8.6%**	**3.5%**	**6.8%**	**-0.6%**	**-3.6%**	**-5.2%**	**2.2%**	**-7.6%**	**0.0%**
Females	0.756***	0.520***	0.188**	0.235**	0.682***	0.173**	0.257	0.385***	-0.157***	-0.047**
	(0.272)	(0.185)	(0.086)	(0.091)	(0.187)	(0.082)	(0.193)	(0.144)	(0.043)	(0.020)
	9.6%	**6.6%**	**4.4%**	**5.5%**	**16.0%**	**4.1%**	**2.5%**	**3.8%**	**-2.7%**	**-0.8%**
Whites	0.751**	1.778***	0.408***	0.840***	0.252**	0.265***	0.680***	2.432***	-0.094**	0.337**
	(0.294)	(0.346)	(0.151)	(0.154)	(0.112)	(0.081)	(0.222)	(0.482)	(0.043)	(0.139)
	7.2%	**17.1%**	**8.4%**	**17.3%**	**3.3%**	**3.4%**	**4.8%**	**17.2%**	**-1.1%**	**3.8%**
Nonwhite/Hispanics	0.207***	0.767***	0.015	0.180**	0.040**	-0.082**	1.357***	2.423***	-1.735***	-1.506***
	(0.078)	(0.269)	(0.010)	(0.071)	(0.018)	(0.040)	(0.314)	(0.574)	(0.402)	(0.382)
	1.7%	**6.1%**	**0.2%**	**2.6%**	**0.5%**	**1.1%**	**6.1%**	**10.9%**	**-9.6%**	**-8.3%**
20-59 Years Old	0.544***	1.409***	0.228	0.561***	0.528***	-0.057***	-0.653***	0.656*	-0.704***	0.001***
	(0.208)	(0.439)	(0.149)	(0.172)	(0.192)	(0.020)	(0.213)	(0.338)	(0.180)	(0.000)
	3.2%	**8.5%**	**3.0%**	**7.4%**	**4.4%**	**-0.5%**	**-3.1%**	**3.1%**	**-6.2%**	**0.0%**
Whites: Aged 20-59	1.475***	3.488***	0.622***	1.520***	0.586***	0.842***	0.830***	3.594***	-0.148**	0.435
	(0.464)	(0.658)	(0.233)	(0.275)	(0.217)	(0.242)	(0.253)	(0.761)	(0.071)	(0.344)
	7.7%	**18.3%**	**7.1%**	**17.4%**	**4.1%**	**6.0%**	**3.4%**	**14.8%**	**-1.1%**	**3.2%**
Whites: Aged 45-54	0.943	3.159***	0.917**	1.898***	0.400**	0.517**	0.604	3.048***	1.498**	1.606***
	(0.645)	(0.907)	(0.434)	(0.511)	(0.185)	(0.202)	(0.439)	(1.116)	(0.604)	(0.549)
	3.4%	**11.4%**	**6.3%**	**13.0%**	**2.6%**	**3.3%**	**1.6%**	**7.9%**	**5.6%**	**6.0%**
≤ High School	0.962**	0.650***	0.589***	0.371***	0.352**	-1.103***	0.269*	-0.026***	-0.744**	-0.042***
	(0.438)	(0.200)	(0.214)	(0.116)	(0.152)	(0.282)	(0.153)	(0.010)	(0.291)	(0.015)
	4.2%	**2.9%**	**6.0%**	**3.8%**	**2.0%**	**-6.3%**	**0.9%**	**-0.1%**	**-4.1%**	**-0.2%**
Some College	0.660**	0.546**	0.381**	0.112	0.254**	0.004***	-0.242	-0.092	0.020	0.501
	(0.335)	(0.242)	(0.191)	(0.092)	(0.112)	(0.002)	(0.242)	(0.131)	(0.013)	(0.317)
	5.3%	**4.4%**	**6.0%**	**1.8%**	**3.4%**	**0.1%**	**-1.2%**	**-0.5%**	**0.1%**	**3.2%**
College Graduate	0.334**	0.762*	0.019	0.248*	0.080**	0.129**	0.024*	1.391***	0.155**	1.283***
	(0.138)	(0.422)	(0.012)	(0.132)	(0.037)	(0.058)	(0.012)	(0.486)	(0.077)	(0.421)
	3.0%	**6.7%**	**0.3%**	**4.5%**	**1.6%**	**2.6%**	**0.1%**	**6.5%**	**0.8%**	**6.9%**
Other Controls	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{\mathbf{I}}$	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{\mathbf{I}}$	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{\mathbf{I}}$	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{\mathbf{I}}$	$\Delta\mathbf{X}$	$\Delta\mathbf{X}^{\mathbf{I}}$

Note: See notes on Tables 1 through 3. Top entry for each group shows the multiple proxy estimate of the effect of economic conditions on changes in the specified death rate, per 100,000 from 1999-2015. Robust standard errors clustered by commuter zone are in parentheses. All models include 1999 supplementary covariates as well as changes in either actual or instrumented values from 1999-2015. The percentage of the total change in specified drug mortality rate growth explained by economic conditions is in bold. *** p<0.01, ** p<0.05, * p<0.1

Table 7: Estimated Effect of Economic Conditions on 1999-2015 Changes in Various Death Rates, By Type of County

	All Drugs		Opioid Analgesics		Illicit Opioids		DSA		Suicide/Alcohol	
	(a)	(b)	(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***	-0.701***	-0.022***
	(0.227)	(0.314)	(0.121)	(0.122)	(0.131)	(0.002)	(0.175)	(0.260)	(0.173)	(0.006)
Dependent Var. Mean [SD]	10.08 [8.51]		3.34 [3.57]		6.44 [6.68]		14.62 [10.82]		4.55 [5.30]	
% of Total Δ Explained	6.4%	14.2%	10.5%	14.5%	5.3%	0.1%	-4.1%	6.5%	-13.2%	-0.4%
Urban Counties										
Multiple Proxy Estimate	0.393**	-0.018*	0.176*	0.509***	0.676***	-0.345***	-0.131***	0.358**	-0.470***	0.305**
	(0.186)	(0.009)	(0.091)	(0.185)	(0.189)	(0.133)	(0.043)	(0.168)	(0.155)	(0.144)
Dependent Var. Mean [SD]	12.35 [10.55]		4.86 [5.89]		5.70 [6.44]		20.13 [15.91]		7.78 [11.34]	
% of Total Δ Explained	3.7%	-0.2%	3.0%	8.6%	10.5%	-3.5%	-0.8%	2.3%	-4.1%	2.7%
Rural Counties										
Multiple Proxy Estimate	0.091***	0.061***	0.167**	0.271**	0.107***	0.200***	-0.464***	-0.179***	0.188***	0.106**
	(0.031)	(0.021)	(0.074)	(0.121)	(0.037)	(0.070)	(0.129)	(0.055)	(0.070)	(0.046)
Dependent Var. Mean [SD]	11.31 [14.18]		5.37 [8.58]		4.10 [6.73]		19.20 [24.08]		7.90 [19.47]	
% of Total Δ Explained	0.6%	0.4%	1.9%	3.2%	1.6%	3.0%	1.9%	0.7%	1.0%	0.5%
Additional Controls (ΔX's)	Δ**X**	Δ$\mathbf{X}^{I}$	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 through 3. All models include 1999 supplementary covariates as well as changes in either actual or instrumented values from 1999-2015. Top panel estimates for 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

Table 8: 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)
<u>All Drugs</u>					
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}$	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
<u>Opioid Analgesics</u>					
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}$	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
<u>Illicit Opioids</u>					
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}$	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	$< \tilde{R}$
<u>DSA</u>					
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}$	-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
<u>Nondrug Suicide/Alcohol</u>					
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}$	-0.533	-2.770	-37.7%	<0.00	$< \tilde{R}$
$\mathbf{X}_{1999}$, $\Delta\mathbf{X}^{\mathbf{I}}$	-0.053	-1.822	-24.8%	<0.00	$< \tilde{R}$

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 an estimated zero treatment effect, with R_{max}=0.75, and column (e) shows the R_{max} value that would do so, with δ=0.5. $R_{max} < \tilde{R}$ 0.75 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.

Table 9: 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. 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 10: 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: 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

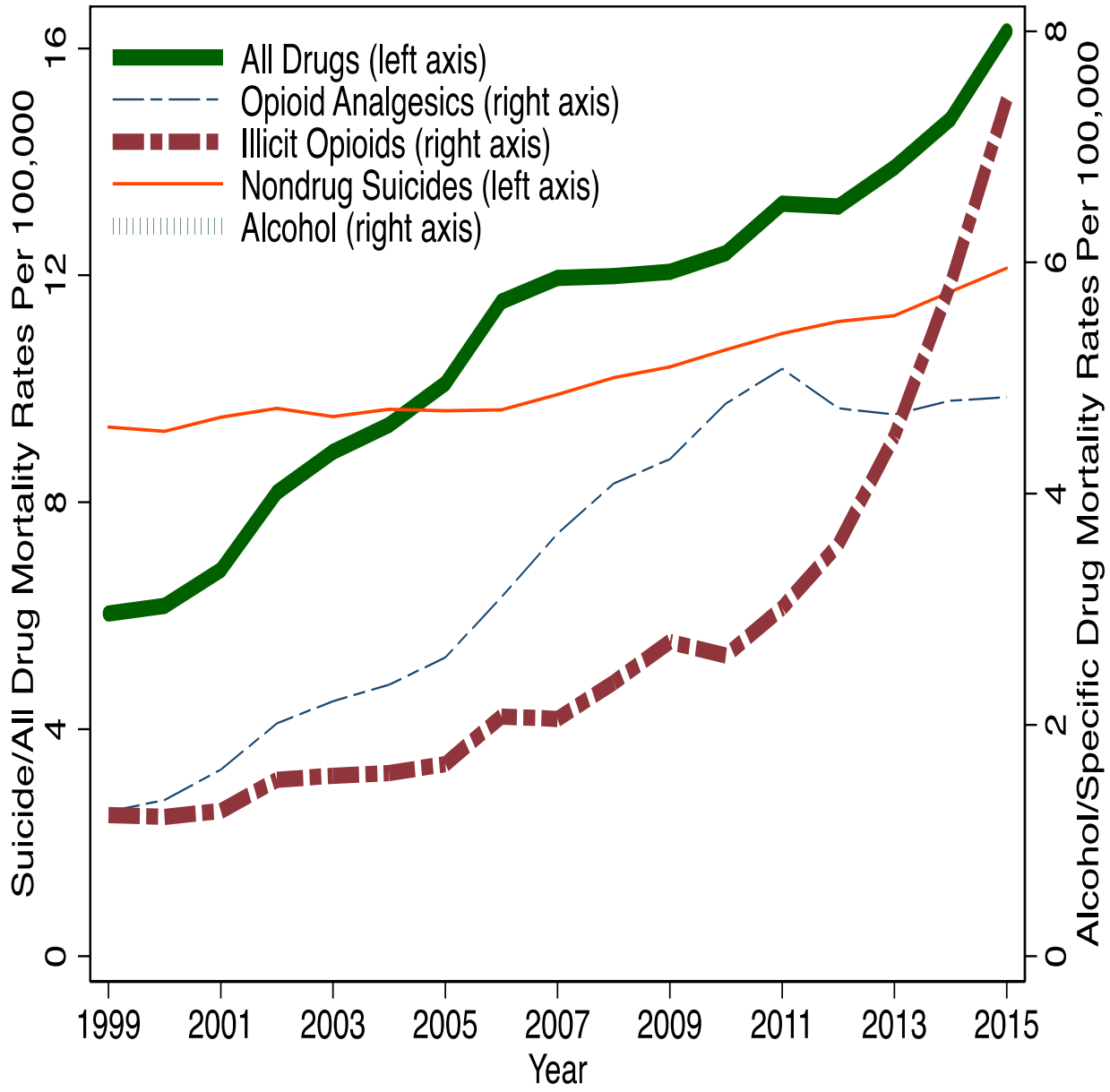


Figure 2: Drug Mortality Rates For Population Subgroups

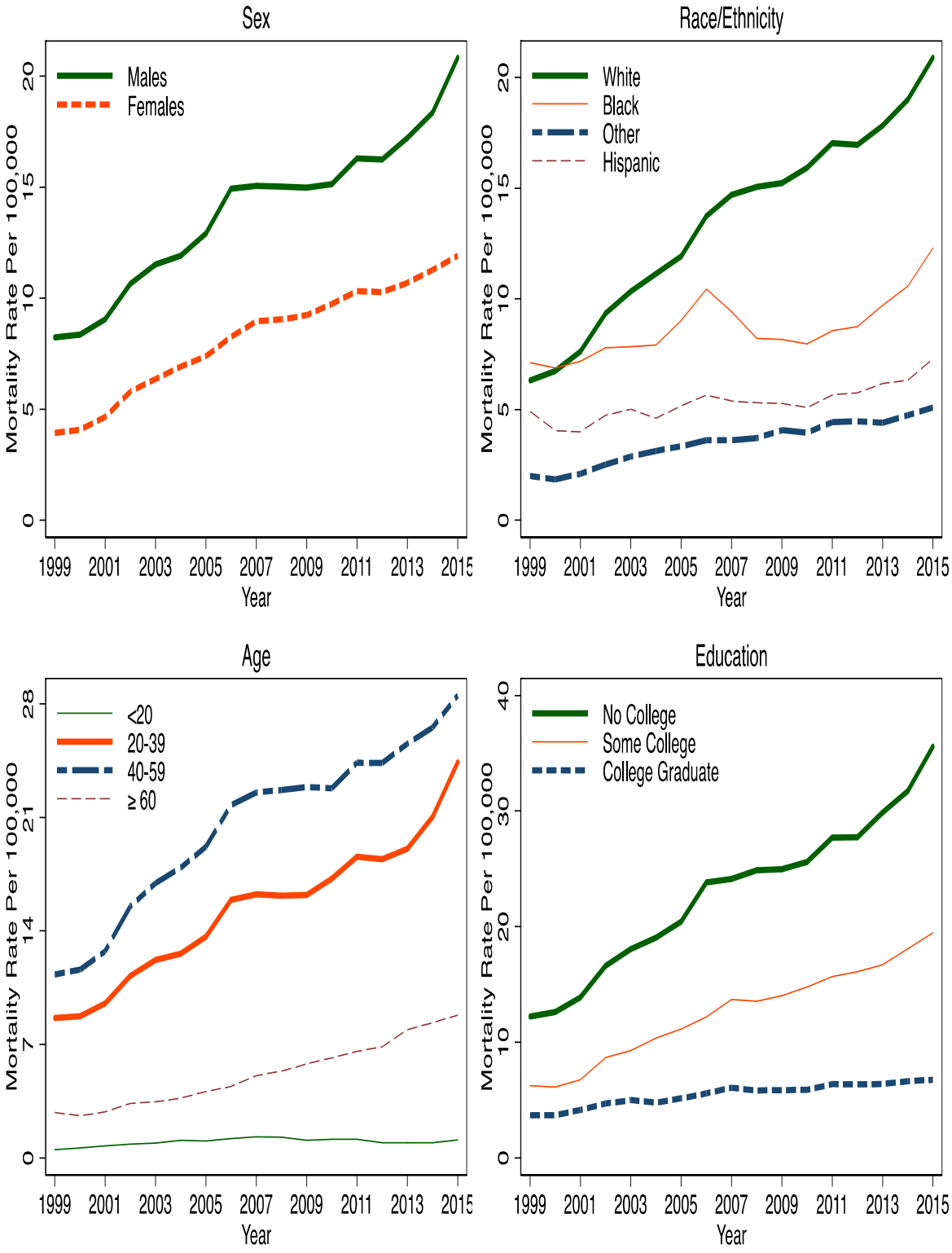


Figure 3: Nondrug DSA Mortality Rates for Population Subgroups

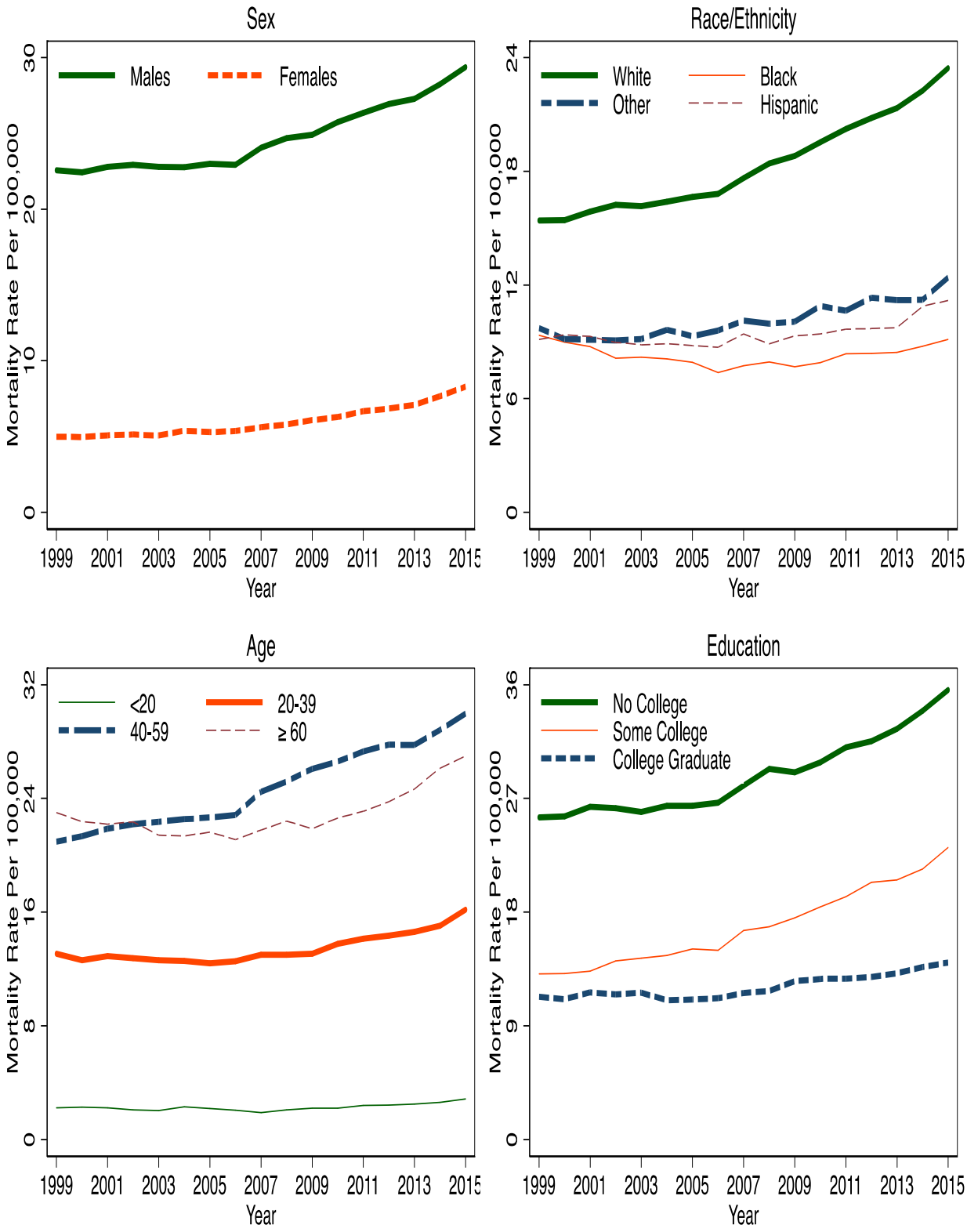


Figure 4: Opioid Analgesic and Illicit Opioid Mortality Rates for Selected Population Subgroups

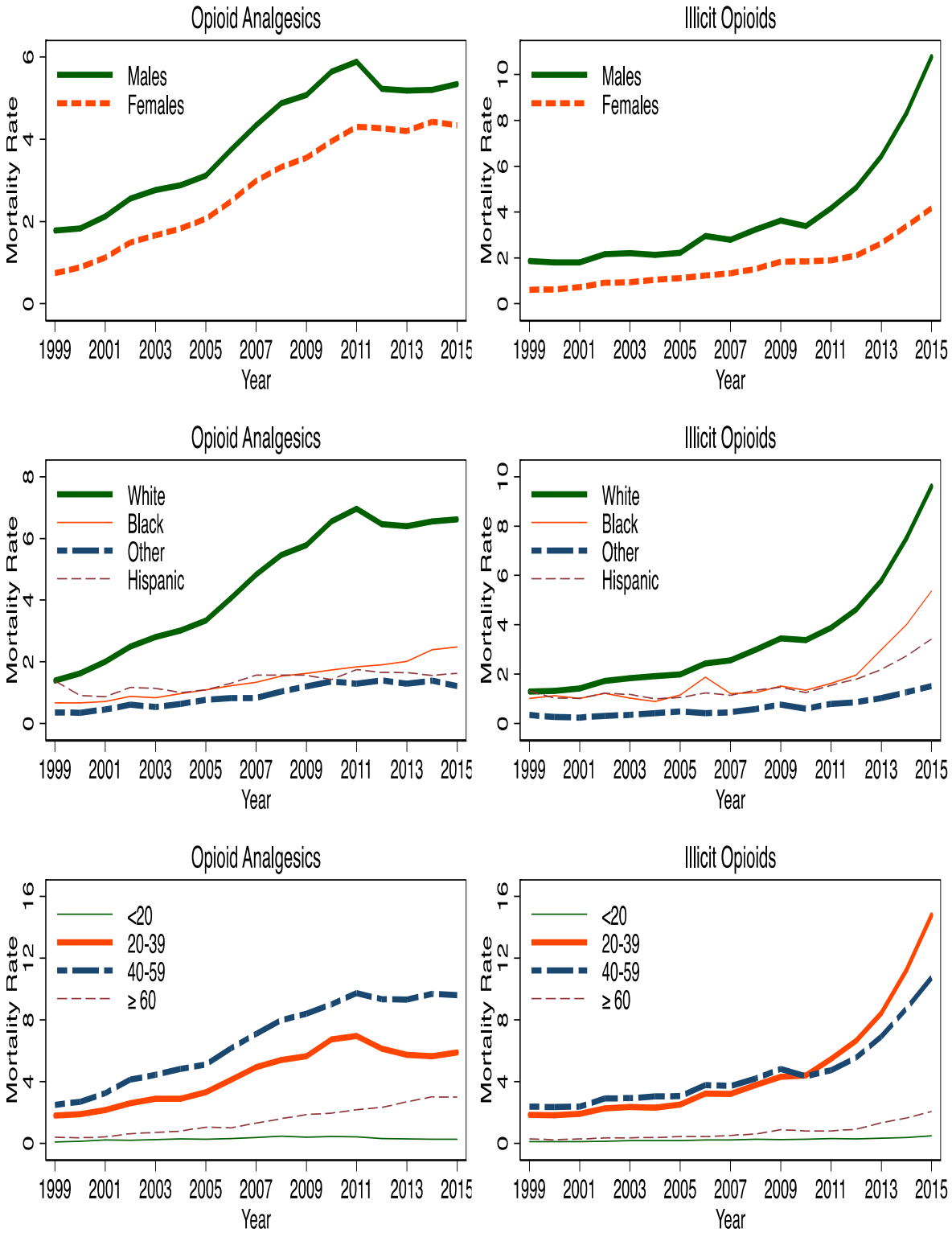
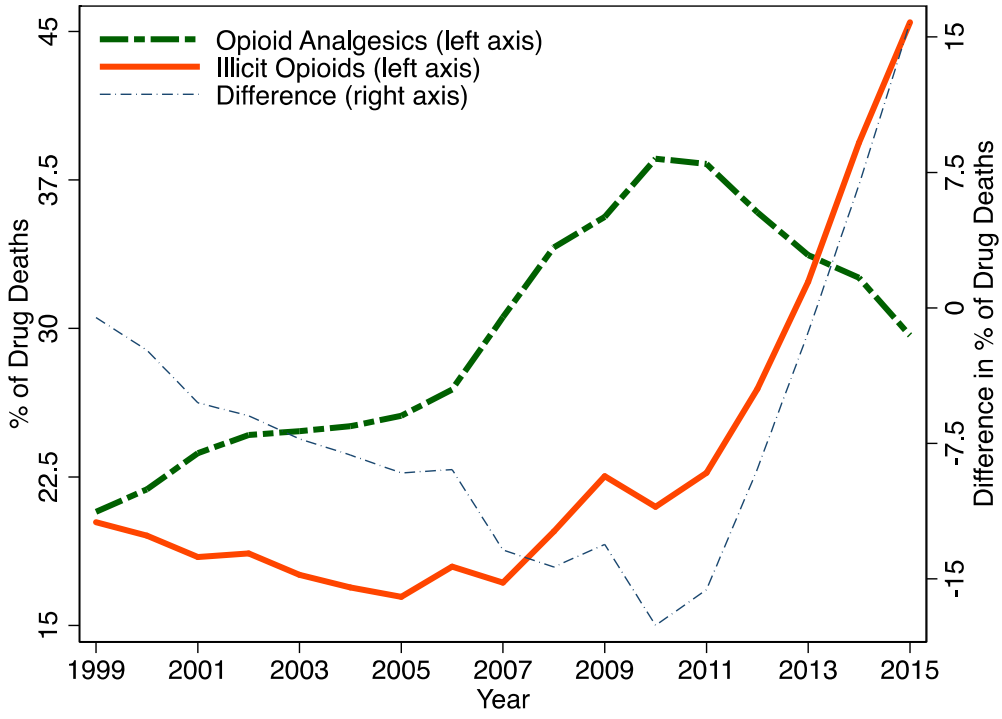
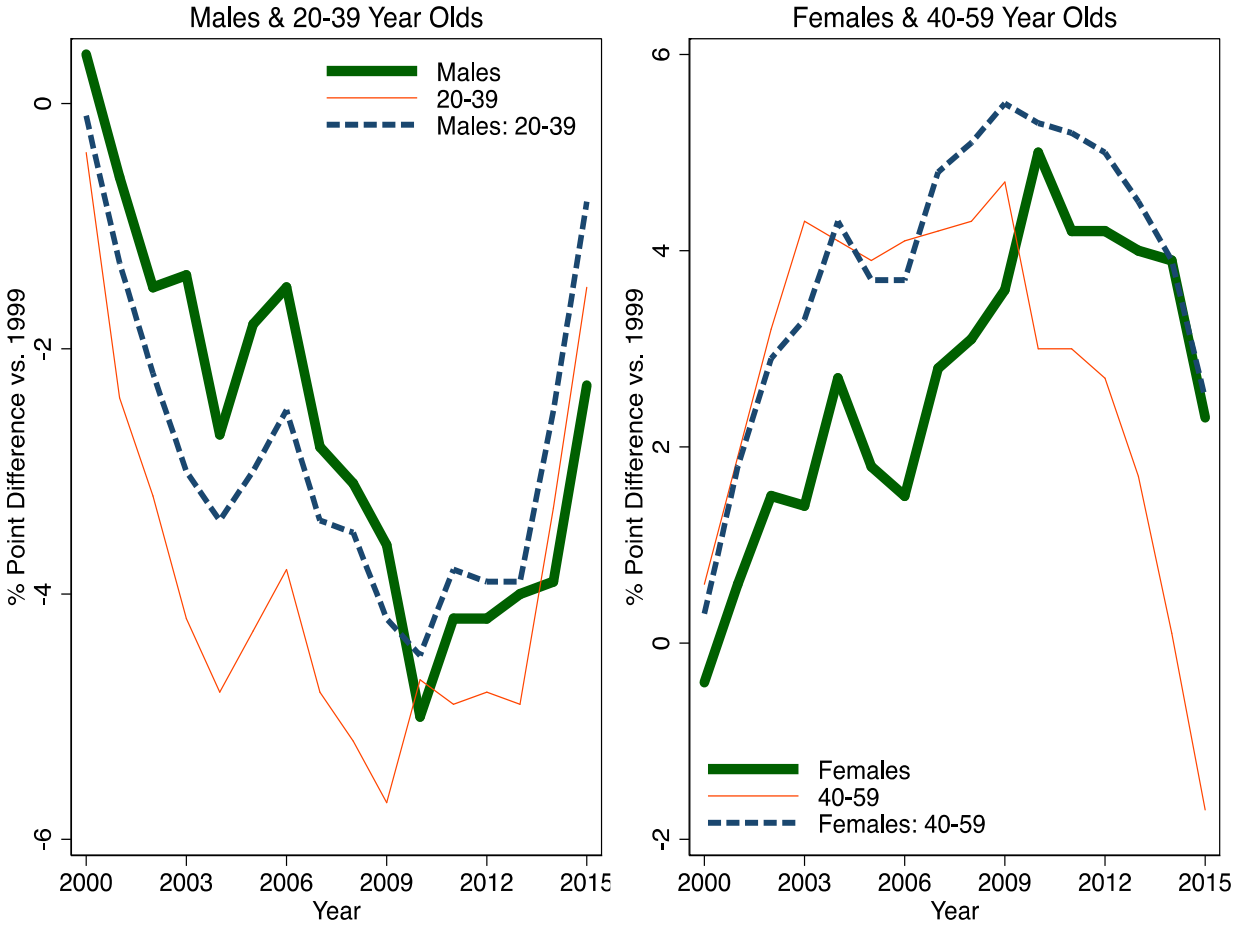


Figure 5: Percent of Drug Deaths Involving Opioid Analgesics and Illicit Opioids, 1999-2015



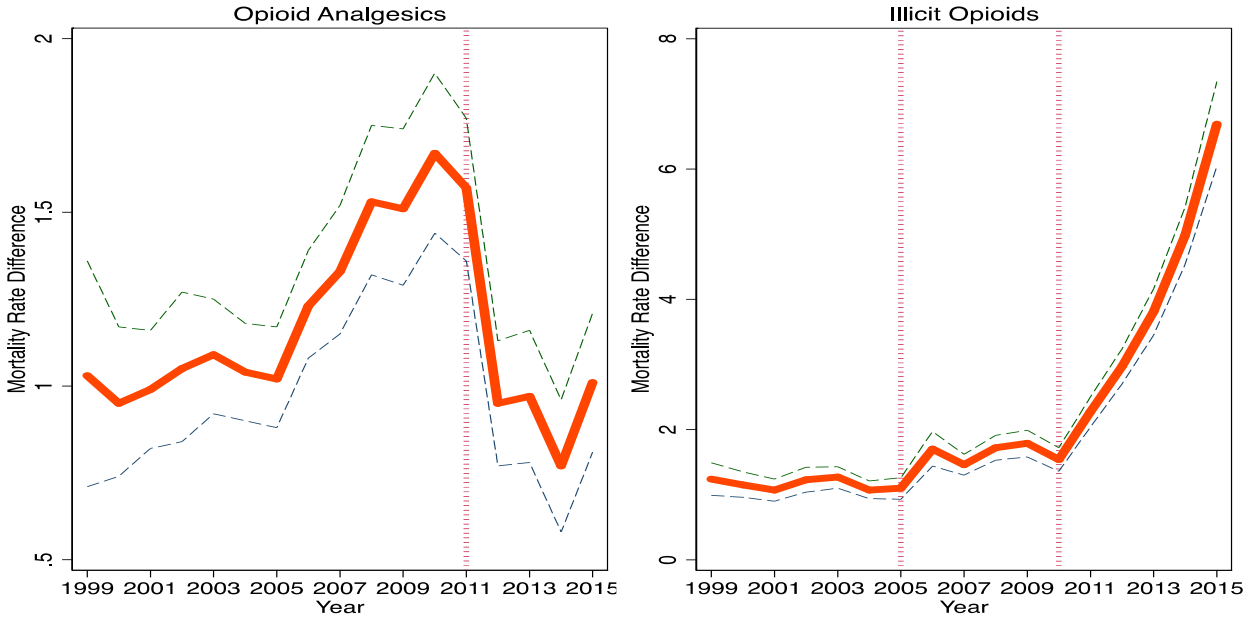
Note: Figure shows the percentage of drug poisonings involving opioid analgesics and illicit opioids, as well as the difference between the two.

Figure 6: Regression-Adjusted Changes Since 1999 in Share of Drug Poisoning Deaths For Selected Sex and Age Groups, 2000-2015



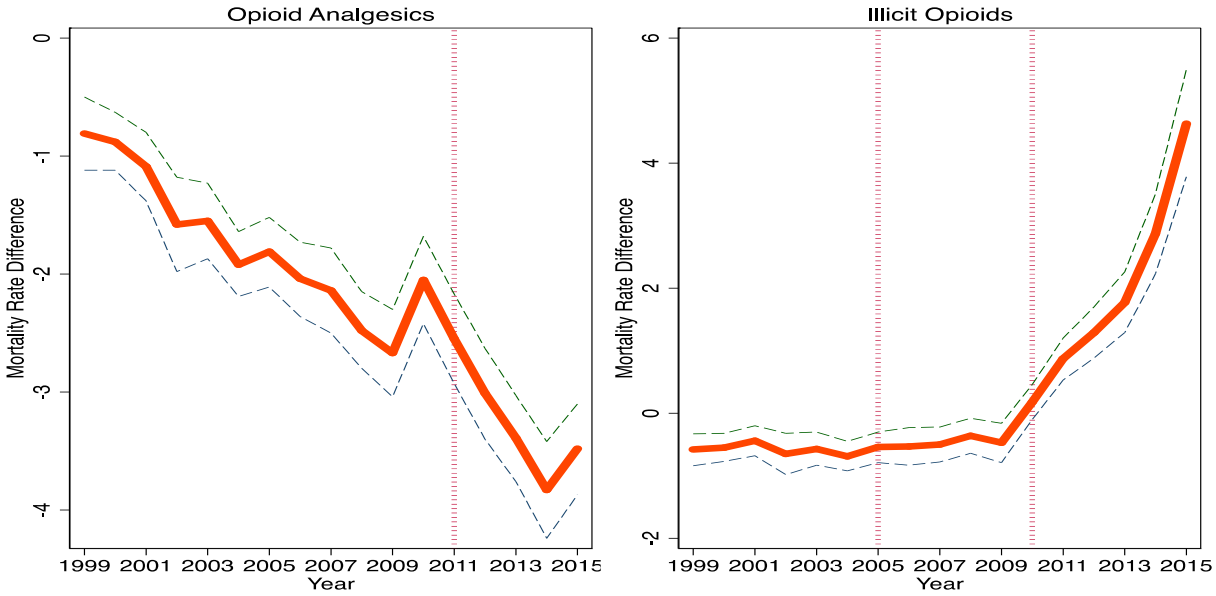
Note: Figure shows coefficients on year dummy variables from county-level regressions that also control for county fixed-effects, the group population share, as well as the county unemployment and poverty rates, and median household incomes. Data are weighted by 2015 county populations.

Figure 7: 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 8: 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.