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Article

Free trade and opioid overdose death in the United States

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ABSTRACT

Opioid overdose deaths in the U.S. rose dramatically after 1999, but also exhibited substantial geographic variation. This has largely been explained by differential availability of prescription and non-prescription opioids, including heroin and fentanyl. Recent studies explore the underlying role of socioeconomic factors, but overlook the influence of job loss due to international trade, an economic phenomenon that disproportionately harms the same regions and demographic groups at the heart of the opioid epidemic. We used OLS regression and county-year level data from the Centers for Disease Controls and the Department of Labor to test the association between trade-related job loss and opioid-related overdose death between 1999 and 2015. We find that the loss of 1000 trade-related jobs was associated with a 2.7 percent increase in opioid-related deaths. When fentanyl was present in the heroin supply, the same number of job losses was associated with a 11.3 percent increase in opioid-related deaths.

The United States suffers roughly 100 opioid-related overdose deaths every day. Drug overdose deaths are now the leading cause of death for adults under 50, two-thirds of which are caused by opioids (Ahmad, LM Rossen, Warner, & Sutton, 2016; O'Donnell, 2017; Rudd, Seth, David, & Scholl, 2016; Williams & Bisaga, 2016). The rise in opioid overdose deaths was originally explained by increased opioid prescriptions, which contributed to the development of opioid use disorders and the initiation of non-prescribed opioids such as heroin (Baker, 2017; Barnett, Olenski, & Jena, 2017; Botticelli, 2016; Carlson, Nahhas, Martins, & Daniulaityte, 2016; Cicero, Ellis, & Kasper, 2017; Compton, Jones, & Baldwin, 2016; Han et al., 2017; Jones, Mack, & Paulozzi, 2013; Mack & Centers for Disease Control and Prevention, 2013). Increasingly, people who develop opioid use disorders initiated with heroin (Cicero et al., 2017). The gradual introduction of fentanyl into heroin markets in 2013 led to a dramatic increase in overdose deaths (O'Donnell, 2017; Rudd et al., 2016; Somerville et al., 2017).

These factors do not fully explain why opioid-mortality rates vary across regions and between socioeconomic groups (Dasgupta, Beletsky, & Ciccarone, 2018). In 2015, the overdose mortality rate in Appalachia was 65 percent higher than the rest of the country (Meit, Heffernan, Tanenbaum, & Hoffmann, 2017). Less-educated white males suffer overdose deaths at such a high rate that it has lowered their overall life expectancy (Case & Deaton, 2015). Recent studies argue that socio-economic factors such as unemployment, low social capital, economic or family distress, and high dependence on mining industries explain this variation. (Hollingsworth, Ruhm, & Simon, 2017; Monnat, 2018; Rigg, Monnat, & Chavez, 2018; Zoorob & Salemi, 2017). This study contributes to this growing debate by exploring the impact of a previously overlooked economic factor: job losses caused by international trade. Trade-related job loss is a distinct phenomenon that represents the closing of local factories and the loss of relatively well-paid manufacturing jobs, and also disproportionately harms the same region and demographic group at the heart of the opioid epidemic (Autor & Dorn, 2013; Davis & Harrigan, 2011; Kletzer, 2001; Margalit, 2011). This study also investigates how the association between trade-related job losses and opioid-related overdose deaths changes when fentanyl - a powerful synthetic opioid - is present in the local heroin supply.

This study also contributes to debates in the social sciences concerning the negative consequences of free trade. Scholars have long focused on the positive effect of international trade on the overall economy, while also noting that it causes layoffs and bankruptcy for some groups (Smith, 1776; Colgan & Keohane, 2017). Recent influential work by Autor, Dorn, and Hanson (2013, 2016), demonstrates that these negative impacts of trade are actually highly localized, with layoffs, unemployment, and lower wages concentrated in specific labor markets. This study furthers our understanding of the local consequences of international trade by looking beyond wages and employment levels to the potential impact on opioid-related overdose death.

In this paper we review existing research on the socioeconomic factors associated with opioid overdose before describing a theory for the unique importance of trade-related job losses. We then present quantitative analysis of county-level data from the United States from 1999 through 2015, including numerous robustness tests. We argue that understanding the opioid epidemic requires interdisciplinary work on economic policy, just as understanding the negative consequences of

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free trade requires interdisciplinary research on public health (e.g. Monnat, 2018; Pierce & Schott, 2016).

Free trade, fentanyl, and opioid overdose deaths

The opioid overdose epidemic is a national public health emergency affecting all regions, races, and genders, but the crisis is heavily concentrated in Appalachia and among less-educated white males (Dasgupta, Beletsky, & Ciccarone, 2018). We argue that it is not a coincidence that the same region and socioeconomic group have suffered the brunt of the negative impact of international trade. U.S. trade policies place an uneven burden across the country, putting specific regions (those with manufacturing employment) and socioeconomic classes (low-skilled workers) at greater risk for harm from the opioid crisis. Likewise, trade puts downward pressure on the wages and job prospects of less-educated workers in manufacturing (Dean, 2016; Wood, 1995), the majority of which are white men (Pierce & Schott, 2016).

In general, job loss and unemployment increase the risk of depression and drug misuse, especially among less-educated workers (Becker, Sullivan, Jeanette, Desai, & Fiellin, 2008; Gossop, Green, & Bradley, 1989; Han et al., 2017; Mossakowski, 2009). In the U.S., the short duration of unemployment benefits leads some laid-off workers indirectly to opioids. This happens when unemployed workers seek disability benefits, an application process that requires medical examination and increases the likelihood of being prescribed opioids (Autor et al., 2013; Morden et al., 2014). Once introduced to prescribed opioids, patients sometimes initiate the use of non-prescribed opioids such as heroin (Botticelli, 2016; Carlson et al., 2016).

However, there are at least three reasons why trade-related job loss may have an even larger impact on opioid misuse than other types of economic distress. First, the jobs lost to international trade are overwhelmingly concentrated in manufacturing, a sector of the economy that provides relatively "good" jobs (Davis & Harrigan, 2011). In 2016, manufacturing workers earned 13 percent more than comparable workers in the rest of the private sector and enjoyed better health insurance, retirement benefits, and higher rates of union membership (Mishel, 2018). These workers end up facing lower wages and benefits even when they find new employment, especially in the low-wage service sector (Kletzer, 2001; Autor & Dorn, 2013). In 2010, for example, 76 percent of net job growth in the U.S. was in service industries that paid between 9 and 15 dollars an hour (Bernhardt, 2012).

Second, trade-related job losses are associated with the closing of local factories that inflict costs well beyond the workers who are actually laid off. In the wake of trade shocks, youth entering the labor market for the first time also find their employment and educational opportunities diminished in ways that negatively impact their future (Dean, 2018). Previous research finds that family economic hardship leads to inconsistent parental discipline and increased drug use among adolescents (Lempers, Clark-Lempers, & Simons, 1989). Scholars also find that manufacturing employment is of unique economic and social significance to local communities (Danson, 2005; Harrison & Bluestone, 1982), and that intense media coverage of trade-related factory closures may make such job losses particularly impactful (Margalit, 2011).

Third, the physical labor required of manufacturing employees leads many to suffer from chronic pain, use opioids during employment, and therefore face an increased risk of transitioning from prescribed opioids to heroin (Cicero et al., 2017; Franklin, Bert, Turner, Fulton-Kehoe, & Wickizer, 2008). In short, the jobs lost due to trade are relatively good jobs, and even when workers find new employment the resulting dislocation increases the risk of opioid-related overdose deaths (Dasgupta, Beletsky, & Ciccarone, 2018; Monnat, 2018). We therefore expect trade-related job losses to be positively associated with opioid-related overdose deaths, even when controlling for local economic conditions, such as the unemployment rate and other types of job losses.

The idea that economic hardship can harm public health is not new. In their seminal study of de-industrialization, Bluestone and Harrison (1982) argued that when northern factories in the "frost belt" closed down and relocated to the southern "sun belt," they left behind more than just unemployment; job losses devastated local tax bases, decreased spending on education, and increased alcoholism, suicide, and other public health problems. Recent research by Pierce and Schott demonstrates that trade with China has a similar impact, leading to increases in suicides and accidental drug poisoning deaths in the United States from 2001 to 2013 (Pierce & Schott, 2016). This paper complements these findings by focusing directly on opioid-related overdose deaths and analyzing more recent data, which permits us also to examine how the association between trade-related job loss and opioid-related overdose death has changed since the uneven introduction of fentanyl in 2013 (Rudd et al., 2016).

Data and methods

We conducted a time-series cross-sectional regression analysis study using publicly available data from the Centers for Disease Control (CDC) and the Department of Labor (DOL) for the years 1999 through 2015, the most recent year for which data is available for trade-related job loss.

Dependent variable

We use county-level data on opioid-related overdose deaths available from the CDC's National Vital Statistics System multiple cause-of-death mortality files. Following previous studies of the opioid epidemic, we classified drug overdose deaths using the International Classification of Disease, Tenth Revision (ICD-10), based on the ICD-10 underlying cause-of-death codes X40-44 (accidental poisoning), X60-64 (intentional self-harm), and Y10–Y14 (undetermined intent). Among the deaths with drug overdose as the underlying cause, we focus on those caused by opioids, as indicated by the following ICD-10 multiple cause-of-death code: opioids (T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6); natural and semisynthetic opioids (T40.2); methadone (T40.3); synthetic opioids, other than methadone (T40.4); and heroin (T40.1). This data captures deaths from both prescribed and non-prescribed opioids. Since the CDC suppresses data for all county-years in which the number of deaths is fewer than 10, data is available for 820 counties.[1]

The study's main dependent variable - *Opioid Deaths* - therefore measures the number of opioid-related overdose deaths at the county-year level. According to the CDC, there were 308,846 opioid-related deaths across all US counties from 1999 through 2015. The 820 counties for which county-year data is available account for 238,876, or 77 percent, of these deaths. The highest absolute number of opioid-related overdose deaths hit Chicago and the surrounding townships in 2015, where there were 547 such deaths. In terms of per capita opioid-related overdose deaths, the highest rates are in the rural counties of West Virginia and Kentucky, where there was 1 death for every one thousand residents in recent years.

The total number of opioid-related overdose deaths in the U.S. has increased dramatically over time. In 1999, there were roughly seven thousand opioid-related overdose deaths throughout the country. By 2010, the number grew to nearly twenty thousand. In 2015, more than thirty thousand deaths were recorded. While some of this increase came from the counties initially reporting opioid-related overdose deaths in 1999, the epidemic has also spread to new counties. In 1999, only 153

[1] For county-years that have non-suppressed data for opioid-related overdose deaths (more than 9), but the previous year's number of deaths is suppressed (less than 10), we impute 9 opioid-related overdose deaths for that observation. This represents a conservative approach, as it assumes the smallest possible increase from the previous year. Additional approaches are discussed in the Appendix.

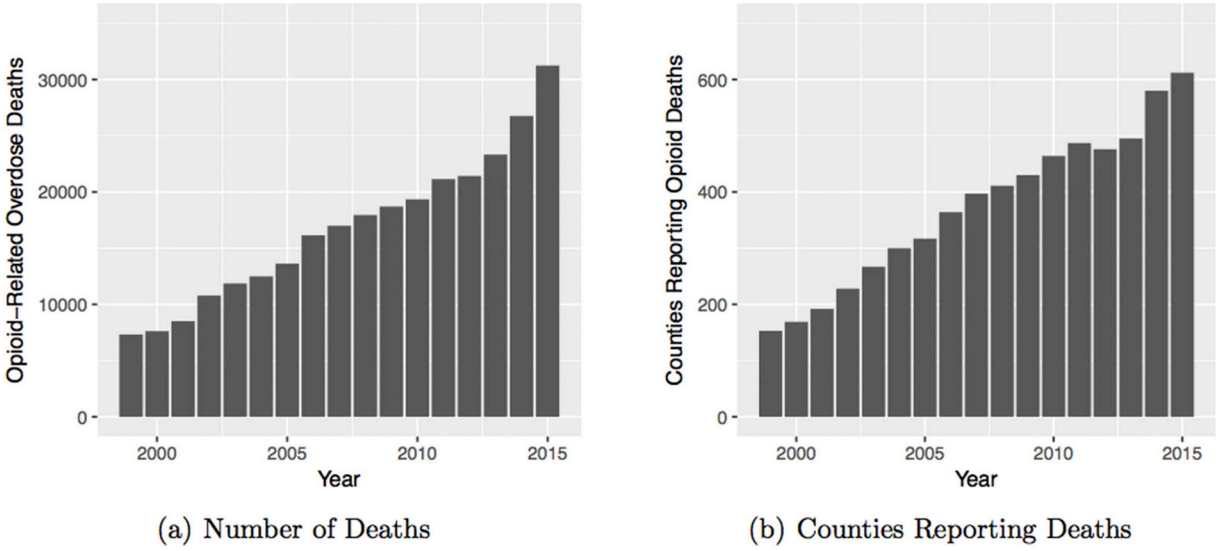

Fig. 1. The growth and spread of the opioid epidemic.

counties reported opioid-related overdose deaths; by 2015 there were deaths reported in 612 different counties. The increase in total opioid-related overdose deaths, as well as the number of counties reporting such deaths, are displayed in Fig. 1.

Independent variable

To measure trade-related job losses, we use plant-level data from the DOL's Trade Adjustment Assistance (TAA) program (Margalit, 2011). This data includes every application submitted requesting compensation for trade-related job losses over a 17-year period (1999–2015). If the DOL determines that the layoffs were caused by international trade, it certifies the application and makes all included workers eligible to receive adjustment assistance from the federal government. The TAA data therefore provides a conservative estimate of trade-related job losses. There are high hurdles to clear for workers seeking to convince the federal government that their layoff was due to international trade (Kletzer, 2001; Kapstein, 1998). We can therefore be fairly confident that the regression results reported below are driven by trade-related job losses rather than technological change or a cyclical downturn in the business cycle.

The study's main independent variable - *Trade Layoffs* - represents the number of trade-related job losses at the county-year level. This variable is generated by aggregating all 24,732 certified petitions at the county-year level. According to this measure, there were 2,273,543 trade-related job losses during this period. While many county-years do not contain a single trade-related job loss, others witness tremendous layoffs. The largest shock of trade-related job losses hit Wayne County - home of Detroit, Michigan - in 2008; the county suffered 9859 trade-related job losses as U.S. Steel, General Motors, and other manufacturing firms decided to offshore jobs. International trade is associated with local plant closings and large layoffs; when counties lost jobs due to trade between 1999 and 2015, the average loss amounted to 235 jobs. Shocks of one thousand or more trade-related job losses hit individual counties 381 times, or roughly twice every month.

Despite the common narrative about trade shuttering factories in the rust belt, the negative effects of international trade are not concentrated in the post-industrial Midwest. Instead, as can be seen in Fig. 2, the burden disproportionately falls on Appalachia, a region made up of 420 counties across Alabama, Georgia, Kentucky, Maryland, Mississippi, New York, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, Virginia, and West Virginia. The cluster of dark-black counties in North Carolina, for example, tells the story of the dramatic decline of the region's furniture industry since the 1990s. This region once manufactured the majority of furniture produced in the United States and many counties in North Carolina relied heavily upon this industry for employment (Nwagbara, Buehlman, & Schuler, 2002). The loss of these jobs, combined with the region's high dependence on a specific industry, resulted in the country's highest levels of per capita trade-related job losses.

We estimate the presence of fentanyl using a binary measure for whether or not a county reported overdose deaths caused by synthetic opioids, the most prominent of which is fentanyl. To construct this proxy measure, we obtained county-level data on overdose deaths caused by synthetic opioids from 1999 to 2015. All counties that reported such deaths during this period were coded as having fentanyl present from 2013 to 2015, when recent research suggests fentanyl entered the heroin supply in the United States (Gladden, Martinez, & Seth, 2016). This binary measure of fentanyl is used in the models presented in the body of this paper.

As robustness tests, we also constructed three additional measures of fentanyl. First, we used CDC data on overdose deaths caused by synthetic opioids to construct a continuous, county-level measure of the relative presence of fentanyl. We calculated the percentage of opioid-related overdose deaths that the CDC attributed to synthetic opioids and used this ratio as a county-level measure of fentanyl from 2013 onward. Second, following recent research on synthetic opioids, we estimate that fentanyl was present in the heroin supplies of New England and Appalachia from 2013 onward (Gladden et al., 2016). This operationalization represents a simplified picture of fentanyl's more complex spread through regional heroin markets. Third, we code fentanyl as present from 2013 to 2015 in only those New England and Appalachia counties that reported synthetic opioid-related overdose deaths during the study period.

Control variables

We obtained county-year level data on population and income per capita from the Bureau of Economic Analysis, and racial demographics and population density from the U.S. Census Bureau. All of these variables vary at the county-year level and are available from 1999 through 2015. We also control for state-level labor union density

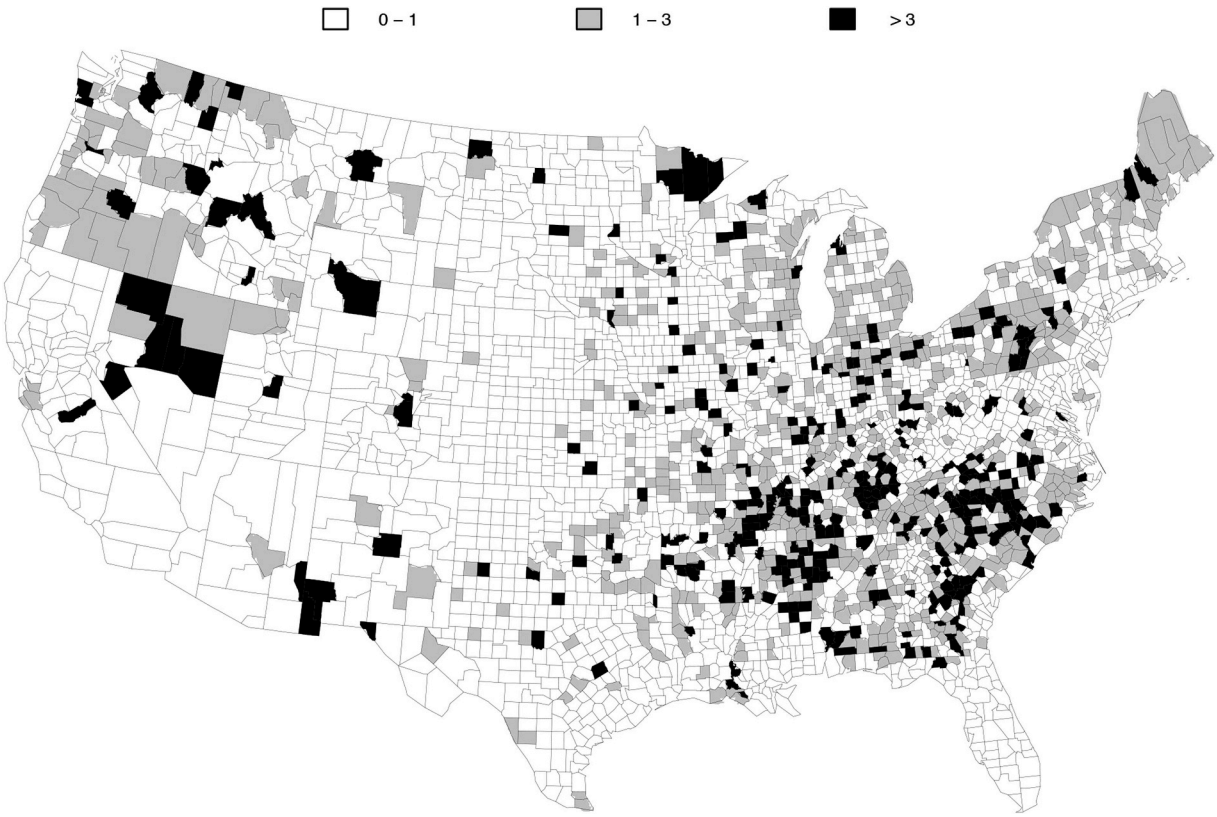

Fig. 2. Trade-Related Job Losses (per 10,000 Population) 1999–2015.

throughout the study period, since unions may influence workers' knowledge of the TAA program and their ability to apply for benefits (Magee, 2001). In order to control for variation in opioid prescription rates we use data available from the Center for Medicaid and Medicare Services (CMS). This data is only available starting in 2006, so we use prescription rates from one year (2013) to capture county-level variation.[2]

In order to control for access to treatment for opioid dependency, we gathered data on the number of physicians certified to prescribe buprenorphine from the Substance Abuse and Mental Health Services Administration.[3] We also obtained unemployment rates and mass layoffs from the Bureau of Labor Statistics (BLS). By subtracting the number of trade-related job losses from this measure of mass layoffs we constructed a variable that measures mass layoffs unrelated to trade. Unemployment rates are available from 1999 through 2015, but BLS stopped collecting data on mass layoffs in 2012. Descriptive statistics for all variables used in the model are presented in Table 1.

Statistical analysis

We first compared the opioid-related overdose death rate in county-years that experienced above-average trade-related job losses to the death rate in county-years that did not. To control for other covariates, we examined the association between opioid-related overdose deaths and trade-related job losses using time-series cross-sectional regression analyses. Opioid-related overdose deaths and trade-related job losses both vary from year to year within each county, therefore the county-year is the basic unit of analysis. The dataset for the full model has 820 units (counties) and a maximum of 17 time periods (years). Due to missing observations for some county-years, the dataset is an unbalanced panel. The ordinary least squares (OLS) regression models reported below address the cross-sectional heteroskedasticity and autocorrelation associated with panel data by including a one-year lag of the dependent variable, state and year-level fixed effects, and robust standard errors clustered at the county-level.

In these OLS models, the dependent variable is logarithmically transformed so that the coefficients represent the relationship between a one-unit increase in the independent variable and a percentage change in opioid-related overdose deaths.

The main OLS regression model is:

$$\log(OpioidDeaths)_{ijt} = \alpha + \beta_1 \log(OpioidDeaths)_{ijt-1} + \beta_2 TradeLayoffs_{ijt} + \sum_k \beta_k Controls_{ijt} + \sum_n \beta_n Controls_{jt} + \sum_m \beta_m Controls_i + \eta_j + \mu_t + \epsilon_{ijt}$$

where i denotes the county, j denotes the state, and t denotes the year. The η_j represent fixed effects at the state-level and the μ_t represent fixed effects and the year-level. The state fixed effects help address the possibility that opioid-related overdose deaths are driven by cultural, political, or healthcare-related factors that vary from state to state. The year fixed effects control for exogenous shocks that may increase opioid-related overdose deaths in any given year, such as the great recession, and also address the well-document secular worsening of the opioid epidemic. The year fixed effects also help to control for the possibility that the Department of Labor's tendency to approve TAA petitions may vary from year to year.

The coefficient associated with *Trade Layoffs*, β_2, represents the county-level association between trade-related job losses and opioid-related overdose deaths. To the extent that laid-off workers may ultimately die in a different county, the model underestimates the total impact of trade-related

[2] In the Appendix, we demonstrate that the results are robust to including county-year level opioid prescription rates from 2006 to 2015, despite the large decrease in the number of observations available.

[3] This data is only available starting in 2002. In the Appendix, we demonstrate that the results are robust to including the state-level number of buprenorphine providers from 2002 to 2015, despite the decrease in the number of observations available.

Table 1
Descriptive Statistics.

Trade Layoffs	Mass Layoffs	Unemployment	Population	Income per capita
(in thousands)	(in thousands)	(percent)	(log transformed)	(in thousands $)
Min.: 0.0 1st Qu.: 0.0 Median: 0.002 Mean: 0.180 3rd Qu.: 0.150 Max.: 9.859 N: 6138	Min.: 0.0 1st Qu.: 0.0 Median: 0.331 Mean: 1.497 3rd Qu.: 1.299 Max.: 239.448 N: 6138	Min.: 1.40 1st Qu.: 4.50 Median: 5.70 Mean: 6.30 3rd Qu.: 7.60 Max.: 23.60 N: 5250	Min.: 9.42 1st Qu.: 11.91 Median: 12.55 Mean: 12.59 3rd Qu.: 13.32 Max.: 16.13 N: 6020	Min.: 16.37 1st Qu.: 32.72 Median: 37.76 Mean: 39.75 3rd Qu.: 44.15 Max.: 156.71 N: 6020
Pop. Density	**CMSPrescribeRate**	**Opioid Deaths**	**Union**	**$Fentanyl_1$**
(per $mile^2$)	(percent filled)		(percent)	(binary)
Min.: 0.002 1st Qu.: 0.174 Median: 0.364 Mean: 1.046 3rd Qu.: 0.891 Max.: 48.959 N: 6020	Min.: 1.681 1st Qu.: 5.235 Median: 6.355 Mean: 6.282 3rd Qu.: 7.273 Max.: 16.432 N: 6138	Min.: 10.00 1st Qu.: 13.00 Median : 21.00 Mean: 37.67 3rd Qu.: 41.00 Max.: 547.00 N: 6138	Min.: 1.90 1st Qu.: 5.80 Median: 11.70 Mean: 11.47 3rd Qu.: 16.10 Max.: 26.70 N: 6124	Min.: 0.0 1st Qu.: 0.0 Median: 0.0 Mean: 0.2435 3rd Qu.: 1.0 Max.: 1.0 N: 6138
$Fentanyl_2$	**$Fentanyl_3$**	**$Fentanyl_4$**	**White**	
(binary)	(binary)	(percent)	(percent)	
Min.: 0.0 1st Qu.: 0.0 Median: 0.0 Mean: 0.061 3rd Qu: 0.0 Max.: 1.0 N: 6138	Min.:0.0 1st Qu.: 0.0 Median: 0.0 Mean: 0.06 3rd Qu: 0.00 Max.: 1.00 N: 5919	Min.:0.0 1st Qu.: 0.0 Median: 0.0 Mean: 3.91 3rd Qu: 0.00 Max.: 41.38 N: 6138	Min.: 20.40 1st Qu.: 74.30 Median:84.24 Mean: 80.75 3rd Qu: 94.53 Max.: 99.40 N: 6138	

Based on county-years for which CDC data is available on opioid-related overdose deaths.

job losses on opioid-related overdose deaths. This coefficient estimates the localized effect of trade-related job losses across counties, but it does not capture the effect of trade-related job losses on national opioid-related overdose deaths. Such national trends in total deaths are captured by the year-fixed effects; however, the model cannot distinguish the effect of trade openness from other national trends that influence opioid-related overdose deaths. Similarly, the analysis should not be interpreted as estimating the total effect of international trade on opioid-related overdose deaths. It is possible that counties that lose manufacturing jobs due to international trade also benefit from new investments and opportunities made possible by trade liberalization. The findings therefore only capture how the opioid-related overdose deaths are impacted by one aspect of international trade: the loss of local jobs.

We performed numerous robustness tests. First, we test three alternative measures of the presence of fentanyl. Second, to address possible selection bias generated by the suppressed CDC observations we performs three tests: propensity score matching; imputation of the suppressed observations; and substitution of the missing values with the extreme values of 0 and 9.[4] Third, we control for county-year opioid prescriptions rates and state-year buprenorphine providers, two variables that are not available for the entire period of study and thus significantly decrease the number of observations available. Last, we replicate the main findings using Poisson and negative binomial regression. These tests are further discussed in the Appendix.

Main results

Trade-related job losses and opioid-related overdose deaths are both disproportionately concentrated in Appalachia. Although the region only contains 8 percent of the total U.S. population, it suffered 16 percent of trade-related job losses and 10 percent of opioid-related deaths from 1999 through 2015. We compared each region's percentage of national trade-related job losses to its percentage of total U.S. population, and Appalachia had a ratio (1.97) that was more than double the ratio for the rest of the country. Similarly, the region's percentage of national opioid-related overdose deaths to its percentage of the total U.S. population (1.19) is the highest in the country.

The positive association between trade-related job losses and opioid-related overdose deaths can be seen clearly in Fig. 3. This plot displays how county-level opioid-related overdose death rates differ between two subsets of American counties: those with trade-related job losses that are above average and those below. While the opioid epidemic has worsened over time for both groups, counties with higher levels of trade-related job losses consistently experience higher rates of opioid-related overdose deaths.

Beyond this bivariate relationship, the regression analysis controls for numerous factors identified by previous studies as markers of risk for harm from opioids. The regression analyses present strong empirical support for this study's core argument: trade-related job losses are positively associated with opioid-related overdose deaths, and this relationship grows significantly stronger when fentanyl is present in the local heroin supply. On average, one thousand trade-related job losses are associated with a 2.7 percent increase in opioid-related overdose

[4] For propensity score matching, we defined the treatment as county-years that experienced trade-related job losses above the mean shock of 235 jobs. We matched these treatment observations with control observations based on county-year level population, income per capita, and unemployment rates. For data imputation, we obtained state-year data on opioid-related overdose deaths in order to calculate the number of such deaths suppressed from the county-year level data. We then imputed those suppressed deaths into the corresponding suppressed county-years based on population size. For further description of all robustness tests, see the Appendix.

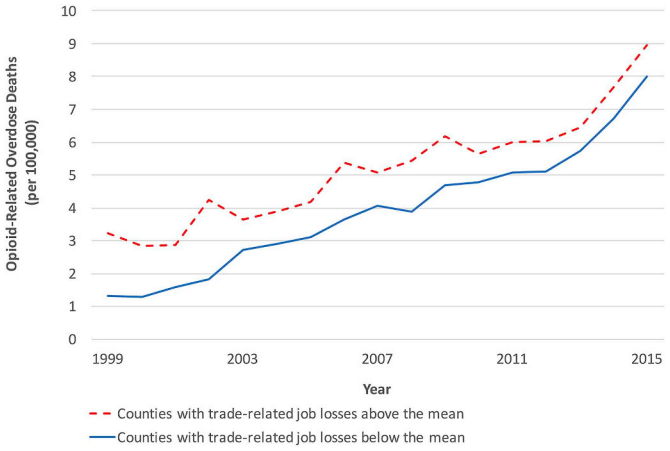

Fig. 3. The opioid epidemic and trade shocks.

Table 2
OLS Regression Analysis of Opioid Mortality, 1999-2015. The dependent variable is the logarithmic transformation of county-level opioid-related overdose deaths.

	Model 1	Model 2	Model 3
	1999–2015	1999–2012	1999–2015
LagDV	0.673***	0.649***	0.671***
	(0.015)	(0.018)	(0.015)
Population	0.213***	0.216***	0.211***
	(0.014)	(0.017)	(0.014)
Income per capita	−0.001	−0.001	−0.001
	(0.001)	(0.001)	(0.001)
Unemployment	0.011***	0.014***	0.012***
	(0.003)	(0.004)	(0.003)
Trade Layoffs	0.027**	0.023*	0.022*
	(0.009)	(0.009)	(0.009)
CMSPrescribeRate	0.014**	0.015**	0.013**
	(0.005)	(0.006)	(0.005)
Pop. Density	0.004*	0.004*	0.004*
	(0.002)	(0.002)	(0.002)
Percent White	0.002**	0.002*	0.002**
	(0.001)	(0.001)	(0.001)
Union	−0.003	0.003	−0.002
	(0.005)	(0.006)	(0.005)
Mass Layoffs (non-trade)		0.003	
		(0.002)	
Fentanyl			0.085**
			(0.028)
Trade Layoffs:Fentanyl			0.073**
			(0.025)
State Fixed Effects	*yes*	*yes*	*yes*
Year Fixed Effects	*yes*	*yes*	*yes*
N	5312	3962	5312
R^2	0.857	0.850	0.857
adj. R^2	0.855	0.847	0.855
Resid. sd	0.299	0.301	0.299

Robust standard errors, clustered at county-level, in parentheses.
† significant at $p < .10$; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

deaths. When fentanyl is present in the local heroin supply, the same number of trade-related job losses are associated with an 11.3 percent increase in opioid-related overdose deaths.

The main findings are presented in Table 2. Model 1 presents estimates from the main model, which includes *Trade Layoffs*, a one-year lag of the dependent variable, controls for various socioeconomic factors, and year and state-level fixed effects, and is estimated using data from 1999 to 2015. The positive and statistically significant coefficient on *Trade Layoffs* suggests that an increase of one thousand trade-related job losses is associated with a 2.7 percent increase in county-level opioid-related overdose deaths.

Model 2 estimates the same model with the addition of a control for mass layoffs unrelated to trade. Since BLS stopped collecting and reporting this data in 2013, this model is estimated using the subset of data from 1999 through 2012. As predicted, trade-related job losses have a stronger association with opioid-related overdose death than do mass layoffs unrelated to trade. While the coefficient on *Trade Layoffs* remains positive and statistically significant, the coefficient on *Mass Layoffs* is only one-seventh the magnitude and is statistically insignificant. These first two models demonstrate a positive relationship between trade-related job losses and opioid-related overdose deaths that cannot be explained by differences in population, per capita income, unemployment rates, opioid prescription patterns, population density, racial demographics, mass layoffs unrelated to trade, serial correlation of death rates, overall time trends, or time-invariant characteristics of different states.

Model 3 introduces an interaction term between trade-related job losses (*Trade Layoffs*) and the presence of fentanyl in the heroin supply (*Fentanyl*), a binary variable that measures the presence or absence of fentanyl in the local heroin supply. The positive and statistically significant coefficient on the interaction term suggests that the relationship between trade-related job loss and opioid-related overdose deaths is stronger when fentanyl is present.

The results in Table 2 are driven by variation in opioid-related deaths and trade-related job losses within, as well as between, counties. This approach is especially appropriate due to the nature of trade-related job losses. While dozens of counties suffered tens of thousands of trade-related job losses from 1999 to 2015, many counties were completely spared. A third of all counties did not suffer a single trade-related job loss during this period. Roughly half of counties suffered trade-related job losses in only one year during this period. Since so much of the variation in trade-related job losses is between counties, modeling strategies that focus narrowly on within county variation effectively discard large portions of the available data. In general, these models represent conservative tests of the basic relationship between trade-related job losses and opioid-related overdose deaths. As Achen (2000) explains, including a one-year lag of the dependent variable on the right hand side of the regression equation can drastically reduce the estimated effect of other independent variables. Although this approach may lead us to incorrectly overlook some effects, we are unlikely to draw incorrect positive conclusions regarding the effect of trade-related job losses. As discussed further and presented in the Appendix, these main results are consistent across a series of robustness tests.

The statistical analysis discussed above has several limitations. First, since individual-level data on trade-related job loss is not available, we analyzed data at the county-level. Further research is therefore needed to explore if the associated increase in opioid-related overdose deaths is driven by the individuals who lost jobs due to trade, or through effects on family or other community members. In addition, although the data for trade-related job losses is from certified TAA petitions to DOL, there may be regional or demographic biases that lead some eligible workers not to apply.

Second, the CDC suppresses data on opioid-related overdose deaths in the majority of U.S. counties. We addressed this data limitation with four different approaches - dropping suppressed county-years, propensity score matching, imputing the suppressed observations, and substituting the suppressed observations with the extreme values of 0 and 9 - all of which produced similar statistical results. The suppression of data also led us to choose a modeling strategy that analyzes variation within, as well as between counties, and leaves the analysis vulnerable to potential omitted variable bias. However, our findings are robust to including a one-year lag of opioid-related overdose deaths, which suggests that our results are not solely driven by cross-county differences.

Third, we used opioid prescription rate data from CMS that only covers Medicare and Medicaid patients and may not be representative of other types of patients. Last, our measure of access to treatment for opioid dependency - state-year-level number of buprenorphine

providers - is unable to capture how such access varies within states. However, it is also possible that buprenorphine treatment during our period of study simply was not extensive enough to impact overdose outcomes.

Conclusion

From 1999 through 2015, over three hundred thousand Americans died from opioid-related overdoses, with the highest per capita death rates hitting rural counties in Appalachia (Rigg et al., 2018). During this same period, over two million American workers lost their jobs due to international trade, with the highest concentration of job losses impacting the same region of the country. We used county-level quantitative data to further explore the relationship between international trade and the opioid epidemic in the United States. We found that one thousand trade-related job losses are associated with a 2.3 percent increase in county-level opioid-related overdose deaths. However, when fentanyl - a powerful synthetic opioid - was present in the local heroin supply, the same magnitude of trade-related job losses was associated with an 11.3 percent increase in opioid-related overdose deaths.

The positive relationship between trade-related job loss and opioid-related overdose death is well illustrated by Forsyth County, North Carolina. In March 2006, less than a year after the U.S. Congress approved the Dominican Republic-Central American Free Trade Agreement, Hanes closed a knit fabric factory, laid off 610 workers, and relocated production to plants in El Salvador, Honduras, and the Dominican Republic. This was just one of many factory closures in Forsyth County, which suffered 2215 trade-related job losses from 2006 to 2008. An increase in opioid-related deaths occurred following these job losses. From 2000 through 2005, the county averaged only 12 opioid-related deaths a year. Between 2006 through 2008, the county suffered an average of 25 deaths per year, a sudden doubling of opioid-related deaths. The number of annual deaths remained at roughly the same level over the next four years, until jumping to an average of 42 deaths after the introduction of fentanyl in 2013. As local Sheriff, Dane Mastin, explained to the Winston-Salem Journal, "the trend is getting worse in part because the bad economy, job losses and other problems are driving more people to seek escape in narcotics" (*Winston-Salem Journal*, 2009).

Although further research is needed to establish a causal connection, the above analyses demonstrate a positive association between trade-related job losses and opioid-related overdose, and that this association is significantly stronger when fentanyl is present in the local heroin supply. Though a framework was proposed, additional studies are needed to further explore the mechanism for this relationship. In addition to proximal strategies to reduce overdose including naloxone distribution, expanded treatment with pharmacotherapy for opioid use disorder, and judicious opioid prescribing, policy makers should also consider the role of macroeconomic factors - such as international trade - on opioid-related overdose mortality.

Ethics approval

The Institutional Review Boards at our Universities (George Washington University and Boston University Medical Center) determined that the analysis of this data does not constitute human subjects research.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2019.100409.

References

Achen, Christopher H. (2000). *Why lagged dependent variables can suppress the explanatory power of other independent variables.* Mimeo: University of Michigan.
Ahmad, F. B., LM Rossen, MR Spencer, Warner, M., & Sutton, P. (2016). *Provisional drug overdose death counts.* National Center for Health Statistics.
Autor, David H., & Dorn, David (2013). The growth of low-skill service jobs and the polarization of the US labor market. *The American Economic Review, 103*(5), 1553–1597.
Autor, David, Dorn, David, & Hanson, Gordon H. (2013). The China syndrome: Local labor market effects of import competition in the US. *The American Economic Review, 103*(6), 2121–2168.
Autor, David H., Dorn, David, & Hanson, Gordon H. (2016). The china shock: Learning from labor market adjustment to large changes in trade. *Annual Review of Economics, 8*(1), 205–240.
Baker, David W. (2017). History of the joint commission's pain standards. *Journal of the American Medical Association, 317*(11), 1117.
Barnett, Michael L., Olenski, Andrew R., & Anupam, B Jena (2017). Opioid-prescribing patterns of emergency physicians and risk of long-term use. *New England Journal of Medicine, 376*(7), 663–673.
Becker, William C., Sullivan, Lynn E., Jeanette, M. Tetrault, Desai, Rani A., & Fiellin, David A. (2008). Non-medical use, abuse and dependence on prescription opioids among U.S. adults: Psychiatric, medical and substance use correlates. *Drug and Alcohol Dependence, 94*(1–3), 38–47.
Bernhardt, Annette (2012). *The low-wage recovery and growing inequality.* Technical report National Employment Law Project.
Botticelli, Michael P. (2016). *National drug control strategy: Data supplement 2016*Technical report.
Carlson, Robert G., Nahhas, Ramzi W., Martins, Silvia S., & Daniulaityte, Raminta (2016). Predictors of transition to heroin use among initially non-opioid dependent illicit pharmaceutical opioid users: A natural history study. *Drug and Alcohol Dependence, 160*, 127–134.
Case, Anne, & Deaton, Angus (2015). Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proceedings of the National Academy of Sciences of the United States of America, 112*(49), 15078–15083.
Cicero, Theodore J., Ellis, Matthew S., & Kasper, Zachary A. (2017). Increased use of heroin as an initiating opioid of abuse. *Addictive Behaviors.*
Colgan, Jeff D., & Keohane, Robert O. (2017). The liberal order is rigged. *Foreign Affairs.*
Compton, Wilson M., Jones, Christopher M., & Baldwin, Grant T. (2016). Relationship between nonmedical prescription-opioid use and heroin use. *New England Journal of Medicine, 374*(2), 154–163.
Danson, Mike (2005). Old industrial regions and employability. *Urban Studies, 42*(2), 285–300.
Dasgupta, Nabarun, Leo, Beletsky, & Ciccarone, Daniel (2018). Opioid crisis: No easy fix to its social and economic determinants. *American Journal of Public Health, 108*(2), 182–186.
Davis, Donald R., & Harrigan, James (2011). Good jobs, bad jobs, and trade liberalization. *Journal of International Economics, 84*(1), 26–36.
Dean, Adam (2016). *From conflict to coalition: Profit-sharing institutions and the political economy of trade.* Cambridge University Press.
Dean, Adam (2018). "NAFTA's army: Free trade and and U.S. Military enlistment. *International Studies Quarterly, 62*(4), 845–856.
Franklin, Gary M., Bert, D. Stover, Turner, Judith A., Fulton-Kehoe, Deborah, & Wickizer, Thomas M. (2008). Early opioid prescription and subsequent disability among workers with back injuries. *Spine, 33*(2), 199–204.
Gladden, R. Matthew, Martinez, Pedro, & Seth, Puja (2016). "Fentanyl law enforcement submissions and increases in synthetic opioid–involved overdose deaths — 27 states, 2013–2014." MMWR. *Morbidity and Mortality Weekly Report, 65*(33), 837–843.
Gossop, M., Green, L., G Phillips, & Bradley, B. (1989). Lapse, relapse and survival among opiate addicts after treatment. A prospective follow-up study. *The British Journal of Psychiatry: The Journal of Mental Science, 154*(3), 348–353.
Han, Beth, Compton, Wilson M., Blanco, Carlos, Crane, Elizabeth, Lee, Jinhee, Christopher, M., et al. (2017). Prescription opioid use, misuse, and use disorders in U.S. Adults: 2015 national survey on drug use and health. *Annals of Internal Medicine, 167*(5), 293–301.
Harrison, Bennett, & Bluestone, Barry (1982). *The deindustrialization of America.* New York: Basic Books.
Hollingsworth, Alex, Ruhm, Christopher J., & Simon, Kosali (2017). Macroeconomic conditions and opioid abuse. *Journal of Health Economics, 56*, 222–233.
Jones, Christopher M., Mack, Karin A., & Paulozzi, Leonard J. (2013). Pharmaceutical overdose deaths, United States, 2010. *Journal of the American Medical Association, 309*(7), 657.
Kapstein, Ethan (1998). Trade liberalization and the politics of trade adjustment

assistance. *International Labor Review, 137*, 501.
Kletzer, Lori G. (2001). *Job loss from imports: Measuring the costs.* Peterson Institute.
Lempers, Jacques, D., Dania, Clark-Lempers, & Ronald, L Simons (1989). Economic hardship, parenting, and distress in adolescence. *Child Development,* 25–39.
Mack, Karin, A., & Centers for Disease Control and Prevention (2013). Drug-induced deaths - United States, 1999-2010. *Morbidity and Mortality Weekly Report,* 161–163 Surveillance summaries (Washington, D.C. : 2002) 62 Suppl 3(3).
Magee, Christopher (2001). Administered protection for workers: An analysis of the trade adjustment assistance program. *Journal of International Economics, 53*(1), 105–125.
Margalit, Yotam (2011). Costly jobs: Trade-related layoffs, government compensation, and voting in US elections. *American Political Science Review, 105*(01), 166–188.
Meit, Michael, Heffernan, Megan, Tanenbaum, Erin, & Hoffmann, T. (2017). *Appalachian diseases of despair.* Report for the Appalachian Regional CommissionThe Walsh Center for Rural Health Analysis National Opinion Research Center (NORC) at the University of Chicago.
Mishel, Lawrence (2018). *Yes, manufacturing still provides a pay advantage, but staffing firm outsourcing is eroding it.* Technical reportEconomic Policy Institute.
Monnat, Shannon M. (2018). Factors associated with county-level differences in U.S. Drug-related mortality rates. *American Journal of Preventive Medicine, 54*(5), 611–619.
Morden, Nancy E., Munson, Jeffrey C., Carrie, H Colla, Skinner, Jonathan S., PW Bynum, Julie, Zhou, Weiping, et al. (2014). Prescription opioid use among disabled medicare beneficiaries: Intensity, trends and regional variation. *Medical Care, 52*(9), 852.
Mossakowski, Krysia N. (2009). The influence of past unemployment duration on symptoms of depression among young women and men in the United States. *American Journal of Public Health, 99*(10), 1826–1832.
Nwagbara, Ucheoma, Buehlmann, Urs, & Schuler, Al (2002). *The impact of globalization on North Carolina's furniture industries.* Technical reportRaleigh, NC: NC Department of Commerce.
O'Donnell, Julie K. (2017). "Deaths involving fentanyl, fentanyl analogs, and U-47700 — 10 states, July–December 2016." MMWR. *Morbidity and Mortality Weekly Report, 66*(43), 1197–1202.
Pierce, Justn R., & Schott, Peter K. (2016). *Trade liberalization and mortality: Evidence from U.S. Counties*.
Rigg, Khary K., Monnat, Shannon M., & Chavez, Melody N. (2018). Opioid-related mortality in rural America: Geographic heterogeneity and intervention strategies. *International Journal of Drug Policy, 57*, 119–129.
Rudd, Rose A., Seth, Puja, David, Felicita, & Scholl, Lawrence (2016). "Increases in drug and opioid-involved overdose deaths — United States, 2010–2015." MMWR. *Morbidity and Mortality Weekly Report, 65*(5051), 1445–1452.
Smith, Adam (1776). *An inquiry into the nature and causes of the wealth of nations*.
Somerville, Nicholas, J., O'Donnell, Julie, Gladden, R. Matthew, Jon, E. Zibbell, Traci, C. G., et al. (2017). Characteristics of fentanyl overdose - Massachusetts, 2014-2016. *MMWR. Morbidity and mortality weekly report, 66*(14), 382–386.
Williams, Arthur R., & Bisaga, Adam (2016). From AIDS to opioids—how to combat an epidemic. *New England Journal of Medicine, 375*(9), 813–815.
Wood, Adrian (1995). How trade hurt unskilled workers. *The Journal of Economic Perspectives, 9*(3), 57–80.
Zoorob, Michael J., & Salemi, Jason L. (2017). Bowling alone, dying together: The role of social capital in mitigating the drug overdose epidemic in the United States. *Drug and Alcohol Dependence, 173*, 1–9.