Assessing Supply and Demand-Side Factors to Explain Geographic Variation in U.S. Drug Mortality Rates

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ABSTRACT

Objectives. To examine associations of county-level demographic, socioeconomic, and labor market characteristics on overall drug mortality rates and specific classes of opioid mortality.

Methods. We used National Vital Statistics System mortality data (2005-07 and 2014-16) and county-level U.S. Census data. We examined associations between several Census variables and drug mortality deaths for 2014-16. We then identified specific classes of counties characterized by different levels of and rates of growth in mortality from specific types of opioids. We ran multivariate regression models to predict the probabilities of membership in each specific "opioid mortality class" based on several county-level Census measures.

Results. Overall, drug mortality rates are higher in more economically disadvantaged, working-class, metropolitan counties. High rates of prescription opioid mortality cluster in economically-disadvantaged rural counties with larger concentrations of blue-collar and service industry workers. High heroin and "syndemic" opioid mortality counties (high rates across all major opioid types) are more urban, have larger concentrations of professional workers, and are less economically disadvantaged.

Conclusions. Census data are an important tool for helping us understand the importance of place-level characteristics on opioid mortality.

Introduction

Rates of fatal drug overdose increased 250% in the U.S., from 6.1 deaths per 100,000 population in 1999 to 21.7 in 2017.[1] Opioids (prescription opioids, heroin, and fentanyl) have been the primary contributor to this increase, accounting for 47,600 deaths in 2017 alone,[1] making opioids among the greatest public health threats of the 21st century. There is widespread geographic variation in fatal opioid overdose rates,[2-5] and prescription opioids, heroin, and fentanyl are differentially implicated in overdoses across different parts of the U.S.[6-8]

Our analysis of county-level variation in opioid mortality is grounded in literature emphasizing the importance of ecological factors on population health and reflects and embraces the importance of counties as population health units of analysis.[9] Counties are both small enough to reflect local economic and social conditions and large enough to be meaningful for policy.[10] County governments provide political and economic structure, which ultimately affects health and well-being. Moreover, the county represents the delivery context of most social and health services and where states administer funding for most social programs[10]. Counties are also largely responsible for covering the costs of the drug crisis, in the form of criminal justice, social services, and emergency service provider expenditures.

Census data can be an essential tool for helping us understand geographic variation in drug mortality rates and therefore in driving policy responses to the crisis. Multiple prior studies have used Census data to understand the roles of demographic, socioeconomic, and labor market conditions on county-level variation in life expectancy,[9,11] all-cause mortality[12-16], premature mortality,[17,18] and cause-specific mortality from cardiovascular diseases,[19] cancers,[19] chronic obstructive pulmonary disease (COPD),[19] diabetes,[20] and unintentional injury[21] in the U.S. Using county-level Census data and pooled county-level mortality rates for 2006-15, Monnat[22] found that drug mortality rates varied across different types of labor markets, and were higher in counties characterized by greater economic disadvantage and lower in places that attracted recent in-movers. However, that study pooled 10-years of mortality data into one rate and did not examine how county characteristics were differentially associated with different classes of opioid mortality. Rather, it focused on the socioeconomic correlates of the drug mortality rates overall. Because prior research has primarily focused on an omnibus measure of drug mortality deaths, there is limited information about the ecological correlates of mortality linked to various forms of opioids.

In this study, we extend prior research on geographic differences in opioid mortality by using the Census (1) to describe the county-level demographic, economic, labor market, and housing characteristics that are associated with overall drug mortality rates in 2014-16 and (2) to analyze how these characteristics vary across what we refer to as "opioid mortality classes" – classes of counties characterized by differential levels and rates of growth in mortality from specific types of opioids (i.e., prescription, heroin, synthetic) and drug combinations.

Methods

Data

Mortality data came from the restricted-use death certificate files from the National Center for Health Statistics National Vital Statistics System, 2005-2016. These data identify causes of death and decedent county of residence from all death certificates filed in the U.S., enabling us to calculate county-level drug mortality rates (deaths per 100,000 population). We categorized drug deaths based on the International Statistical Classification of Diseases, 10th revision (*ICD-10*) codes as any death that included an underlying cause (UCD) of accidental poisoning, intentional poisoning, poisoning of undetermined intent by exposure to drugs, assault by drugs, drug-induced diseases, finding of drugs in the blood, and mental/behavioral disorders due to drugs. The specific ICD-10 codes are listed in Appendix A Table A1. Overall opioids deaths and deaths due to specific opioids (i.e., heroin, prescription, synthetic) were identified as those with an UCD reflecting accidental, intentional, or undetermined intent poisoning or assault along with any multiple-cause-of-death opioid-specific ICD-10 code (T40.0-T4.04, T40.6) or any mental and behavioral disorder due to opioids (F11.0-F11.9). We calculated rates for heroin, prescription opioids, synthetic opioids, and multiple-cause (those that included two or more opioids). Because opioid deaths are known to be underreported on death certificates with substantial geographic variation in underreporting,[6,23] we calculated a fifth measure representing all drug overdoses, minus those that included an opioid on the death certificate.

To smooth potentially large fluctuations from small changes in death counts in small population counties, we pooled deaths across a three-year period. Consistent with CDC methods, we then calculated age-adjusted rates with the direct method using the 2000 U.S. standard population.

County-level population (demographic), socioeconomic, labor market, and housing measures came from the 2000 U.S. Census. All Census variables included in the analysis are listed in Table 1. The use of data from 2000 reduces the risk of reverse causality bias and allows for a lagged relationship between county-level conditions and mortality. In supplemental analyses, we substituted data from the 2008-12 and 2012-16 American Community Survey (ACS) 5-year estimates. Findings were robust to these alternative specifications.

To control for opioid supply factors, we also included county-level retail opioid prescribing from QuintilesIMS Transactional Data Warehouse (CDC, 2018). These data report retail opioid prescriptions dispensed per 100 persons. A limitation is that they include only prescriptions obtained from retail pharmacies and exclude high-volume prescribing pain clinics (i.e., "pill mills"). Prescribing information was missing for between 6% and 13% of counties, depending on year. We imputed average missing prescribing values using a Markov Chain Monte Carlo model with 500 imputations.[24] The analyses we present includes the average prescribing rate for 2009-2011 to capture years of peak prescribing, but we tested alternate models with prescribing rates for 2006-08 and 2012-14. Findings were robust to these substitutions.

Analyses included 3,079 U.S. counties. Analyses were restricted to the 48 conterminous states and Washington, D.C. Values for Broomfield County, CO, newly created in 2003, were disaggregated back into its pre-2003 counties for analysis over time. We also merged 29 independent cities in Virginia with populations under 65,000 back into their respective counties. This reduces the potential for ACS measurement error in small cities.

Statistical Analysis

For the first part of the analyses, we examined relationships between year 2000 county-level Census characteristics (with sensitivity tests using 2008-12 and 2012-16 ACS estimates) and overall drug mortality rates for 2014-16. Using negative binomial regression, we modeled overall drug mortality counts for 2014-16, offset by the log of the county population, as a function of each of the Census characteristics. We standardized all variables prior to including them in regression models, enabling us to compare the relative strength of associations across different factors. We adjusted each model only for county racial and age composition. We do not attempt to tease out the mechanisms through which each of these variables are associated with drug mortality. We simply aim to show the relative importance of several Census variables for understanding county-level differences in drug mortality rates. Because mortality rates and U.S. Census estimates for counties with small populations are at risk of instability and large margins of error, we weighted regression analyses by county population (logged) for 2014-16.

For the second part of the analyses, we describe variation in county-level Census characteristics across specific classes, or groupings of counties, of opioid-specific mortality. We identified opioid-specific mortality classes using latent profile analysis (LPA). LPA offers several advantages over more common classification techniques like hierarchical cluster analysis.[25] LPA provides hypothesis tests of class structure and model fit statistics, whereas cluster analysis relies on subjective heuristics. Cluster analysis can result in very different solutions depending on the type of distance metrics and linkage rules used, whereas LPA relies on a single estimation technique. Most importantly, LPA estimates classification uncertainty using posterior probabilities obtained using Bayesian methods. By contrast, cluster analysis incorrectly assumes perfect certainty in classification, failing to recognize that cases may fit well into multiple clusters.

We used LPA to create county classifications based on age-adjusted opioid mortality rates for 2014-16 and the change in rates between 2005-07 and 2014-16 using the opioid specific mortality rates described above (e.g., prescription opioids, heroin, synthetic, multiple), including rates for drug overdose deaths that did not specify an opioid on the death certificate. We normalized mortality rates using z-scores to remove scale differences and allow for comparisons across categorizes. Like all classification techniques, LPA is sensitive to extreme scores that can result in a large number of classes with few cases. To minimize this, we Winsorized extreme scores at the 0.5 and 99.5 percentiles, roughly corresponding to ±2.6 standard deviations (SD). We found evidence for six classes based on fit indices and examination of latent class means (see Appendix B Table B1). Specific criteria used to assess fit are described in Appendix B.[26-28] We discuss the six classes in the Results section.

We first compared the means of the same Census characteristics from the overall drug mortality analysis across the different opioid mortality classes. We then modeled the probability of membership in each of the opioid mortality classes as a function of the Census variables using multivariate multinomial logistic regression. Models included adjusted standard errors for the clustering of counties within states.

Because there are strong correlations between several Census variables, they are ideal for generating indices that capture latent constructs. We used exploratory factor analysis to identify which of the 38 Census variables grouped together under common constructs. Initial eigen values indicated that the first four factors, representing 28 of the Census variables collectively explained 70% of the variance. We created four factor-weighted indices that combined the variables loading highly onto their respective factors (factor loading of $\geq$.40). We then standardized all factors to a mean of 0 and standard deviation of 1. The first index, termed *urban professional* (alpha=0.88) is a construct reflecting the presence of a large professional middle class, and includes population density, percentage of renter-occupied housing units, percentage employed in business and professional industries, percentage employed in finance, insurance, and real estate (FIRE) industries, percentage of workers employed in professional and technical, executive and managerial occupations, retail sales, and administrative/clerical occupations. The second index, termed *economic disadvantage* (alpha=0.90), captures percent poverty, percentage of households receiving public assistance, inverse of the labor force participation rate, Thiel's L (inequality at the bottom of the income distribution), the Gini coefficient of income inequality, the ratio of federal-to-state median household income, percentage of single parent families, and percent divorced/separated. The third index, termed *blue collar presence* (alpha=0.84), which reflects a large presence of working-class and manual laborers, includes percentage age 25+ without a four-year college degree, percentage of workers employed in production, extraction, and construction occupations, percentage employed in transportation and material moving occupations, and percentage employed in the manufacturing industry. The final index, termed *service economy* (alpha=0.68), includes percentage of workers in personal service occupations, percentage employed in retail, personal sales, food, and accommodations; construction; and public administration industries, percent veterans, and percent vacant housing units.

Multivariate regression models simultaneously included these four indices and controlled for racial/ethnic and age composition, metropolitan status, percentage of new residents to the county in past 5 years, and average opioid prescribing in 2009-11.

Results

A map of drug mortality rates by county for 2014-16 is shown in Appendix A, Figure A1. High rates are concentrated throughout New England, central Appalachia, parts of the Industrial Midwest, eastern Oklahoma, and the desert southwest. Concentrations of low rates are observed throughout the southern black belt, Texas, and the northern Great Plains.

The regression models reveal that several demographic, socioeconomic, and labor market Census characteristics are associated with overall drug mortality rates, net of county racial/ethnic and age composition (Table 1). County population density; percent veterans; multiple markers of economic disadvantage, percentages separated/divorced and single parent families; percentages working in administrative/clerical, personal services, and retail occupations; and percentages employed in business/professional, communications, information, and utilities, health service, retail, personal services, food, and accommodations, mining, and public administration industries are all associated with significantly higher drug mortality rates in 2014-16. Nonmetro status, percent recent in-movers, percentage employed in farming, fishing, or forestry occupations or industries, and percentage employed in education and manufacturing industries are associated with significantly lower drug mortality rates. Counties with higher opioid prescribing rates have significantly higher ($p<.001$) drug mortality rates in 2014-16.

Turning to the LPA results, means of opioid-specific mortality rates and standardized rates across the six latent opioid classes are shown in Appendix B Tables B2 and B3. The majority of counties (1,791, 58%) are in a *low-or-average opioid mortality* class. These are counties with comparatively low death rates and lower change rates between 2005-07 and 2014-16 from each of the specific opioid types and other drugs. The LCA classified 232 counties

(7.5%) into the *high prescription opioid* class, characterized by high rates of prescription opioid mortality in 2014-16 that grew much faster than the national average since 2005-07. The *high heroin* class (N=150, 4.9%) is characterized by sharply-rising heroin mortality rates between 2005-07 and 2014-16, with rates in 2014-16 the highest in the nation. The *emerging heroin* class (N=453, 14.7%) incorporates counties with slightly lower and slower-growing heroin mortality rates than the high heroin class, but heroin rates in the emerging class still outpace most other classes. There are two multi-opioid classes, representing counties where deaths involve multiple opioids, including fentanyl. The *synthetic+* class (N=213, 6.9%) has high and fast-growing mortality rates from synthetic opioids alone or in combination with prescription opioids, and to a lesser extent, heroin. By contrast, counties in the final class (N=141, 4.6%) are in the depths of the opioid crisis, having very high and rapidly-growing mortality rates from all types of opioids: heroin, synthetic, prescription opioids, and combinations. We term this class the *syndemic opioid* class because it reflects an aggregation of multiple concurrent or sequential epidemics, in which the combination of high rates of death from multiple opioids greatly exacerbates the crisis.[29] The remaining counties (N=99, 3.2%) were unclassified.

The geographic distribution of opioid classes is show in Figure 1. The specific opioids or combinations of opioids implicated in high drug mortality rates vary substantially across the U.S. High prescription opioid class counties are concentrated in southern Appalachia, eastern Oklahoma, parts of the desert southwest and Mountain West and sprinkled throughout the Great Plains. High heroin and emerging heroin counties are geographically distinct from the prescription opioid class and are concentrated throughout parts of New York, the Industrial Midwest, central North Carolina, and parts of the southwest and northwest. The synthetic+ and syndemic classes are concentrated throughout New England, central Appalachia, and central New Mexico.

Mean overall drug and opioid-specific mortality rates and means of all county characteristics are shown in Appendix C, Table C1. Overall drug mortality and opioid-specific mortality rates in 2014-16 were highest in the syndemic class (41.3 overall drug and 31.7 opioid-specific deaths per 100,000 population), followed by synthetic+ (29.4, 20.0), prescription opioid (27.9, 17.6), high heroin (25.2, 16.7), emerging heroin (19.5, 11.1), and low/average overdose class (11.4, 3.). On average, the low/average mortality class has lower percent black, lower population density, and lower percent veterans than the opioid classes. Nonmetro counties are most heavily represented in the prescription opioid class; 76% of nonmetro counties are in the prescription opioid class, whereas they are only 35% of counties in the syndemic class. On average, the prescription opioid class counties are the most economically disadvantaged, have the highest blue collar and service economy index scores, and have the lowest urban professional index score. These counties also have the highest average prescribing rates. The emerging heroin and syndemic class counties have the highest urban professional index scores and the lowest blue-collar index scores.

Relative risk ratios of opioid mortality class membership (compared to the low/average reference group) are presented in Table 2. While economic disadvantage was associated with higher overall drug mortality rates, it was not significantly associated with specific cluster membership, net of controls. Supplemental analyses revealed that the addition of opioid prescribing eliminated the significance of economic disadvantage for the prescription opioid class. The blue-collar index and service economy index are associated with significantly greater odds of being in any of the five opioid classes versus the low/average mortality class. The urban professional index is associated with significantly greater odds of being in the heroin, synthetic+, or syndemic classes versus the low/average mortality class. Percent black is associated with lower odds of being in any of the five opioid classes versus the low/average class. Percentage of recent in-movers to the county is associated with lower odds of being in the heroin, synthetic+, and syndemic classes. Finally, opioid prescribing in 2009-11 is associated with significantly greater odds of being in the prescription opioid class, supporting the validity of our opioid class construction. Although relative risk ratios are useful for assessing risk of cluster membership compared to the reference class, they do not compare relative risk across all classes.

Predicted probabilities of opioid mortality class membership by levels of the four Census-variable derived indices are presented in Figure 2. Probabilities are from fully-adjusted models with all other variables held at their means. Higher levels of county economic disadvantage (A) are associated with lower probability of membership in both heroin classes but greater probability of membership in the prescription opioid and synthetic+ classes. Greater blue-collar worker presence (B) is associated with rapidly declining probability of membership in the low/average mortality class and higher probabilities of membership in the emerging heroin and syndemic classes. Higher values on the urban professional index (C) are related to rapidly declining probabilities of membership in the low/average mortality class and in the prescription opioid class and higher probabilities of membership in the emerging heroin, synthetic+, and syndemic classes. Finally, higher values on the service economy index (D) are associated with lower probability of membership in the low/average mortality class and greater probability of membership in each of the five opioid classes. Appendix D shows that opioid prescribing is only associated with increased probability of membership in the prescription opioid class.

Discussion

Counties are important analytical units for understanding how ecological conditions relate to population health. Our findings support the contention that place matters not only for understanding drug mortality rates overall, but for specific classes of opioid mortality. Consistent with recent research on drug overdose trends in the U.S., we found substantial geographic variation in overall drug mortality rates.[4,7,22] Net of demographic controls, overall drug mortality rates (2014-16) were higher in counties characterized by more economic disadvantage, greater concentrations of blue-collar and working-class occupations and industries, counties with higher rates of opioid prescribing, and in metropolitan counties.

Our study also shows important geographic variation in mortality rates from specific types and combinations of opioids. Using innovative latent profile analysis methods, we found that counties cluster into six distinct "classes of opioid mortality", characterized by differential mortality rates and changes in rates from different types of opioids. We found substantial variation in the importance of different place-level factors for specific classes of opioid mortality – an empirical observation not considered in previous research on geographic differences in opioid mortality.[30,31]

For example, we found that high rates of prescription opioid deaths and deaths from combinations of synthetic and prescription opioids (the synethic+ class) cluster in more economically disadvantaged rural counties with comparatively larger concentrations of blue-collar and service industry workers. High blue collar and service worker presence – what we might collectively think of as the working class – was associated with increased odds of being in *all five* high opioid mortality classes versus the low/average mortality class. The nature of blue collar and service work might increase risk for work-related injury or physical wear and tear, thereby increasing demand for pain treatments within these contexts. Moreover, numerous in-depth accounts show that declines in good-paying and secure employment opportunities for the working-class have manifested in collective psychosocial despair, family and community breakdown, and social disorders like substance misuse [32-34]. Graham and Pinto[35] show that working-class whites are less hopeful and optimistic about their futures than any other group in the U.S., and that optimism among this group started to decline in the 1970s. Interventions aimed at helping individuals suffering from addiction in these places must consider the likely absence of alternative pain treatment services, underfunded public services resulting from community economic disinvestment, and the need for "wraparound" services that address not just drug addiction but chronic pain and despair in these places.

In contrast to the high prescription opioid and synthetic+ class, the heroin and syndemic opioid classes (counties with high mortality across all types and combinations of opioid), is more urban, represents larger concentrations of professional workers, and is less economically disadvantaged. Interventions in these places should be structured differently based on their relatively advantaged social and economic contexts. However, it is possible that the same infrastructural and locational advantages that allow for prosperous urban contexts also contribute to early adoption and distribution of new opioid products, which disproportionately harm the disadvantaged residents of these counties. Counties characterized by high rates of death from combinations of opioids require a multifaceted supply and demand-based response from policymakers and public health professionals.

Collectively, our findings highlight the importance of Census data for understanding geographic variation in a timely and important population health crisis. Census data allow for a more complete understanding of the ecological correlates of drug mortality, helping to inform development of place-specific policies to address drug crises. Our findings support the contention that population health crises and their causes and consequences follow different trajectories across places. The opioid crisis is not monolithic across U.S. Rather, there are four specific crises: prescriptions alone, heroin alone, synthetics mixed with heroin, and a syndemic opioid group involving high rates of death from all three major opioids. Each class of counties is distinct in its socioeconomic and labor market conditions, suggesting different causes and policy responses to address the crisis. We call on public health researchers to explore place-based trajectories and to use historical and forthcoming 2020 Census and American Community Survey data to better understand heterogeneity in other population health crises.

Limitations

There are important limitations to consider when interpreting this study's findings. First, because this is ecological research, we do not distinguish between place-based and individual effects, and we cannot account for individual decedents' duration of residence. Second, aggregate measures of county-level conditions mask important and often substantial within-county differences. Third, death certificates may misclassify cause of death, leading to an undercount of opioid deaths.[6] We attempt to minimize this concern by including in our LPA a measure mortality from deaths where an opioid was not specified on the death certificate. Fourth, the available prescribing data include prescriptions from retail pharmacies only and exclude prescriptions that came from high-volume prescribing pain clinics (i.e., pill mills). Fifth, relationships between county environments and drug mortality rates likely play out over an extended period, but this study considered only relatively recent county conditions and did not consider changes in county environments over time. Future research should examine the role of changing labor markets since the 1980s and concomitant socioeconomic changes on drug mortality rates. Finally, it was beyond the scope of this paper to examine variation in mortality rates across demographic subgroups (i.e., sex, race/ethnicity, age, educational attainment). Future research should examine whether relationships between the ecological measures assessed here and opioid mortality rates apply equally to opioid and other drug mortality across different demographic subgroups.

Public Health Implications

National policy strategies to combat the opioid crisis cannot be assumed universally applicable. For example, policies targeting the prescription opioid supply are unlikely to be effective in places characterized by high rates of heroin and synthetic opioid overdose. Counties are embedded within state contexts that can constrain or enhance local efforts to address the opioid crisis. Understanding that certain combinations of place-level factors put some counties at greater risk of high drug mortality rates, and that similar risks are often shared by neighboring counties, could facilitate regional responses and better resource targeting. In addition to important national policies to combat the opioid and larger drug crisis, emphasis should be placed on developing locally- and regionally-tailored interventions. Moreover, interventions are unlikely to be effective if they do not consider the diverse social and economic profiles of places.

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Table 1. Census Variable Descriptive Information and Coefficients from Minimally-Adjusted Negative Binomial Regressions of County-Level Drug Deaths (2014-16) on County Census Characteristics (2000)

	Mean (SD)	IDR	95% CI	p
Population Characteristics				
Non-Hispanic white, %	81.69 (18.71)	1.10	1.05 to 1.14	<.001
Non-Hispanic black, %[a]	8.64 (14.44)	0.86	0.82 to 0.90	<.001
Hispanic, %[a]	6.18 (12.16)	0.96	0.92 to 1.01	.088
Age 65+, %	14.82 (4.11)	0.97	0.94 to 1.01	0.094
Veterans, %	13.97 (2.92)	1.09	1.05 to 1.13	<.001
Moved into county in last 5 years, %[b]	19.78 (6.58)	0.90	0.87 to 0.94	<.001
Population density[b]	3.73 (1.65)	1.14	1.07 to 1.16	<.001
Nonmetro (0/1)[c]	62.97%	0.91	0.85 to 0.98	0.013
Socioeconomic Characteristics				
Not working (unemp. or not in labor force), %[c]	55.65 (5.81)	1.11	1.06 to 1.16	<.001
No 4-year college degree, %	83.56 (7.69)	1.06	1.02 to 1.10	<.001
Ratio of federal-to-county median household income, %	125.9 (28.79)	1.06	1.02 to 1.10	0.007
Poverty, %	14.18 (6.53)	1.08	1.03 to 1.13	0.001
Public assistance receipt, %	0.94 (0.65)	1.12	1.08 to 1.16	<.001
Thiel's L (inequality at bottom of income distribution)	0.33 (0.07)	1.02	0.98 to 1.06	0.377
Gini coefficient of income inequality	0.43 (0.04)	1.06	1.02 to 1.11	0.004
Separated or divorced, %	11.27 (2.27)	1.29	1.24 to 1.34	<.001
Single parent families, %	25.05 (7.38)	1.21	1.15 to 1.27	<.001
Vacant housing units, %	14.21 (9.56)	1.02	0.99 to 1.06	0.234
Renter-occupied housing units, %	22.32 (7.40)	1.02	0.99 to 1.06	0.218
Occupational Composition				
Administrative/clerical, %	13.48 (2.09)	1.07	1.03 to 1.11	<.001
Executive and managerial, %	9.04 (2.94)	0.99	0.95 to 1.02	0.425
Farming, fishing, forestry, %[b]	5.44 (6.40)	0.84	0.81 to 0.88	<.001
Personal services, %	13.27 (2.76)	1.07	1.03 to 1.11	<.001
Production, extraction, construction, %	22.73 (6.50)	1.00	0.96 to 1.04	0.999
Professional/technical, %	18.61 (3.83)	1.03	1.00 to 1.06	0.090

Retail sales, %	9.68 (2.02)	1.07	1.03 to 1.11	<.001
Transportation and material moving, %	7.74 (2.14)	1.02	0.98 to 1.05	0.390
Industry Composition				
Agriculture, fishing, forestry, % [b]	6.13 (7.03)	0.84	0.81 to 0.88	<.001
Business & professional, %	5.27 (2.63)	1.05	1.02 to 1.09	0.004
Construction, %	7.72 (2.37)	1.02	0.99 to 1.06	0.200
Communication, information, utilities, % [b]	3.11 (1.36)	1.07	1.03 to 1.11	<.001
Finance, insurance, real estate, %	4.57 (1.86)	1.01	0.97 to 1.04	0.712
Education, %	9.16 (3.13)	0.96	0.93 to 0.99	0.033
Health, %	11.08 (2.66)	1.09	1.05 to 1.13	<.001
Retail, personal services, food, accommodations, %	23.33 (4.24)	1.09	1.06 to 1.13	<.001
Mining, %	1.16 (2.71)	1.06	1.02 to 1.11	0.001
Manufacturing, %	15.90 (9.07)	0.95	0.91 to 0.99	0.014
Public administration, %	5.35 (3.01)	1.04	1.00 to 1.08	0.038
Transportation, %	4.22 (1.52)	1.02	0.99 to 1.05	0.224
Wholesale Trade, %	3.00 (1.13)	0.97	0.94 to 1.01	0.110
Opioid prescribing [c]				
Retail opioid prescribing per 100 pop, 2006-08	82.51 (40.88)	1.21	1.17 to 1.26	<.001
Retail opioid prescribing per 100 pop, 2009-11	89.45 (44.31)	1.21	1.17 to 1.26	<.001
Retail opioid prescribing per 100 pop, 2012-14	89.33 (42.78)	1.24	1.20 to 1.28	<.001
Retail opioid prescribing per 100 pop, 2015-16	75.84 (40.69)	1.25	1.21 to 1.30	<.001

N=3,079

SD= standard deviation; IDR=incidence density ratio; CI=confidence interval, p=p-value

Notes: All variables are standardized at a mean of 0 and standard deviation of 1. The regressions model death counts (offset by the log of the county population size) using random effects negative binomial models. All models are adjusted for county age 65+ and percent NH white and are weighted by the log of the county population. Means are unweighted.

[a] Models for percent non-Hispanic black and percent Hispanic control only for percent age 65+

[b] Due to non-normality, this variable was logged for regression analysis

[c] Metro status, labor force participation rate, and opioid prescribing are not from Census 2000.

Table 2. Relative Risk Ratios of Opioid Class Membership

	High Rx Opioid		Emerging Heroin		High Heroin		Synthetic+		Syndemic	
	RRR	95% CI	RRR	95% CI	RRR	95% CI	RRR	95% CI	RRR	95% CI
Economic disadv. index	1.34	0.94 to 1.91	0.72	0.56 to 0.93	0.60	0.38 to 0.94	1.24	0.88 to 1.74	0.72	0.40 to 1.27
Blue collar index	1.54	1.14 to 2.09	2.42	1.80 to 3.27	2.15	1.36 to 3.39	2.09	1.56 to 2.80	3.07	1.49 to 6.30
Urban professional index	0.70	0.48 to 1.03	3.44	2.57 to 4.61	2.49	1.50 to 4.14	3.26	1.95 to 5.44	5.70	2.59 to 12.55
Service economy index	1.47	1.19 to 1.83	1.71	1.45 to 2.02	1.93	1.43 to 2.62	1.97	1.59 to 2.43	3.09	2.15 to 4.43
Non-Hispanic black, %	0.55	0.39 to 0.78	0.76	0.58 to 1.00	0.72	0.47 to 1.10	0.49	0.30 to 0.82	0.55	0.29 to 1.06
Hispanic, %	0.63	0.45 to 0.89	0.97	0.77 to 1.22	1.18	0.91 to 1.53	0.54	0.24 to 1.19	0.83	0.32 to 2.19
Age 65+, %	1.12	0.90 to 1.38	0.92	0.74 to 1.14	0.85	0.63 to 1.15	0.82	0.62 to 1.08	0.76	0.56 to 1.03
New residents, past 5 years, % (logged)	1.15	0.86 to 1.54	0.77	0.64 to 0.93	0.52	0.39 to 0.68	0.61	0.46 to 0.81	0.32	0.19 to 0.52
Nonmetro	0.70	0.46 to 1.07	1.11	0.76 to 1.62	1.00	0.66 to 1.51	1.10	0.73 to 1.67	0.58	0.30 to 1.12
Opioid prescribing, 2009-11	1.60	1.29 to 1.97	0.89	0.74 to 1.07	1.02	0.79 to 1.30	1.04	0.84 to 1.29	1.31	0.97 to 1.75

Reference category=low/average overdose
RRR=relative risk ratio; CI=95% confidence interval
RRRs based on multinomial logistic regression model with clustered standard errors. Model weighted by the log of the county population.
All variables except metro status are z-score standardized.
Pseudo R^2=0.92

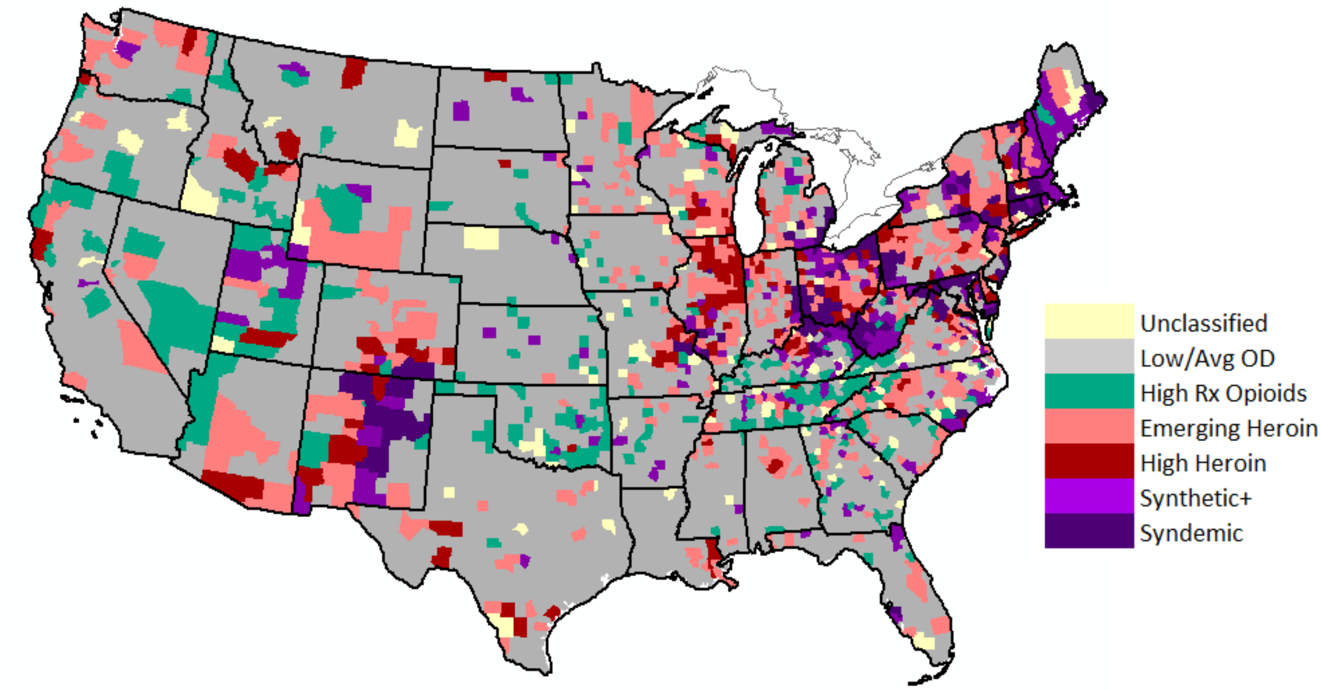
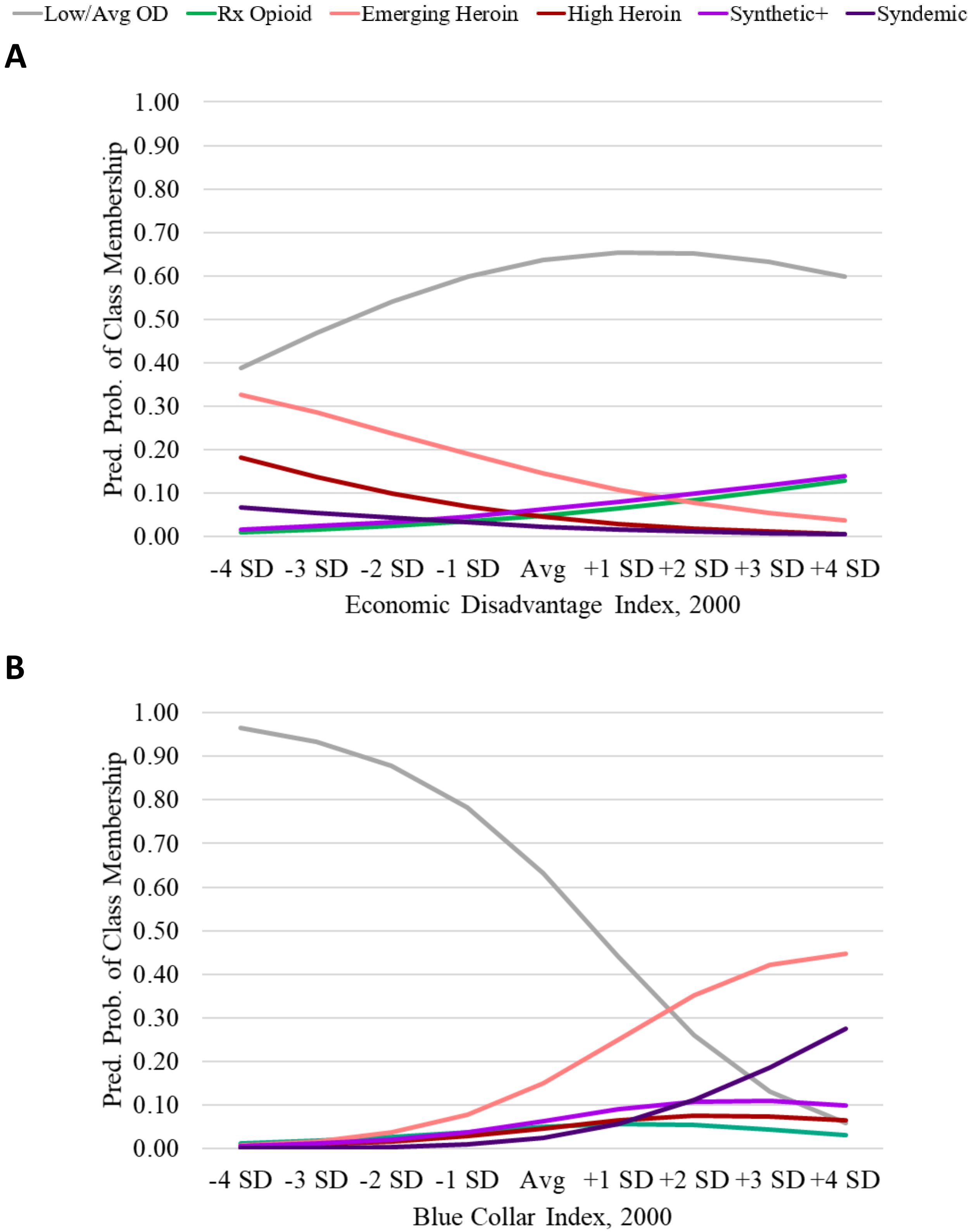


Figure 1. Opioid Mortality Classes

Note: Based on absolute mortality rates in 2014-16 and change in rates between 2005-07 and 2014-16

Figure 2. Predicted Probabilities of Opioid Mortality Class Membership by Levels of Census-Variable Derived Indices



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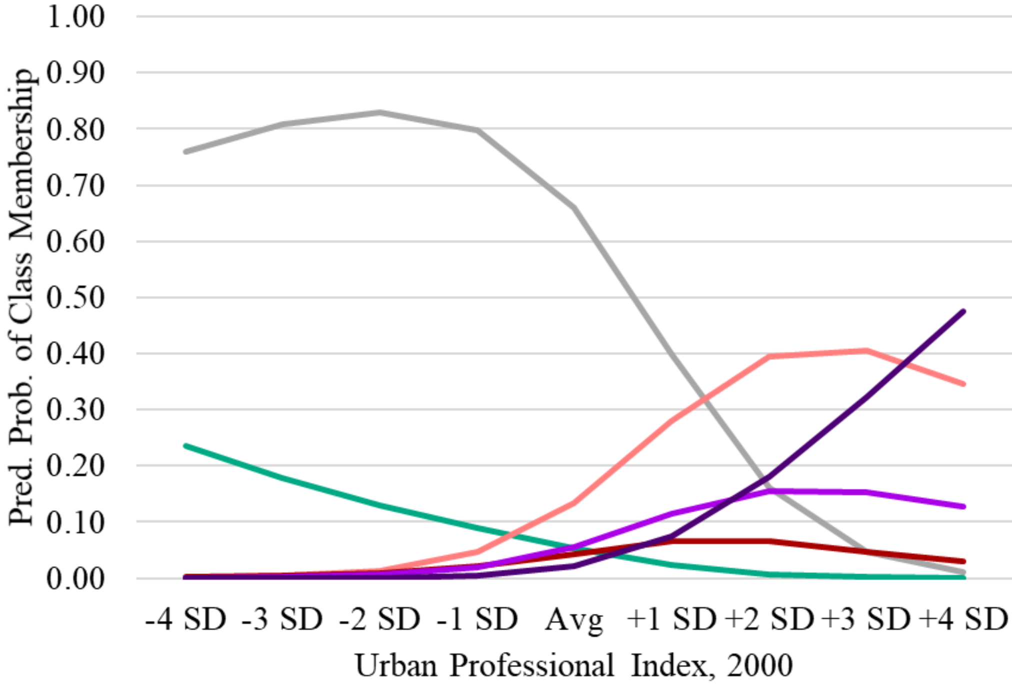

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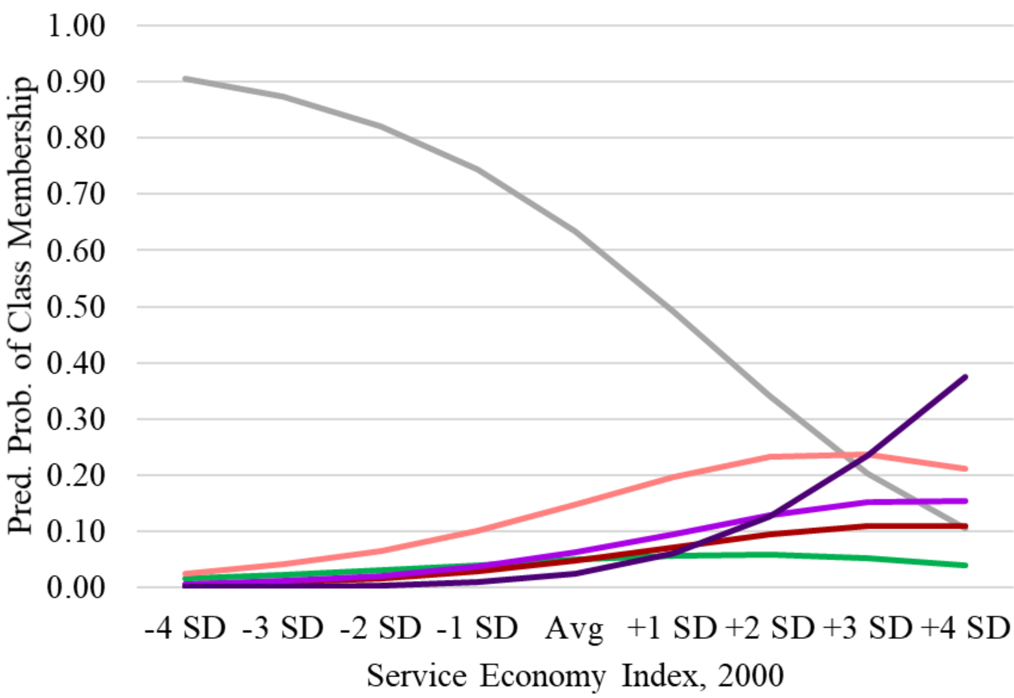

SD=standard deviation

Note: predicted probabilities are calculated from fully-adjusted multinomial logistic regression models with all other variables held at means.

APPENDIX A

Table A1. ICD-10 codes identified as drug-related

Category	**ICD-10 code**
Poisoning due to drugs (accidental, intentional, assault, underdetermined intent)	X40-X44, X60-64, X85, Y10-Y14
Drug-induced diseases	D52.1, D59.0, D59.2, D61.1, D64.2, E06.4, E16.0, E23.1, E24.2, E27.3, E66.1, G21.1, G24.0, G25.1, G25.4, G25.6, G44.4, G62.0, G72.0, I95.2, J70.2-J70.4, K85.3, L10.5, L27.0, L27.1, M10.2, M32.0, M80.4, M81.4, M83.5, M87.1, R50.2
Finding of drugs in the blood	R78.1-R78.5
Mental and behavioral disorders due to drugs	F11.0-F11.5, F11.7-F11.9, F12.0-F12.5, F12.7-F12.9, F13.0-F13.5, F13.7-F13.9, F14.0-F14.5, F14.7-F14.9, F15.0-F15.5, F15.7-F15.9, F16.0-F16.5, F16.7-F16.9, F18.0-F18.5, F18.7-F18.9, F19.0-F19.5, F19.7-F19.9
Opioid specific	(X40-X44, X60-64, X85, Y10-Y14 *plus* any of T40.0-40.4, T40.6) *or* F11.0-11.9
Heroin	T40.0 and T40.1
Prescription	T40.2 and T40.3
Synthetic or unknown narcotic	T40.4 and T40.6

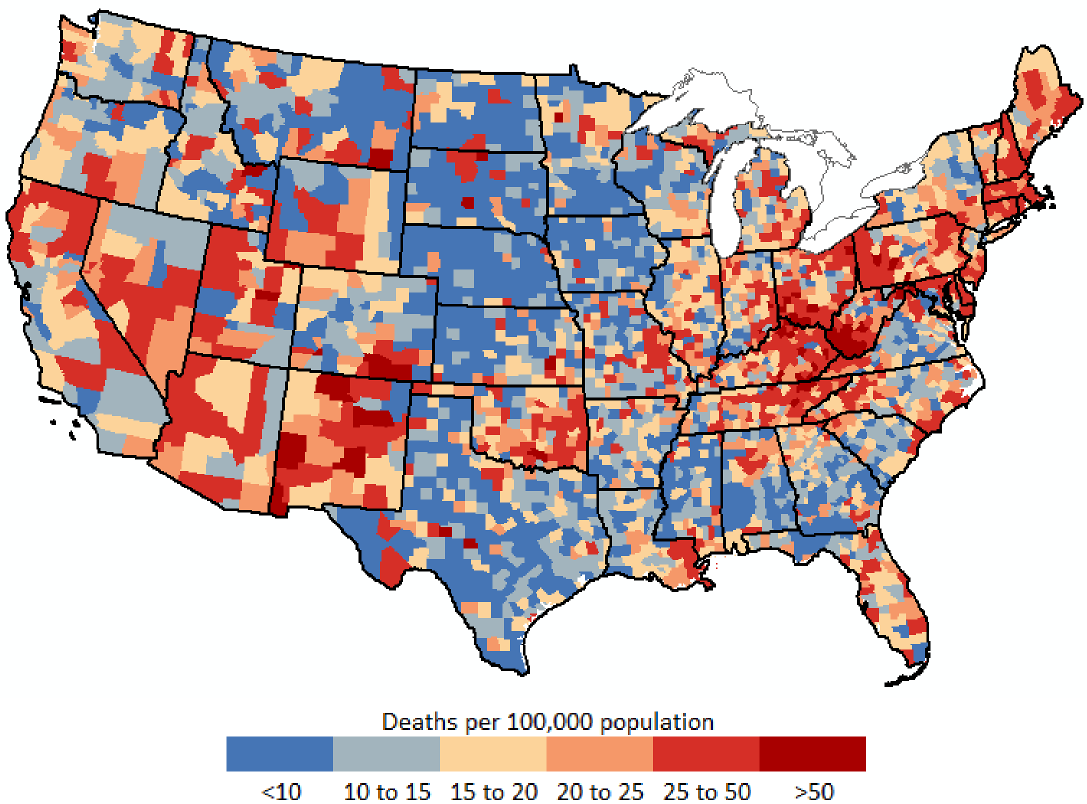

Figure A1. Age-Adjusted County-Level Drug Mortality Rates, 2014-16

APPENDIX B

Explanation of Latent Profile Analysis (LPA) Methods

Latent profile analysis (LPA) is part of a broader technique of finite mixture models. Although LPA is used for continuous indicators and latent class analysis for categories ones, we refer to the profiles as classes. LPA assumes the observed data is a multivariate mixture collected from a number of mutually exclusive classes, each with its own distribution (Lanza, Tan, and Bray, 2013). The estimated LPA density function is presented in equation 1, where $\mathbf{x}_i$ are the opioid mortality variables, $\boldsymbol{\lambda}_k$ are the mixture weights for each variable in class k, and $\boldsymbol{\theta}_k$ are the mean vectors and covariance matrices for each class or $\boldsymbol{\theta}_k = (\boldsymbol{\mu}_k , \boldsymbol{\Sigma}_k)$ (Collier and Leite, 2017). The LPA is identified by having positive degrees of freedom, an information matrix that is positive definite, and the assumption of uncorrelated indicators or cov ($\mathbf{x}_i$, $\mathbf{x}_i$) = 0 (Abar and Loken, 2012; McLachlan and Peel, 2000). Expectation-maximization is used to obtain maximum likelihood a posterior (MAP) estimates. To avoid the issue of local maxima, we estimate 5,000 initial starting values and optimize 10 in the final stage (Marsh et al., 2009).

(1) $$f\left(x_i \mid \theta\right) = \sum_{1}^{K} \lambda_k f_k\left(x_i \mid \theta_k\right)$$

The sample-size adjusted Bayesian information criterion is a relative fit index based on the -2LL, adjusted for parameters and sample size, with lower values indicating better fit. The rate of decrease in BICs slows down at class-6, indicating this is an ideal solution. The relative entropy index is the degree of uncertainty in classification, with values above 0.8 indicating good separation across classes (Collier and Leite, 2017). All classes exhibit good separation. The Lo-Mendell-Rubin (LMR) adjusted likelihood ratio tests the null hypothesis that k number of classes fits just as well and k classes, with failure to reject indicating one fewer class is needed. The LMR test is non-significant at class-8, indicating the presence of seven classes. However, examination of latent means shows little additional information is provided by adding a seventh class, with the two being identical in shape and only slightly different in elevation. Therefore, we chose the six-class solution based on fit, interpretability and parsimony.

Table B1. Results of the Latent Profile Analysis (LPA) on Opioid Mortality Rates in 2014-16 and Change from 2005-07.

Class	BIC	BIC-SSA	Relative Entropy	LMR Test	LMR p
1	75,460.03	75,396.48	n.a.	n.a.	<.001
2	67,852.61	67,754.11	0.969	7,609.66	<.001
3	65,141.08	65,007.63	0.952	2,768.55	<.001
4	62,687.81	62,519.41	0.966	2,513.19	<.001
5	61,285.18	61,081.83	0.960	1,474.30	<.004
6	60,060.55	59,822.25	0.943	1,298.29	<.001
7	58,823.22	58,549.97	0.947	1,272.13	<.001
8	57,857.77	57,549.56	0.954	1,042.02	0.127
9	56,903.32	56,560.16	0.944	951.94	0.355
10	55,978.41	55,600.29	0.945	890.214	0.711

BIC = Bayesian information criteria

BIC-SSA = sample-size adjusted BIC

LMT = Lo-Mendell-Rubin test.

Description of the Opioid Classes

Means of opioid-specific mortality rates and standardized rates across the six latent opioid classes are presented in Tables B2 and B3 below. The majority of counties (1,791) are in a *low-to-average opioid mortality* class. These are counties having comparatively low rates of death and slower rates of change between 2005-07 and 2014-16, with all opioid mortality rates being below average, but non-opioid drug deaths at the national average. LCA classified 232 counties into the *prescription opioid* class, characterized by high rates of prescription opioid mortality in 2014-16 (13.58/100,000 population, z=1.70), that has grown much faster than the national average since 2005-07 (7.84 gain per 100,000 population, z=1.34). The *high heroin* class (N=150) saw heroin mortality rates rise sharply between 2005-07 and 2014-16, with rates in 2014-16 at 8.22 per 100,000 population (z=1.90), up from the 2005-07 death rate of only 0.38. The *emerging heroin* class (N=453) includes counties with slightly lower (3.61/100,000 population, z=0.65) and slower growing (3.29 gain per 100,000 population, z=0.64) heroin mortality rates than the high heroin cluster, but heroin rates in the emerging class still outpace most other classes. There were two multi-opioid class, representing counties where deaths involved multiple opioids. The *synthetic*+ class (N=213) has high and fast growing mortality rates from synthetic opioids alone or in combination with prescription opioids or heroin. Deaths from multiple combinations of opioids rose from 0.75 to 6.87 per 100,000 population (z=1.56, change z=1.52); and deaths from synthetic opioids alone rose by 3.91 per 100,000 population (z=0.68) to the current rate of 5.68 per 100,000 (z=0.86). By contrast, counties in the *syndemic opioid* class (N=141) are in the depths of the opioid crisis, having very high and fast growing mortality rates from all major types of opioids: heroin, synthetics, prescription opioids, or any combination of the three. Deaths where multiple opioid were present jumped from 0.85 to 9.71 per 100,000 population (z=2.11, change z=2.07), heroin mortality also jumped from 0.82 to 8.51 per 100,000 (z=1.88, change z=1.78). Among counties in this class, synthetic opioid deaths rose by 5.47 deaths since 2005-07 (z=1.10) to a rate of 7.11 per 100,000 (z=2.11) in 2014-16.

Table B2. Opioid Mortality Rates by Latent Classes in 2014-16 and Change from 2005-07.

	Low/Avg OD (n=1,791)		High Rx Opioid (n=232)		Emerging Heroin (n=453)		High Heroin (n=150)		Synthetic+ (n=213)		Syndemic (All Opioids High) (n=141)	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Heroin	0.35	0.62	0.34	0.66	3.61	0.98	8.22	4.94	1.38	1.36	8.51	4.68
Change	0.21	0.78	0.25	0.81	3.29	0.98	7.84	5.02	1.02	1.25	7.69	4.37
Prescription Opioid	2.10	2.39	13.58	5.79	3.93	3.05	3.92	4.68	6.87	7.75	7.00	6.47
Change	-0.76	3.97	7.84	6.32	0.76	3.37	0.04	4.69	0.64	6.50	1.53	5.72
Synthetic/Unknown Opioid	1.16	2.17	3.33	4.10	2.31	2.13	3.02	2.53	5.68	5.18	7.11	4.07
Change	0.35	2.81	1.73	4.55	1.29	2.33	1.43	3.00	3.91	4.89	5.47	4.40
Multiple-Causes	0.49	0.88	0.96	1.28	1.68	1.40	2.15	1.72	6.87	3.40	9.71	4.69
Change	0.24	1.05	0.15	1.87	1.26	1.62	1.67	1.77	6.12	3.23	8.87	4.37
OD w/ No Opioid Specified	7.24	6.71	9.48	6.79	7.81	6.55	7.78	6.34	8.50	6.57	8.81	5.95
Change	1.62	7.74	0.83	7.78	1.82	5.57	1.56	6.70	2.01	6.71	1.48	5.99
Avg. Posterior Probability	0.98	0.06	0.94	0.10	0.95	0.09	0.96	0.09	0.97	0.08	0.98	0.07

SD = standard deviation. Excludes 99 unclassified counties with posterior probabilities below 0.60.

Table B3. Standardized Opioid Mortality Rates by Latent Classes in 2014-16 and Change from 2005-07.

	Low/Avg OD (n=1,791)		High Rx Opioid (n=232)		Emerging Heroin (n=453)		High Heroin (n=150)		Synthetic+ (n=213)		Syndemic (All Opioids High) (n=141)	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Heroin	-0.46	0.21	-0.46	0.22	0.65	0.33	1.90	0.45	-0.11	0.46	1.88	0.64
Change	-0.44	0.25	-0.43	0.27	0.64	0.34	1.90	0.48	-0.16	0.44	1.78	0.65
Prescription Opioid	-0.38	0.48	1.70	0.64	-0.01	0.61	-0.05	0.70	0.41	0.94	0.49	0.82
Change	-0.21	0.66	1.34	0.93	0.07	0.65	-0.09	0.85	0.03	1.09	0.19	0.94
Synthetic/Unknown Opioid	-0.34	0.54	0.26	0.92	0.02	0.63	0.24	0.75	0.86	1.10	1.32	0.87
Change	-0.23	0.61	0.11	1.01	0.03	0.65	0.06	0.83	0.68	1.12	1.10	0.96
Multiple-Causes	-0.41	0.30	-0.25	0.44	0.00	0.48	0.16	0.59	1.56	0.62	2.11	0.51
Change	-0.36	0.34	-0.40	0.63	-0.01	0.56	0.14	0.62	1.52	0.64	2.07	0.56
OD w/No Opioid Specified	-0.10	0.88	0.24	0.92	-0.01	0.82	-0.01	0.86	0.10	0.91	0.14	0.79
Change	-0.01	0.86	-0.11	1.03	0.02	0.69	-0.01	0.88	0.04	0.87	-0.02	0.79
Avg. Posterior Probability	0.98	0.06	0.94	0.10	0.95	0.09	0.96	0.09	0.97	0.08	0.98	0.07

SD = standard deviation. Excludes 99 unclassified counties with posterior probabilities below 0.60.

APPENDIX C

Table C1. Differences in County Characteristics across Opioid Mortality Classes, Mean (SD)

	Low/Avg. OD (N=1791)	High Rx Opioid (N=232)	Emerging Heroin (N=452)	High Heroin (N=150)	Synthetic+ (N=213)	Syndemic (N=141)	Non-Classified (N=99)
Overall drug mortality rate, 2005-07	9.7 (8.5)	17.0 (10.7)	11.0 (6.5)	12.6 (8.1)	15.6 (10.6)	16.1 (8.3)	12.4 (7.9)
Overall drug mortality rate, 2014-16	11.4 (8.1)	27.9 (11.5)	19.5 (8.3)	25.2 (9.5)	29.4 (14.8)	41.3 (14.6)	20.1 (7.5)
Opioid mortality rate, 2005-07	3.7 (4.9)	7.7 (7.8)	4.4 (4.1)	5.8 (5.5)	8.3 (8.2)	8.1 (6.5)	5.3 (5.2)
Opioid mortality rate, 2014-16	3.8 (3.7)	17.6 (7.9)	11.1 (4.6)	16.7 (7.0)	20.0 (11.5)	31.7 (11.9)	11.6 (5.2)
Population Characteristics							
Non-Hispanic white, %	79.6 (19.8)	86.6 (14.1)	83.2 (17.2)	82.8 (17.8)	87.2 (14.8)	85.4 (17.6)	81.4 (19.8)
Non-Hispanic black, %	9.9 (16.1)	5.3 (10.6)	7.5 (12.0)	5.7 (8.5)	6.3 (11.7)	7.2 (11.5)	10.2 (15.0)
Hispanic, %	6.9 (12.7)	3.6 (6.5)	6.0 (11.7)	8.4 (16.1)	3.4 (8.2)	5.0 (13.2)	4.8 (11.3)
Age 65+, %	15.1 (4.4)	16.0 (3.7)	13.8 (3.7)	14.3 (3.2)	14.6 (3.4)	14.1 (2.8)	14.6 (3.6)
Veterans, %	13.7 (2.9)	14.5 (3)	14.3 (3.1)	14.4 (2.8)	14.3 (2.8)	14.2 (1.9)	13.8 (3.3)
Population density	3.4 (1.6)	3.3 (1.3)	4.6 (1.5)	4.2 (1.8)	4.2 (1.5)	5.1 (1.5)	4.2 (1.6)
Nonmetro (0/1)	68.8%	75.9%	47.2%	56.7%	60.6%	34.8%	54.5%
Socioeconomic Characteristics							
Not in labor force, %	56.0 (6.1)	57.7 (4.7)	53.8 (5.1)	54.8 (4.9)	56.2 (6.0)	54.5 (4.7)	55.4 (5.6)
No 4-year college degree, %	83.9 (7.5)	86.6 (5.5)	81.1 (8.6)	83.3 (6.8)	83.7 (8.1)	82.7 (7.1)	82.8 (9.4)
Ratio of federal-to-county median household income, %	129.8 (28.2)	139.0 (24.1)	111.4 (25.1)	116.9 (25.9)	125.1 (33.4)	113.2 (26.5)	124.5 (28.9)
Poverty, %	15.0 (6.9)	15.6 (5.3)	11.7 (5.4)	12.4 (5.5)	13.9 (6.8)	12.1 (5.2)	14.1 (6)
Public assistance receipt, %	1.0 (0.7)	1.2 (0.6)	0.7 (0.4)	0.8 (0.5)	1.1 (0.8)	0.9 (0.6)	1.0 (0.6)
Thiel's L (inequality at bottom of income distribution)	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)
Gini coefficient of income inequality	0.4 (0.0)	0.4 (0.04)	0.4 (0.04)	0.4 (0.04)	0.4 (0.04)	0.4 (0.04)	0.4 (0.04)
Separated or divorced, %	11.0 (2.5)	11.8 (2.2)	11.4 (1.9)	11.5 (1.9)	11.6 (1.8)	12 (1.4)	11.6 (1.9)
Single parent families, %	24.9 (7.9)	24.5 (6.5)	25 (6.4)	25.3 (5.8)	25.3 (6.6)	26.8 (6.9)	26.2 (6.9)
Vacant housing units, %	14.4 (8.9)	17.1 (11.1)	12.5 (9.5)	14.2 (11.8)	15.6 (10.9)	11.7 (9.4)	13.1 (8.9)
Renter-occupied housing units, %	22.4 (7.2)	19.8 (5.3)	23.1 (8.2)	22.1 (7.1)	21 (7.5)	23.8 (7.0)	24.1 (10.1)

Occupational Composition							
Administrative/clerical, %	13.2 (2.1)	12.7 (1.6)	14.3 (2.0)	13.9 (2.1)	13.6 (2.2)	14.7 (1.8)	13.4 (1.9)
Executive and managerial, %	8.7 (2.8)	7.9 (1.8)	10.3 (3.4)	9.4 (2.7)	9.3 (3.1)	10.1 (2.8)	9.2 (3.2)
Farming, fishing, forestry, %	6.9 (7.4)	5.4 (5.0)	2.7 (2.8)	3.8 (4.3)	3.3 (3.7)	1.8 (1.8)	4.0 (4.5)
Personal services, %	13.3 (2.8)	13.5 (3.0)	13.1 (2.5)	13.3 (2.5)	13.3 (2.7)	13.5 (2.7)	13.1 (2.7)
Production, extraction, construction, %	22.3 (6.5)	25.4 (6.9)	22.5 (6.3)	23.3 (6.0)	23.7 (6.4)	22.2 (6.1)	23.5 (7.0)
Professional/technical, %	18.3 (3.7)	17.5 (3.7)	19.5 (4.1)	19 (3.8)	19 (3.6)	19.9 (3.9)	19.2 (5.1)
Retail sales, %	9.5 (2.1)	9.4 (1.9)	10.2 (1.8)	9.5 (1.9)	9.9 (1.9)	10.3 (1.7)	10.1 (1.8)
Transportation and material moving, %	7.8 (2.1)	8.2 (1.9)	7.4 (2.2)	8 (2.4)	7.9 (2.3)	7.5 (2.1)	7.5 (2.0)
Industry Composition							
Agriculture, fishing, forestry, %	7.7 (8.1)	6.2 (5.6)	3.1 (3.1)	4.3 (5.0)	3.8 (4.2)	2.0 (2.0)	4.4 (4.8)
Business & professional, %	4.9 (2.5)	4.5 (1.9)	6.3 (2.7)	5.7 (2.5)	5.8 (2.7)	6.8 (2.5)	5.6 (2.8)
Construction, %	7.6 (2.4)	8.4 (2.3)	7.7 (2.3)	7.6 (2.2)	8.2 (2.5)	7.7 (2.4)	7.7 (2.4)
Communication, info., utilities, %	3.1 (1.4)	2.9 (1.3)	3.3 (1.1)	3.1 (1.3)	3.3 (1.5)	3.4 (1.1)	2.9 (1.3)
Finance, insurance, real estate, %	4.4 (1.7)	3.8 (1.1)	5.2 (2.3)	4.8 (1.9)	4.7 (2.0)	5.2 (1.8)	4.7 (2.1)
Education, %	9.4 (3.2)	8.9 (2.3)	8.9 (3.6)	8.9 (3.0)	9 (2.4)	8.6 (2.2)	8.9 (3.2)
Health, %	11.0 (2.7)	10.8 (2.5)	11 (2.5)	10.9 (2.4)	11.4 (2.2)	11.7 (2.5)	11.8 (3.5)
Retail, personal services, food, accommodations, %	22.9 (4.4)	23.6 (4.6)	24.1 (3.9)	23.2 (3.6)	23.9 (3.7)	24.7 (3.7)	23.7 (3.9)
Mining, %	1.2 (2.6)	1.5 (2.8)	0.7 (2.7)	1.3 (3.7)	1.4 (3.1)	0.7 (1.9)	0.9 (2.1)
Manufacturing, %	15.1 (9.2)	17.2 (9.7)	17.3 (8.5)	17.5 (9.4)	16.2 (8.3)	16.5 (8.1)	17.6 (8.7)
Public administration, %	5.5 (3.1)	5.4 (3.5)	5 (2.9)	5.4 (2.8)	5.3 (2.4)	5.3 (2.6)	4.8 (1.8)
Transportation, %	4.3 (1.6)	4.1 (1.2)	4.1 (1.6)	4.2 (1.2)	4.2 (1.3)	4.4 (1.9)	4.0 (1.5)
Wholesale Trade, %	3.0 (1.2)	2.7 (1.0)	3.1 (1.1)	3 (1.2)	2.9 (0.9)	3.1 (0.9)	3.1 (1.0)
Census Variable Derived Indices							
Urban professional index	-0.16 (0.94)	-0.42 (0.60)	0.48 (1.07)	0.15 (1.04)	0.16 (1.05)	0.62 (0.94)	0.19 (1.10)
Economic disadvantage index	0.07 (1.04)	0.31 (0.89)	-0.34 (0.83)	-0.25 (0.83)	0.07 (1.06)	-0.15 (0.90)	0.05 (0.96)
Blue collar index	-0.04 (0.98)	0.35 (0.96)	-0.09 (1.03)	0.10 (1.00)	0.08 (1.00)	-0.06 (0.98)	0.04 (1.09)
Service economy index	-0.06 (0.96)	0.26 (1.15)	-0.01 (1.04)	0.03 (0.98)	0.17 (1.05)	0.06 (0.95)	-0.07 (1.04)
Opioid prescribing							
Retail opioid prescribing, 2006-08	78.0 (37.7)	105.1 (53.6)	78.6 (34.2)	80.5 (33.8)	94.9 (53.6)	97.1 (42.3)	84.7 (38.7)

Retail opioid prescribing, 2009-11	84.6 (42.1)	114.1 (58.9)	85.7 (36.8)	87.2 (37.1)	100.5 (51.9)	106.3 (43.1)	91.9 (42.0)
Retail opioid prescribing, 2012-14	85.3 (41.8)	111 (54.7)	86.7 (36.1)	85.5 (34.5)	98.7 (47.6)	99.4 (37.0)	94.7 (44.7)
Retail opioid prescribing, 2015-16	71.6 (41.1)	94.2 (51.8)	76.4 (31.9)	71.8 (32.6)	83.2 (44.1)	84 (28.2)	85.2 (40.4)

SD=standard deviation

APPENDIX D

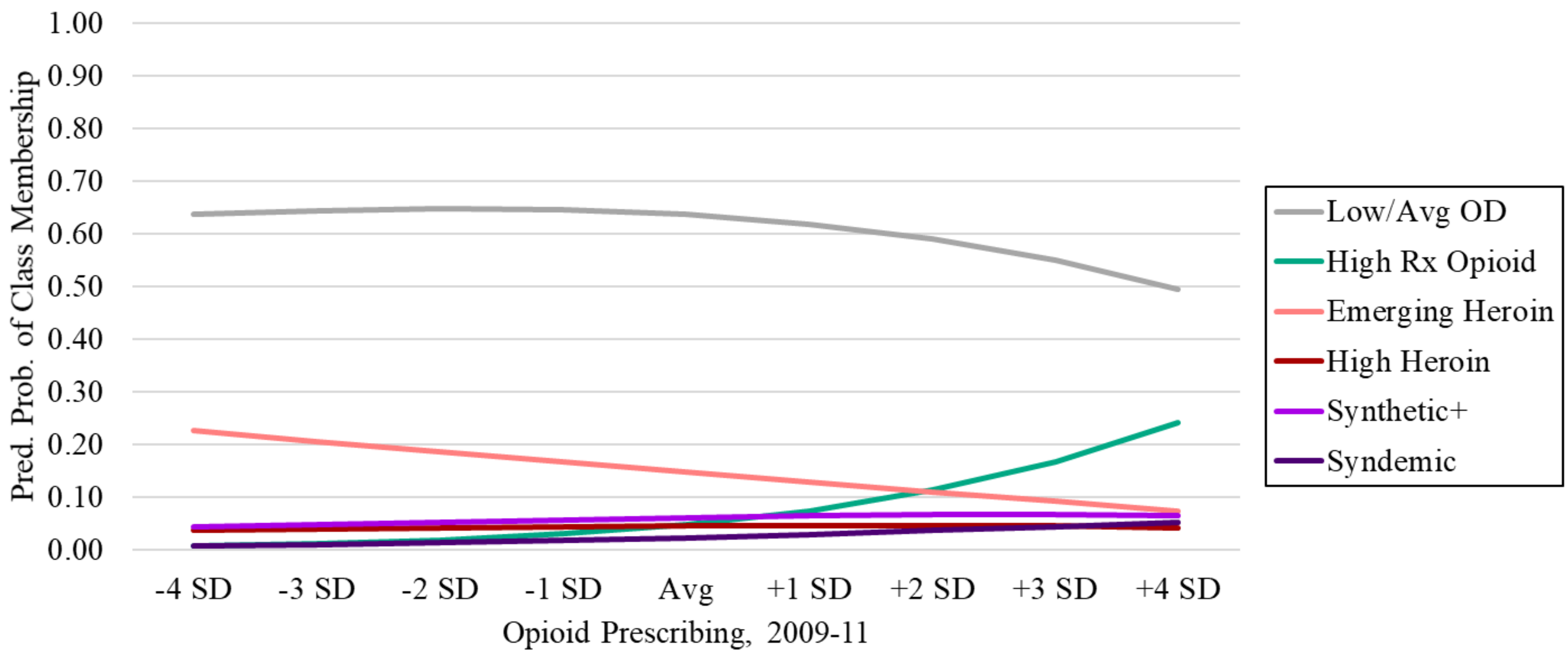

Figure D1. Predicted Probabilities of Opioid Mortality Class Membership by Levels of Opioid Prescribing in 2009-11

Predicted Probabilities based on fully adjusted model. All other variables held at means.
SD=standard deviation