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A MULTIVARIATE SPATIOTEMPORAL CHANGE-POINT MODEL OF OPIOID OVERDOSE DEATHS IN OHIO

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Abstract

Ohio is one of the states most impacted by the opioid epidemic and experienced the second highest age-adjusted fatal drug overdose rate in 2017. Initially it was believed prescription opioids were driving the opioid crisis in Ohio. However, as the epidemic evolved, opioid overdose deaths due to fentanyl have drastically increased. In this work we develop a Bayesian multivariate spatiotemporal model for Ohio county overdose death rates from 2007 to 2018 due to different types of opioids. The log-odds are assumed to follow a spatially varying change point regression model. By assuming the regression coefficients are a multivariate conditional autoregressive process, we capture spatial dependence within each drug type and also dependence across drug types. The proposed model allows us to not only study spatiotemporal trends in overdose death rates but also to detect county-level shifts in these trends over time for various types of opioids.

Key words and phrases.

Multivariate conditional autoregressive; change point; Bayesian; spatial rates

1. Introduction.

The United States is in the midst of a public health crisis due to opioid misuse and overdose death (Drug Enforcement Agency (2016), Office of National Drug Control Policy Executive, Office of the President of the United States (2011)). The rate of overdose death increased 200% from 2000 to 2014 (Rudd et al. (2016)) and in 2017 became the leading cause of injury-related death in the United States (Centers for Disease Control and Prevention (2019)). Nationally, in 2016, the Substance Abuse and Mental Health Services Administration (SAMHSA) estimated that 11.8 million people aged 12 and over misused

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SUPPLEMENTARY MATERIAL

Supplement A: A multivariate spatiotemporal change point model of opioid overdose deaths in Ohio: Supplementary material (DOI: [10.1214/20-AOAS1415SUPPA](https://doi.org/10.1214/20-AOAS1415SUPPA); .pdf). The pdf file contains tables and figures of additional results from the analysis.

Supplement B: A multivariate spatiotemporal change point model of opioid overdose deaths in Ohio: Data and code (DOI: [10.1214/20-AOAS1415SUPPB](https://doi.org/10.1214/20-AOAS1415SUPPB); .zip). The zipped folder contains all data and code needed to implement the model and obtain the results of the analysis.

opioids in the past year which represents 4.4% of the population (SAMHSA (2017)). In addition, it is estimated that 2.1 million people aged 12 and over had an opioid use disorder in 2016 (SAMHSA (2017)). Opioid misuse is accompanied by increased risks of morbidity and mortality as well as social, economic and legal consequences (Centers for Disease Control and Prevention (2012), Degenhardt et al. (2015), Evans et al. (2015), Hser et al. (2014), Teesson et al. (2015)) which create both short and long term public health and policy problems.

The opioid epidemic has been particularly severe in the state of Ohio. In 2017, Ohio had the nation's second highest overdose mortality rate (Division of Unintentional Injury Prevention (2017)). The rate of overdose death in Ohio was 39.1 per 100,000 which is approximately double the national rate of 19.8 per 100,000 (Division of Unintentional Injury Prevention (2017)). In 2015, it was estimated that the opioid epidemic and related problems cost the state between \$6.6 to \$8.8 billion (Rembert et al. (2017)). In 2011, the state launched the Governor's Cabinet Opiate Action Team and implemented various policies in an effort to stem the tide of the ongoing epidemic (Governor's Cabinet Opiate Action Team (2012)). These policies included enforcement against pill mills (i.e., clinics where opioids are inappropriately prescribed (Rigg, March and Inciardi (2010))), increased access to naloxone and strengthening of the prescription drug monitoring program, among others (Penm et al. (2017)). These policies helped to reduce the prescribing and supply of prescription opioids in the state (Winstanley et al. (2018)).

While it is estimated nationally that 92% of opioid misusers only misuse prescription opioids or pain relievers, the estimated rate of heroin misuse significantly increased in 2016 compared to annual estimates from 2002–2013 (SAMHSA (2017)). It is also estimated that more than 77% of heroin users first used prescription opioids (Jones (2013)). While the reasons for the transition from prescription opioids to heroin are likely complex, the decrease in the availability of prescription opioids (Dart et al. (2015), Delcher et al. (2015)) and the increased availability of low-cost, high-purity heroin (Compton, Jones and Baldwin (2016)) may be contributing factors. In Ohio and around the country, illicit suppliers of opioids are responding to demand by turning to fentanyl to reduce costs and maintain a supply of strong, fast-acting drugs (Mars, Rosenblum and Ciccarone (2019)) which has led to unprecedented rates of overdose (Daniulaityte et al. (2017)). This progression from the initial prescription opioid epidemic to heroin and then to fentanyl reflects the three waves of the opioid epidemic (Ciccarone (2019)).

In this work we estimate local trends in overdose deaths due to prescription opioids, heroin and fentanyl in Ohio to address three main questions. First, we are interested in modeling the waves of the epidemic and the timing of changes in the death rates attributed to the three drug types. We estimate spatially varying change points in each of the death rate trends to identify when the waves of the epidemic affected each county. This helps illuminate where the initial impacts are observed and how the changes in death rates proliferate to the rest of the state. Second, we estimate county-specific intercepts and slopes before and after the change point to describe local differences in trajectory. It is important to assess trends at the county-level because Ohio is a geographically heterogeneous state with urban, rural, Appalachian and Rust Belt regions that have experienced the epidemic differently.

In addition, counties have health departments that are allocated resources and coordinate local responses to the epidemic, making them a meaningful unit of analysis. Finally, we estimate correlation between slopes and intercepts across drug types to explore how trends in overdose may be interrelated. Together, these insights illuminate differences across the state that can then be taken into consideration while formulating policies and interventions.

To accomplish the above goals, we propose a Bayesian model that builds on techniques for multivariate disease mapping and change-point regression models for binomial data. The multivariate disease mapping framework allows us to jointly analyze deaths due to the three types of opioids. This improves estimation by borrowing strength across drug types in addition to across space (Martinez-Beneito, Botella-Rocamora and Banerjee (2017)). Warren, Pingali and Weinberger (2017) developed a spatially-varying change-point regression model to model the probability that invasive pneumococcal disease is caused by a targeted serotype. Berchuck, Mwanza and Warren (2019) used a similar change-point regression model to study glaucoma progression. Our proposed model extends these to the case of multivariate outcomes. We assume the death rate trend, due to each type of opioid considered, has its own spatially varying change-point regression model, and correlations among the three drug types are induced by assuming a multivariate conditional autoregressive (MCAR) model for the regression coefficients (Gelfand and Vounatsou (2003)).

The rest of the paper is organized as follows. Section 2 describes the data and statistical methodology. The results of the analysis are presented in Section 3. In Section 4 we close with a discussion of findings and their public health implications.

2. Methods.

2.1. Data.

We acquired routinely collected county-level mortality data for the state of Ohio. The Ohio Department of Health makes state mortality data publicly available via the Ohio Resident Mortality Data (Ohio Public Health Data Warehouse (2020)). For this study we limit deaths to those categorized as *unintentional drug poisonings*. We then specifically focus on those deaths coded by the state with the poisoning indicator for prescription opioids, heroin and fentanyl. International Classification of Diseases, Revision 10 (ICD 10) codes listed in the multiple cause codes on the death certificate are used to classify whether prescription opioids (T40.2-T40.4, T40.6) and heroin (T40.1) are mentioned. The involvement of fentanyl is determined via a text search of the literal cause of death statements. Annual counts of deaths involving the three types of drugs were obtained from 2007–2018 for each of Ohio's 88 counties. A death can be attributed to multiple drugs, and so a single death can be included in the count for multiple drug types. We follow the practice of the Ohio Department of Health and the recommendation by Seth et al. (2018) and exclude deaths involving fentanyl from the count for prescription opioid deaths which removes double counting of fentanyl related deaths in the prescription category. Annual estimates of the population for each county were also obtained from the Ohio Department of Health website listed above and were provided by the National Center for Health Statistics (Ohio Public Health Data Warehouse (2020)). Maps and a scatterplot matrix of the annual observed death

rates involving each drug per 100,000 residents are included in the Supplementary Material (Hepler, Waller and Kline (2021a), Figures 1–2).

2.2. Model.

Our goal is to jointly model counts of overdose death by type of drug from 2007–2018 for each county in Ohio. We focus on the three most common types of opioids associated with overdose and the waves of the epidemic: prescription opioids, heroin and fentanyl. We introduce a novel multivariate model that allows for county-specific trends and local change points in the trajectories and can quantify the relationship between outcomes and their respective trends. As in Berliner (1996), let $[Y/Z]$ denote the conditional probability density of Y given Z . We assume a three-stage Bayesian hierarchical model of the form:

Stage 1: [Data|Process, Parameters],

Stage 2: [Process|Parameters],

Stage 3: [Parameters],

and specify the model accordingly in the following subsections.

2.2.1. Data model.—For the death counts associated with each drug type, we assume a binomial logistic regression model. That is, for drug type ℓ ($\ell = 1, 2, 3$) in county i ($i = 1, \dots, 88$) at year t ($t = 1, \dots, 12$),

$$Y_{it}^{(\ell)} | p_{it}^{(\ell)} \stackrel{\text{ind}}{\sim} \text{Binomial}(N_{it}, p_{it}^{(\ell)}), \quad (2.1)$$

where $Y_{it}^{(\ell)}$ is the death count, N_{it} is the population and $p_{it}^{(\ell)}$ is the death rate. Using the canonical logit link, we specify the following mixed effects logistic regression model:

$$\text{logit}(p_{it}^{(\ell)}) = \mu_{it}^{(\ell)} + \epsilon_{it}^{(\ell)}, \quad (2.2)$$

where $\mu_{it}^{(\ell)}$ is a spatiotemporal mean trend and $\epsilon_{it}^{(\ell)}$ an independent error term to account for uncorrelated heterogeneity and overdispersion.

The mean function $\mu_{it}^{(\ell)}$ is assumed to be linear before and after the change point with county-specific intercepts and slopes. That is,

$$\mu_{it}^{(\ell)} = \begin{cases} \beta_{0i}^{(\ell)} + \beta_{1i}^{(\ell)}t, & t \leq \theta_i^{(\ell)}, \\ \beta_{2i}^{(\ell)} + \beta_{3i}^{(\ell)}t, & t > \theta_i^{(\ell)}, \end{cases} \quad (2.3)$$

where $\beta_{0i}^{(\ell)}$ and $\beta_{1i}^{(\ell)}$ are the intercept and slope before the change point, $\theta_i^{(\ell)}$ is the change point and $\beta_{2i}^{(\ell)}$ and $\beta_{3i}^{(\ell)}$ are the intercept and slope after the change point for drug ℓ in county i . These parameters characterize the county-level heterogeneity in overdose trends and allow us to estimate the local onset of the waves of the epidemic.

2.2.2. Process model.—We assume the random error terms are independently distributed as mean zero normal random variables, $\epsilon_{it}^{(\ell)} \sim N(0, \sigma_{\epsilon}^2)$. For the mean function, we assume:

$$\begin{aligned}\beta_{0i}^{(\ell)} &= \beta_0^{(\ell)} + u_{0i}^{(\ell)}, \\ \beta_{1i}^{(\ell)} &= \beta_1^{(\ell)} + u_{1i}^{(\ell)}, \\ \beta_{2i}^{(\ell)} &= \beta_2^{(\ell)} + u_{2i}^{(\ell)}, \\ \beta_{3i}^{(\ell)} &= \beta_3^{(\ell)} + u_{3i}^{(\ell)},\end{aligned}\tag{2.4}$$

where $\beta_0^{(\ell)}, \beta_1^{(\ell)}, \beta_2^{(\ell)}$ and $\beta_3^{(\ell)}$ are overall means and, for each $h \in \{0, 1, 2, 3\}$,

$\mathbf{u}_{hi} = (u_{hi}^{(1)}, u_{hi}^{(2)}, u_{hi}^{(3)})'$ is a vector of spatial random effects that quantify county-level deviations from the overall mean and account for correlation between parameters across drug types.

Since we are jointly modeling deaths due to multiple drug types, one source of dependence is between the different drug types. In our model we assume this dependence is captured through each regression parameter. For example, we assume that the intercepts before the change point are correlated across each drug type. Similarly, we assume that the slopes after the change point are correlated across each drug type and so on. To account for both spatial dependence and dependence across drug types, we assume an intrinsic MCAR model (Carlin and Banerjee (2003)) for each regression parameter. Let $N(\mathbf{m}, \mathbf{C})$ denote a multivariate normal distribution with mean $\mathbf{m}$ and covariance $\mathbf{C}$. For parameter h our model assumes

$$\mathbf{u}_{hi} \mid \mathbf{u}_{h(-i)} \sim N\left(\sum_j \frac{w_{ij}}{w_{i+}} \mathbf{u}_{hj}, \frac{1}{w_{i+}} \boldsymbol{\Sigma}_h\right),\tag{2.5}$$

where $\mathbf{u}_{h(-i)} = \{\mathbf{u}_{hj} : j \neq i\}$, $w_{ij} = 1$ if counties i and j are neighbors (share a border) and $w_{ij} = 0$ otherwise and w_{i+} is the total number of neighbors of county i . The matrix $\boldsymbol{\Sigma}_h$ is a 3×3 random matrix that captures the conditional covariance between elements of $\mathbf{u}_{hi}$. The intrinsic MCAR model is improper, as the precision matrix of the joint distribution is not of full rank; however, it can be used as a process model when a mean zero centering constraint is enforced (Banerjee, Carlin and Gelfand (2004)).

2.2.3. Parameter model.—We fit our model in the Bayesian paradigm and, therefore, must specify prior distributions for all parameters. The prior distributions for the overall means $\beta_0^{(\ell)}, \beta_1^{(\ell)}, \beta_2^{(\ell)}$ and $\beta_3^{(\ell)}$ are independent and uniform on the real line for each drug type. For each $\boldsymbol{\Sigma}_h$, we assign independent inverse Wishart prior distributions with five degrees of freedom and a 3×3 identity scale matrix. For each county and drug type we independently assign the change point $\theta_i^{(\ell)}$, a discrete uniform distribution over the years 2008–2016. Finally, for σ_{ϵ}^2 we assume independent inverse gamma distributions with shape and scale of 0.5.

2.3. Computation.

We implemented our model using the R package NIMBLE (de Valpine et al. (2017)) to perform an adaptive Metropolis-within-Gibbs Markov chain Monte Carlo (MCMC) algorithm. The MCAR process models are specified following the approach outlined in Lawson (2020). The centering requirement for the intrinsic CAR processes are enforced within NIMBLE through a commonly used ad hoc approach that samples these latent variates without the mean-zero constraint and then empirically enforces the constraint by subtracting the mean after the random vector is updated. While this approach results in sampling from a stationary distribution that approximates, but is not exactly equal to, the desired posterior distribution (Rue and Held (2005), page 37); in practice, the departure may be minimal (Paciorek (2009)). The MCMC sampler was performed for 2,000,000 iterations with the first 1,000,000 discarded as a burn-in. For storage considerations and to reduce auto-correlation, the samples were thinned with only every 50th iteration included in the sample. Convergence was assessed by visually inspecting trace plots of model parameters. The data and R NIMBLE code are provided in the Supplementary Material (Hepler, Waller and Kline (2021b)).

2.4. Alternative models for comparison.

To evaluate the added benefit of our multivariate change-point model, we also fit our data using two simpler spatiotemporal models. The first comparison model specifies intrinsic univariate CAR models for the spatial random effects instead of intrinsic MCAR models. This assumes the spatial random effects are independent across the three drug types and is equivalent to assuming Σ_h is a diagonal matrix for each $h \in \{0, 1, 2, 3\}$ in equation (2.5). The second comparison model uses an interrupted time series instead of a change-point regression model by including an indicator variable for year 2011 or later. As discussed in Section 1, various state policies were implemented in Ohio starting in 2011 with the goal of slowing the opioid epidemic (Governor's Cabinet Opiate Action Team (2012)). Thus, a reasonable comparison model is the model that assumes all counties experience a change in the trend at this time. More specifically, this model assumes equation (2.3) is replaced by

$$\mu_{it}^{(\ell)} = \beta_{0i}^{(\ell)} + \beta_{1i}^{(\ell)}t + \left(\beta_{2i}^{(\ell)} + \beta_{3i}^{(\ell)}t\right)I(t \geq 5).$$

As in the proposed model, the regression coefficients are decomposed into an overall mean component and a spatial random effect, and an MCAR model is assumed for the spatial random effects.

3. Results.

3.1. Goodness of fit.

We assessed the appropriateness of our proposed model for the observed data by computing posterior predictive p-values for five different test quantities including the mean, standard deviation, maximum, proportion of observations that equal zero and the chi-square discrepancy function (Gelman et al. (2014)). These test quantities were chosen to assess different features of the posterior predictive distributions including the center, spread, tail

behavior and also to assess whether the binomial model adequately captures the number of zeros in the data. The posterior predictive p-values of the five tests for each of the three drug types are included in the Supplementary Material and range from 0.22 to 0.57 (Hepler, Waller and Kline (2021a), Table 1). Thus, there is no strong evidence of lack of fit for our proposed model. In addition, maps of the estimated rates for each drug type from the proposed model are presented in the Supplementary Material and look very similar to the corresponding maps of the observed rates, indicating appropriate model fit (Hepler, Waller and Kline (2021a), Figure 3).

3.2. Comparison to alternative models.

We compared our proposed model to the two baseline models described in Section 2.4 using WAIC (Watanabe (2010)). WAIC is a more recently developed alternative to DIC for Bayesian model comparison and is more desirable since it averages over the posterior distribution (Gelman, Hwang and Vehtari (2014)). Small values for WAIC indicate better model fit. Our proposed model resulted in a WAIC of 11382.79. The comparison model that assumed drug types were independent yielded a WAIC of 11406.52 and the interrupted time series model 11531.53. Thus, we can see that while our model is more complicated, the flexibility afforded by our more general dependence and trend structures resulted in a better fit to the observed data.

3.3. Change points.

The first objective of the study was to assess the waves of the epidemic by estimating spatially varying change points. Looking across the three drug types, we observe evidence of these waves in the ordering of the changes. Figure 1 shows the number of counties whose most likely (mode) change point was each year. In general, we see earlier estimated change points for prescription with a statewide median estimated change point of 2012. For heroin, 40 of the 88 counties had an estimated change between 2011 and 2013, with roughly 27 counties experiencing a later change in 2015 or 2016. The statewide median estimated change point for heroin is 2013. Fentanyl shows less variability in the most likely change point across the state, with roughly 63% of counties having an estimated change point of 2013 or 2014, and the statewide median estimated change point is 2013.

Our goal was not just to capture the overall waves of the epidemic but to see how they varied across the state. Figure 2 shows the county-specific cumulative posterior probabilities that the change point occurred at or prior to each year. Based on our parameterization, a county with a change point estimated in year t has a different linear trend starting in year $t + 1$. Thus, the years in Figure 2 reflect the final year before a change occurs in the trend of overdose death rates. The color scheme for Figure 2 is designed so that the change from blue to red at the midpoint of the scale reflects the posterior median change point.

We notice there is spatial heterogeneity in the estimated change points. For prescription, early changes in trends generally occur in more rural parts of the state, including counties in southern Ohio where there was an emphasis on pill mills. These early changes can be observed starting in 2009 and 2010. In contrast, we notice the initial changes in heroin in 2010 and 2011 in counties in the western, southwestern and central regions of the state

which are around Dayton, Cincinnati and suburban Columbus. We also see evidence of changes in the northwestern and northeastern regions around Toledo and Cleveland. This is consistent with the idea that heroin spreads out from cities and then into the rest of the state. Similarly, with fentanyl we see the early changes in the western, southwestern and northwestern parts of the state which are the areas of Dayton, Cincinnati and Toledo. We observe some early changes in fentanyl trends in southern Ohio along the border with Kentucky and West Virginia. Through the maps in Figure 2, we gain insights in how changes in overdose trends have moved through space and time across the three drugs of interest.

3.4. County-specific effects.

The second objective of the study was to estimate county-specific trends in overdose rates attributed to the three drug types. In Figure 3 we plot the estimated conditional posterior mean intercept before and after each county's respective mode change point, where we estimate this quantity for each county using only the draws for which the change point was equal to its mode. We also plot the conditional posterior mean difference in the trend at the change point which reflects a shift in the level following the change point. The color scale for each plot is centered at the estimated state average for each parameter which can be found in the Supplementary Material (Hepler, Waller and Kline (2021a), Table 2). Before the change point we observe very similar relative spatial patterns across the three drug types with higher values in the southwestern and central parts of the state and slightly above average values in the northeastern part of the state. This reflects the region around Cincinnati, Columbus and Cleveland, respectively. After the change point all three drug types remain higher than average in southwestern Ohio. We observe fentanyl is also above average in the northeast. After the change point the estimated differences in the trend for prescription are relatively small with the largest positive shifts in eastern Ohio. For heroin we see positive estimated differences in eastern and northwestern Ohio. For fentanyl we see large, upward shifts after the change point with the largest increases in western and southwestern Ohio. Posterior means and 95% credible intervals (CI) for the intercept parameters are presented in the Supplementary Material (Hepler, Waller and Kline (2021a)).

In Figure 4 we plot the estimated posterior mean slope before and after each county's respective mode change point, conditioning on the change point equaling the mode. Each slope plotted reflects the change in log odds for an increase of one year in time. Posterior means and 95% CIs for the slope parameters are presented in the Supplementary Material (Hepler, Waller and Kline (2021a)). For prescription we generally see positive slopes before the change point, reflecting increasing rates of overdose deaths. The posterior mean state average slope before the change point is 0.06 (95% CI: [0.02, 0.10]) which corresponds to an 6% increase in the odds of overdose death per year. The highest rates of increase are in southern and northwestern Ohio. After the change point we see slopes that are typically less than or equal to zero which reflect decreasing rates of overdose. The posterior mean state average slope after the change point is -0.11 (95% CI: [-0.14, -0.08]) which corresponds to a 10% decrease in the odds of overdose death per year. In the eastern part of the state we still observe increasing rates. Looking at the difference in the slopes, we see the smallest decreases in the slope in the southwestern and eastern parts of the state and the largest decreases in the northwest.

The slopes for heroin in Figure 4 show different trends than were observed for prescription. Before the change point, slopes were positive across the state reflecting increasing rates of heroin overdose deaths. The posterior mean state average slope was 0.26 (95% CI: [0.21, 0.31]) which corresponds to a 30% increase in the odds per year. The rates of increase were generally highest in the northeastern part of the state. After the change point, rates of increase slowed and even began decreasing across the eastern, western and northwestern parts of the state. However, rates continued to increase in southern Ohio with little change in the slope from before the change point. The posterior mean state average slope after the change point was -0.07 (95% CI: $[-0.12, -0.01]$) which corresponds to a 7% decrease per year in odds of heroin overdose deaths. While all Ohio counties showed reduced rates of change in heroin deaths, counties on the southeastern border tended to have slopes more similar to those before the change point, indicating that they remained on a similar trajectory.

For fentanyl, Figure 4 shows the explosion in the rate of overdose deaths after the change point. Before the change point the slopes were fairly flat with a posterior mean state average slope of -0.03 (95% CI: $[-0.12, 0.06]$). However, after the change point we see rapid increases in the rates of fentanyl deaths. The posterior mean state average slope after the change point is 0.49 (95% CI: $[0.44, 0.55]$) which corresponds to a 63% increase in the odds per year. The entire state has positive slopes with the largest values in the southwest, around Cincinnati and Dayton, and in the northeast, around Cleveland. Looking at the change in the slope from before the change point, we see the biggest increases in the northern, western and southwestern regions of the state. These plots make it clear how devastating fentanyl overdose deaths have been to the state of Ohio over the latter part of the study period.

Putting all of these estimates together, we examine the estimated log odds of overdose death for each drug across the study period. In Figure 5 we plot the posterior mean estimates of the mean function for each county and the posterior mean for the state average for each drug. For fentanyl we see the large jump at the change point followed by rapid growth in the log odds of overdose deaths. We also observe the growth and flattening of the log odds of heroin overdose death. Finally, we see that the log odds for prescription overdose are fairly flat and then slightly decreasing over the study period.

3.5. Correlations.

The final objective was to estimate the correlation in the intercepts and slopes between drug types. The posterior median correlation estimates are shown in Table 1. Note that each correlation is residual to the statewide trends and spatial dependence, as they are parameters in Σ_h from equation (2.5). As we observed above, the posterior median correlations for the intercepts before the change point reflect positive, moderately strong correlation. There is little correlation in the slopes before the change point. After the change point, correlation in the intercepts is positive but not as strong as it was prior to the change point. While not particularly strong, we do see positive correlations in the slopes after the change point. In particular, we see the strongest correlation between the slopes for the log odds of heroin and fentanyl which makes sense as fentanyl is commonly an addition to the heroin supply (Mars, Rosenblum and Ciccarone (2019)).

We believe these estimates are likely a reflection of the fact that counties struggling with addiction are likely to exhibit similar trends across drug types. That is, the positive correlations likely reflect that there are underlying addiction problems in a county that can be satisfied by consumption of any of these drug types, so we generally see positive correlations in the behavior of overdose trends. While very reasonable, this is not entirely what we expected to observe. In addition to borrowing strength to improve model fit, we were initially curious whether the correlation estimates might reflect hypothesized substitution of drug types (Compton, Jones and Baldwin (2016)). We hypothesized we would observe negative correlations in the slopes between prescription and the other two drugs as the regulation of prescribing has increased and people began to turn to other substances. However, while there is some evidence of this in the larger examination of the statewide mean trends in Figures 4 and 5, there was not evidence of this relationship in the residual county-level correlation structure.

3.6. Summary.

In summary, we observed county-level heterogeneity in trends of drug overdose and the timing of changes to those trends. For prescription we estimated a general slightly increasing trend until around 2012 when we started to observe a decreasing trend. For heroin we observed increasing trends until 2013 when a slightly decreasing trend began. Finally, for fentanyl we observed the start of a quickly increasing trend around 2013.

While our analysis is not causal or a formal policy evaluation, the timing and direction of the changing trends fit with larger policy interventions taking place in Ohio (Governor's Cabinet Opiate Action Team (2018), Penm et al. (2017)). In 2011 and 2012, policies targeting "pill mills," new prescribing guidelines, expansion of medication assisted treatment and secure drug disposal programs were enacted. Ohio also saw the creation and expansion of a naloxone distribution program starting in 2012 and the expansion of Medicaid in 2014. While these interventions likely contributed to the slowing of prescription and heroin overdoses during this time period, our model captured the onset and rapid growth of the illicit fentanyl market which has driven overdose in more recent years. Thus, our model seems to have captured the waning of the first wave (prescription), the peak of the second wave (heroin) and the beginning of the third wave (fentanyl) during this study period.

4. Discussion.

In this study we developed a novel multivariate spatiotemporal model with spatially varying change points. We used the model to estimate the trends and changes in trends in county-level overdose death rates attributed to prescription opioids, heroin and fentanyl. By doing so, we are able to better understand how the opioid epidemic has changed over time and better describe heterogeneity across counties in Ohio. Our model includes a rich parameterization that allows us to learn about when trends changed, how they changed and how they were related across drug types.

While developing the model, we identified a few areas for future research. We did not explicitly include spatial dependence in the change points. However, we noted in the results that there appeared to be some spatial structure to the estimates such that the model may

benefit from devising a way to incorporate such dependence. In addition, more work could be done to explore changes in the dependence structure around the change point. For example, we assume that, while the timing may be different, neighboring counties will experience similar trends once they hit a change point. In our application we believe this is reasonable, as the change points likely reflect changes in the statewide policy or drug market environment that may take time to propagate throughout the state but should have similar effects. In other applications this may not be as reasonable, and there may need to be additional complexity added into the modeling of the dependence structure.

There are several limitations to our study. This study was based on cause of death classification from death certificates. We recognize that this is often imperfect (Slavova et al. (2015)); however, we believe that it still provides valuable information about the evolution of the epidemic. This analysis was also conducted at the county level, and so all estimates must be interpreted at the county level to avoid the ecological fallacy (Pianntadosi, Byar and Green (1988)).

In conclusion, our multivariate spatiotemporal change-point model provided a wealth of information regarding spatiotemporal trends in opioid overdose. This work illuminates where changes began, and it highlights areas that changed more or less rapidly than others in the state. This information can be used to target areas for interventions or further investigations into what may be driving overdose in those counties. Our work has added valuable insights into the spatiotemporal epidemiology of the opioid epidemic that can be utilized by public health practitioners and policymakers to continue to combat the epidemic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

- Banerjee S, Carlin BP and Gelfand AE (2004). Hierarchical Modeling and Analysis for Spatial Data. Chapman & Hall/CRC, Boca Raton, FL.
- Berchuck SI, Mwanza J-C and Warren JL (2019). A spatially varying change points model for monitoring glaucoma progression using visual field data. *Spat. Stat* 30 1–26. MR3921304 10.1016/j.spasta.2019.02.001 [PubMed: 30931247]
- Berliner LM (1996). Hierarchical Bayesian time series models. In *Maximum Entropy and Bayesian Methods. Fund. Theories Phys* 79 15–22. Kluwer Academic, Dordrecht. MR1446713

- Carlin BP and Banerjee S (2003). Hierarchical multivariate CAR models for Spatio-temporally correlated survival data. *Bayesian Statistics* 7 45–63.
- Centers for Disease Control and Prevention (2012). HIV infection and HIV-associated behaviors among injecting drug users—20 cities, United States, 2009. *Morb. Mort. Wkly. Rep* 61 133–138.
- Centers for Disease Control and Prevention (2019). National survey on drug use and health, 2013 and 2014. Internet. Available at <https://www.cdc.gov/opioids/index.html>.
- Ciccarone D (2019). The triple wave epidemic: Supply and demand drivers of the US opioid overdose crisis. *Int. J. Drug Policy* 71 183–188. 10.1016/j.drugpo.2019.01.010 [PubMed: 30718120]
- Compton WM, Jones CM and Baldwin GT (2016). Relationship between nonmedical prescription-opioid use and heroin use. *N. Engl. J. Med* 374 154–163. [PubMed: 26760086]
- Daniulaityte R, Juhascik MP, Strayer KE, Sizemore IE, Harshbarger KE, Antonides HM and Carlson RR (2017). Overdose deaths related to fentanyl and its analogs—Ohio, January–February 2017. *Morb. Mort. Wkly. Rep* 66 904–908. 10.15585/mmwr.mm6634a3
- Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher-Bartelson B and Green JL (2015). Trends in opioid analgesic abuse and mortality in the United States. *N. Engl. J. Med* 372 241–248. 10.1056/NEJMs1406143 [PubMed: 25587948]
- de Valpine P, Turek D, Paciorek CJ, Anderson-Bergman C, Temple Lang D and Bodik R (2017). Programming with models: Writing statistical algorithms for general model structures with NIMBLE. *J. Comput. Graph. Statist* 26 403–413. MR3640196 10.1080/10618600.2016.1172487
- Degenhardt L, Larney S, Kimber J, Farrell M and Hall W (2015). Excess mortality among opioid-using patients treated with oral naltrexone in Australia. *Drug Alcohol Rev.* 34 90–96. 10.1111/dar.12205 [PubMed: 25302627]
- Delcher C, Wagenaar AC, Goldberger BA, Cook RL and Maldonado-Molina MM (2015). Abrupt decline in oxycodone-caused mortality after implementation of Florida’s prescription drug monitoring program. *Drug Alcohol Depend.* 150 63–68. [PubMed: 25746236]
- Division of Unintentional Injury Prevention (2017). Drug overdose data. Internet. Available at <https://www.cdc.gov/drugoverdose/data/statedeaths.html>.
- Drug Enforcement Agency (2016). 2016 national drug threat assessment. Internet. Available at <https://www.dea.gov/resource-center/2016%20NDTA%20Summary.pdf>.
- Evans E, Li L, Min J, Huang D, Urada D, Liu L, Hser YI and Nosyk B (2015). Mortality among individuals accessing pharmacological treatment for opioid dependence in California, 2006–10. *Addiction* 110 996–1005. [PubMed: 25644938]
- Gelfand AE and Vounatsou P (2003). Proper multivariate conditional autoregressive models for spatial data analysis. *Biostatistics* 4 11–25. 10.1093/biostatistics/4.1.11 [PubMed: 12925327]
- Gelman A, Hwang J and Vehtari A (2014). Understanding predictive information criteria for Bayesian models. *Stat. Comput* 24 997–1016. MR3253850 10.1007/s11222-013-9416-2
- Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A and Rubin DB (2014). *Bayesian Data Analysis*, 3rd ed. Texts in Statistical Science Series CRC Press, Boca Raton, FL. MR3235677
- Governor’s Cabinet Opiate Action Team (2012). Attacking Ohio’s opiate epidemic. Online. Available at <https://mha.ohio.gov/Researchers-and-Media/Combating-the-Opioid-Crisis>; accessed 6-September-2017.
- Governor’s Cabinet Opiate Action Team (2018). Combating the opiate crisis in Ohio. Online. Available at https://mha.ohio.gov/Portals/0/assets/ResearchersAndMedia/Combating%20Opiate%20Abuse/Combating-the-Opiate-Crisis_SEPT-2018.pdf?ver=2018-11-29-113014-833; accessed 25-February-2020.
- Hepler SA, Waller LA and Kline DM (2021a). Supplement to “A multivariate spatio temporal change-point model of opioid overdose deaths in Ohio.” 10.1214/20-AOAS1415SUPPA.
- Hepler SA, Waller LA and Kline DM (2021b). Data Files and Code for “A multivariate spatio-temporal change point model of opioid overdose deaths in Ohio” 10.1214/20-AOAS1415SUPPB.
- Hser YI, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, Jacobs P, Teruya C, McLaughlin P et al. (2014). Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction* 109 79–87. [PubMed: 23961726]

- Jones CM (2013). Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers—United States, 2002–2004 and 2008–2010. *Drug Alcohol Depend.* 132 95–100. [PubMed: 23410617]
- Lawson AB (2020). NIMBLE for Bayesian disease mapping. *Spat. Spatio-Tempor. Epidemiol* 33.
- Mars SG, Rosenblum D and Ciccarone D (2019). Illicit fentanyl in the opioid street market: Desired or imposed? *Addiction* 114 774–780. 10.1111/add.14474 [PubMed: 30512204]
- Martinez-Beneito MA, Botella-Rocamora P and Banerjee S (2017). Towards a multidimensional approach to Bayesian disease mapping. *Bayesian Anal* 12 239–259. MR3597574 10.1214/16-BA995 [PubMed: 29707101]
- Office of National Drug Control Policy Executive, Office of the President of the United States (2011). Epidemic: Responding to America's prescription drug abuse crisis. Internet. Available at <https://www.hsdl.org/?view&did=4609>.
- Ohio Public Health Data Warehouse (2020). Ohio resident mortality data. Available at <http://publicapps.odh.ohio.gov/EDW/DataCatalog>; accessed February 2, 2020.
- Paciorek C (2009). Technical Vignette 5: Understanding intrinsic Gaussian Markov random field spatial models, including intrinsic conditional autoregressive models. Technical Report. Dept. Statistics, Univ. California, Berkeley and Dept. Biostatistics, Harvard School of Public Health.
- Penm J, Mackinnon NJ, Boone JM, Ciacchia A, McNamee C and Winstanley EL (2017). Strategies and policies to address the opioid epidemic: A case study of Ohio. *J. Am. Pharm. Assoc* 57 S148–S153. 10.1016/j.japh.2017.01.001
- Pianntadosi S, Byar DP and Green SB (1988). The ecological fallacy. *Am. J. Epidemiol* 127 893–904. [PubMed: 3282433]
- Rembert M, Betz M, Feng B and Partridge M (2017). Taking measure of Ohio's opioid crisis. Available at https://aede.osu.edu/sites/aede/files/publication_files/Swank%20-%20Taking%20Measure%20of%20Ohios%20Opioid%20Crisis.pdf.
- Rigg KK, March SJ and Inciardi JA (2010). Prescription drug abuse & diversion: Role of the pain clinic. *J. Drug Issues* 40 681–702. 10.1177/002204261004000307 [PubMed: 21278927]
- Rudd RA, Aleshire N, Zibbell JE and Gladden RM (2016). Increases in drug and opioid overdose deaths—United States, 2000–2014. *Morb. Mort. Wkly. Rep* 64 1378–1382. 10.15585/mmwr.mm6450a3
- Rue H and Held L (2005). Gaussian Markov Random Fields: Theory and Applications. Monographs on Statistics and Applied Probability 104. CRC Press/CRC, Boca Raton, FL. MR2130347 10.1201/9780203492024
- SAMHSA (2017). Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health. HHS Publication No. SMA 17–5044, NSDUH Series H-52 Available at <http://www.samhsa.gov/>.
- Seth P, Rudd RA, Noonan RK and Haegerich TM (2018). Quantifying the epidemic of prescription opioid overdose deaths. *Am. J. Publ. Health* 108 500–502. 10.2105/AJPH.2017.304265
- Slavova S, O'Brien DB, Creppage K, Dao D, Fondario A, Haile E, Hume B, Largo TW, Nguyen C et al. (2015). Drug overdose deaths: Let's get specific. *Public Health Reports* 130.
- Teesson M, Marel C, Darke S, Ross J, Slade T, Burns L, Lynskey M, Memedovic S, White J et al. (2015). Long-term mortality, remission, criminality and psychiatric comorbidity of heroin dependence: 11-year findings from the Australian treatment outcome study. *Addiction* 110 986–993. 10.1111/add.12860 [PubMed: 25619110]
- Warren JL, Pingali SC and Weinberger DM (2017). Spatial variability in the persistence of pneumococcal conjugate vaccine-targeted pneumococcal serotypes among adults. *Epidemiology* 28 119–126. 10.1097/EDE.0000000000000551 [PubMed: 27541841]
- Watanabe S (2010). Asymptotic equivalence of Bayes cross validation and widely applicable information criterion in singular learning theory. *J. Mach. Learn. Res* 11 3571–3594. MR2756194
- Winstanley EL, Zhang Y, Mashni R, Schnee S, Penm J, Boone J, McNamee C and MacKinnon NJ (2018). Mandatory review of a prescription drug monitoring program and impact on opioid and benzodiazepine dispensing. *Drug Alcohol Depend.* 188 169–174. [PubMed: 29778769]

FIG. 1.
Counts of the number of counties whose mostly likely change point occurred in the given year.

FIG. 2. Cumulative probability of the change point occurring at or prior to each year for each drug type.

FIG. 3.

County-specific intercepts before the mode change point, after the mode change point and the immediate difference at the mode change point.

FIG. 4.

County-specific slopes before the mode change point, after the mode change point and the change from before to after.

FIG. 5.

County-specific mean functions $\mu_{it}^{(\ell)}$ (dotted lines) and the statewide average mean function (solid lines) for each drug type.

TABLE 1

Posterior median correlation between parameters across pairs of drug types after accounting for the statewide trend

Drug type pair	Before		After	
	Intercept	Slope	Intercept	Slope
Prescription and Heroin	0.7694	0.0669	0.4371	0.1925
Prescription and Fentanyl	0.6546	0.1044	0.2978	0.1328
Heroin and Fentanyl	0.6073	0.0225	0.4860	0.2339