Investigating the Social Ecological Contexts of Opioid Use Disorder and Poisoning Hospitalizations in Pennsylvania

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ABSTRACT. Objective: Opioid use disorder (OUD) and overdose rates have been sharply on the rise in the United States. Although systematic patterns of geographic variation in OUD and opioid overdose have been identified, the factors that explain why opioid-related hospitalizations increase in certain areas are not well understood. **Method:** We examined Pennsylvania Health Care Cost Containment Council (PHC4) hospital inpatient discharge data at the ZIP code level to measure the geographic growth and spread of OUD as measured by 44 quarters of inpatient hospitalization data (from 2004 through 2014) for the entire state of Pennsylvania ($n = 16,275$ ZIP codes). We assessed the relative contribution of specific attributes of areas (e.g., population density) to patterns of OUD, heroin poisonings, and non-heroin opioid poisonings. Unit misalignment

and spatial autocorrelation were corrected for using Bayesian space-time conditional autoregressive models. **Results:** The associations between a greater density of manual labor establishments and all opioid-related hospitalizations were well supported and positive. A dose-response relationship between population density and opioid-related hospitalizations existed, with a stronger association for heroin poisonings (relative rate, densest quintile vs. least dense: 3.40 [95% credible interval 2.68, 4.39]). **Conclusions:** Posterior distributions from these models enabled the identification of locations most vulnerable to problems related to the opioid epidemic in Pennsylvania. Understanding spatial patterns of OUD and poisonings can enhance the development and implementation of effective prevention programs. (*J. Stud. Alcohol Drugs*, 79, 899–908, 2018)

OPIOID USE DISORDER (OUD) and overdose rates in the United States have increased at a startling rate in the past decade (Warner et al., 2011). The age-adjusted rate for drug poisoning deaths involving heroin nearly quadrupled between 2000 and 2013 (Hedegaard et al., 2015), and deaths from drug overdose are now the top cause of injury-related death in the United States (Centers for Disease Control and Prevention [CDC], 2014). The impact of opioids can also be seen in the growth of use disorders: OUD-related hospital stays increased by more than 150% per year from 1993 to 2012 (Owens et al., 2014). There is significant variation in the impact of the opioid epidemic across regions within the United States, in both the rate of increase and the patterns of heroin versus prescription opioid use (Cicero et al., 2015; O'Donnell et al., 2017). In 2014, there were more than 2,497 overdose deaths in Pennsylvania; overdoses were the leading cause of death for ages 25–44 (Rudd et al., 2016). These rates have increased sharply over the past 20 years statewide, from 5.4 per 100,000 in 1996 to 18.9 per 100,000 in 2014, an average increase of more than 75 deaths per year.

Although systematic patterns of geographic variation in opioid overdose have been identified in the literature (e.g., Unick et al., 2013, 2014), the ways in which areas with the greatest rates of increase and largest overall burden develop and spread across space, and the contextual, ecological factors that explain why specific locations are at greatest risk, are not well understood. As has been established in the alcohol literature, increased availability to substances via both legal (Anderson et al., 2009; Gruenewald, 2011) and illegal (Dent et al., 2005) sources increases use and use disorders. Growth in the rate of opioid overdose is strongly correlated with an increase in supply at the national and local levels (Wright et al., 2014). Although the increase in legal access to opioids has been partially driven by overprescribing practices (Compton et al., 2015; Modarai et al., 2013), it may also represent true medical need for prescription opioids for workplace-related physical injuries (Leff et al., 2003; Van Hasselt et al., 2015). Locations with a greater increase in supply may therefore correspond to areas with a greater medical need for opioids. Medical need for opioids for the most common pain-related chronic conditions, such as cancer and arthritis, may also increase supply and off-label use (Cerdá et al., 2017).

Increased access to legal (e.g., prescription opioids), semi-legal (e.g., doctor shopping), and illegal (e.g., heroin) opioids is just one part of the puzzle, however. In the past several decades, economic and social environmental factors have combined to create communities with greater vulnerability to substance use (Boardman et al., 2001). Communities

Received: March 7, 2018. Revision: September 4, 2018.

This research was supported by National Institutes of Health Grant R03 DA043373.

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with a higher concentration of economic stressors (e.g., low median household income) may be particularly vulnerable to abuse of opioids, as they may be using as a way to manage stress and mental health disorders (Cerdá et al., 2017; King et al., 2014). Understanding the role of economic conditions in the development and spread of the opioid epidemic is crucial.

A number of other demographic and environmental conditions may play an important role in the spatial patterning of OUD and overdose. In particular, the potentially distinct epidemics occurring in rural versus urban communities warrant investigation. Opioid use, OUD, and overdose have risen sharply in non-urban areas in states such as Pennsylvania (Drug Enforcement Agency, 2015). However, there is also evidence that the bulk of the current epidemic of both heroin and prescription opioid-related overdoses is still occurring in urban as compared to rural environments (Unick et al., 2014). Several factors might explain the rapid growth of opioid use, OUD, and overdose in rural communities. For example, the economic environments and stressful living conditions often experienced in rural America may put these groups at increased risk (Keyes et al., 2014). On the other hand, the more dramatic rate of increase within rural communities may simply be a function of the historically lower rates of opioid use and OUDs as compared to urban environments.

Detailed assessments of spatial patterns of OUD and overdose growth, and their associations with population subgroups and environmental predictors, require consistently collected and geographically well-resolved space-time data (Gruenewald, 2013; Gruenewald et al., 2013). In the United States, there is no systematic monitoring of drug abuse and dependence at either a regional or state level. The only existing estimates of incidence and prevalence rates are meant to represent the entire country (e.g., National Survey on Drug Use and Health [Center for Behavioral Health Statistics and Quality, 2014]; Monitoring the Future [Johnston et al., 1999]), or are limited to a small number of communities (Gruenewald, 2013). Publicly available hospital discharge data are a source of consistently collected, adequately resolved diagnostic information that can be used to assess the incidence and prevalence of OUD and overdose at the local (i.e., ZIP code) level across a larger region over the span of years, making them a relatively rare commodity.

The goals of this study were to investigate whether hospitalizations due to OUD (abuse and/or dependence), heroin poisoning, and non-heroin opioid poisoning spread across space over a 10-year period in Pennsylvania and to assess the relative contributions of medical need-related conditions, economic circumstances, and demographic and environmental covariates to patterns of opioid-related hospital discharges. We hypothesized that rural ZIP codes with greater medical need for opioids, greater availability of

prescription opioids, and worse economic conditions would have the highest rates of OUD and overdose in Pennsylvania. We also demonstrate how posteriors from spatial random effects models can be used to identify communities with the greatest predicted probabilities of epidemic outbreak in order to target high-risk regions.

Method

Data sources and variables

We analyzed annual spatial panel population data using Bayesian space-time models to relate hospitalizations for opioid use disorders (i.e., abuse and/or dependence), heroin poisonings, and non-heroin opioid poisonings to indicators of medical need-based, economic, and demographic and environmental conditions. As ZIP codes refer to point-based features such as street addresses, whereas others exclusively contain post office boxes, ZIP codes were spatially joined to create year-specific contiguous areas appropriate for spatial analyses. The resulting residential polygons consisted of 16,275 space-time units in Pennsylvania from 2004 through 2014.

Hospital discharge data: Opioid use disorders and poisonings. We obtained patient-level records of all hospitalizations between 2004 and 2014 through the Pennsylvania Healthcare Cost Containment Council (PHC4) (<http://www.phc4.org>) (PHC4, 2016). The PHC4 collects approximately 1.9 million inpatient records per year, aggregated to quarters. These data include 70 fields with information on each patient's ZIP code and county of residence, admitting diagnosis, principal diagnosis code and up to 17 secondary diagnosis codes, principal E-code (external causes of injuries and poisonings codes), and up to two additional E-codes. We included 19,889,285 of 20,840,763 observations from 2004 through 2014. The 951,478 excluded observations (4.6% of total observations) were either missing ZIP code of residence or had a residential ZIP code outside Pennsylvania.

Three opioid-related hospitalization variables, representing OUD, heroin poisoning, and non-heroin opioid poisoning, were generated. OUDs were defined using ICD-9-CM codes representing opioid abuse (305.5x), dependence (304.0x), and dependence with combinations of opioids with other drugs (304.7x). Heroin poisoning was defined as an ICD-9-CM code for poisoning by heroin (965.01) and/or an E-code for accidental heroin poisoning (E850.0). Non-heroin opioid-related poisoning included ICD-9-CM codes 965.00, 965.02, and 965.09, and E-codes E850.1 and E850.2. Both primary and secondary codes were included (12.35% of abuse and dependence codes, 76.42% of heroin poisoning codes, and 59.24% of other opioid poisoning codes were primary). Because only eight secondary codes were permitted before 2011, we excluded any additional secondary codes (9 through 17) allowed as of 2011.

Medical need for opioids: Density of manual labor industries, density of pharmacies, and percentages of cancer- and arthritis-related hospitalizations. The concentration of manual labor industries in a ZIP code was used to represent medical need for prescription opioids due to workplace-related physical injury, since areas with a higher proportion of individuals involved in manual labor tend to have higher rates of self-reported injury and chronic pain (Cerdá et al., 2017). Counts were calculated using the North American Industry Classification System (NAICS) codes from Zip Code Business Patterns data (U.S. Census Bureau, 2016). We included six industries that involve manual labor: Agriculture, Forestry, Fishing and Hunting (NAICS Sector 11); Mining, Quarrying, and Oil and Gas Extraction (Sector 21); Construction (Sector 23); Manufacturing (Sectors 31–33); Wholesale Trade (Sector 42); Transportation and Warehousing (Sectors 48–49); and Utilities (Sector 22). These manual labor establishment densities do not necessarily represent individuals working in these fields who live in a given ZIP code, but the number of establishments in these fields. The number of establishments per square mile was calculated for each ZIP code in each year. NAICS code 446110 (Pharmacies and Drug Stores) was used to generate the density of pharmacies per square mile for each ZIP code in each year.

To represent overall medical need for prescription opioids, we calculated the percentage of cancer- and arthritis-related hospital discharges. These were chosen as they are leading age-related sources of chronic pain and have been used to represent aging-related medical need for opioids in prior research (Cerdá et al., 2017). Cancer ICD-9-CM codes included malignant neoplasms (140.xx–209xx), whereas arthritis codes included osteoarthritis and allied disorders (715.xx). The percentages of cancer hospitalizations were calculated as the number of primary and secondary (up to eight) diagnoses per ZIP code divided by the total number of hospitalizations. For arthritis hospitalization percentages, only primary diagnosis codes were used because secondary codes jumped between 2010 and 2011 due to changes in the use of specific codes and diagnostic updates.

Economic conditions. Three variables available via the U.S. Census representing economic resources were used. These included median household income (per \$10,000), the percentage of the population below 150% of the poverty level, and the percentage of unemployed individuals. Annual (inter-censal) estimates were generated from GeoLytics publicly available projections at the Census block group level (GeoLytics, 2014). Each of these variables was aggregated from the Census block group level up to the ZIP code boundaries specific to each year (as they are not available at the ZIP code level) using a method we have successfully used in other ZIP code-level analyses (Mair et al., 2013).

Demographic and environmental conditions. Several other annual ZIP code-level demographic data from the U.S. Census were generated from block group-level estimates.

These included racial distributions (percentage non-Hispanic White, Black, and Hispanic), age distributions (percentage ages 0–19, 20–24, 25–44, and 45–64), percentage male, and population density. To identify and investigate differential patterns between urban and rural ZIP codes, population density was categorized into quintiles (0–52.5 people/mi², 52.6–124.1, 124.2–333.3, 333.4–1414.2, ≥1414.3). A variable representing the overall retail environment of a ZIP code was calculated as the number of establishments with NAICS Sectors 44–45 (Retail Trade) and 72 (Accommodation and Food Services) per square mile. Furthermore, the overall hospitalization rate, calculated as the number of discharges per capita per ZIP code, was included to control for access to inpatient care in each community.

ZIP code misalignment. To determine whether there were any biasing effects of changes in the number and shape of ZIP codes from one year to the next, we included a measure of the geographic instability of a ZIP code's population between consecutive years (Mair et al., 2013). This was calculated as the percentage of all year-2000 Census block populations within a given year's ZIP code definition that would not have fallen within the boundaries of the best-matched ZIP code in the prior year. Large values of this measure correspond to substantial changes in population covered by a misaligned ZIP code (i.e., high instability).

Eighty-three of the 16,275 ZIP codes had a population value of zero. To allow for nonzero population risks in all areas, these ZIP codes were assigned a minimal population of five. Furthermore, these 83 areas were given the average value for all other ZIP codes in the same year for Census-derived variables.

Data analysis

We used hierarchical Bayesian space-time Poisson misalignment models to perform analyses at the ZIP code level. The shape and number of ZIP code polygons varies across years (in Pennsylvania there were 1,469 ZIP codes in 2004 vs. 1,490 in 2014), requiring an approach that takes this nonnesting spatial misalignment into account (Zhu et al., 2013). Misalignment models account for the similarity of unexplained risks among neighboring geographic units (spatial autocorrelation) by introducing a separate conditional autoregressive (CAR) random effect for each year-specific map of spatial adjacencies, while also including a second, separate, random effect that is not spatially autocorrelated. Poisson regression was used, since the outcome measures are counts of hospitalizations in a given ZIP code in each year:

$$Y_{i,t} | \mu_{i,t} \sim \text{Poisson}(E_{i,t} \exp(\mu_{i,t})) \quad (\text{Equation 1})$$

$Y_{i,t}$ is the count of hospital discharges in ZIP code i in year t , and $E_{i,t}$ is the expected number of hospital discharges under the assumption that hospital discharges are distributed among ZIP codes across the state in direct proportion to

TABLE 1. Descriptive statistics, ZIP codes in Pennsylvania, 2004–2014 ($n = 16,275$ ZIP codes)

Covariate	<i>M</i>	<i>SD</i>	Min.	Max.	<i>M</i> change 2014 vs. 2004
Population size	8,490.78	11,258.67	5.00	73,131.91	221.08
No. of opioid use disorder hospitalizations	17.93	43.92	0	868	8.66
No. of opioid poisoning hospitalizations (any)	1.97	3.79	0	79	0.88
Heroin	0.45	1.34	0	41	0.39
Non-heroin	1.54	2.83	0	38	0.51
Medical need for opioids					
Manual labor, no. of establishments per mi ² (x10)	65.22	170.89	0.00	2,697.41	-12.40
Pharmacies, no. of establishments per mi ² (x10)	2.97	15.04	0.00	410.63	-0.04
Arthritis diagnoses, % of total hospitalizations	3.08	2.20	0.00	100.00	1.19
Cancer diagnoses, % of total hospitalizations	7.88	3.99	0.00	100.00	0.54
Economic conditions					
Median household income, per \$10,000	4.48	1.67	0.00	18.46	0.86
Population below 150% of poverty level, %	21.33	10.03	0.00	86.65	3.50
Unemployment, %	7.42	5.24	0.00	100.00	2.30
Demographic and environmental covariates					
Race/ethnicity, %					
Black	4.28	11.77	0.00	98.01	-0.07
Hispanic	2.24	5.50	0.00	71.45	0.37
White	89.12	15.27	0.40	100.00	-6.27
Age, %					
0–19	24.02	3.71	0.00	50.00	-1.69
20–24	6.60	1.34	0.00	35.53	0.19
25–44	24.81	3.56	0.00	77.43	-1.83
45–64	27.41	3.15	0.43	68.75	0.80
Male, %	49.42	2.73	5.26	100.00	0.01
Population density, per mi ²	1,278.49	3,111.11	0.10	36,466.28	21.50
No. of retail establishments, per mi ² (x10)	104.20	584.60	0.00	18,565.47	-6.49
Overall hospitalization rate, per 100 people	18.83	54.48	0.00	1,780.00	-2.30

Notes: Min = minimum; max. = maximum; no. = number; mi = mile.

ZIP code population size. The relative rate associated with spatial unit i at time t is $\exp(\mu_{i,t})$. The log relative rate, $\mu_{i,t}$, is modeled as:

$$\mu_{i,t} = \alpha_t + X'_{i,t}\beta + \theta_{i,t} + \phi_{i,t} \quad (\text{Equation 2})$$

This is a linear combination of fixed covariate effects and random effects that take account of spatial and/or temporal correlation. Vector α_t is a set of year-specific intercepts that control for statewide changes in opioid hospitalization risks that are not explained by other covariates. Matrix $X'_{i,t}$ contains space- and time-specific covariates, and β is a vector of fixed-effects estimates of those covariates. $\theta_{i,t}$ and $\phi_{i,t}$ denote the pair of random effects capturing spatially unstructured heterogeneity and CAR spatial dependence, respectively. As these models allow for different spatial adjacencies in each year, they do not allow for an examination of temporal shifts or patterns.

We estimated models separately for each of our three outcomes (OUD, heroin poisoning, non-heroin opioid poisoning). All models included the density of manual labor industries, density of pharmacies, percentages of hospitalization with cancer and primary arthritis diagnoses, economic conditions (median household income, percentage of population below 150% of poverty level, percentage unemployed), population demographics (age distribution categories, racial/ethnic composition, percentage male), and other ZIP code environmental and demographic covariates (population den-

sity, retail environment, overall hospitalization rate). Models were estimated using WinBUGS 1.4.3 software (Lunn et al., 2000). Non-informative priors were specified for all fixed and random effects and allowed to burn in for 50,000 Markov Chain Monte Carlo (MCMC) iterations, by which point all model estimates between two chains with different initial values had converged. After this burn-in period, posterior estimates were sampled for an additional 40,000 MCMC iterations to provide model results. Traces of MCMC iterations demonstrated good convergence for all parameters. Sensitivity analyses were run with separate codes (e.g., abuse or dependence alone), with primary codes only, and combining all codes together.

Results

There were an average of 17.93 OUD hospitalizations per ZIP code per year in Pennsylvania ($SD = 43.92$), 0.45 ($SD = 1.34$) heroin poisonings, and 1.54 ($SD = 2.83$) non-heroin opioid poisoning hospitalizations (Table 1). These numbers increase from 2004 to 2014, by 8.66 (OUD), 0.39 (heroin poisoning), and 0.51 (non-heroin opioid poisoning) per ZIP code per year. The percentage of all hospitalizations with a primary or secondary opioid abuse or dependence ICD-9-CM code rose from 1.22% in 2004 (22,806 total hospitalizations) to 2.18% in 2014 (36,032 total hospitalizations). The proportion of all opioid-related poisonings with a heroin

TABLE 2. Relative rates (RRs) [95% CIs] and Ln(RR), opioid use disorders and opioid poisoning hospitalizations, Bayesian spatial misalignment models ($n = 16,275$ ZIP codes)

Variable	Model 1: Opioid use disorders		Model 2: Heroin poisoning		Model 3: Non-heroin opioid poisoning	
	RR [95% CI]	Log(RR)	RR [95% CI]	Log(RR)	RR [95% CI]	Log(RR)
Medical need for opioids						
Manual labor, no. of establishments per mi ² (x10)	1.057 [1.045, 1.068] ^a	0.056	1.070 [1.047, 1.096] ^a	0.046	1.042 [1.026, 1.057] ^a	0.025
Pharmacies, no. of establishments per mi ² (x10)	1.010 [0.994, 1.023]	0.010	1.028 [0.999, 1.058]	0.028	1.006 [0.985, 1.027]	0.006
Arthritis diagnoses, % of total hospitalizations	0.943 [0.933, 0.954] ^a	-0.059	0.913 [0.878, 0.949] ^a	-0.091	0.898 [0.881, 0.914] ^a	-0.108
Cancer diagnoses, % of total hospitalizations	0.975 [0.970, 0.981] ^a	-0.026	0.964 [0.945, 0.984] ^a	-0.037	0.971 [0.962, 0.981] ^a	-0.029
Economic conditions						
Median household income, per \$10,000	0.843 [0.833, 0.854] ^a	-0.171	0.926 [0.899, 0.956]	-0.079	0.842 [0.824, 0.859] ^a	-0.170
Population below 150% of poverty level, %	1.017 [1.015, 1.019] ^a	0.017	1.013 [1.007, 1.018]	0.013	1.008 [1.004, 1.011] ^a	0.008
Unemployment, %	1.003 [0.999, 1.006]	0.003	1.011 [1.003, 1.020] ^a	0.011	1.003 [0.999, 1.008]	0.003
Demographic and environmental covariates						
Race/ethnicity, %						
Black	1.010 [1.007, 1.013] ^a	0.010	1.004 [0.998, 1.011]	0.004	0.995 [0.991, 0.999] ^a	-0.005
Hispanic	1.016 [1.013, 1.020] ^a	0.016	1.011 [1.004, 1.019] ^a	0.011	0.993 [0.988, 0.998] ^a	-0.007
White	1.018 [1.015, 1.020] ^a	0.018	1.018 [1.012, 1.025] ^a	0.018	1.005 [1.001, 1.009] ^a	0.006
Age, %						
0–19	0.999 [0.994, 1.006]	-0.001	1.006 [0.995, 1.018]	0.007	0.995 [0.989, 1.003]	-0.005
20–24	0.964 [0.952, 0.974] ^a	-0.037	1.016 [0.983, 1.046]	0.016	0.968 [0.949, 0.987] ^a	-0.033
25–44	0.978 [0.973, 0.983] ^a	-0.022	0.977 [0.964, 0.989] ^a	-0.024	0.967 [0.961, 0.975] ^a	-0.033
45–64	1.019 [1.012, 1.030] ^a	0.019	1.024 [0.999, 1.042]	0.023	1.008 [0.998, 1.020]	0.008
Male, %	0.993 [0.988, 0.997] ^a	-0.007	1.004 [0.988, 1.015]	0.004	0.999 [0.991, 1.007]	-0.001
Population density, per mi ^{2b}						
Quintile 2	1.214 [1.161, 1.270] ^a	0.194	1.416 [1.104, 1.851] ^a	0.348	1.138 [1.040, 1.247] ^a	0.130
Quintile 3	1.428 [1.361, 1.505] ^a	0.356	1.756 [1.387, 2.301] ^a	0.563	1.387 [1.262, 1.522] ^a	0.327
Quintile 4	1.773 [1.681, 1.879] ^a	0.573	2.517 [1.999, 3.254] ^a	0.923	1.528 [1.381, 1.682] ^a	0.424
Quintile 5	1.972 [1.858, 2.114] ^a	0.679	3.404 [2.680, 4.393] ^a	1.225	1.749 [1.569, 1.939] ^a	0.559
No. of retail establishments, per mi ² (x10)	0.995 [0.991, 0.998] ^a	-0.006	0.992 [0.984, 0.999] ^a	-0.008	0.995 [0.990, 1.001]	-0.005
Overall hospitalization rate, per 100 people	1.001 [1.001, 1.001] ^a	0.001	1.000 [0.999, 1.001]	-0.001	1.001 [<1.001, 1.001] ^a	<0.001
Misalignment effects						
ZIP code instability	1.001 [0.997, 1.004]	0.001	0.991 [0.973, 1.007]	-0.009	1.000 [0.993, 1.007]	<0.001
Random effects						
Spatial random effects (s.d. CAR process)	0.613 [0.593, 0.633]		0.467 [0.363, 0.532]		0.324 [0.292, 0.355]	
ZIP code-level random effects (s.d.)	0.177 [0.150, 0.204]		0.241 [0.148, 0.318]		0.226 [0.171, 0.268]	
Spatial to total random variability ratio ^c	0.923 [0.896, 0.946]		0.795 [0.580, 0.920]		0.668 [0.553, 0.803]	

Notes: Log(RR) = natural log of median relative rate; CI = credible interval; no. = number; mi = mile; CAR = conditional autoregressive. ^aIndicates findings that are well supported by the data as evidenced by CIs that exclude one for relative risks. ^bPopulation density was divided into approximately equal quintiles as follows: 1 (reference; <52.5 people/square mi); 2 (52.6–124.1); 3 (124.2–333.3); 4 (333.4–1,414.2); and 5 (≥1,414.3). ^cCalculated as the variance ratio of spatial to spatial and nonspatial random effects.

code increased from 23.68% to 31.56% from 2004 through 2014. Overall, there was notable spatial clustering of OUD, heroin poisonings, and non-heroin opioid poisonings (e.g., Moran's I values in 2014 ranged from 0.409 to 0.517) (data not shown in table). This indicates that there is significant spatial autocorrelation at the ZIP code level of opioid-related hospitalizations.

The number of manual labor establishments per square mile fell by 1.24 from 2004 through 2014, although the range across ZIP codes was highly variable (range: 0–270) and spatially patterned (e.g., Moran's I value in 2014 = 0.468) (data not shown). Economic conditions also differed by ZIP code, with an average unemployment rate of 7.42% ($SD = 5.24$) (increasing by 2.30% from 2004 through 2014), 21.33% ($SD = 10.03$) of population below 150% of poverty level, and a median household income of \$44,812.44 (range: \$0–\$184,588.10). Pennsylvania is a mainly rural state with two large urban metropolitan areas (population density

mean = 1,278.49, $SD = 3,111.11$). The state has a small minority population (mean 89.12% White; percentage White decreased by 6.27% over the study period).

Table 2 displays the results of the Bayesian space-time misalignment models for each of the three primary outcomes (OUD, heroin poisoning, and non-heroin opioid poisoning hospitalizations). Each of the three models had substantial spatial autocorrelation, with the CAR spatial random effect explaining anywhere from 66.8% (non-heroin opioid poisoning) to 92.3% (OUD) of the overall error variance (Cressie, 1993). This demonstrates the importance of properly correcting for spatial CAR effects; the likelihood of Type I errors is high without this correction.

Medical need for opioids. A greater percentage of both cancer- and arthritis-related hospitalizations was associated with fewer OUD and opioid poisoning hospitalizations. A greater density of manual labor establishments was associated with an increase in OUD (relative rate [RR] [95%

FIGURE 1. Median year-specific intercepts and 95% credible intervals, opioid use disorders (OUD) (Model 1). The figure shows the general trends in OUD from 2004 to 2014, after accounting for all other covariates in the model.

credible interval] = 1.057 [1.045, 1.068]) and both types of opioid poisoning hospitalizations. A greater density of pharmacies was not associated with increases in opioid-related hospitalizations.

Economic conditions. Lower median household income and higher poverty level were associated with a greater number of OUD and non-heroin poisonings. An increase in ZIP code-level median household income of \$10,000 was associated with a 16% decrease in hospitalization risk (RR [95% credible interval] = 0.843 [0.833, 0.854], OUD; 0.842 [0.824, 0.859], non-heroin opioid poisonings). Higher unemployment was associated with a greater number of heroin poisonings (RR [95% credible interval] = 1.011 [1.003, 1.020]).

Demographic and environmental covariates. A greater percentage Black and Hispanic in a ZIP code was associated with increased risk for OUD and decreased risk for non-heroin opioid poisonings. A dose-response relationship was found between increasing population density and all three of the opioid-related hospitalization outcomes, with the strongest gradient for heroin poisonings. The relationship between the most urban quintile (population density 1414.3+/mi²) compared to the lowest population density (<52.5/mi²) had the strongest association with each hospitalization type (e.g., heroin poisoning RR [95% credible interval] 3.404 [2.680, 4.393], highest vs. lowest density ZIP code quintile).

Year-to-year trends. Figure 1 displays the median year-specific intercepts for Model 1 (OUD). These represent general trends in OUD from 2004 through 2014, after accounting for all other covariates in the model. Although there is still an increasing trend, the 95% credible intervals greatly overlap. The year-specific intercepts for Models 2 and 3 (not shown) displayed no increasing trend from 2004 to 2014.

Figure 2 displays the quantitative impacts of the medical need-related conditions, economic circumstances, and demographic and environmental covariates for the ten 2014 ZIP codes with the highest estimated rates (excluding locations with population below 100) and the five 2014 ZIP codes with the lowest estimated rates of OUD (1a), heroin poisoning (1b), and non-heroin opioid poisoning (1c), using posteriors from Models 1, 2, and 3 (Table 2). This allows us to view the relative contribution of different environmental and demographic covariates on opioid hospitalizations across ZIP codes and visually represents the varying impacts seen in different geographic locations across the state, as well as the different (and similar) profiles of areas with the highest and lowest risks. For example, the density of manual labor businesses has a large positive effect on OUD in several of the highest risk ZIP codes (e.g., 19134), whereas the risk in other ZIP codes is driven by a greater percentage White, higher poverty level, and an older age distribution (e.g., 15190). Income appears to play a large protective effect in the lowest risk regions, coupled with a large percentage White (e.g., ZIP code 19350).

Discussion

Opioid use disorders, heroin poisonings, and non-heroin opioid poisonings all have observable spatial patterns in Pennsylvania, which are partially explained by medical need for opioids and economic conditions within a geographic location (operationalized as ZIP codes). The results of this study highlight key ecological predictors of the epidemic, some of which match current rhetoric (e.g., manual labor occupations leading to injuries leading to prescription opioid use leading to OUD), whereas others highlight aspects that are largely missed (e.g., although the rate of growth may be largest in rural communities, communities with dense populations still carry the vast majority of the burden). These findings contribute to our understanding of the spatial trends of the opioid epidemic and the ecologic conditions within a given region that might contribute to (or act as indicators of) this spread.

Some of the strongest associations with opioid hospitalizations were for indicators of medical need associated with work-related injuries (i.e., density of manual labor establishments), economic conditions (i.e., lower median household income and unemployment rate), percentage White, and greater population density. Viewing the posterior maps in Figure 2 enables us to visualize how combinations of co-

FIGURE 2. Quantitative impacts of economic, demographic, and medical need-based covariates on opioid abuse/dependence, heroin poisoning, and non-heroin opiate poisoning hospitalizations across the highest- and lowest-risk ZIP codes in Pennsylvania. Covariate-specific posterior effects for the 2014 ZIP codes with the five lowest and ten highest RRs, (a) OUD, (b) heroin poisoning, and (c) non-heroin opiate poisoning. The figure displays the median RR contributions of the fixed effects in the models. Each bar represents a single ZIP code in 2014; the effects of covariates that raise risks are above the zero-risk line and those that lower risks are below the line. For example, for ZIP code 18101, the effect of manual labor establishments on OUD was associated with an RR increase of 1.45, whereas the same effect in ZIP code 15901 was negligible (relative rate = 1.08).

variates create patterns of risk within specific ZIP codes. For example, although both the highest and lowest risk ZIP codes show increased risk associated with a large percentage White, the low-risk regions have a large decreased risk via high median household income, whereas the high-risk areas contain a high proportion of manual labor businesses, low median household incomes, and high population density. Some of the other highest risk ZIP codes (e.g., 18101) had a greater increased risk connected to percentage Hispanic, poverty level, and low median household income. Figure 2 can be viewed as an illustration that the opioid epidemic comprises “multiple” epidemics. Each of these communities may require different approaches to effectively combat the opioid epidemic.

Somewhat surprisingly, a greater percentage of arthritis- and cancer-related hospitalizations were associated with fewer OUD and poisoning hospitalizations. This may indicate that the misuse of prescription opioids where the need for illness-related pain relief is greatest is not a significant contributor to the epidemic. In contrast, the proportion of manual labor establishments had a well-supported association with OUDs and poisonings, suggesting that pain management for occupational injuries may play a role.

The strong dose-response relationship that emerged between population density and OUD, non-heroin opioid poisoning, and heroin poisoning was another unexpected result of our analyses. The greatest risks of OUD and opioid poisoning hospitalizations still accrue in the most dense, urban communities in Pennsylvania, with heroin poisoning hospitalizations having the strongest association with urban environments. Heroin has been a consistent problem in the urban communities of the Northeast in the past 50 years and was historically viewed as an urban problem (Schneider, 2008). The attention focused on rural Appalachian communities (Keyes et al. 2014; Young et al., 2012) has been largely driven by the more rapid rates of overdose increase in these areas rather than the overall burden of opioid-related problems. It is important not to lose sight of the communities shouldering the greatest overall burden of the opioid epidemic as well as those who have only been affected in recent years.

Focusing these analyses on Pennsylvania is important, given the huge burden of the epidemic within the state (PHC4, 2016) and the governor’s recent classification of the opioid epidemic as a disaster emergency (Governor Tom Wolf’s Office of Communications, 2018). It is important to note that although the conditions within Pennsylvania are likely applicable to other regions of Appalachia, such as West Virginia, they may differ from other parts of the United States. A similar analysis conducted in California found that age-related medical need for prescription opioids (i.e., cancer and arthritis hospitalizations) was associated with a greater number of prescription opioid-related hospitalizations, whereas the poverty rate and manual labor occupations

had a lesser impact than in Pennsylvania (Cerdá et al., 2017). It will be important for similar analyses to be conducted in other regions of the United States where data are available at a relatively fine spatial resolution.

Using hospital inpatient discharge data to track the opioid epidemic limits the generalizability of our results, since many opioid users (and those who overdose) will not end up in a hospital setting. Those who end up in an inpatient hospital setting (vs. emergency department or with no medical care) are likely to be older and with a greater number of comorbid conditions than the general population of opioid users, limiting the generalizability of these findings. These limitations are somewhat offset by the consistency over both time and space within a given state of hospital discharge data. Substance use and use disorder surveillance data with spatial resolution below the level of states or counties do not exist in the United States. Hospitalization data, although imperfect in many ways, can fill this gap with much better spatial resolution. Our analyses are population based and cannot tell us how the social environment affects an individual’s risk for OUD or overdose, or whether there are high-risk individuals within specific communities that have a disproportionate impact on the epidemic. Still, understanding population patterns and predictors of the epidemic has the potential to be of great public health importance.

The majority of the efforts to combat the opioid epidemic have focused on treatment and secondary prevention (e.g., provision of naloxone to prevent overdose death) and have not accounted for the ecologically specific nature of the epidemic. The National Heroin Task Force recently issued a report with recommendations that included ensuring safe prescribing practices, increasing strategic enforcement, preventing overdose deaths through the use of naloxone, and increasing access to treatment (National Heroin Task Force, 2015). In each of these cases, it is easy to imagine how a statement with ecological validity, e.g., “treatment for young adults in poor, rural regions is most needed,” is more useful than a general statement that “better access to treatment is needed.” Our findings demonstrate how the results from spatial random effects models can be used to identify communities with the greatest predicted probabilities of epidemic outbreak. Additionally, information provided by analyses of this type can be used to ask, and answer, the question of where we should put resources to try to reduce the number of opioid-related hospitalizations, as well as the relative contribution in predicting this risk of specific publicly available markers of social and demographic environmental conditions. We need to continue the conversation about smart primary prevention and explicitly address the social ecological contexts of opioid use and overdose, or we will have to continue to rely on treatment and prevention of secondary consequences as our only strategy.

Potential Competing Interests

The Pennsylvania Health Care Cost Containment Council (PHC4) is an independent state agency responsible for addressing the problem of escalating health costs, ensuring the quality of health care, and increasing access to health care for all citizens regardless of ability to pay. PHC4 has provided data to this entity in an effort to further PHC4's mission of educating the public and containing health care costs in Pennsylvania. PHC4, its agents, and staff have made no representation, guarantee, or warranty, express or implied, that the data—financial, patient, payor, and physician-specific information—provided to this entity are error free, or that the use of the data will avoid differences of opinion or interpretation. This analysis was not prepared by PHC4. This analysis was done by all listed authors. PHC4, its agents, and staff bear no responsibility or liability for the results of the analysis, which are solely the opinion of this entity.

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