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Geographic patterns of prescription opioids and opioid overdose deaths in New York State, 2013-2015

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ABSTRACT

Objectives: To examine the relationship between prescription opioid rates and prescription opioid overdose deaths using spatial cluster and regression analyses.
Methods: Publicly available county-level data were obtained from the New York State Health Department and the Centers for Disease Control and Prevention, 2013–2015. Kulldorff's spatial scan statistic was used to investigate spatial clustering of New York State opioid prescription overdose death rates, as well as opioid prescription rates. A Poisson regression was used to analyze opioid prescriptions as a predictor of mortality accounting for spatial autocorrelation in the residuals.
Results: We report 1440 overdose mortalities and 26.8 million opioid prescriptions throughout New York State in 2013–2015. Multiple significant clusters were found for both opioid prescription mortalities as well as prescriptions, although the locations of the elevated rates did not strongly overlap. Poisson regression showed a significant, small, negative relationship between prescriptions and opioid mortalities, wherein for every 10,000 prescriptions increased, the number of opioid mortalities decreased approximately 0.12%; therefore, essentially a null relationship.
Conclusions: Simply reducing the number of prescriptions may not be effective in reducing prescription related mortality; although opioid prescription dosing information should be made available to engender a better evaluation of the epidemic. Geographical differences in opioid mortalities exist above and beyond what can be explained by prescription rate data; identifying these locations may help inform and guide public health interventions. Despite the recent reduction in opioid prescription rates, the overall population is still inundated with prescriptions.

1. Introduction

Opioid related deaths in the United States have been steadily increasing over the past 15 years, and have become one of the most recognizable public health crises of today. Despite a concerted effort to decrease prescription availability, prescribed natural and semi-synthetic opioids are still major drivers of mortality, accounting for a third of opioid-related mortalities in the US (Center for Disease Control and Prevention, 2017a).

The opioid landscape is evolving. From 2007–2012, physician prescription rates for prescribed opioid pain relievers (i.e., buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, propoxyphene, tapentadol, and tramadol) consistently rose in the US. In 2012, the rate hit a peak value of 81.6 retail opioid prescriptions per 100 people (Center for Disease Control and Prevention, 2017c). Unsurprisingly, prescription related opioid deaths rose concurrently and accounted for the majority of opioid mortalities (Center for Disease Control and Prevention, 2017b).

As the CDC declared this an epidemic in late 2011, states began implementing legislation to reduce prescription opioid volume. By 2016, opioid prescription rates were on the decline but remained relatively high at 66.5 per 100 people (Center for Disease Control and Prevention, 2017c). This translated into 19.1% of individuals in the US with an opioid prescription filled in 2016, and an average of 3.5 prescriptions per individual who possessed at least one prescription (Centers for Disease Control and Prevention; US Department of Health and Human Services, 2017).

Measuring how this reduction impacted prescription related

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mortalities, however, is challenging. Starting around 2012, illicitly manufactured fentanyl began to gain traction and has since created a conundrum in estimating the true rate of prescription related opioid deaths. Traditionally, deaths from prescribed synthetic opioids like fentanyl and tramadol were included in prescription mortality rates. But prescription fentanyl and illicitly manufactured fentanyl cannot be distinguished from one another in a toxicology report or death certificate (Rudd et al., 2016a; Seth et al., 2018), rendering it impossible to categorize these mortalities as either prescription or non-prescription related.

The surge in synthetic opioid overdose deaths has been shown to correlate with law enforcement seizure of drug products that test positive for illicit fentanyl, and not with fentanyl specific prescription rate data (Gladden et al., 2016). Therefore, it can be inferred that most synthetic opioid mortalities are related to illicit fentanyl, and not prescribed fentanyl or tramadol (Centers for Disease Control and Prevention, 2015; Rudd et al., 2016b; Schuchat et al., 2017; Seth et al., 2018). Thus, recent evidence suggests that excluding deaths related to synthetic opioids is a reasonable approach for estimating prescription mortality rates.

While it is harder to control the amount of illicit opioids available in the population, prescription opioids are a modifiable factor, as evidenced by the reduction of prescription rates over the past few years. At this critical time point, it is important to understand the role and relationship that prescription opioids continue to play in the epidemic as it relates to prescription opioid related deaths.

Research examining the spatial relationship between prescription drug mortalities and prescribing patterns is not common. Cerda et al. (Cerda et al., 2017) examined geographic distribution of prescription opioid poisonings in California by using hospital discharge data. Hospital discharges were higher in postal codes with a higher density of pharmacies, higher number of arthritis-related hospital discharges, lower income, and higher number of manual labor industries. Prescription rate data were not included, and mortality was not considered. McDonald et al. (McDonald et al., 2012) report considerable geographic variation in 2008 county level opioid prescription rates across the US, but unrelated to prevalence of conditions most likely requiring analgesics. They did not examine prescription opioid related mortalities. Hot-spots in drug poisoning within the US were examined at the county level (Rossen et al., 2014), but this included all drug poisoning deaths as opposed to isolated prescription opioid specific mortalities. Most notably, two area-level studies in Canada (Gladstone et al., 2015; Gomes et al., 2011) found positive associations between opioid prescriptions and prescription related mortality and noted a wide variety of prescribing practices that exist within Canada. Both studies were conducted in a time period prior to the need to consider whether synthetic opioid mortalities are caused by illicit fentanyl, or prescribed fentanyl or tramadol. It is unknown if this relationship holds in other countries, or whether it still persists using more recent data where synthetic opioid mortalities are excluded.

County level prescription opioid mortality data, with information on the specific class of opioids related to mortality, are not easily ascertained. Our analysis focuses on one state, New York, where this information was available via the state health department website. New York State was identified as one of 7 states with a statistically significant increase in drug overdose death rates involving prescription pain relievers from 2014 to 2015 (Center for Disease Control and Prevention, 2017b). It is unknown if spatial clusters of prescription opioid-related mortality exist within NYS, and whether these clusters could be explained by differential prescription drug rates within the State. To the extent of our knowledge, no work has been done to investigate the spatial distribution of county level prescription opioid related mortality rates in NYS. Assessing potential spatial patterns could help researchers generate hypotheses regarding underlying social or environmental risk factors for prescription opioid overdose deaths.

Our aims for this study are twofold: First, to determine the existence of statistically significant spatial clusters of pain reliever prescription opioid overdose deaths (using natural and semi-synthetic opioids) or prescription opioid rates within New York State; and second, to evaluate the relationship between opioid prescription availability and prescription opioid overdose deaths.

2. Materials and methods

2.1. Data

All data were publically available for download from either the Centers for Disease Control and Prevention (https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html) (Center for Disease Control and Prevention, 2017c) or the New York State Department of Health (NYSDOH) (https://www.health.ny.gov/statistics/opioid/) (New York State Department of Health, 2018).

2.2. Mortality data

Opioid overdose mortality cases (natural and semi synthetic opioids) from 2013 to 2015 were extracted from NYSDOH at the county level. NYSDOH collects and compiles vital statistic data from death certificates, using ICD 10 codes for the underlying cause of death. NYSDOH defines prescription related opioid overdose deaths in three ways: 1) as “any painkiller”, defined as any pharmaceutically and illicitly produced naturally-occurring, semi-synthetic, and synthetic opioids such as codeine, oxycodone, fentanyl, and methadone; 2) as “involving synthetic opioids other than methadone”, which includes overdose deaths due to pharmaceutically and illicitly produced synthetic opioids such as fentanyl and tramadol; and 3) Methadone as a standalone category, which cannot distinguish methadone received as a prescription pain reliever, or methadone received from a methadone maintenance treatment program. In order to reduce the possible noise generated from both methadone and illicitly made synthetic opioids, and to best match prescription related data from the CDC, we extracted all variables related to the three overdose prescription related opioid death categories, and calculated a new pain-reliever mortality numerator variable by subtracting total methadone and synthetic opioid deaths from all opioid pain reliever deaths (in other words, 1-(2 + 3) using the death definitions described earlier in this paragraph). Final ICD10 codes included can be summarized as the following: underlying cause of death X40-X44, X60-64, X85, Y10-Y14, AND opioid pain reliever (T40.2 only) in all other causes of death.

While data suggest that the synthetic opioid overdose mortalities are more likely to be related to illicit fentanyl as opposed to prescribed synthetic opioids (Gladden et al., 2016), we are less confident about the dichotomy that exists in the methadone-related deaths. Methadone-related mortalities cannot be distinguished by the source of methadone (i.e., from prescription pain relievers, or methadone received from a methadone maintenance treatment program). However, prescription rate data (described below) include only methadone prescriptions that were not distributed from a treatment program. To examine the possible discrepancy between the different data, a sensitivity analysis for both the clustering and regression analyses was performed using an opioid mortality variable which includes methadone related mortalities.

The 2013–2015 average age adjusted death rates were also provided for each county; however, age adjustments were made according to the 2000 U.S. population. (More recent age adjusted county level populations were not available.) To estimate the underlying age-adjusted population at risk, we divided the number of mortalities by the age adjusted rates in each county.

2.3. Prescription data

Opioid prescription data from 2013 to 2015 were extracted at the

Table 1
Summary Descriptive Statistics for NYS 2013–2015 Opioid Mortality and Prescription Opioids.

Classification	Cases and Rates	Mean	Std Dev	Median	Q1	Q3
Mortality - Excluding Methadone and Synthetic overdoses	Total Cases, 2013-2015	23.61	36.5	7	3	24
	Average Age Adjusted Mortality Rate per 100,000 people	2.73	1.74	2.75	1.44	3.72
Sensitivity Analysis: Mortality - excluding synthetic overdoses only	Total Cases - 2013-2015	35.64	57.11	10	4	30
	Average Age Adjusted Mortality Rate per 100,000 people	3.78	2.1	3.6	2.25	5.19
Opioid Prescriptions	Total Number of Opioid Prescriptions, 2013-2015	438,755	612,497	157,524	95,124	437,592
	Average Opioid Prescription Rate per 100 people	55.38	16.27	55.07	41.9	63.43

Descriptive statistics for mortality total cases as well as age adjusted mortality rates for both the primary and sensitivity analysis are presented below Descriptive Statistics are also presented for total number of opioid prescriptions and rate of prescriptions.

county level, including the following variables: opioid prescription rate (defined as the number of opioid prescriptions per 100 residents per county), and county population data. Prescription data were compiled by QuintilesIMS TDW, which uses a sample of retail (non-hospital) pharmacies dispensing approximately 88% of all retail prescriptions in the United States. Opioid prescription rates include retail prescriptions for "butrans (buprenorphine), codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, propoxyphene, tapentadol, and tramadol. Methadone dispensed through methadone maintenance treatment programs are not included in QuintilesIMS TDW data" (Center for Disease Control and Prevention, 2017c). Denominator estimates for the annual resident population were obtained from the U.S. Census Bureau's Population Estimates Program, using the 2010–2016 Postcensal Estimates of the Resident Population for Counties. The number of prescriptions was then calculated by multiplying the prescription rates by the population data.

2.4. Data merging

Data were cleaned, matched and merged using SAS 9.4© Software (Cary, NC, USA). A United States County boundaries shapefile from the US Census Bureau's Cartographic Boundary Shapefiles repository was clipped to include only New York counties and joined with the opioid data using the 'FIPS County Code' common field in ESRI's ArcMap 10.5.1. Prescription rate data were missing for one county (Hamilton), and therefore, the polygon was deleted; treated, in essence, as a body of water in this spatial analysis. Centroids of remaining polygons were exported from ArcMap and saved as a "County Centroids" point feature class (ESRI shapefile).

2.5. Analyses

Choropleth maps were generated in Geoda v. 1.1.2 (Chicago, IL, USA) to visualize both mortality and prescription opioid rates by New York State County. Kulldorff's spatial scan statistic in SaTScan v. 9.5 (Boston, MA, USA) was used to assess spatial clustering of opioid prescription overdose deaths at the county level. A discrete Poisson model was chosen, using total 2013–2015 county prescription related overdose deaths as the numerator, and age adjusted county population as the denominator. We chose a maximum inclusion of up to 25% of the population at risk, with no centers of clusters overlapping other clusters. Under the null hypothesis, the observed number of cases follows a uniform distribution in the study area, so that the expected number of cases in an area is proportional to its population size. Clusters of interest are selected on the basis of the p-value associated to their likelihood under the null hypothesis using Monte Carlo simulations at a p-value of < 0.05. SaTScan is considered a state-of-the-art approach to spatial cluster analysis (Sherman et al., 2014) because it examines possible clusters throughout the study area, includes numerator and denominator in the algorithm (not just a rate), and accounts for the possibility of false positives arising from multiple testing. Clustering of opioid prescription rates was also examined separately using similar methods.

A Poisson regression was performed in SAS v. 9.4 (Cary, NC) to evaluate the relationship between prescriptions and mortalities. Because prescription numbers far exceeded opioid mortalities, prescriptions were rescaled by dividing by 10,000. The number of opioid mortalities was then set as the outcome, and the "per 10,000 prescriptions" variable as the predictor, with the log of the total age adjusted population as an offset.

Raw residuals from the Poisson regression were explored for overall spatial autocorrelation in Geoda using Moran's I with first order Queen Contiguity weights. Given the possibility of spatial autocorrelation in the residuals which could indicate a possible spatial confounder in the analysis, the residuals were smoothed using the Empirical Bayes Smoother (EBS) in Geoda. EBS residuals were imported into SAS and included as a covariate in a subsequent Poisson regression to control for the potential spatial confounding in opioid mortalities.

3. Results

A total of 1440 overdose mortalities related to natural and semi-synthetic prescription opioids (excluding methadone) were reported in New York State from 2013 through 2015. Approximately 26.8 million opioid prescriptions were distributed throughout New York State in that same period.

The average age adjusted mortality rate varied within the state, with an average rate of 2.73 deaths per 100,000 per county (min = 0; max = 7.65), (Table 1). Rates are mapped in Fig. 1a. Twelve significant spatial clusters were detected: 5 had higher than expected rates (Fig. 2a), and seven had lower than expected rates (Fig. 2b). Some clusters overlapped one another; the highest probability clusters are ranked from 1 to 12 in Fig. 2. Clusters of high mortality rates were found in the Hudson Valley, Catskills, western Central New York, eastern Finger Lakes, and Thousand-Islands Seaway regions, as well as Richmond County and Long Island. Low mortality rate clusters were found in the New York City region (excluding Richmond County), as well as in the Capital, eastern Central New York, and lower Adirondacks regions. Similar results were seen when methadone mortalities were included (results not shown).

The average county opioid prescription rate varied within the state, with statewide average of 55.38 prescriptions per 100 people (min = 25.1; max = 102.57), (Table 1). Rates are mapped in Fig. 1b. SaTScan cluster analysis detected 14 significant clusters across the state: 6 had higher than expected rates, and eight had lower than expected rates (Fig. 3a, b). High prescription rate clusters were found throughout most of the state north of Westchester County. Low rate clusters were found in the New York Metropolitan area, excluding Richmond County. (Please see Supplemental Table 1 and Supplemental Fig. 1* for cluster ranking details and county locations.)

In results from a Poisson regression, there was a significant inverse relationship between prescriptions and opioid mortalities, with a beta

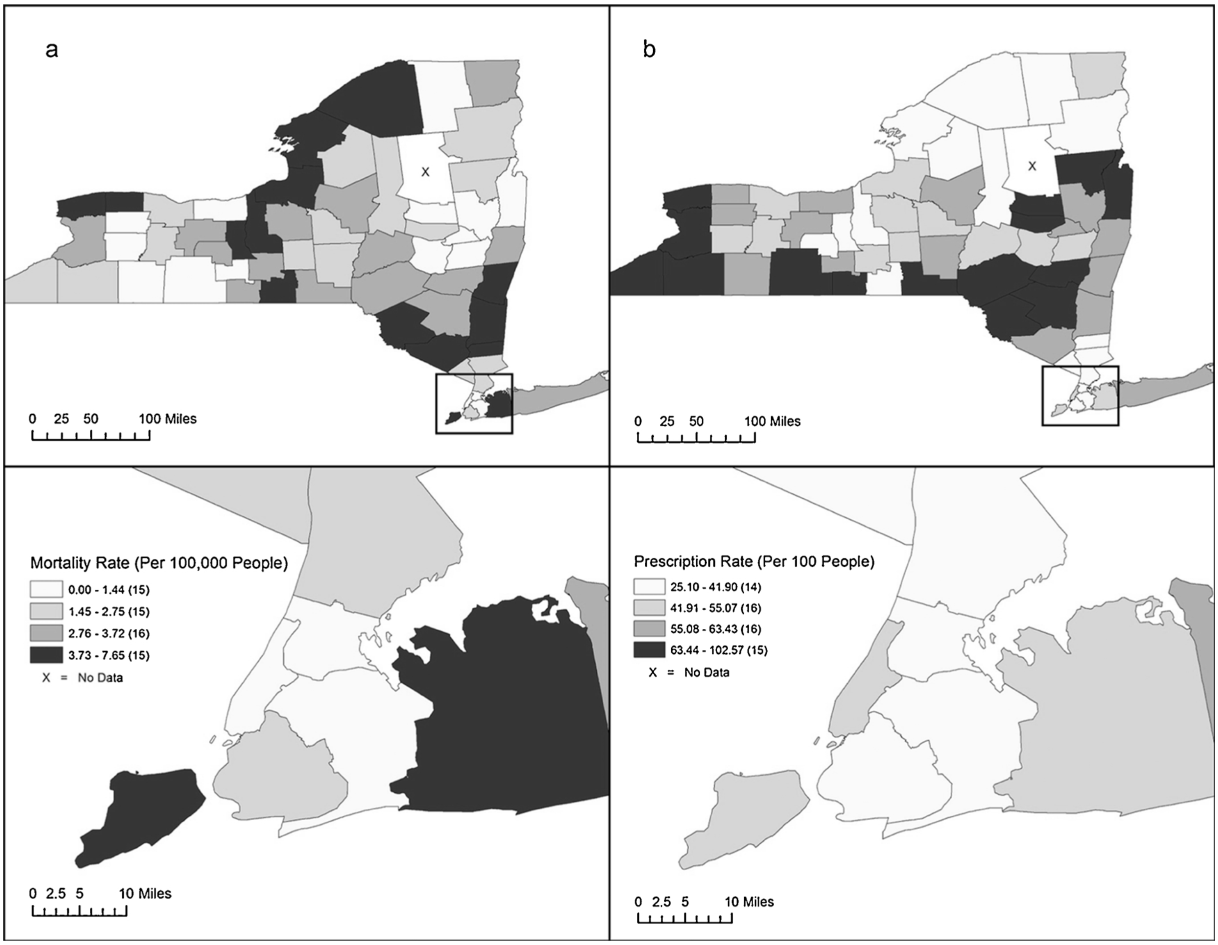

Fig. 1. Geographic Distribution of (a) Opioid Prescription Mortality Rate Quantiles and (b) Opioid Pain Reliever Prescription Rate Quantiles, County Level: New York State, 2013–2015. County level data for both mortality rates and prescription rates are displayed in quantiles, ranging from low/light colors to high/dark colors. Actual mortality rates in NYS range from 0 to 7.65 per 100,000 people, while prescription rates range from 25.1 to 102.57 per 100 people.

coefficient value of -0.0016. Counterintuitively, for every 10,000 prescriptions increased, the number of opioid mortalities decreased by approximately [1-exp(-0.0016)] 0.16%. This relationship is very small, but significant ($p < 0.001$). Similar results were seen when methadone mortalities were included, with a [1-exp(-0.008)] 0.80% case decrease per 10,000 prescription increase.

Residuals from the Poisson regression were examined for spatial autocorrelation using univariate Moran's I. Moderate to high significant spatial autocorrelation was found ($I = 0.499$, $p = 0.001$), indicating potential spatial confounding by an unidentified other variable. To account for this potential spatial factor, residuals were smoothed and included as a covariate in the Poisson regression. The prescription coefficient estimates attenuated slightly but remained significant. After accounting for spatial autocorrelation in the residuals, for every 10,000 prescriptions increased, the number of opioid mortalities decreased approximately [1-exp(-0.0012)] 0.12%. Similar results were seen when methadone mortalities were included, with a Moran's $I = 0.256$, $p = 0.002$. Poisson regression revealed a [1-exp(-0.0015)] 0.15% case decrease per 10,000 prescription increase.

4. Discussion

This study investigates the spatial relationship between opioid prescriptions and opioid mortality in the current context of the opioid epidemic. We applied spatial clustering and Poisson regression analyses at the county level in NYS. Several areas were identified with elevated and lower rates of spatial clusters for both opioid prescriptions and prescription opioid mortalities; however, prescription and mortality clusters did not overlap in corresponding directions. Elevated clusters of prescription rates often overlapped with decreased clusters of mortality rates, and vice versa. Contrary to our hypothesis, regression results did not show a positive relationship between prescriptions and mortality. A significant relationship was seen between these variables, but the relationship was incredibly small and negative. After we controlled for spatial autocorrelation in the residuals, the relationship attenuated slightly, but was still significant. The small predictive capability of prescription rates suggests there are geographical differences in opioid mortalities above and beyond what can be explained by prescription rate data alone. Perhaps most critical, across the three-year time period, we observed 1440 overdose mortalities compared with 26.8 million opioid prescriptions distributed across NYS. Given the overwhelming amount of prescription opioids in circulation compared with death events, modest reductions in the number of prescriptions were not associated with a decrease in prescription related mortalities.

When visually examining mortality rates versus prescription rates (Fig. 1a and b), several areas with discrepancies are notable. For instance, in the Thousand Islands-Seaway region and Central NY (located in the north north-western/north-central parts of NY), most counties have higher opioid related mortality rates but lower opioid prescription rates. This relationship is similar in the Hudson Valley region (located north of New York City). The westernmost region of the state appears to have the opposite relationship - with higher prescription rates and lower mortalities. This is similar for central eastern counties. New York City seemed to be the one location that had both lower mortality rates

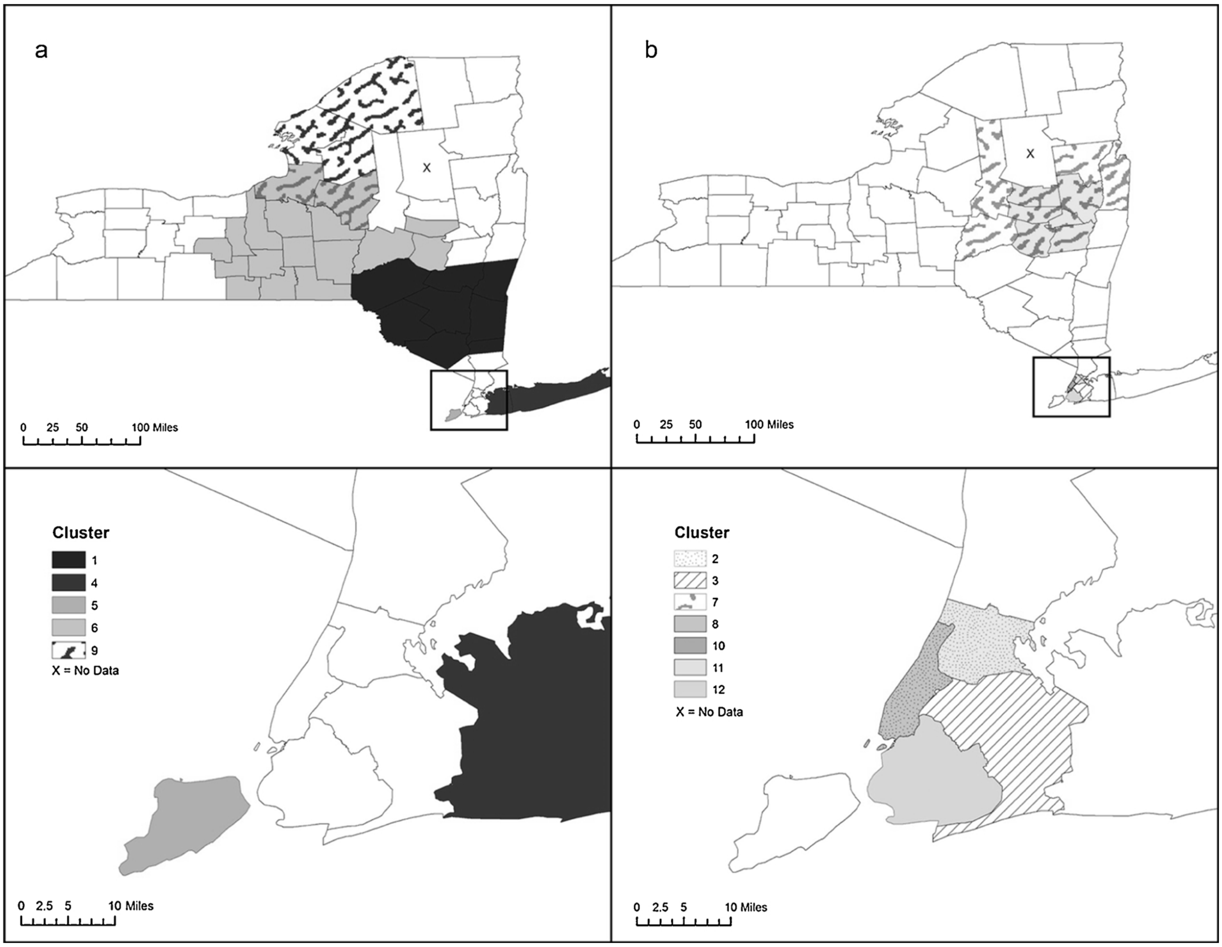

Fig. 2. Geographical Clustering of Natural & Semi-Synthetic Opioid Mortality by (a) High and (b) Low Rates: New York State, 2013–2015. Five significantly higher than expected mortality rate clusters (a), and seven significantly lower mortality rate clusters (b) were detected across New York state counties.

and lower prescription rates.

There are several hypotheses as to what may be driving these geographical differences. Prescribing methods related to dosing and duration may vary by geographic area. Interestingly, one case-control study showed that high doses of prescription opioids do not necessarily indicate a higher risk of death for the individual with the prescription (Gwira Baumblatt et al., 2014). Those authors suspected that these types of high daily dose prescriptions were linked to diversion, i.e., the transfer of a prescription drug from someone who was lawfully prescribed that drug, to another who was not (Green et al., 2013). In fact, a Canadian study found that 50% of individuals who suffered a prescription opioid mortality did not have an opioid prescription filled in the past year (Gladstone et al., 2015). It is possible that diversion plays a role in the prescription/mortality rate discrepancies within our analysis. As diversion and drug dose appear to be an interwoven issue, it would be important to understand how average dosing rates, not just average prescription rates, may either vary by geographic region or account for the geographic differences in regions. Further understanding of these differences might also shed light on the shifting patterns from prescription opioid use to illicit drug use such as heroin (Stewart et al., 2017).

Our findings are discordant with two prior studies (Gladstone et al., 2015; Gomes et al., 2011) – which found a positive correlation between opioid prescription rates and opioid-related mortalities. While Gomes looked at prescription rates, Gladstone was able to quantify prescriptions using morphine equivalent dosing rates. Unfortunately, since this type of data was not available to us, prescription rates must serve as the best proxy in our analysis.

Our findings are not necessarily at discord when placed in the context of US national trends. Even though prescription rates began to decrease in 2012 and have continued through present day across the US, the corresponding natural and semi-synthetic opioid mortality rate did not follow suit. Rates showed a small initial decrease in 2012, but rebounded again by 2015 (Center for Disease Control and Prevention, 2017a). This may indicate that prescribing rates need to decrease even more to show a corresponding effect. It may also indicate that there are additional geographically varying predictors of prescription-related mortality other than prescription rates. Certain geographic areas could be obtaining additional prescription drugs from outside of their immediate surroundings. In the lower Hudson Valley region, for example, mortality rates were higher, and prescription rates were lower. Proximity to New York City, Connecticut, and Pennsylvania may provide a source of prescriptions outside of the county. Similarly, counties in the North may be receiving prescriptions from Canada, which would not be accounted for in this data, but may explain a higher mortality rate.

There are limitations in the data used for the analysis. In addition to the lack of available dosing data, prescription data for retail opioid prescriptions included synthetic opioids (e.g., fentanyl) and certain methadone prescriptions, both of which we excluded from the mortality data used in the primary analysis. Detailed rates for each type of opioid were not provided, so synthetic (fentanyl) and methadone prescriptions could not be teased out and excluded. By including these in the prescription data and excluding mortalities from synthetic and methadone prescriptions, we may have reduced the strength of the relationship between opioid prescriptions and mortality. As previously stated though, it is likely that most synthetic opioid mortalities are related to

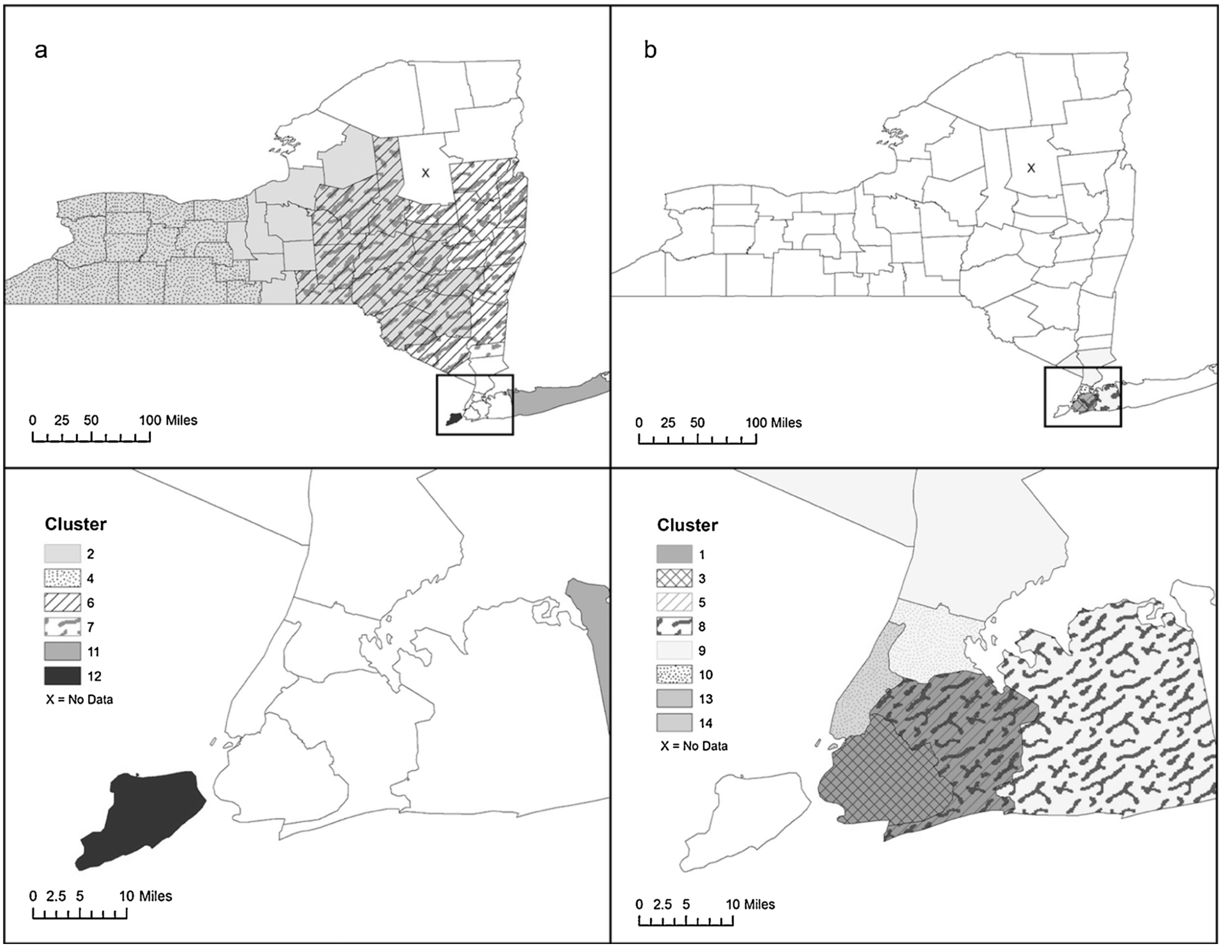

Fig. 3. Geographical Clustering of Opioid Prescriptions by (a) High and (b) Low Rates: New York State, 2013–2015. Six significantly higher than expected clusters of prescription rates (a), and eight significantly lower than expected clusters of prescription rates (b) were detected across New York state counties.

illicit fentanyl, and not prescribed fentanyl or tramadol (Centers for Disease Control and Prevention, 2015; Gladden et al., 2016). If we had included mortalities for synthetic opioids, we would not be capturing the current drug landscape, which would mask the true relationship between opioid prescriptions and prescription related death. Second, we could not find a reasonable estimate for the approximate proportion of methadone mortalities that were attributable to physician prescribed pain relief methadone as opposed to methadone received from a treatment clinic. Since the prescription data was comprised of only non-treatment center prescriptions, but mortality data included all methadone related mortalities, we performed a sensitivity analysis with and without the methadone overdose mortalities. We found little difference in results of any of the analyses. Prescription data also do not include prescriptions obtained from within a hospital, which has been estimated to account for about 10% of all opioid prescriptions dispensed (McDonald et al., 2012). However, it is unclear if some New York state hospitals were allowed to dispense opioid prescriptions over this time period. Even so, if 10% were to remain unaccounted for, it would not equate to a severe underestimate of the available opioids in the public, and it remains unclear what role this would play in the spatial relationship between prescriptions and deaths.

In SaTScan, 'ellipsoid' is a cluster detection option for scan window shape when using the Bernoulli model, but is not yet available for use in Poisson models. Therefore, our analyses were conducted using a circular search window since there were no alternatives. This is not ideal because it is more realistic to expect true clusters to be ellipsoid or amoeboid in shape. Since we were unable to utilize an ellipsoid shape, alternative clusters may not have been detected. However, allowing clusters to overlap permits the identification of more amoeba-like cluster regions.

Finally, sparse mortality data introduce the possibility of a small numbers problem. Counties with small populations might have unstable mortality rates. The variable size scanning window used by SaTScan, the Poisson regression approach, and including three years of data, all help alleviate these concerns.

5. Conclusions

In summary, the widened use of illicit fentanyl has revised how we define prescription-related mortalities. Examining spatial patterns in mortalities from natural and semi-synthetic opioid prescriptions is an important step to understanding the dynamic opioid epidemic. There are obvious spatial patterns in opioid prescription rates and mortality rates within NYS. While there continues to be an ever important reduction in opioid prescribing over the last few years, the overall population appears to essentially remain flooded with opioid prescriptions. Thus, while small reductions in the number of prescriptions may not be enough to elicit a decrease in prescription related mortalities, further reductions may yet stem the tide of the epidemic. Opioid prescription drug-specific dosing information at both the US State and County levels would be helpful to allow both national and local evaluation of the epidemic and engender a broader understanding of the issue as well as illuminate areas for locally targeted interventions. It is also worth acknowledging that the opioid epidemic may not have stagnant predictors over time. We must continue to examine this issue as the epidemic changes, in hope of shedding new light for future public health interventions.

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Contributors

Authors contributed to the conception, design, analysis, interpretation, and writing of the manuscript. All authors approved of the final version of the manuscript.

Conflict of Interest

No conflicts declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2018.11.027.

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