ABSTRACT

Title of Dissertation:	THE SPATIAL ANALYSIS OF OPIOID-RELATED HEALTH OUTCOMES AND EXPOSURES IN THE UNITED STATES OPIOID OVERDOSE CRISIS
	Jeffery SAUER, Doctor of Philosophy, 2022
Dissertation directed by:	Professor Kathleen Stewart Department of Geographical Sciences

The United States continues to endure the Opioid Overdose Crisis. Yet the burden of the crisis is not experienced uniformly across the United States. The discipline of geography offers a framework and spatial analysis methodology that are direct ways to investigate placed-based differences in opioid-related outcomes, exposures, and proxy measures. This dissertation combines the contemporary frameworks of health geography and geographic information science to provide novel studies on both the geographic patterns in opioid-related health measures at different scales across the United States as well as the actual spatial analytic methods that provide evidence on the Opioid Overdose Crisis. Three main research objectives are addressed over the course of the dissertation: 1) Model the space-time risk of heroin-, methadone-, and cocaine-involved emergency department visits in the greater Baltimore metropolitan area from January 2016 to December 2019 at the Zip Code Tabulation Area-level; 2) Estimate the local and neighboring relationship between prescription opioid volume and treatment admissions involving a prescription opioid across the United States from 2006 to 2014 at the county-level; and 3) Investigate and provide a framework as to how geographic information science has been used to provide knowledge over the duration of the crisis from 1999 to 2021. The first study demonstrates how a recently proposed spatio-temporal Bayesian model can produce disease risk surfaces for opioid-related health outcomes in data constrained scenarios. The second study executes spatial lag of X models on a nationwide prescription opioid distribution dataset, allowing for estimates on the relationship between neighboring prescription opioid volume and nonfatal treatment admissions involving a prescription opioid at the county-level. The third and final study of the dissertation developed and implemented a scoping review methodology, ultimately analyzing the study design and geographical elements of 231 peer-reviewed publications using geographic information science on research questions related to the crisis. Examination of the geographical components of these studies reveals a lack of evidence available at sub-state scales and in the Midwest, north Rocky Mountains, and non-continental United States. Several important future research directions - such as geographic meta-analyses and geographical machine learning - are identified. Taken as a whole, the dissertation provides a contemporary geographical framework to understand the ongoing United States Opioid Overdose Crisis.

THE SPATIAL ANALYSIS OF OPIOID-RELATED HEALTH OUTCOMES AND EXPOSURES IN THE UNITED STATES OPIOID OVERDOSE CRISIS

by

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Dissertation submitted to the Faculty of the Graduate School of the
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Dedication

To my family: Mary Lynn Yakel, Jeff Sauer, Caroline Sauer, Margaret Skoglund, and Elizabeth Yakel

To those close to me for helping at various points along the journey: Aleksandra Busic-Conevska, Joey Wong, Sean Boyle, Chelsea Ayukawa, Andres Ruiz-Tagle, Tuviere Onookome-Okome, Allison Baer, Rebecca Traldi, Elisabeth Powell, Amber Liang, Xinyuan Li, Eric Gao, Rene Iwo, Maxwell McClarty, Midori Huguenin, Georgia Channing, and Sarah Knill

To all those who have encountered addiction in its manifold forms

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List of Abbreviations

US: United States

OOC: Opioid Overdose Crisis

ED: Emergency department

GIScience: Geographic Information Science

EDDS: Emergency Department Drug Surveillance system

SMR: standardized mortality rate or ratio

ZCTA: ZIP code tabulation area

ARCOS: Automated Reports and Consolidated Ordering System

DEA: Drug Enforcement Administration

SAMHSA: Substance Abuse and Mental Health Services Administration

TEDS-A: Treatment Episode Dataset

ADAI: University of Washington Addictions, Drug & Alcohol Institute

MME: Morphine milligram equivalents

SLX: Spatial lag of X model

PDMP: Prescription Drug Monitoring Program

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses - Scoping Review Extension

OSF: Open Science Framework

WOS: Web of Science

IEEE: Institute of Electrical and Electronics Engineers

ACM: Association for Computing Machinery

Chapter 1: Introduction and research context

1.1 Dissertation overview

Since the early 2000s in the United States (US), physicians, researchers, and government entities have observed increases in opioid-involved mortality (death) and morbidity (disease) (King et al. 2014; Hasegawa et al. 2014). In 1999, the national age-adjusted rate of drug overdose deaths was 6.1 per 100,000, yet by 2018 the rate had more than tripled to 20.7 per 100,000 (Hedegaard, Minino, and Warner 2020). Similar increases have been observed in opioid-related morbidity. During the period of 1999 to 2010, nonfatal treatment admissions for opioid use disorder increased more than 300% (L. Paulozzi et al. 2011). These increases in mortality and morbidity have coalesced into a public health emergency called the Opioid Overdose Crisis (OOC). A commonly used framework describes the OOC as occurring over three distinct phases (also called ‘waves’) (Figure 1). These waves include a rise in prescription opioid prescribing and death from 1999-2010 (Wave 1), a transition to heroin use and subsequent rise in heroin overdose deaths from 2010 to 2014 (Wave 2), and a rise in synthetic opioid overdose deaths from 2013 onwards (Wave 3). While each of the individual waves describes a specific period and opioid, taken as a whole the waves provide a cogent narrative that helps to explain how the OOC has continued for more than two decades.

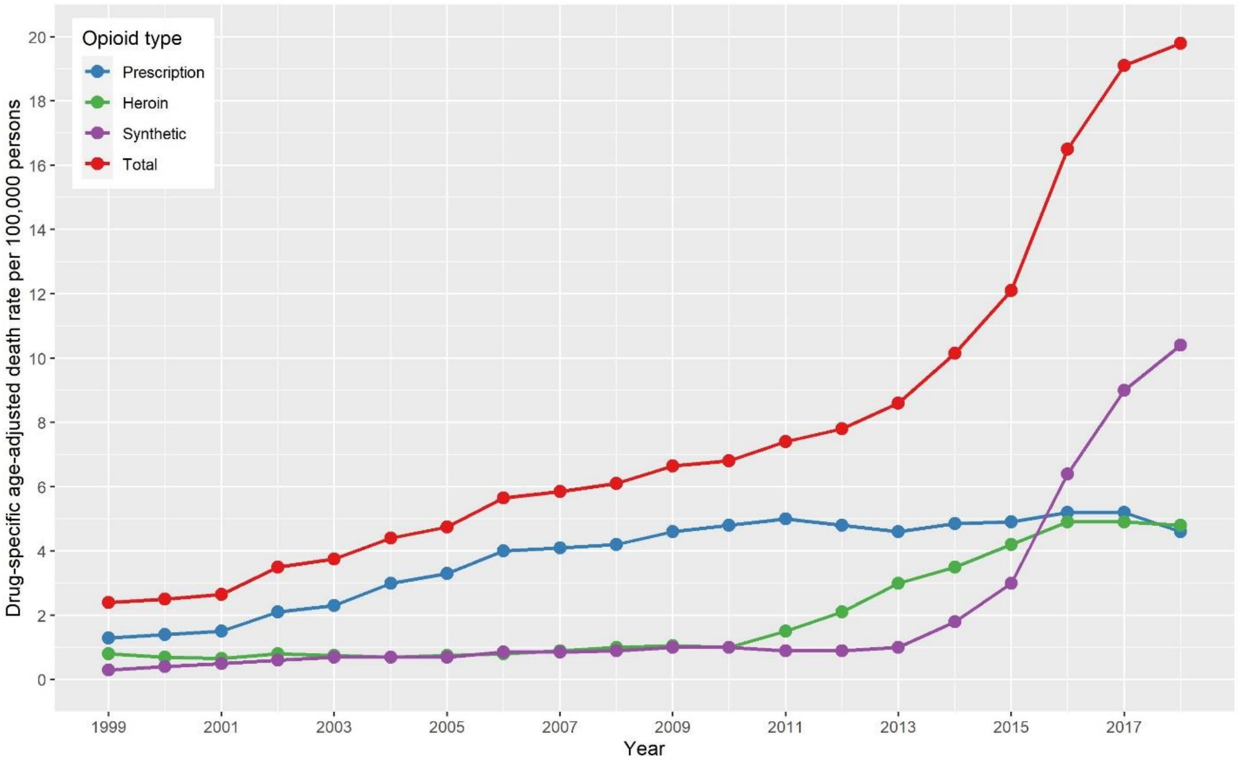

Figure 1. Nationwide drug-specific age-adjusted death rates for various opioid types, 1999-2018. Data from the National Vital Statistics System (NVSS) Mortality File and organized by the by the Centers for Disease Control and Prevention. Data available from NCHS Data Brief No. 365.

Situated within the broader discipline of geography, this dissertation will apply and critically examine geographic information science (GIScience) as it relates to pertinent research questions of the ongoing OOC. The dissertation is comprised of five chapters: an introduction, three associated studies, and a conclusion. The associated studies are presented in the order in which they were completed. Chapter 1 introduces the core concepts found throughout the dissertation. Chapter 2, the first study, uses a geospatial model that accounts for space and time to compare disease risk surfaces for heroin-, methadone-, and cocaine-related emergency department visits from 2016 to 2019 in the greater Baltimore metropolitan area (thematically related to Wave 2 of the OOC). Chapter 3, the second study, deploys spatial models at the national scale from 2006 to 2014 to investigate the relationship between local and neighboring prescription opioid distribution and nonfatal admissions to opioid-related recovery programs (thematically related to Wave 1 of the OOC). Chapter 4, the third and final study, provides a quantitative, scoping review of publications using GIScience between 1999 and 2021 to analyze how geospatial analyses have provided evidence for opioid-related health measures, capturing evidence across Wave 1 to Wave 3 of the OOC. Chapter 5 concludes the dissertation.

The remainder of Chapter 1 is organized as follows. Section 1.2 provides a primer on the US OOC, highlighting how fundamental changes in medical and pharmaceutical practices produced lasting impacts on opioid-related health measures. Section 1.3 describes the outcome-exposure disease model of health geography and explains how this model relates to each study of the dissertation. As the final dissertation study is a systematic literature review, Section 1.4 describes changes in GIScience publishing and the need for evidence synthesis in the context of ever-increasing scholarship. Finally, Section 1.5 sets out the research objectives of each of the three associated studies in the dissertation and previews the concluding chapter.

1.2 A Primer on the United States Opioid Overdose Crisis

The medical profession uses several vital signs to determine the general health of a patient. Historically, these have included temperature, blood pressure, heart rate, and respiratory rate. However, beginning in the mid-1990s, coincident changes between the medical profession and pharmaceutical industry led to the unofficial addition of a fifth vital sign: pain. On the medical side, a notable 1995 presidential address of the American Pain Society brought widespread attention to the idea that pain could be a fifth indicator of patient health, and by 1996 leading medical professional organizations issued joint statements advocating for treating chronic pain via opioids (Campbell 1995; Consensus Statement from the American Academy of

Pain Medicine and the American Pain Society 1997). Opioids had previously been reserved for the treatment of acute pain. Using opioids to treat chronic pain was a subtle yet significant paradigm shift that greatly expanded how opioids could be used. At the same time, new opioid formulations and marketing tactics from pharmaceutical companies began to act on changes in the medical practice around pain. In particular, Purdue Pharma would introduce and aggressively market OxyContin, an extended release painkiller based on the semi-synthetic opioid oxycodone, directly to medical professionals starting in 1996 (Van Zee 2009). Purdue Pharma placed heavy emphasis on a first-of-its-kind Food and Drug Administration (FDA) label describing OxyContin as having a low risk of addiction. By the time the label would change in 2001 – when the FDA refined the label to indicate that not enough data was available to understand OxyContin's impact on addiction – the practices of Purdue Pharma were already being mimicked by other pharmaceutical companies, and high-dose opioid prescriptions were becoming a staple across medical, dental, and therapeutic professions (Van Zee 2009).

Changes in the medical treatment of pain and new pharmaceutical products had clear and immediate effects on the use of prescription opioids in the US (Figure 1). From 1991 to 2011 the annual number of opioid prescriptions increased from 76 million to 211 million, and by 2011 oxycodone-based medications comprised nearly 25% of the prescription opioid supply (Evans, Lieber, and Power 2019). The overall annual rate of opioid prescribing would peak in 2012 with 81.3 prescriptions per 100 people (Guy Jr. et al. 2017). Although opioid prescribing in the US has been on the decline since 2012, levels in 2015 were triple that of 1999 (Guy Jr. et al. 2017). The most recent data from 2020 indicates that the opioid prescribing rate continues to decline (43.3 opioid prescriptions per 100 people as of 2020). Nevertheless, these levels of prescription opioid distribution, in terms of total number of prescriptions and the potency of the average prescription, are exceptionally high compared to other countries with similar demographic and income profiles (International Narcotics Control Board (INCB) 2020). Efforts to curtail the distribution of prescription opioids has included reformulating opioid tablets with abuse-deterrent mechanisms, implementing prescription drug monitoring programs (PDMP), and the federal government fining pharmaceutical companies for fraudulent and misleading marketing (Evans, Lieber, and Power 2019; Puac-Polanco et al. 2020; "'The Role of Purdue Pharma and the Sackler Family in the Opioid Epidemic' Full Hearing Transcript - Rev" 2021).

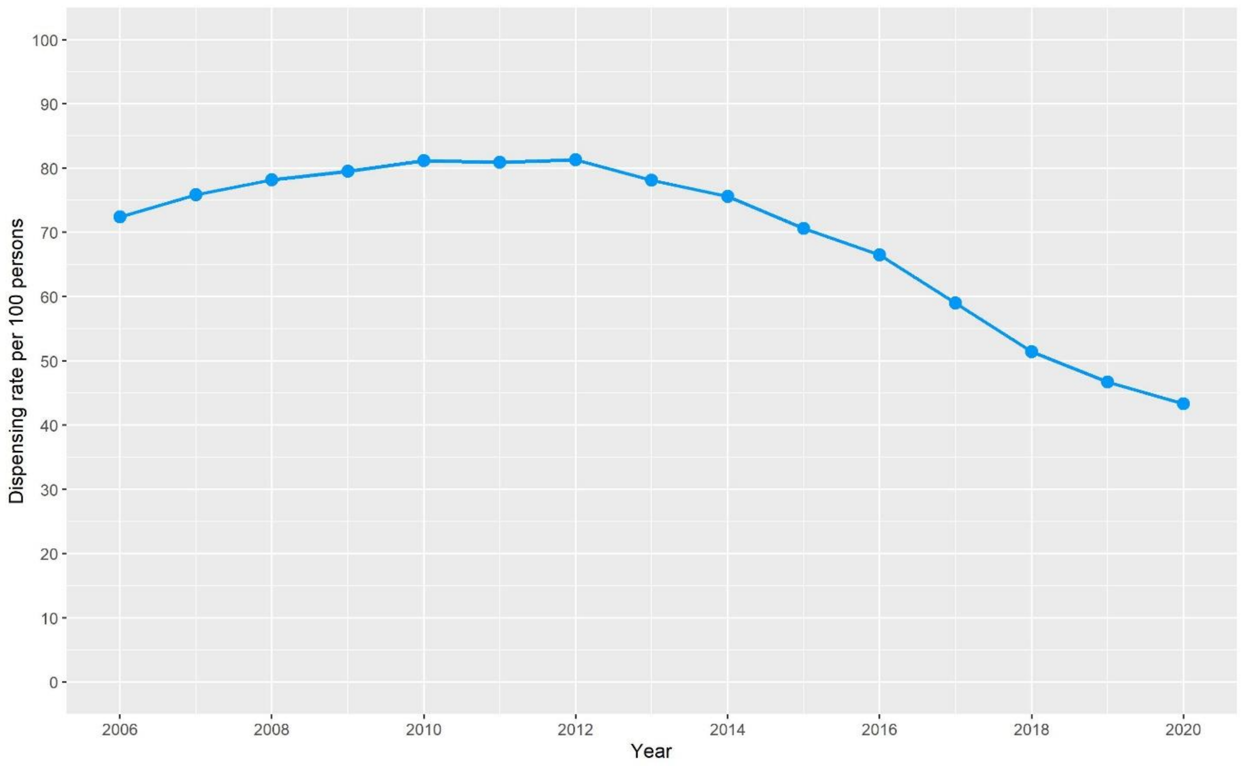

Figure 2. Changes in the overall nationwide rate of opioid dispensing per 100 persons, 2006 to 2020. Data originally from the IQVIA Xponent 2006-2020 Sample, organized by the Centers for Disease Control and Prevention. Opioid prescriptions include all prescriptions with at least one days' supply for the twelve leading active opioid ingredients distributed in the United States. Data available from CDC US Opioid Dispensing Rate Maps.

These curtailing measures have significantly reduced the distribution of prescription opioids in the US since the late 2010s. The reduction put a pressure on individuals who developed a dependence on prescription opioids, prompting some to transition to illicit opioids like heroin (Mars et al. 2014). This transition has been documented extensively in popular reporting (Meier 2018; Quinones 2015; Vuong 2019; The New York Times 2022). There are several reasons for transitioning from prescription opioids to illicit opioids, such as an individual using all of their prescription refills, a dealer expending their supply of prescription opioids, and, most generally, heroin having a lower financial cost compared to OxyContin (Meier 2018). These transitions are reflected in national surveys and research. For example, analysis of National Survey on Drug Use and Health (NSDUH) data spanning 2002 to 2011 found that the recent (within the past 12 months) heroin incidence rate was nearly 20 times higher for people who had previously used prescription opioids compared to those who had not (Muhuri, Gfroerer, and Davies 2013). In addition, four out of five recent heroin users reported ever having used prescription opioids (Muhuri, Gfroerer, and Davies 2013). The transition from prescription opioids to illicit opioids has generated additional mortality. Since 2014, the frequency and rate of drug overdose deaths has been higher in heroin compared to natural and semisynthetic opioids (e.g., prescription opioids) (Hedegaard, Minino, and Warner 2020). While the frequency and rates involving heroin have held steady since 2015 – at around 15,000 deaths and an age-adjusted rate of around 4.9 per 100,000 – these levels are more than quintuple those observed in 1999 and show no indication of decreasing (Hedegaard, Minino, and Warner 2020).

In addition to the prescription opioid and heroin dynamics, since 2014 there has been a sharp uptick in drug overdose death rates involving synthetic opioids other than methadone (Hedegaard, Minino, and Warner 2020). The uptick is largely attributed to an influx of the synthetic opioid fentanyl into the illicit drug use landscape (Zoorob 2019). Since 2013, the age-adjusted drug overdose death rate for synthetic opioids has increased from 1.0 per 100,000 to 9.9 per 100,000 in 2018 (Hedegaard, Minino, and Warner 2020). Increases in mortality are thought to be due to a combination of fentanyl’s overdose potential in extremely small doses as well as individuals in the drug use landscape lacking the ability, financial means, or incentives to distinguish between substances (Mars, Ondocsin, and Ciccarone 2018). The extent of fentanyl use is difficult to measure as testing for fentanyl is not yet standardized in national surveillance programs, but regional results indicate that fentanyl is likely underrepresented in surveys of adverse drug events (Z. Dezman et al. 2020; Zoorob 2019).

1.3 Applying a Health Geography Framework to the United States Opioid Overdose Crisis

This dissertation builds upon a health geography framework to investigate geographic patterns of opioid-related health measures. Health geography is fundamentally concerned with understanding the spatial relationships between human health and the surrounding social or biophysical environment (Dummer 2008). A health geography framework helps provide context to observed geographic patterns of opioid-related health measures and relates the patterns to broader concepts in health sciences research. For example, modeling spatial differences in opioid-related health outcomes can be used to identify *inequalities* between places or assess environmental *determinants of health* (Dummer 2008; Dasgupta, Beletsky, and Ciccarone 2018). Another avenue of research might measure travel time to opioid treatment programs to provide information on *health service utilization* (Dummer 2008; Luo and Wang 2003).

A unifying concept across these broad research interests is the outcome-exposure disease model used to investigate health across space (K. Jones and Moon 1987). This model posits that opioid-related health *outcomes* must be caused by opioid-related *exposures*, and the relationship between outcomes and exposures may be altered by *confounding* factors (Figure 3).

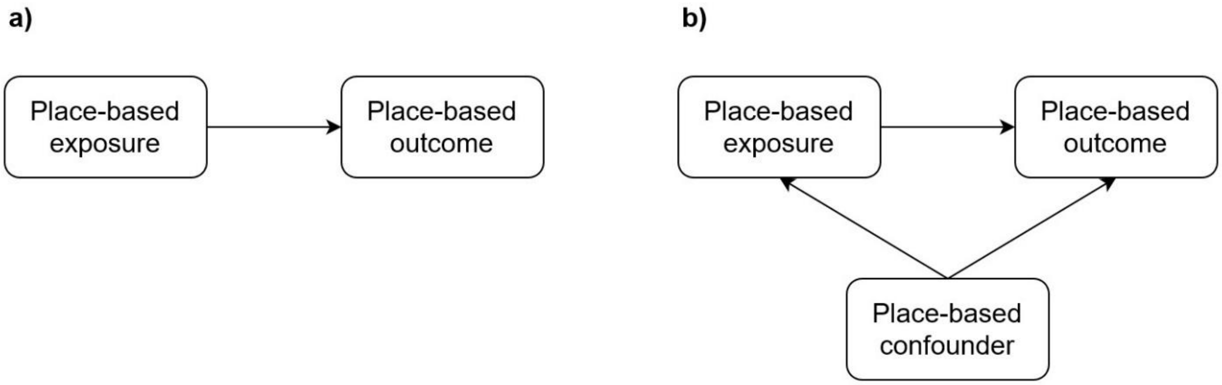

Figure 3. Basic representation of outcome-exposure model underlying health geography research. Researchers may be interested in exposures, outcomes, or confounders in isolation, as well as the relationship between concepts. Figure 3a) represents a naïve outcome-exposure disease relationship that considers a single exposure as the driver of a disease outcome. Figure 3b) represents a more complex and commonly used outcome-exposure disease relationship wherein confounding factors alter the relationship between an exposure and disease outcome.

While not always explicitly diagrammed, the outcome-exposure disease model remains fundamental as to how health geographers craft investigations on the OOC. Furthermore, the outcome-exposure disease model can be used to more clearly identify what aspect of the OOC a study purports to address (e.g., opioid-related outcome, opioid-related exposure, or proximal measure). The outcome-exposure disease model provides an analytic framework for each study of the dissertation. Chapter 2 applies a spatio-temporal model to estimate place-based opioid-related health outcomes. Chapter 3 uses spatial regression models on a placed-based opioid-related exposure. Lastly, Chapter 4 uses the outcome-exposure disease models as a heuristic for identifying studies using GIScience on opioid-related health measures.

There are numerous opioid-related measures that can be considered as outcomes, exposures, confounders, and proxies. An outcome in one study may be considered as an exposure in another, and the methods used to investigate these measures can take a multitude of forms depending on the research objectives. Significant attention has been paid to health outcomes, specifically opioid-related mortality, in the post-2000s (Netherland and Hansen 2016; Walden 2018). This focus is understandable given that opioids in prescription, heroin, and synthetic form have been the leading cause of drug-involved death in the US since 2006 (Stewart et al. 2017; Jalal et al. 2018). However, the twin public health concept to *mortality* is that of *morbidity*: the population that actively manages a disease and uses health resources. Opioid-related morbidity can be conceptualized in a multitude of ways including nonfatal overdose events, the population living with a substance use disorder, or the uptake of addiction treatment programs. These measurements of morbidity are especially important as they are a known risk factor for an eventual fatal overdose (Mars et al. 2014; Gaines et al. 2020). Both opioid-related disease burden and cost on the healthcare system have worsened over the course of the OOC. Nationwide, the proportion of all nonfatal treatment admissions where the primary substance of abuse at admission was opioids increased from 18% in 2005 to 34% in 2015 (Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality 2017). Moreover, data from the National Inpatient Sample indicates that hospitalization for opioid use disorder, as measured by the number of insurance claims for OUD and the rate of claims within the sample, increased from 62,010 in 1998-2000 to 136,240 in 2015-2016 (Singh and Cleveland 2020). Research from the late 2000s estimated that opioid-related poisoning accumulated more than $2 billion direct medical costs, with substantial additional costs ($18.2 billion) due to lost future earnings from mortality (Inocencio et al. 2013). Later research conducted from 2017, a much more severe year of the crisis, estimated much higher nonfatal medical costs of $31.3 billion (Florence, Luo, and Rice 2021). Chapters 2 and 3 focuses on outcome measures of opioid-related morbidity, whereas Chapter 4 considers a variety of measures for opioid-related morbidity, mortality, and proxy measures.

1.4 Evolution of GIScience research during the United States Opioid Overdose Crisis

The 2000s also saw changes in the frequency and magnitude of academic research. Geographic research has expanded dramatically since the early 2000s (Larsen and von Ins 2010). The total number of geoscience journals, as indexed by the Institute for Scientific Information, has increased from 128 in 2003 to 200 in 2019 (an increase of 56%), and the cumulative number of articles has increased from 12500 in 2003 to 26845 in 2019 (an increase of 114%) (Figure 4, data retrieved from Clarivate InCites Journal Citation Reports, jcr.clarivate.com). These increases are also evident in the sub-discipline of GIScience. A survey of twenty select GIScience journals from 2000 to 2014 found the annual number of publications to have increased from 537 to 1357 (an increase of 153%) (Biljecki 2016). Given this widespread increase in academic research, there is ample opportunity to review specific domain areas, such as GIScience on the OOC, to critically reflect on what evidence is available.

However, the growth of academic literature poses several challenging questions as to how evidence can best be gathered and synthesized. Tracking academic literature is essential for both translating research into positive societal benefits and setting forth future areas for innovative research. The importance of knowledge synthesis is increasingly recognized and carried out by federal funders of research (Graham 2012; “Systematic Review Service | NIH Library” n.d.) as well as professional organizations (Stevens 2001) for its role in knowledge translation and agenda-setting.

This dissertation develops a systematic scoping review methodology that can reliably retrieve GIScience evidence on the OOC. This collection of evidence is then interrogated to understand trends in GIScience research on the OOC since 1999. The analytical elements of each piece of GIScience evidence - such as the geospatial methods, units of analysis, and scales of study - receive special attention. Identifying what analytical elements are missing from the collection of evidence points to existing research gaps and critical areas for future research.

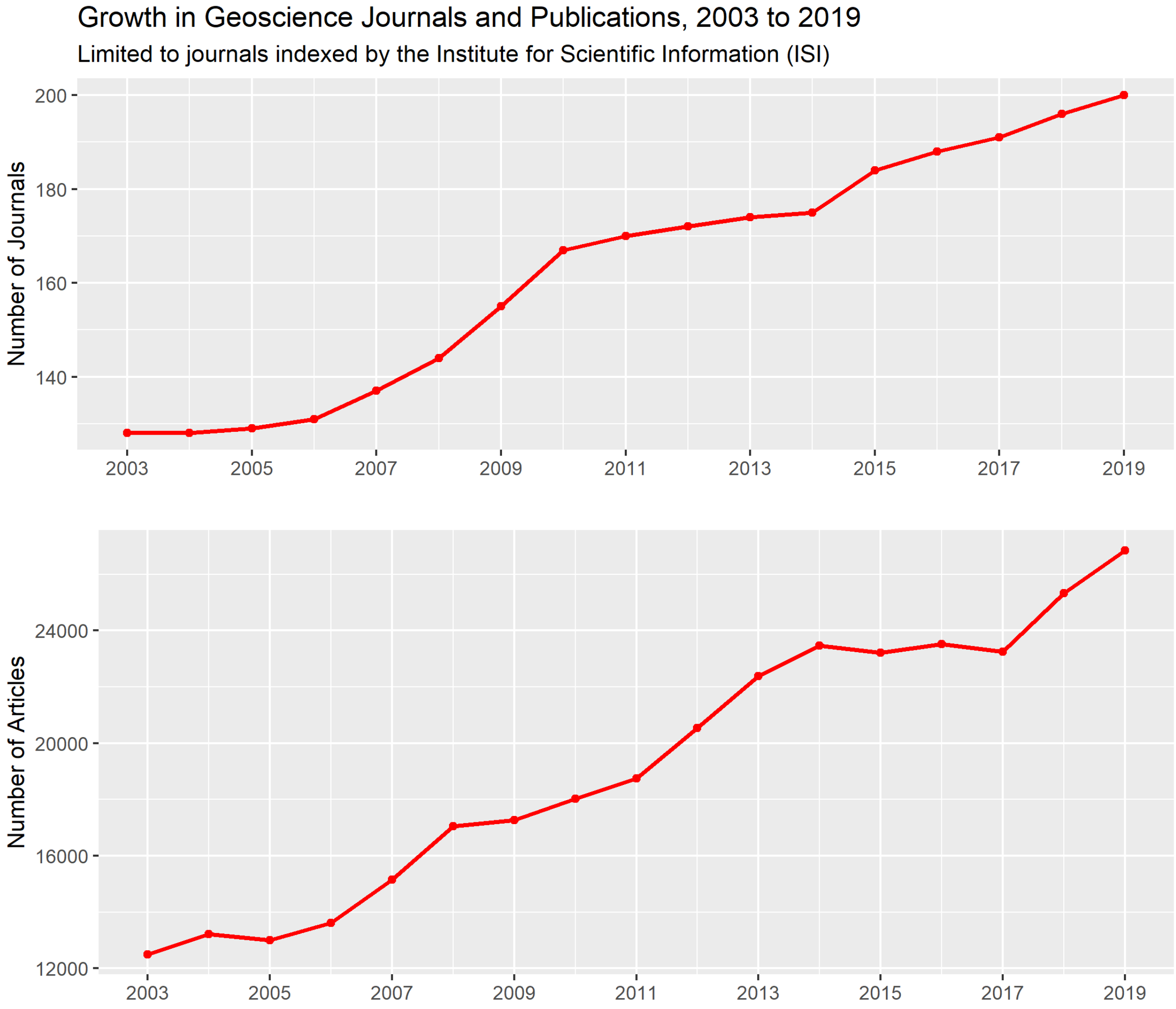

Figure 4. Publishing trends in journals belonging to the category of 'geoscience' by the Institute for Scientific Information, 2003 to 2019. Trends describe the growth in the total number of journals (top) as well as the absolute number of articles (bottom). Geoscience includes journals belonging to human geography, geographic information science, remote sensing, and more.

GIScience research offers a variety of methodologies to investigate the OOC. The increase in geographic and GIScience publishing occurred during the evolution of the OOC and over this period several distinct avenues of GIScience research emerged. Reasonably, GIScience efforts from the early 2000s through the early 2010s focused on understanding geographic variation in prescription opioid-related health measures like distance to community pharmacies, signals of prescription opioid abuse, the sufficiency of the supply of opioid analgesics, prescription opioid mortality, among others (Lin, Crawford, and Salmon 2005; Cicero, Inciardi, and Muñoz 2005; Green et al. 2005; L. H. Curtis et al. 2006). A general shift toward studies of heroin and injection drug use followed the second wave of the OOC in the mid-2010s, with GIScientists exploring heroin purity, measures of accessibility in relation to heroin-injection rates, spatial patterns in heroin overdoses, and the legal space for syringe programs in urban areas to name just a few examples (Cunningham et al. 2010; Kao et al. 2014; Meiman, Tomasallo, and Paulozzi 2015; Allen et al. 2016). GIScience was also used in relatively early studies highlighting the emergence of illicit fentanyl in drug overdose deaths. For example, Alexander et al. applied descriptive mapping and hot spot analysis to toxicology data and found clear fentanyl-involved outbreak patterns in data from as early as 2013 (Alexander et al. 2016). In addition, innovation in computation and novel data sources have advanced GIScience research on the OOC. In particular, advances in Bayesian computation, namely the Markov chain Monte Carlo (MCMC) family of algorithms in the 1990s, greatly expanded the feasibility of proposed spatio- and spatio-temporal models (Julian Besag and Green 1993). Versions of these models were applied to the OOC as early as 2008 to detect signals of opioid analgesic abuse (M. Y. Smith et al. 2008) and are increasingly applied to investigate area-level covariates on opioid-related health outcomes (Bohnert, Nandi, et al. 2011; Wolf et al. 2016) or, more recently, generate spatial risk surfaces (Cobert et al. 2020; Ransome et al. 2020). In addition, novel user-generated data has allowed for the analysis of opioid-related phenomenon that was previously difficult to measure, such as discarded needle location, black-market opioid sales, and internet traffic relating to opioids (Bearnot, Pearson, and Rodriguez 2018; Hswen, Zhang, and Brownstein 2020; Buntain and Golbeck 2015).

GIScience is increasingly seen a multidisciplinary methodology, and the use of GIScience towards understanding the OOC is no exception (Blaschke and Merschdorf 2014). GIScience uses a variety of study designs, methods, technologies, and datasets, ultimately offering a great diversity of evidence. Yet this strength makes tracking trends in study characteristics, as well as exact study-to-study comparison, challenging (Munn et al. 2018). In addition, open questions remain as to whether GIScience on the OOC reflects publishing trends in GIScience more broadly. Critically examining the available body of GIScience evidence is important to guide future research, especially given a lack of improvement in opioid-related health measures across the US. Therefore, there is a need to synthesize the available GIScience research on the OOC to understand how the discipline can best assist in improving health measures and reducing harm.

1.5 Dissertation structure

The overall goal of this dissertation is to demonstrate how spatial analytic techniques can improve understanding of the geographic variation observed for opioid-related measures in the context of the US OOC. Each dissertation chapter expands upon a set of research objectives relating to opioid-related health outcomes (Chapter 2), opioid-related exposures (Chapter 3), and the extant analytical trends of GIScience research investigating the OOC (Chapter 4). A conceptual diagram displaying the relationship between these chapters is presented in Figure 5.

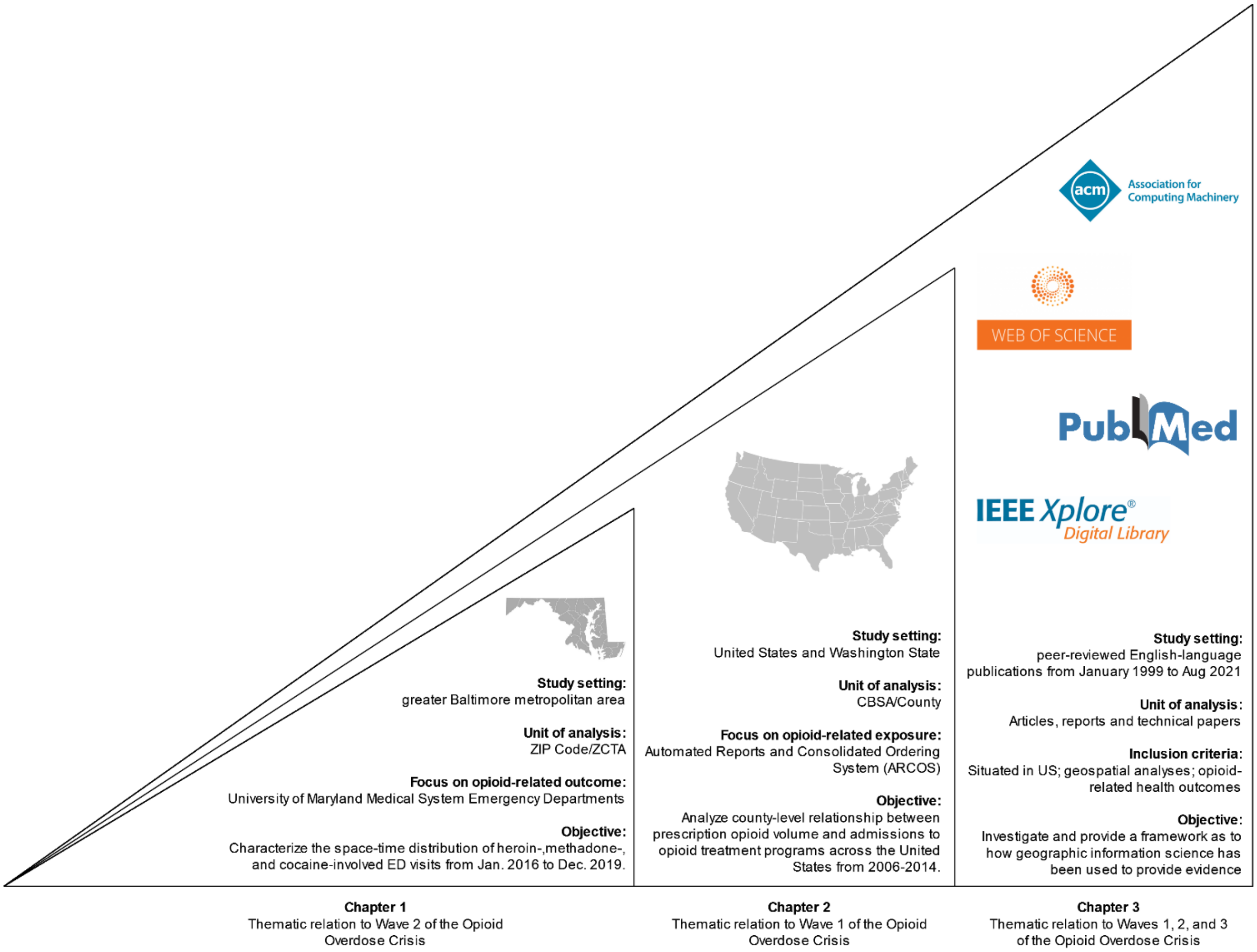

Figure 5. Conceptual framework of the dissertation. Each chapter has a thematic relation to both a wave of the Opioid Overdose Crisis, as well as a focus on opioid-related outcome, exposure, and GIScience analytics used to investigate opioid-related measures.

These research objectives directly address the dissertation's overall goal and are designed to contribute novel evidence to the broader scientific understanding of the OOC. The core research objectives of each analytical chapter are as follows, and the specific research questions are elaborated upon in each chapter:

Chapter 2) Characterize the space-time distribution of heroin-, methadone-, and cocaine-involved emergency department (ED) visits in the greater Baltimore metropolitan area from January 2016 to December 2019 at the Zip Code Tabulation Area (ZCTA)-level.

Chapter 3) Analyze both the state-level patterns in prescription opioid distribution as well as the county-level relationship between prescription opioids and admissions to opioid-related treatment programs across the United States from 2006 to 2014.

Chapter 4) Investigate and provide a framework as to how GIScience has been used to provide knowledge on the OOE, from the early the turn of the century to the present day.

Chapter 2 develops from the Emergency Department Drug Surveillance (EDDS) study, a collaboration between the Center for Substance Abuse Research (CESAR) and scholars at the University of Maryland Baltimore (Center for Substance Abuse Research 2020). EDDS provides a unique sample of electronic health records for all patients presenting with a drug-related health issue to four urban ED situated in the greater Baltimore metropolitan area. Research questions for Chapter 2 explore the standardized morbidity rate of heroin-, methadone-, and cocaine-involved-involved ED visits at the ZCTA-level using univariate and bivariate spatial statistics, as well as a recently developed spatio-temporal Bayesian model. Chapter 2 is fundamentally concerned with understanding the local distribution of drug-related health events. These scarcer health events present a small area problem, wherein a small number of events of interest can cause instability in traditional statistical approaches. Building on previous research using EDDS data that used Bayesian spatial smoothing (Cao et al. 2019), Chapter 2 goes further by applying a recently proposed spatio-temporal Bayesian model to estimate the adjusted rates and risk of presenting to ED across the greater Baltimore metropolitan area region. Results indicate that the spatio-temporal Bayesian model can produce locally sensitive estimates from a limited number of sample hospitals, and several ZCTA-level socioeconomic characteristics were associated with an elevated risk of presenting to the ED (Sauer, Stewart, and Dezman 2021).

Chapter 3 is motivated by an increasing recognition of the relationship between high opioid prescribing and negative opioid-related health outcomes. In addition, a newly released portion of the Drug Enforcement Administration’s (DEA) Automated Reports and Consolidated Ordering System (ARCOS) database was made publicly available in late 2018 and provides granular location information on prescription opioid shipments across the US (*The Washington Post* 2020; Rich et al. 2020). This motivation and new access to ARCOS data allowed for the identification of several novel research questions relating to state-level trends in the distribution of prescription opioids, sub-state patterns of spatial autocorrelation, and the county-level relationship between prescription opioid volume and admissions to treatment facilities involving a prescription opioid. Chapter 3 uses existing theory that suggests an excessive prescription opioid supply allows for extra diversion opportunities (Reisman et al. 2009). Chapter 3 provides evidence on these theoretical underpinnings at a higher spatial compared to previous studies (Reisman et al. 2009). Going further, Chapter 3 extends the theory by using spatial lag of X models to examine the role of excessive prescription opioid supplies in neighboring areas. Model results hold even after adjusting for numerous socioeconomic factors and state-level fixed effects, the latter of which account for factors like differences in PDMP. The analysis is conducted on both nationwide data describing treatment admissions for metropolitan areas of the US as well as on a dataset with complete coverage for the state of Washington as an external validity check.

Chapter 4 is situated in the ever-expanding use of GIScience and available GIScience evidence found across multiple disciplines. Tracking the multidisciplinary use of GIScience is important as GIScience researchers and developers must be able to respond to needs and outline best practices for a broadening set of users (N. Smith 1992). In the context of the OOC, practitioners should critically examine how GIScience can advance the understanding of the crisis and push for GIScience innovations that benefit the public (Pickles 1995). Chapter 4 uses a systematic scoping review methodology to gather and summarize the available GIScience evidence on the OOC. Chapter 4 addresses several novel bibliometric and meta-science research questions relating to publication output, emergent trends in study design, primary application areas of GIScience on the OOC, and evidence gaps to be addressed in future research. The systematic scoping review followed best practices laid out by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), an international scholarly collaboration that aims to improve the quality and reporting of systematic reviews (Page et al. 2021). A scoping review protocol was developed and uploaded to a public platform (Open Science Framework) in advance of the review (Sauer and Stewart 2021). Results reveal dramatic temporal changes in GIScience publishing on the OOC, clear research gaps regarding where sub-national studies are conducted across the US, and what geographic scales and methodologies comprise the available evidence.

Chapter 5 concludes the dissertation with a synthesis of the previous chapters. The synthesis builds through a progression of small discussions including a review of the dissertation, an outline of the significant contributions of each associated study, and a consideration of the major limitations. Following the synthesis are several avenues for future work to advance GIScience on the OOC. Lastly, the dissertation closes with a set of final remarks that reflect its opening and re-centers the motivation for all the work presented here: *pain*. The geographic study of the US OOC is ultimately a study as to how the human reaction to pain varies over space and time. Future scholarship must remain grounded in this reality to ensure that advances in research and technology help to better society’s understanding of and reaction to pain.

Chapter 2: A spatio-temporal Bayesian model to estimate risk and evaluate factors related to drug-involved emergency department visits in the greater Baltimore metropolitan area

Abstract

The ongoing US OOC presents a major public health challenge. Opioid-involved morbidity, especially nonfatal emergency department (ED) visits, are a key opportunity to prevent mortality and measure the extent of the problem in the local substance use landscape. Data on the nationwide rate of ED visits is normally distributed by federal agencies. However, state- and substate-level rates of ED visit demonstrate significant spatial and temporal variation. This study uses an ongoing sample of ED visits from four hospitals in the University of Maryland Medical System (UMMS) from January 2016 to December 2019 to provide locally sensitive information on ED visit rates and disease risk for drug-related health outcomes. Using exploratory spatial data analysis and spatio-temporal Bayesian models, this study analyzes both the frequency and risk of heroin-, methadone-, and cocaine-involved ED visits across the greater Baltimore metropolitan region at the Zip Code Tabulation Area-level (ZCTA). Specific research questions include: 1) What is the space-time distribution of the standardized morbidity rate (SMR) of heroin-, methadone-, and cocaine-involved ED visits in the greater Baltimore metropolitan area region from January 2016 to December 2019 at the ZCTA-level? 2) Do ZCTA-level estimates of the SMR for ED visits demonstrate bivariate spatial association between drugs (e.g., heroin and methadone, heroin and cocaine, methadone and cocaine)? 3) Applying a recently developed spatio-temporal Bayesian model, what is the local, ZCTA-level risk of ED visits for these three drugs? What, if any, are the differences in area-level risk of ED

visits between these three drugs? The Global Moran's *I* for the standardized morbidity ratio (SMR) of total heroin-, methadone-, and cocaine-involved ED visits in 2019 was 0.44, 0.53, and 0.46, respectively, demonstrating strong positive spatial autocorrelation. Spatio-temporal Bayesian models indicated that ZCTA with a higher score in a deprivation index, higher share of CMS claims, and adjacent to a sampled UMMS hospital had an increased risk of presenting patients for drug-related ED visits, with variation in the magnitude of this increased risk depending on the drug-demographic strata. Modeled disease risk surfaces – including posterior median risk and posterior exceedance probabilities – showed distinctly different risk surfaces between the substances of interest, probabilistically identifying ZCTA with a lower or higher risk of ED visits. The modeling approach used a sample of ED visits from a larger health system to estimate recent, locally sensitive drug-related morbidity across a large metropolitan area. Part of this dissertation Chapter was published as "A spatio-temporal Bayesian model to estimate risk and evaluate factors related to drug-involved emergency department visits in the greater Baltimore metropolitan area" in the *Journal of Substance Abuse Treatment* (Sauer, Stewart, and Dezman 2021) and presented at the American Association of Geographers Annual Conference 2021.

2.1 Introduction

Beyond providing direct patient care to patients in need, drug-involved visits to ED present an opportunity to track substance use in the community and develop new public health tools to decrease substance misuse. The Centers for Disease Control (CDC) estimated 577,794 ED visits for drug-involved poisonings (all intents) in 2016, a 5.5% increase from the estimated 547,543 visits in 2015 (Centers for Disease Control and Prevention 2018; 2019). The country-wide rate of drug-related visits exhibits substantial variability by both location and demographic characteristics. For example, the rate of drug-involved poisonings (all intents) in the West region of the US is 31.6% lower than the Midwest (156 per 100,000 and 228 per 100,000, respectively) (Centers for Disease Control and Prevention 2019). The sub-regional variation is reflected in the risk factors known to drive drug-related ED visits, such as the prescribing rate of opioid medications (L. J. Paulozzi, Mack, and Hockenberry 2014). Considering the rate of ED visits at the level of individual states, health systems, and metropolitan areas should reveal further variation that is important for informing local health care practice (Vivolo-Kantor et al. 2018).

National policy initiatives have focused on the dramatic increases in opioid-involved mortality witnessed since 2000 (Netherland and Hansen 2016; Walden 2018). Licit (oxycodone, hydrocodone) and illicit opioids (heroin, illicit fentanyl) have been the leading cause of drug-involved mortality in the US since 2006 (Stewart et al. 2017; Jalal et al. 2018). Among those patients living with a substance use disorder, nonfatal medical events like overdoses and ED visits offer a crucial opportunity to prevent avoidable deaths (Mars et al. 2014; Gaines et al. 2020). Additionally, nonfatal medical events may be caused by multiple substances used at the same time and the user’s local environment. Early surveys of heroin users revealed that the use of multiple substances alongside opioids was associated with an increase in nonfatal overdose events (Gossop et al. 1996). Additionally, the simultaneous use of opioids and benzodiazepine is a well-known risk factor for both fatal and non-fatal overdose (Dowell, Haegerich, and Chou 2016; J. D. Jones, Mogali, and Comer 2012). In Baltimore, Maryland, the use of heroin and/or cocaine has been an area of frequent and recent study, with studies demonstrating that local conditions like neighborhood socioeconomic status as well as exposure to substance use in expanded social networks associate with heroin and/or cocaine use (Bohnert, Bradshaw, and Latkin 2009; Williams and Latkin 2007; Artigiani and Wish 2014). States have attempted to address their local opioid crisis by increasing funding for and access to substance use treatment programs, such as the Maryland Heroin and Opioid Prevention Effort (HOPE) and Treatment Act of 2017 (Klausmeier et al. 2017). In addition, since 2014 Maryland has expanded Screening, Brief Intervention, and Referral to Treatment (SBIRT) services to more than 24 hospitals across the state, screening more than one million individuals in an attempt to scale up treatment and referral for those exhibiting disordered substance use (Monico et al. 2020). Although important, treatment is not a panacea for all health outcomes related to substance use. The risk of overdose resulting in an ED visit persists even after patients enter treatment (Lo-Ciganic et al. 2016).

Efforts to understand the risk factors for drug-involved ED visits increasingly point to the role of the social determinants of health and how patient residence changes the ability to access to health services (McLafferty 2008). Spatial analyses involving geocoded patient data and location-based technologies are routinely used to examine the relationship between location and substance use. Data from GPS-tracking technologies have been used to estimate substance users' exposure to psychosocial stress, and geocoded social media data related to substance use has been associated with area-level estimates of drug-related health phenomenon like ED visits (Kwan et al. 2019; Cao et al. 2020). Statistical techniques directly and indirectly accounting for space have been used to quantify geographical differences in drug-related health outcomes across neighborhood, regional, and national scales. Rowe et al. compared census tracts adjacent and not adjacent to naloxone distribution sites in San Francisco, showing how census tracts that contained or were immediately adjacent to naloxone distribution sites were associated with a greater number of opioid overdose reversal events (Rowe et al. 2016). Stewart et al.'s space-time cluster analysis demonstrated how drug poisoning deaths involving heroin shifted from the West Coast in 2000 to the Midwest and North Atlantic by 2014 (Stewart et al. 2017). Statistical techniques to adjust for spatial autocorrelation can both compliment traditional regression methods as well as allow for spatially explicit modeling. For example, Jennings et al. used Moran's *I* to adjust their regression specification in an assessment of neighborhood alcohol outlet density and violent crime in Baltimore, whereas Goedel et al. used spatial error models to evaluate the relationship between racial/ethnic segregation with treatment capacity across the US (Jennings et al. 2014; Goedel et al. 2020). Spatio-temporal Bayesian models are a subset of spatial regression models that are increasingly used for their analytical flexibility, interpretability in terms of probability, and the ability to produce model estimates even when the underlying spatial phenomenon of interest may not adhere to a normal distribution (Cressie 1993). Ransome used spatio- and spatio-temporal Bayesian approaches to examine the relationship of alcohol outlet density and area-level prevalence of drinking on both alcohol-related complaints and drug- and alcohol fatal overdoses across New York City (Ransome et al. 2020; 2019). Another study examined the relationship between a neighborhood deprivation index and drug-related admissions to EDs in Durham County, North Carolina (Cobert et al. 2020). Other researchers have applied Bayesian models for entire states, such as Kline and Hepler in their estimation of both opioid-related deaths and treatment admissions at the county-level across the state of Ohio (Kline and Hepler 2021). Many of these studies rely on surveillance programs maintained by state or metropolitan departments of health. There remains a need to investigate the applicability, sensitivity, and utility of spatio-temporal Bayesian models when the data source represents a limited sample of a larger health system.

This analysis uses a spatio-temporal Bayesian model to quantify the local area-level risk of presenting to an ED for a drug-involved health event. The analysis covers the greater Baltimore metropolitan area, utilizing an ongoing sample of ED patients who presented to four

EDs affiliated with the University of Maryland Medical System (UMMS). The present data comes from the Emergency Department Drug Surveillance (EDDS) system in which the four UMMS hospitals participate. EDDS was established by the Center for Substance Abuse Research (CESAR) at the University of Maryland College Park and provides de-identified encounter data and routine urine drug screen results for all drug-related visits to these four ED (Center for Substance Abuse Research 2020). This study focuses on patients that presented with a heroin-, methadone-, or cocaine-involved ED visit between January 2016 and December 2019. These substances were of interest because of 1) the high frequency of occurrence among all ED visits, 2) the potential for interaction with other substances across the life course, such as methadone in a treatment program or cocaine via polydrug use, and 3) the changing distribution of these drugs in the greater Baltimore metropolitan area over recent years (Z. D. W. Dezman et al. 2018; Mars, Ondocsin, and Ciccarone 2018). This study characterizes the spatial distribution of ED visits rates for heroin, methadone, and cocaine from 2016 to 2019 and investigates the extent to which ED visit rates for each drug exhibit univariate and bivariate spatial autocorrelation. In addition, this study models patterns of ED visit rates across the study area using hierarchical Bayesian Poisson models that can account for space-time patterns, adjust for area-level confounding factors, and produce risk surfaces that can be compared between drugs. These models reveal local, area-level differences in the risk of ED visits for heroin, methadone, and cocaine, with the potential to directly inform the provision of services by the health system.

2.2 Methods

2.2.1 Study design

Encounter data for all individuals who presented with a drug-related health issue was gathered from the four UMMS ED participating in EDDS from 2016 to 2019 (Figure 6). Because this ED data represents a convenience, non-random sample, the present study focuses on the greater Baltimore metropolitan area and the UMMS Primary Service Area, although these ED see patients from across the Delaware-Maryland-Virginia area (University of Maryland Medical System Foundation 2020). Other hospitals in the Baltimore metropolitan area include seven non-UMMS hospitals managed by Johns Hopkins University and MedStar Health, although ED visit data from these other hospitals was unavailable. These non-UMMS health facilities share similar service areas (Johns Hopkins Medicine 2018; MedStar Health 2018).

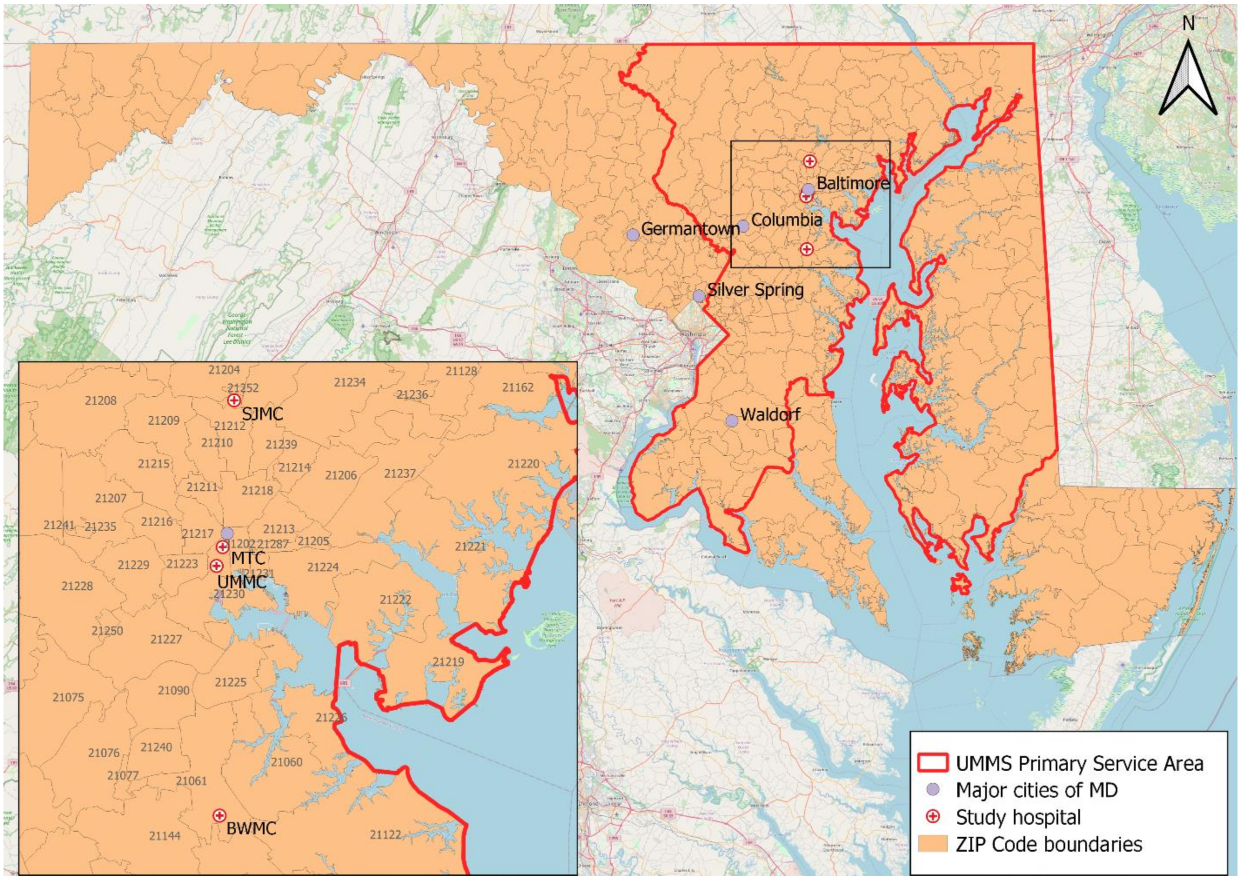

Figure 6. Location of study hospitals and ZIP Code boundaries used in the present study. Hospitals include University of Maryland (UM) St. Joseph Medical Center (SJMC), University of Maryland Medical Center - Midtown Campus (MTC), University of Maryland Medical Center (UMMC), and UM Baltimore Washington Medical Center (BWMC). The University of Maryland Medical System (UMMS) Primary Service Area (outlined in red) spans 14 counties across the state of Maryland.

This analysis includes all ED visits that 1) tested positive via urinalysis or received an ICD-10 diagnosis corresponding to opiates (hereafter interpreted as as heroin), methadone, or cocaine, and 2) reported a ZIP Code of residence within the state of Maryland. These criteria resulted in 1925 visits for 2016, 2176 visits for 2017, 2020 visits for 2018, and 1757 visits for 2019. Patient-level summary statistics of the ED visits show that the sample was stable across the study period (Table 1). Most patients were aged 25 to 34 or 45 to 54, and the majority of patients were male. Nearly all patients reported White or Black for race. Anonymized data comes from the UMMS Epic Electronic Healthcare Records system.

Table 1. Patient-level demographic characteristics for drug-related emergency department visits to four UMMS hospitals from 2016 to 2019.

	2016		2017		2018		2019	
	N	%	N	%	N	%	N	%
Age Group								
15-19	23	1.2	37	1.7	32	1.6	33	1.9
20-24	175	9.1	191	8.8	155	7.7	117	6.7
25-34	550	28.6	561	25.8	473	23.4	371	21.1
35-44	330	17.1	353	16.2	343	17.0	301	17.1
45-54	405	21.0	495	22.7	501	24.8	434	24.7
55-64	331	17.2	404	18.6	391	19.4	375	21.3
65+	111	5.8	135	6.2	125	6.2	126	7.2
Race								
White	1069	55.5	1059	48.7	878	43.5	723	41.1
Black	810	42.1	1028	47.2	1068	52.9	948	54.0
Other	30	1.6	68	3.1	49	2.4	64	3.6
Missing or not reported	16	0.8	21	1.0	25	1.2	22	1.3
Sex								
Male	1252	65.0	1414	65.0	1319	65.3	1148	65.3
Female	673	35.0	762	35.0	701	34.7	609	34.7

Visit data was aggregated to the ZIP Code-level for each year in the study (2016, 2017, 2018, and 2019). 2016 reference rates and demographic strata from the CDC Annual Surveillance Report of Drug-related Risks and Outcomes were used to convert the annual ZIP Code-level counts of ED visits for heroin, methadone, and cocaine to indirectly Standardized Morbidity Ratios (SMR) (Table 3A from Centers for Disease Control and Prevention, 2019). The resulting strata include total population, male population, female population, and population grouped into age ranges of 0-14, 15-19, 20-24, 25-34, 35-44, 45-54, 55-64, and 65 or older. ZIP Codes were converted to ZIP Code Tabulation Areas (ZCTA) – a generalized version of ZIP Codes provided by the US Census Bureau – using a 2019 crosswalk from the Uniform Data

System.[1] Considering the data as ZCTA allows merging of demographic information provided by the US Census Bureau. ZIP Code and ZCTA shapefiles were compared from 2016 to check for any discrepancies and to ensure that the 2019 crosswalk was appropriate for previous years.

2.2.2 Model adjustment for area-level risk factors

Literature on individual-, area-, and systemic-level studies of drug-involved health events were reviewed to identify risk factors that may impact ZCTA-level ED visit rates. Table 2 describes the source, timespan, and supporting literature for each of the equivalent or similar adjustment variables identified from the literature.

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[1] The Uniform Data System (UDS) provides a ZIP Code to ZCTA Crosswalk to the public (https://www.udsmapper.org/zcta-crosswalk.cfm). In some states, there may be instances where ZIP Codes and ZCTA do not align.

Table 2. List of adjustment variables identified as potential risk factors for inclusion in spatio-temporal models. Adjustment variables were categorized into three conceptual categories: social determinants of health, propensity for drug issue in an area, and descriptors of an area's location. Each column describes the variable's source, spatial unit, timespan, and supporting citation.

Risk factor	**Data source and spatial unit**	**Timespan**	**Supporting citation**
Social determinants of health			
Messer deprivation index[1]	ACS 5-year estimates, ZCTA[2]	2016-2018	(Messer et al. 2006; Cobert et al. 2020)
Race (% white)	ACS 5-year estimates, ZCTA	2016-2018	(Scott et al. 2007)
Gender (% male)	ACS 5-year estimates, ZCTA	2016-2019	(Ransome et al. 2020)
Access to vehicle	ACS 5-year estimates, ZCTA	2016-2018	(Flanagan et al. 2011)
Share of total Centers for Medicaid Services (CMS) claims	Centers for Medicaid Services Hospital Service Area Files, ZCTA	2016-2018	(Tai, Porell, and Adams 2004)
Propensity for drug issue in an area			
Number of SAMHSA-registered treatment facilities[3]	SAMHSA Treatment Facilities Locator, points aggregated to ZCTA	2019	(Langabeer et al. 2020)
Medicare Part D opioid prescribing rate	Centers for Medicaid Services Part D Prescriber Data, ZCTA	2016-2017	(Barnett, Olenski, and Jena 2017)
EMS calls for overdose in greater Baltimore area	Baltimore Police Department Victim Based Crime Data, points aggregated to ZCTA	2016-2019	(Nandi et al. 2006)
Descriptors of area-level location			
Average ZCTA Euclidean distance to UMMS hospitals (miles)	Calculated, ZCTA	Fixed	(Arthas, Graeme, and Angela 2012; Stephens, Young, and Havens 2017)
ZCTA adjacent to hospital ZCTA	Calculated, ZCTA	Fixed	*Reconceptualization of above*
Rural-Urban Commuting Area (RUCA) classification	University of North Dakota Center for Rural Health, ZCTA	2012	(Davis et al. 2016)

Notes: Models stratified into total, sex, and age groups.

1. Messer Deprivation Index a principal components analysis of area-level percent poverty, percent without high school degree, percent in managerial professions, percent in crowded buildings, percent on public assistance, percent unemployed, and percent with an income under $30,000.
2. ZCTA is an abbreviation for Zip Code Tabulation Area.
3. Gathered using the SAMHSA Treatment Facilities Locator online tool. Included facilities for Substance Use and Buprenorphine Practitioners.

This analysis conceptualizes adjustment variables as belonging to three groups. The first group relates to the social determinants of health, wherein social determinants such as economic status, area-level deprivation, and use of public medical services may impact the likelihood for drug use and dependency (Galea and Vlahov 2002). The second group attempts to adjust for the existing propensity for drug issues in an area, which act as a separate force that may change the availability of drugs and exposure to drug use (Ali et al. 2019; Logan et al. 2013). Lastly, the third and final group focuses on the role of location, namely the ZCTA-level characteristics that describe distance of an individual from health services under consideration (Kelly et al. 2016).

2.2.3 Spatial statistical analysis

Global and Local Moran's *I* analysis was used to assess the presence of spatial autocorrelation in the annual indirect SMR for heroin, methadone, and cocaine. Values of global Moran's *I* can be interpreted with a Moran scatter plot to assess the overall amount of spatial autocorrelation present in the data, as well as classify the patterns of spatial autocorrelation as behaving in a particular way (e.g., areas with high values surrounded by neighbors with high values) (Anselin 1995). The added utility of the local Moran's *I* helps the user to identify areas of substantive interest (e.g., 'clusters' of high and low ED visit rates). Both the location and significance of Moran's *I* values were considered to identify spatial clusters and spatial outliers. Given recent interest and attempts to model multivariate spatial dependence, the ZCTA-level bivariate spatial association was explored using Lee's *L* statistic for each combination of drug-related total SMR (e.g., heroin and methadone, heroin and cocaine, methadone and cocaine) (S. Il Lee 2001; Kline and Hepler 2021; Ransome et al. 2020).

After exploratory spatial data analysis, a series of nonspatial and spatial models were applied to estimate disease risk surfaces and evaluate the associations between area-level risk factors and drug-related ED visits. As a preliminary step, nonspatial Poisson models both with and without covariates were fit for each drug-demographic stratum. The presence of spatial autocorrelation in the residuals of these nonspatial models were assessed via the global Moran's *I* statistic.

Following the preliminary modeling step, hierarchical Bayesian Poisson spatio-temporal models were fit using the R `CARBayesST` package following the modeling strategy outlined by the package authors (D. Lee 2020). In these spatio-temporal models the spatial unit is each ZCTA in Maryland and the temporal unit is each year in the study period. These models employ a spatially autocorrelated first-order autoregressive process and are implemented using the `ST.CARar()` function (D. Lee, Rushworth, and Sahu 2014; D. Lee 2020). These models allow the estimation of spatio-temporal effects on disease risk and spatial disease risk surfaces for specific temporal segments of the study period. Two versions of these spatio-temporal models were fit. The first version included only space and time random effects. The second version included space and time random effects as well as area-level risk factors. Models were estimated using a Markov chain Monte Carlo (MCMC) simulation approach over a set number of samples. If there is large between-chain or within-chain variation in these samples the models are said to demonstrate nonconvergence and estimates from the models will not accurately approximate the reference distribution of the underlying data. Model convergence was evaluated using graphical traceplots, Geweke's diagnostics, and the potential scale reduction factor (PSRF). Goodness of fit was assessed using the Watanabe-Akaike Information Criterion (WAIC) (Gelman, Hwang, and Vehtari 2013). Results from the spatial statistical analysis are presented with a visual emphasis on ZCTA located within the UMMS Primary Service Area based on the location of the ED in downtown Baltimore.

2.3 Results

2.3.1 Spatial autocorrelation in ED visits

Global Moran's *I* statistics for the indirect SMR of ED visit rates at the ZCTA-level demonstrated variation across drug-demographic strata (Table 3). The numerical global Moran's *I* results are presented for all years, although local Moran's *I* visualizations are presented only for 2016 and 2019 in consideration of space. The population stratum for all visits, both male and female visits, age 45-54 visits, and age 55-64 visits demonstrated strong, consistent positive spatial autocorrelation (global Moran's *I* above 0.10) across all three drugs and all years.

Previous research indicated that opioid-involved ED visits peaked among a similar sample in 2017, and the 2017 global Moran's *I* values for heroin-involved ED visits presented here suggest an additional dimension of spatial clustering in the sample (global Moran's *I* of 0.42 for all heroin-related visits, 0.30 for male visits, and 0.49 for female visits) (Cao et al. 2020). The strongest positive spatial autocorrelation tended to appear in the total visits group, the male visits group, and visits by individuals aged 45-54 and 55-64. Visits by individuals aged 20-24, 25-34, and over 65 tended to demonstrate a high variability in the global Moran's *I* values across all three drugs and all years. For example, visits by individuals aged 20-24 demonstrated no clear indication of spatial autocorrelation in any of the drugs in 2016, although the same group demonstrated weakly positive spatial autocorrelation in heroin and methadone in 2017.

Table 3. Global Moran's *I* value for indirect SMR of ED for drugs of interest by demographic stratum, 2016 to 2019. Bolded cells indicate Global Moran's *I* values that were significant at a 0.05 threshold using two tailed test.

Drug	*Total*	*Male*	*Female*	*20-24*	*25-34*	*35-44*	*45-54*	*55-64*	*65 or older*
2016									
Heroin	**0.30**	**0.21**	**0.19**	0.08	**0.11**	0.001	**0.40**	**0.50**	**0.50**
Cocaine	**0.46**	**0.47**	**0.31**	-0.003	0.09	**0.25**	**0.40**	**0.50**	0.03
Methadone	**0.39**	**0.27**	**0.34**	-0.004	-0.007	**0.27**	**0.35**	**0.21**	**0.21**
2017									
Heroin	**0.42**	**0.30**	**0.49**	**0.29**	**0.13**	0.07	**0.43**	**0.45**	**0.23**
Cocaine	**0.46**	**0.36**	**0.52**	0.06	**0.12**	**0.28**	**0.40**	**0.30**	**0.51**
Methadone	**0.46**	**0.45**	**0.30**	**0.14**	0.001	**0.29**	**0.37**	**0.29**	**0.12**
2018									
Heroin	**0.14**	**0.26**	0.03	**0.31**	0.02	0.06	**0.15**	0.09	**0.24**
Cocaine	**0.47**	**0.40**	**0.51**	**0.16**	**0.22**	**0.35**	**0.45**	**0.18**	**0.18**
Methadone	**0.51**	**0.46**	**0.43**	-0.002	**0.14**	**0.29**	**0.40**	**0.24**	**0.22**
2019									
Heroin	**0.44**	**0.39**	**0.35**	0.04	**0.17**	0.10	**0.37**	**0.42**	**0.13**
Cocaine	**0.46**	**0.47**	**0.25**	**0.12**	0.02	**0.28**	**0.41**	**0.34**	0.06
Methadone	**0.53**	**0.46**	**0.43**	-0.004	**0.25**	**0.23**	**0.29**	**0.30**	**0.15**

Subsequent Local Moran's *I* analysis identified ZCTAs that were consistently associated with a high number of ED visit rates and that were surrounded by other ZCTAs with high visit rates (e.g., 'clusters', denoted HH or high-high) in the downtown core of Baltimore across all three drugs in 2016 (Figure 7). There were slight deviations in these clusters across heroin, methadone, and cocaine. The 2016 cluster for heroin extended from Baltimore's center southward along the ZCTA bordering the Patapsco River, whereas the cluster for methadone spread in a West-to-East pattern across Baltimore's city center. The 2016 cluster for cocaine covered the downtown core of Baltimore, with numerous clusters of low ED visit rates occurring in a diagonal pattern across the study area. From 2016 to 2019, these clusters became more scattered and revealed considerably more areas of mixed spatial heterogeneity, indicated by the numerous occurrences of ZCTAs surrounded by dissimilar neighbors (e.g., those ZCTA belonging to HL, or high-low, and LH, or low-high classes in Figure 7).

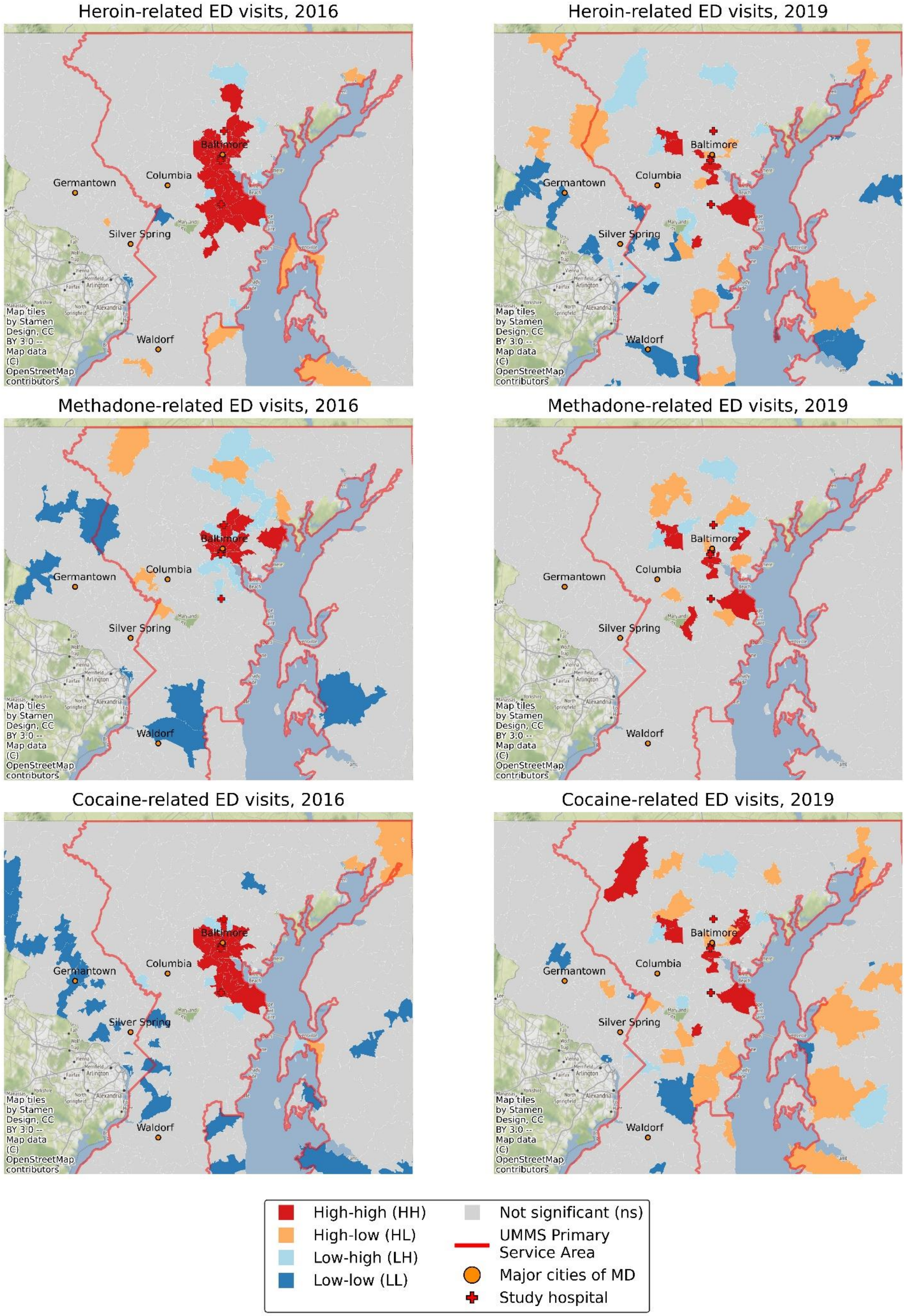

Figure 7. Local Moran's *I* analysis of indirect SMR ED visits rates for heroin, methadone, and cocaine (total visits), 2016 (left) and 2019 (right). Legend labels correspond to high-high (HH), high-low (HL), low-high (LH), low-low (LL), and not significant (ns) patterns of spatial autocorrelation (significance threshold of 0.05).

While the bivariate *L*-statistic for SMR of total ED visits of each paired drug combination indicated moderate to moderately strong association (Table 4), none of the associations were significant using an analytical inference approach. Further inspection of the local *L* values indicated that two ZCTAs in downtown Baltimore – specifically, ZCTA 21223 and 21217 – demonstrated consistently high local *L* values across each paired drug combination. This suggests that these two ZCTA demonstrated a strong bivariate association for SMR of total ED visits for each paired drug combination, although this association was not observed for the majority of ZCTAs in the study area.

Table 4. Lee's *L* statistic applied to the total indirect SMR between different drug combinations, 2016 to 2019.

Year	Heroin and Cocaine (*L*)	Heroin and Methadone (*L*)	Cocaine and Methadone (*L*)
2016	0.29	0.27	0.31
2017	0.34	0.35	0.39
2018	0.19	0.21	0.35
2019	0.38	0.40	0.41

2.3.2 Spatio-temporal modeling results

Assessments of cross-correlation between area-level risk factors indicated that EMS calls for overdose in the greater Baltimore area, percent of population reporting male gender, percent of population with access to transportation, and average ZCTA Euclidean distance to UMMS hospitals demonstrated strong association with other area-level risk factors. Attempting to include these variables in the preliminary models resulted in unstable coefficient estimates. These variables were omitted from the models.

Full results for the nonspatial Poisson models, both with and without covariates, of each drug-demographic stratum are available in the Appendix (heroin Appendix A, cocaine Appendix

B, and methadone Appendix C). Of these nonspatial models, the drug-demographic strata that demonstrated the strongest spatial autocorrelation in the residuals were the total number of visits involving heroin and cocaine, as well as male visits involving heroin and cocaine. Most other nonspatial models demonstrated moderate amounts spatial autocorrelation in the residuals (e.g., global Moran's $I > 0.10$), although certain drug-demographic stratum, especially methadone-related visits in age groups of 25-34, 35-44, 45-54, and 55-64 age groups demonstrated lower amounts of spatial autocorrelation (e.g., global Moran's $I < 0.10$). A full description of the global Moran's *I* for spatial autocorrelation in the residuals of the nonspatial Poisson models is available in Appendix D. Due to high variation in the initial global Moran's *I*, low total visit counts across all substances (space-time observations n=113), and model stability issues, results are not reported for the over 65 age group.

Results from the hierarchical Bayesian Poisson spatio-temporal models are shown in Table 5 for heroin-related ED visits, Table 6 for cocaine-related ED visits, and Table 7 for methadone-related ED visits. These tables provide posterior median coefficient estimates and 95% credible intervals (CI) for area-level risk factors as well as the spatial and temporal fixed effects. Goodness of fit statistics are reported for the null models that included only space and time random effects and the covariate models that included both space and time random effects and area-level risk factors (bottom rows of Table 5, Table 6, and Table 7).

Table 5 Posterior median estimates and 95% credible interval for hierarchical Bayesian Poisson models used to estimate the SMR of ED visits for a heroin-involved health issue in four ED of the UMMS health system, 2016 to 2019.

Model. Coefficient value and 95% credible interval (CI).

Covariate	**Total**	**Male**	**Female**	**Age 25-34**	**Age 35-44**	**Age 45-54**	**Age 55-64**
Race (% white)	2.51 (1.20-5.46)	1.57 (0.74-3.46)	4.34 (1.49-13.02)	7.84 (2.92-21.07)	2.64 (0.84-8.96)	0.83 (0.29-2.53)	0.41 (0.11-1.40)
CMS Total Share	1.31 (1.18-1.48)	1.31 (1.17-1.48)	1.38 (1.20-1.6)	1.36 (1.20-1.54)	1.28 (1.09-1.5)	1.37 (1.17-1.6)	1.33 (1.11-1.59)
ZCTA neighboring hospital location	1.52 (1.08-2.06)	1.69 (1.25-2.36)	1.36 (0.84-2.07)	1.97 (1.33-3.15)	1.80 (1.09-2.89)	1.31 (0.78-2.10)	2.08 (1.25-3.74)
RUCA Classification	0.92 (0.77-1.1)	0.95 (0.76-1.16)	0.82 (0.58-1.04)	0.98 (0.74-1.17)	0.96 (0.77-1.25)	0.83 (0.52-1.12)	0.73 (0.42-1.14)
Opioid Prescribing rate	0.99 (0.97-1.01)	0.99 (0.97-1.02)	0.99 (0.96-1.02)	0.99 (0.96-1.01)	0.99 (0.95-1.03)	0.99 (0.95-1.02)	1.02 (0.98-1.06)
Number of SAMHSA-listed treatment facilities	1.01 (1.00-1.02)	1.01 (1.00-1.02)	1.01 (1.00-1.02)	1.00 (1.00-1.01)	1.01 (1.00-1.02)	1.02 (1.01-1.03)	1.01 (1.00-1.02)
Deprivation index	1.45 (1.18-1.79)	1.41 (1.13-1.75)	1.64 (1.23-2.19)	1.16 (0.86-1.54)	1.56 (1.14-2.15)	1.82 (1.33-2.40)	1.42 (1.02-1.97)
Variance of spatial autocorrelation (τ^2)	1.04 (0.80-1.37)	1.06 (0.80-1.45)	1.46 (0.98-2.15)	1.20 (0.77-1.84)	1.57 (0.97-2.54)	1.40 (0.88-2.15)	1.74 (1.10-2.74)
Spatial parameter (ρ_S)	0.99 (0.97-1.00)	0.99 (0.97-1.00)	0.98 (0.95-1.00)	0.98 (0.95-1.00)	0.98 (0.93-0.99)	0.99 (0.96-1.00)	0.99 (0.95-1.00)
Temporal parameter (ρ_T)	0.94 (0.83-1.00)	0.93 (0.81-1.00)	0.90 (0.75-0.99)	0.833 (0.66-0.98)	0.87 (0.68-0.99)	0.88 (0.70-0.99)	0.87 (0.69-0.99)
WAIC: Null model (space time fixed effects, no adjustment variables)	2356	1990	1396	1463	1050	1044	926
WAIC: Covariate model (space time fixed effects, adjustment variables)	2198	1859	1320	1366	997	994	893

Table 6. Posterior median estimates and 95% credible interval for hierarchical Bayesian Poisson models used to estimate the SMR of ED visits for a cocaine-involved health issue in four EDs of the UMMS health system, 2016 to 2019.

Model. Coefficient value and 95% credible interval (CI).

Covariate	**Total**	**Male**	**Female**	**Age 25-34**	**Age 35-44**	**Age 45-54**	**Age 55-64**
Race (% white)	2.48 (0.84-6.27)	1.74 (0.61-4.92)	2.23 (0.71-7.21)	5.98 (1.78-20.96)	3.53 (0.93-13.39)	0.81 (0.21-3.26)	0.61 (0.13-2.86)
CMS Total Share	1.30 (1.13-1.48)	1.36 (1.18-1.56)	1.33 (1.13-1.55)	1.48 (1.29-1.71)	1.34 (1.11-1.62)	1.28 (1.05-1.55)	1.41 (1.14-1.75)
ZCTA neighboring hospital location	1.76 (1.21-2.75)	1.65 (1.09-2.47)	2.35 (1.47-3.89)	1.84 (1.15-3.15)	2.49 (1.38-4.54)	1.74 (0.99-3.16)	2.19 (1.14-4.05)
RUCA Classification	0.88 (0.68-1.07)	0.86 (0.63-1.14)	0.94 (0.63-1.24)	0.99 (0.75-1.21)	0.66 (0.33-1.15)	0.13 (0.04-0.52)	0.8 (0.35-1.32)
Opioid Prescribing rate	1.00 (0.97-1.03)	1.00 (0.97-1.03)	1.02 (0.98-1.06)	1.00 (0.96-1.04)	1.02 (0.97-1.07)	1.01 (0.97-1.06)	1.03 (0.98-1.08)
Number of SAMHSA-listed treatment facilities	1.01 (1.01-1.02)	1.01 (1.01-1.02)	1.01 (1.01-1.02)	1.01 (1.00-1.02)	1.02 (1.01-1.03)	1.02 (1.01-1.03)	1.02 (1.01-1.03)
Deprivation index	1.68 (1.28-2.13)	1.62 (1.22-2.14)	1.84 (1.34-2.55)	1.33 (0.93-1.84)	2.01 (1.41-2.86)	1.91 (1.37-2.71)	1.64 (1.10-2.42)
Variance of spatial autocorrelation (τ^2)	1.04 (0.71-1.45)	1.02 (0.69-1.51)	1.18 (0.65-1.98)	0.86 (0.42-1.63)	1.56 (0.85-2.90)	1.30 (0.77-2.22)	1.44 (0.79-2.63)
Spatial parameter (ρ_S)	0.98 (0.95-1.00)	0.98 (0.95-1.00)	0.97 (0.90-0.99)	0.95 (0.78-0.99)	0.95 (0.84-0.99)	0.98 (0.93-1.00)	0.98 (0.87-1.00)
Temporal parameter (ρ_T)	0.95 (0.82-1.00)	0.94 (0.81-1.00)	0.90 (0.70-1.00)	0.91 (0.68-1.00)	0.85 (0.61-0.99)	0.95 (0.79-1.00)	0.87 (0.66-0.99)
WAIC: Null model (space time fixed effects, no adjustment variables)	1493	1261	878	872	677	747	540
WAIC: Covariate model (space time fixed effects, adjustment variables)	1383	1162	830	813	646	698	518

Table 7. Posterior median estimates and 95% credible interval for hierarchical Bayesian Poisson models used to estimate the indirect SMR of ED visits for a methadone-involved health issue in four ED of the UMMS health system, 2016 to 2019.

Model. Coefficient value and 95% credible interval (CI).

Covariate	**Total**	**Male**	**Female**	**Age 25-34**	**Age 35-44**	**Age 45-54**	**Age 55-64**
Race (% white)	1.69 (0.50-6.42)	1.01 (0.25-4.19)	2.19 (0.45-10.42)	5.69 (0.98-35.81)	1.95 (0.43-8.56)	0.13 (0.02-1.34)	0.98 (0.23-5.34)
CMS Total Share	1.39 (1.19-1.64)	1.52 (1.29-1.79)	1.38 (1.14-1.66)	1.66 (1.34-2.06)	1.54 (1.23-1.97)	1.60 (1.21-2.18)	1.49 (1.18-1.82)
ZCTA neighboring hospital location	2.01 (1.12-3.23)	2.04 (1.22-3.33)	2.16 (1.16-3.77)	1.3 (0.61-2.74)	3.34 (1.76-7.69)	3.34 (1.48-7.3)	2.07 (1.1-3.78)
RUCA Classification	0.95 (0.55-1.42)	0.82 (0.33-1.22)	0.62 (0.24-1.13)	0.72 (0.3-1.13)	0.78 (0.31-1.2)	0.22 (0-1.18)	0.41 (0.12-0.97)
Opioid Prescribing rate	1.03 (1.00-1.07)	1.02 (0.98-1.06)	1.05 (1.01-1.09)	1.01 (0.94-1.07)	1.07 (1.02-1.11)	1.05 (0.97-1.11)	1.02 (0.95-1.07)
Number of SAMHSA-listed treatment facilities	1.01 (1.01-1.02)	1.01 (1-1.02)	1.02 (1.01-1.03)	1.01 (0.99-1.02)	1.03 (1.01-1.04)	1.02 (1.01-1.04)	1.02 (1.01-1.03)
Deprivation index	1.72 (1.28-2.42)	1.65 (1.16-2.38)	1.99 (1.31-2.92)	1.34 (0.77-2.22)	2.34 (1.56-3.47)	1.69 (1.04-2.95)	2.13 (1.43-3.16)
Variance of spatial autocorrelation (τ^2)	1.31 (0.82-2.09)	1.09 (0.61-1.97)	1.35 (0.69-2.45)	1.42 (0.17-3.56)	1.10 (0.37-2.64)	2.53 (1.16-4.97)	0.92 (0.26-2.32)
Spatial parameter (ρ_S)	0.99 (0.96-1.00)	0.98 (0.93-1.00)	0.97 (0.88-1.00	0.95 (0.07-0.99)	0.67 (0.04-0.97)	0.94 (0.67-0.99)	0.92 (0.18-0.99)
Temporal parameter (ρ_T)	0.90 (0.73-0.99)	0.90 (0.66-0.99)	0.88 (0.65-0.99)	0.84 (0.46-0.99)	0.89 (0.48-1.00)	0.85 (0.55-0.99)	0.83 (0.30-0.99)
WAIC: Null model (space time fixed effects, no adjustment variables)	905	723	591	441	468	422	415
WAIC: Covariate model (space time fixed effects, adjustment variables)	877	697	581	446	449	412	419

Of the covariates relating to the social determinants of health, race, share of total CMS claims, and the Messer deprivation index were included in the final models. ZCTA with a higher proportion of white residents was associated with an increased risk of ED visits across several drug-demographic strata, although this covariate should be interpreted with caution as it had differing point estimates and wide CI that sometimes included 1. However, other covariates in this thematic grouping were associated with an elevated risk of drug-related ED visits. The ZCTA-level Messer deprivation index was consistently associated with a higher risk for presenting ED visits with a drug-involved health problem. For example, estimates suggested that a one standard deviation change in the ZCTA-level Messer deviation index increased risk 45% (CI 18-79%) for total heroin visits, and increased risk more than 100% for methadone visits for individuals in the 35-44 and 55-65 age groups. In addition, ZCTA with a higher share of CMS claims indicated a consistent heightened risk for drug-related ED visits. A one standard deviation change in the ZCTA-level share of CMS claims increased risk 31% (CI 18-48%) in all heroin visits, 30% (CI 13-48%) in all cocaine visits, and 39% (CI 19-64%) in all methadone visits.

The number of SAMHSA-registered treatment facilities and the Medicare Part D opioid prescribing rate were included in the models to evaluate measures of area-level propensity for drug issues. The number of SAMHSA-listed treatment facilities in a ZCTA, including substance use facilities and buprenorphine-waivered practitioners, was not significantly associated with a higher or lower risk of presenting ED visits across the majority of drug demographic stratum, as the CI often included or was near 1. Similarly, the Medicare Part D opioid prescribing rate was not significantly associated with a higher or lower risk of presenting ED as the CI almost always included 1 across drug-demographic stratum.

The location-based covariates included in the final models were RUCA classification and an indicator for whether a ZCTA was adjacent to a ZCTA containing one of the UMMS hospitals sampled in the analysis. ZCTA adjacency was significantly associated with a higher risk for presenting ED visits with a drug-involved health event, demonstrating a range of increased risk depending on drug-demographic strata. ZCTA adjacent to ZCTAs containing one of the UMMS hospitals increased risk 52% (CI 8-106%) in total heroin visits, 76% (CI 21-175%) in total cocaine visits, and 101% (CI 12-223%) in total methadone visits. However, there were also drug-demographic strata where ZCTA adjacency had no clear effect (such as female heroin visits, age 45-54 heroin visits, and age 25-34 methadone visits). Although the point estimate for RUCA classification suggested that ZCTAs with a higher (e.g., more rural) classification had a reduced risk of presenting ED visits for a drug-involved health event, most CI included 1.

2.4.2 Model fit

Nearly all models saw improvement in fit between the null and alternative formulations. For the nonspatial models, all models saw dramatic improvement in the WAIC when including adjustment variables (final rows of Appendix A, B, and C). In addition, nearly all models saw improvement in the WAIC when considered with spatio-temporal effects, although there was variation in the magnitude of improvement. For example, nonspatial and spatio-temporal models for total heroin visits greatly improved fit 3785 to 2198, respectively. Comparatively, the smallest improvement in model fit was observed for methadone models, especially methadone models for patient age groups of 45-54 and 55-64. In general, spatio-temporal models considerably improved fit over nonspatial models across heroin and cocaine demographic strata, especially for total, male, and female visits, although the improvements among methadone models were more modest.

2.4.3 Disease risk surfaces for ED visits

Spatial disease risk surfaces, specifically the posterior median risk and posterior exceedance probabilities (PEP), were estimated for total heroin-, methadone-, and cocaine-involved ED visits in 2019 (Figures 8, 9, and 10, respectively). Results are presented for 2019 because these risk surfaces represent the most recent view of the study area given the data. Disease risk surfaces for earlier years in the study (i.e., 2016, 2017, and 2018) were largely consistent with those observed in 2019. The posterior median risk map shows where the adjusted SMR were highest and lowest, whereas the PEP maps shows areas that had either a low or high probability that risk of a heroin-, methadone-, or cocaine-involved ED visit in an area was greater than one (D. Lee 2020).

The posterior median risk maps for heroin in 2019 (Figure 8) show that the handful of areas with a heightened risk corresponded to ZCTAs located within Baltimore's city limits. This pattern is also reflected in the PEP map, showing that Downtown, Inner Harbor, and South Baltimore were the areas with the highest probability that the risk of heroin-related ED visits exceeded one. The vast majority of the remaining ZCTAs, both within Baltimore's city limits and throughout the rest of the state, had a negligible probability that the risk of heroin-related ED visits exceeded one, suggesting that the key cluster of elevated heroin-related ED visit risk for these hospitals was located in their immediate vicinity.

The risk maps for cocaine (Figure 9) were distinctly different compared to heroin during 2019. Compared to heroin, there were far more ZCTAs with a large posterior median risk (i.e., extending beyond the areas containing or immediately adjacent to the four ED). These areas extended from midtown Baltimore in a path along the Chesapeake Bay. However, there were also notable patches of lower risk in the city, such as areas to the southwest and southeast of SJMC. The PEP map highlights that there were a great many areas with a high probability of risk exceeding one, forming a large North-South pattern across the state.

Lastly, methadone (Figure 10) offered yet another contrast to the modeled risk surfaces of heroin and cocaine. The posterior median risk map for 2019 shows that most areas across Baltimore had heightened risk of visits for methadone, with decreasing risk away from city center. Similar to the risk surfaces for cocaine, the risk surfaces for methadone covered a much larger area compared to the downtown, concentrated areas found in the heroin risk maps. The PEP map also shows that several areas north of Baltimore – extending towards the border of Pennsylvania – had a relatively high probability of the risk of methadone-related ED visits exceeding one.

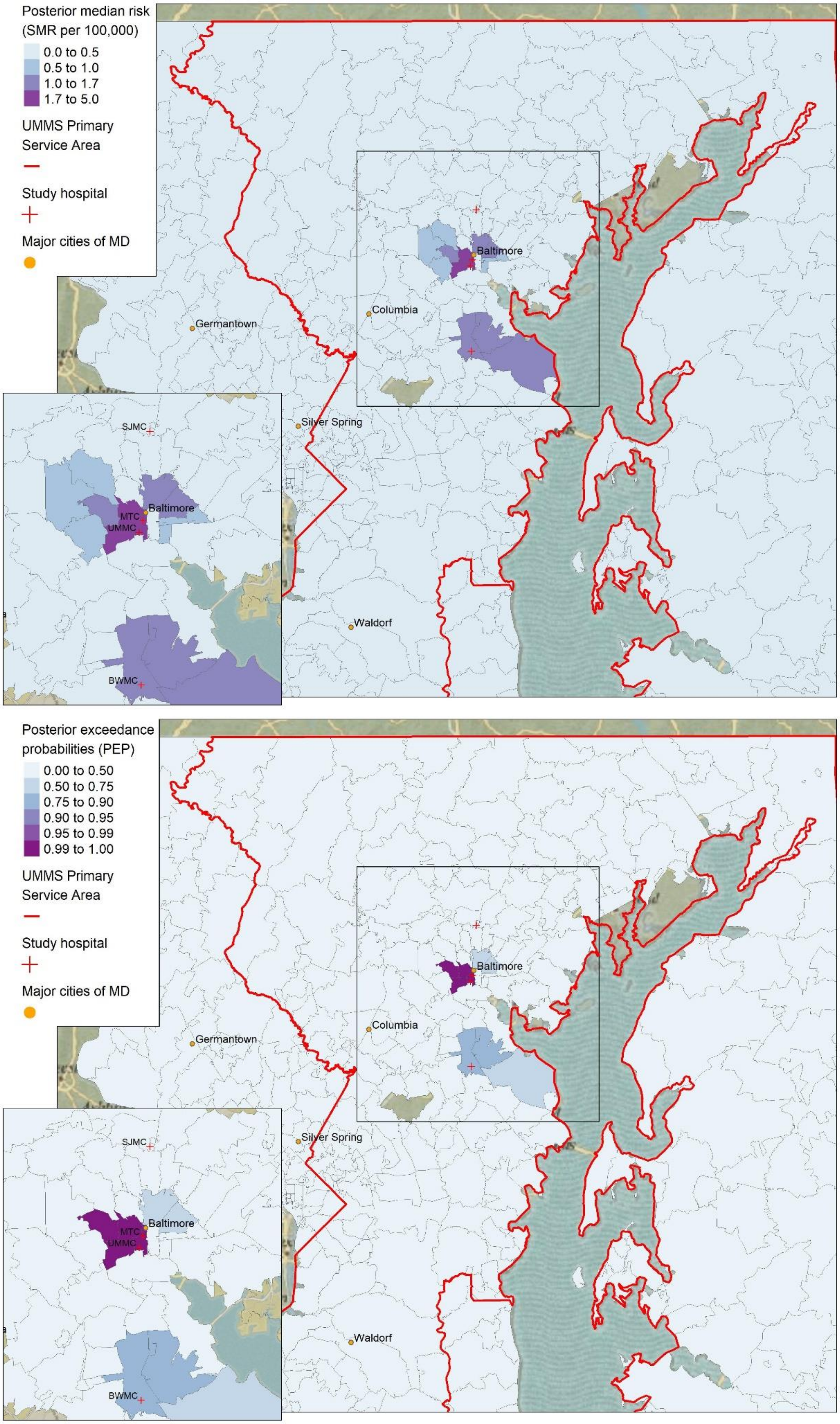

Figure 8. Estimated (posterior median) SMR surface for heroin-involved ED visits in 2019 (top) and posterior exceedance probabilities (PEP) that risk in 2019 is greater than 1 (bottom). Hospitals include University of Maryland (UM) St. Joseph Medical Center (SJMC), University of Maryland Medical Center - Midtown Campus (MTC), University of Maryland Medical Center (UMMC), and UM Baltimore Washington Medical Center (BWMC).

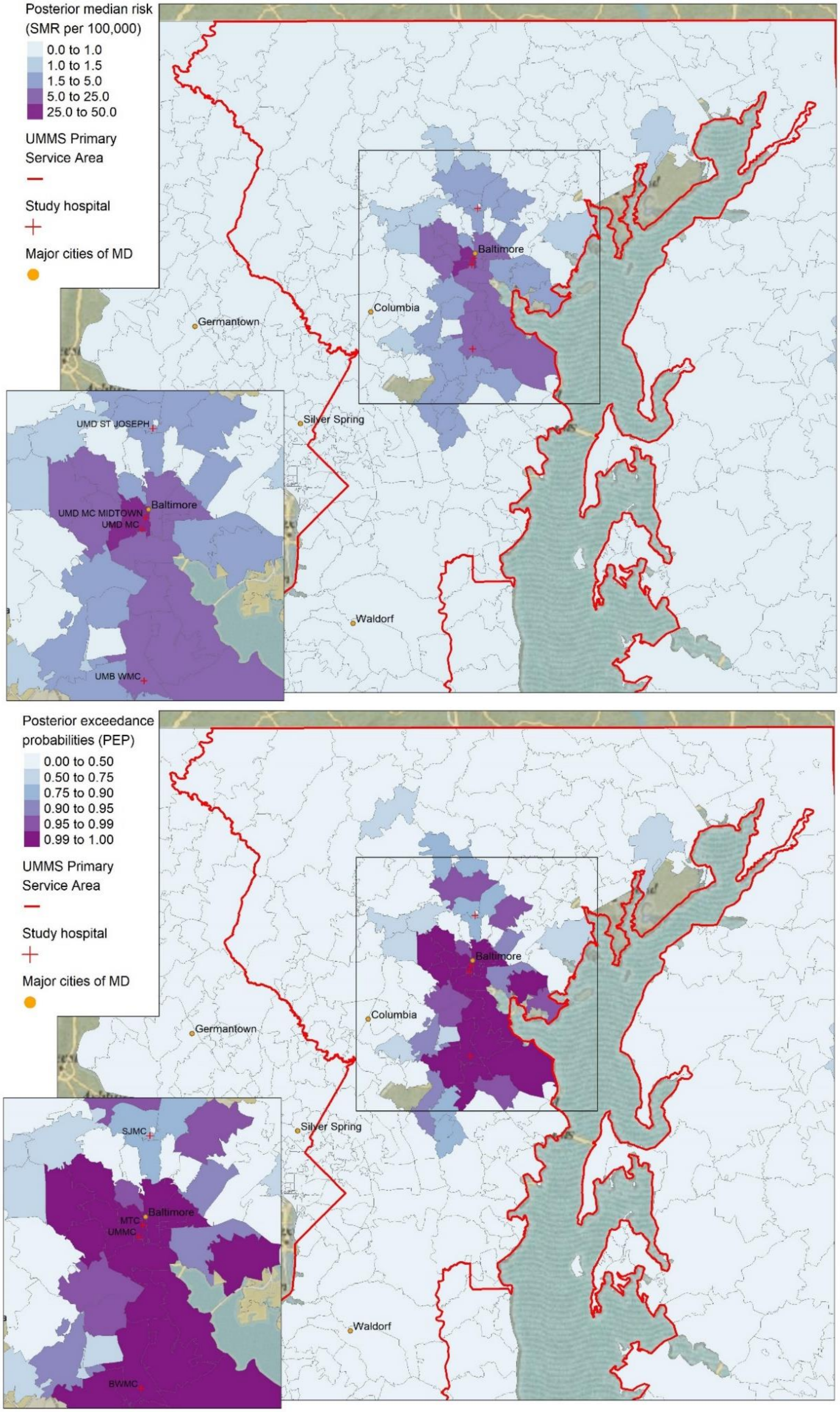

Figure 9. Estimated (posterior median) SMR surface for cocaine-involved ED visits in 2019 (top) and posterior exceedance probabilities (PEP) that risk in 2019 is greater than 1 (bottom). Hospitals include University of Maryland (UM) St. Joseph Medical Center (SJMC), University of Maryland Medical Center - Midtown Campus (MTC), University of Maryland Medical Center (UMMC), and UM Baltimore Washington Medical Center (BWMC).

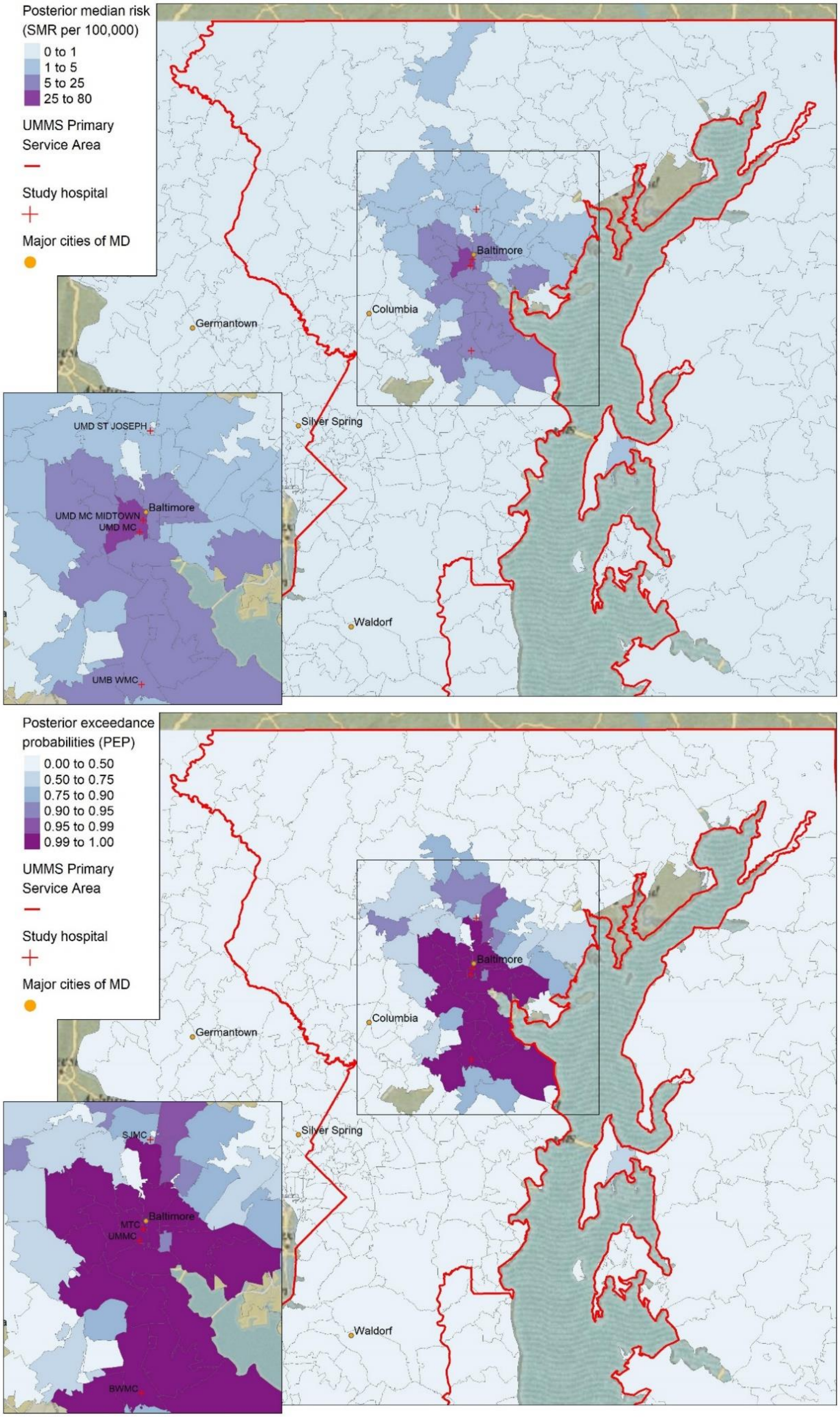

Figure 10. Estimated (posterior median) SMR surface for methadone-related ED visits in 2019 (top) and posterior exceedance probabilities (PEP) that risk in 2019 is greater than 1 (bottom). Hospitals include University of Maryland (UM) St. Joseph Medical Center (SJMC), University of Maryland Medical Center - Midtown Campus (MTC), University of Maryland Medical Center (UMMC), and UM Baltimore Washington Medical Center (BWMC).

2.4 Discussion

This study presents a geospatial analysis of visits to four EDs in a major urban area of the US for drug-involved health issues amid the ongoing OOC. Existing research has focused on using large data collection systems at the national- or state-level to provide a snapshot of drug-related disease burden. A sample of ED visits from an urban health system was used to characterize the spatiotemporal distribution of ED visit rates for heroin, methadone, and cocaine visits, visits by gender, and visits by age at the sub-county spatial resolution.

The history of substance use in Baltimore has led to numerous studies at the individual-, neighborhood-, and city-level. The present study contributes new information by showing ZCTA-level patterns of drug-specific ED visit rates in the greater Baltimore metropolitan area. These results share spatial overlap with previous studies that describe drug-related phenomenon situated in the greater Baltimore metropolitan area. For example, the elevated posterior median risk maps share spatial overlap with studies that have found clusters and elevated frequency of emergency calls involving substance use in West and East Baltimore (Linton et al. 2014; Wooditch, Lawton, and Taxman 2013) as well as drug market arrests occurring across downtown Baltimore in a similar same West-to-East pattern (Jennings, Woods, and Curriero 2013).

The spatio-temporal Bayesian models found higher levels of Messer et al.'s neighborhood deprivation index at the ZCTA-level to associate with an elevated risk of heroin-, methadone-, and cocaine-involved ED visits (Messer et al. 2006). Alternative deprivation indices have also been shown to positively associate with drug-related hospital admissions, drug-related deaths, and opioid dependence in other geographies such as North Carolina, Pennsylvania, and Scotland (Cobert et al. 2020; Sumetsky 2017; Congdon 2019). The present study provides further evidence of the utility of deprivation indices in modeling drug-involved health outcomes in the greater Baltimore metropolitan area. In particular, this study aligns with a recent analysis that focused exclusively on the relationship between an area deprivation index (ADI) and area-level ED admissions for opioid, amphetamines, or psychostimulants for a subset of EDs in Durham, North Carolina (Cobert et al. 2020). While the present models indicate that ZCTA adjacency to ZCTAs containing a sample ED was associated with an elevated risk of ED visits across nearly every drug-demographic stratum, other covariates relating to location, such as rurality captured via RUCA classification, provided less certain results as the credible intervals varied across drug-demographic stratum. This uncertainty is interesting given that the PEP maps for certain drugs, namely cocaine, indicate several ZCTA in the urban periphery and rural areas with relatively high probability exceedance values. These findings on covariates relating to location reflect the importance of identifying an appropriate conceptualization and operationalization of distance measures that may be sensitive to the study setting and design (Apparicio et al. 2008; Yang, Goerge, and Mullner 2006). Such considerations are especially important in studies of drug-related phenomenon that contain both urban and rural geographies if the bulk of the phenomenon tends to concentrate in one geography over the other. For example, a recent statewide study of fentanyl-related deaths across the state of Maryland highlighted how the vast majority of deaths occurred in Baltimore (Alexander et al. 2016).

The results presented here indicate that EDs within health systems of the greater Baltimore metropolitan area are providing emergency health services to different locales depending on the drug, with certain areas of service varying widely in extent. The estimated (posterior median) risk and probability maps for the most recent year of data, 2019, lay out clear differences in ZCTAs that have higher and lower risk of presenting ED visits for these three substances. To the best of my knowledge, such maps have not been produced for specific drug-demographic outcomes at such a refined spatial resolution. These maps allow for the precise estimation of adjusted, gender- and age-specific area-level standardized morbidity ratio, as well as the probabilistic identification of ZIP codes at based on the number of individuals seeking ED care for drug-related health problems.

Modeling of the ED visits revealed specific drug-demographic stratum that demonstrated spatial autocorrelation in the residuals of nonspatial models. The nonspatial models indicated that heroin and cocaine tended to show moderate to strong amounts of positive spatial autocorrelation in the residuals, while models for methadone tended to demonstrate less spatial autocorrelation in the residuals. The latter result may reflect differences in residency patterns for patients on methadone, distances patients on methadone may travel to acquire treatment, or the sensitivity of spatial patterns to the type of medical center under consideration (Rosenblum et al. 2011; Joudrey et al. 2020).

An additional result in the analysis was that variables measuring area-level propensity for underlying drug issues – such as the Medicare Part D opioid prescribing rate and the number of SAMHSA-listed treatment facilities – demonstrated uncertain effects on the area-level risk of presenting patients for a drug-related health issue. These results differ from other studies. For example, Chang et al. found that additional opioid prescriptions and additional benzodiazepine prescriptions all increased the risk for nonfatal opioid overdose (Chang et al. 2019). Hamilton et al. observed that community access to SAMHSA-listed treatment facilities was significantly associated with a lower chance of admission to a hospital after an ED visit (Hamilton et al. 2016). There are several possibilities for the differences in observed effects. Differences in study design and geographic location may vary with the population under study. Additionally, the variables used across studies differed in temporal and geographic scale, potentially altering relationships with the outcome measure used to capture drug-involved health events (e.g., Hamilton et al. operationalized SAMHSA-listed treatment facilities as a binary variable indicating treatment facility presence within a 5-mile radius of an ED).

2.4.1 Limitations

This study has several limitations that should be noted. The ED visit data represents visits for drugs identified via screening or medical diagnosis at four UMMS EDs, yet there are other EDs in the greater Baltimore metropolitan area. Other EDs were not part of the EDDS study under which this analysis was conducted and thus their ED data was unavailable. Given the location of the sampled ED, the spatial statistical results are most applicable to ZCTA located within the UMMS service area. Limiting the interpretation results to ZCTA within the UMMS service area and adjusting for location-based covariates attempts to minimize known issues between distance to care and selection bias, namely that the likelihood of inclusion in a given study may be related to distance from sample health care facilities (Caniglia et al. 2019).

The majority of patients in the analyzed ED data were aged 20 or older, which limits the ability of the analysis to make inference about the population aged 19 and younger. In addition, not all EDs use the exact same screening and testing procedures, so it is possible that the data by drug type could be an underestimate. A recent study indicating that standard hospital opiate screens may miss drugs like fentanyl draws attention to how screening and testing procedures impacts the identification of substances in patients (Z. D. W. Dezman et al. 2020). Beginning in February of 2019, two of the four UMMS EDs added fentanyl to the panel of drugs detected by the urinalysis. Given that only a portion of the EDs in the sample recently began fentanyl testing, fentanyl was not considered in the present study. Recent studies have highlighted both the likely underestimation of fentanyl in routine ED drug screenings as well as the role of fentanyl in drug-related mortality since 2013 (Z. D. W. Dezman et al. 2020; Alexander et al. 2016). Future research plans to examine the spatial patterns of fentanyl in the greater Baltimore metropolitan area for these ED.

While most of the adjustment variables included in the hierarchical Bayesian Poisson models had temporal variation, some variables had static values that did not change for some or all of the study period (e.g., 2016 to 2019). Some of these static values are reasonable – such as whether a ZCTA is adjacent to the ZCTA containing a sample hospital – although others may be subject to changes from year to year that impact the estimated coefficients and risk surfaces. Additionally, not all originally identified adjustment variables were included in the final models due to concerns over multicollinearity, specifically gender, EMS calls for overdose, and ZCTA-to-hospital Euclidean distance. These covariates have been identified as demonstrating a relationship with drug-related health outcomes in external studies and the exclusion of these covariates should be seen as a sensitivity of the modeling process rather than a comment on the covariate's importance as a risk factor. While the use of index-based variables describing neighborhood characteristics like deprivation allow researchers to capture multidimensionality, they also pose challenges when trying to pinpoint specific opportunities for intervention.

Lastly, indirect SMR was used as the outcome disease measure for its ability to compare the morbidity of the observed population to national estimates produced by the CDC, as well as the common use of SMR in spatial disease models (Wakefield 2007). Previous studies have outlined how the use of general population estimates used in the calculation of (in)direct SMR can underestimate the true SMR, especially as the prevalence of exposure in the general population increases (M. E. Jones and Swerdlow 1998). Of more relevance to the present study are recent demonstrations of potential type III errors when using SMR in disease mapping, especially when observed counts for a given areal unit are low (Heinzl and Waldhoer 2012). The primary concern of type III errors is effect reversal, wherein the *estimated* increase or decrease in risk is opposite the direction of the *observed* risk. A sensitivity analysis compared the estimated posterior median SMR and observed SMR of the demographic stratum for total heroin-, methadone-, and cocaine-involved ED visits in 2019 to assess for effect reversal. Effect reversal was defined as an estimated posterior median SMR with a direction (e.g., positive or negative) that did not align with the observed SMR. For example, an estimated posterior median SMR of -5 would be considered not in alignment with an observed SMR of 4. The sensitivity analysis revealed that the estimated posterior median SMR aligned with the direction of the observed SMR in 99.4% of ZCTA for total heroin visits, 93.4% of ZCTA for total cocaine visits, and 96.5% of ZCTA for total methadone visits.

2.5 Conclusions

This analysis quantifies local spatio-temporal patterns of heroin-, cocaine-, and methadone-involved ED visits in the greater Baltimore metropolitan area from 2016 to 2019. Indirectly standardized morbidity ratios (SMR) for heroin-, methadone-, and cocaine-involved ED visits were analyzed across gender and age strata, examining both spatial and spatio-temporal patterns. Exploratory spatial data analysis using Moran's *I* showed relatively consistent ZCTA-level clusters of high ED visit rates in downtown Baltimore in 2016. By 2019, these clusters had considerably changed, revealing heterogeneity in the spatial pattern of SMR for each drug.

The analysis further modeled the ZCTA-level SMR for drug-involved ED visits in 2019 using hierarchical Bayesian Poisson models, adjusting for area-level measures relating to the social determinants of health, the propensity for an underlying drug-issue, and the role of location. The models revealed distinctly different spatial risk surfaces for drugs resulting in an ED visit. These risk surfaces probabilistically identify different areas of the greater Baltimore metropolitan area with a higher or lower risk of presenting to an ED for a health event related to heroin, methadone, and cocaine at four UMMS hospitals. Administrators of multi-ED health systems can use this approach for spatial decision support to aid in managing the distribution of health services, anticipate individual-level needs based on patient residence, or work with other health systems to manage and utilize existing resources more efficiently.

Chapter 3: Spatio-temporal patterns of prescription opioid exposure and its relationship to treatment admissions in the United States

Abstract

Research on the geographic relationship between prescription opioid supply and prescription opioid-related health outcomes is limited. A special data release from the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System (ARCOS) provides information on more than 230 million prescription opioid shipments across the US. New access to detailed ARCOS data allows for novel geographic analyses of prescription opioid distribution amidst the US Opioid Overdose Crisis (OOC). This study examines state- and county-level spatial patterns of prescription opioid exposure across the United States (US) from 2006 to 2014. Specific research questions include: 1) How did the state-level space-time distribution of prescription opioids change across the US from 2006 to 2014? 2) What sub-state (e.g., county-level) patterns underly the distribution of prescription opioids? What does local spatial analysis reveal about these patterns? 3) What is the county-level relationship between prescription opioid volume and treatment admissions involving a prescription opioid? Do neighboring levels of opioid volume (as an exogenous effect) affect this relationship? Geofacet visualization assesses space-time trends at the state-level, while cross-sectional Getis Ord G_i^* statistics evaluate spatial autocorrelation at the county-level. In addition, this study estimates the county-level relationship between direct and neighboring prescription opioid exposure and admissions to treatment facilities involving prescription opioids. These relationships are estimated using nonspatial and spatial lag of X (SLX) regression models. Model estimates are compared between a nationwide survey of major metropolitan areas and a comprehensive dataset for the state of Washington as an external validity check. States with the highest levels of

prescription opioid exposure were consistently located in the southeast and mid-Appalachia region across the study period. There was a large, multi-state cluster of counties with high prescription opioid exposure extending from Tennessee to southern Ohio in 2006, though this cluster shifted southward and expanded in size by 2014. Regression models indicated a strong, positive relationship between prescription opioid exposure, as well as the spatial lag of prescription opioid exposure, and treatment admissions involving prescription opioids that persisted after controlling for socioeconomic characteristics and state-level fixed effects. Estimates from nationwide data indicate that higher levels of prescription opioids in neighboring counties was associated with an 8.9% increase in local treatment admissions in 2006 and 5.0% in 2014. Similar results were obtained for the state of Washington. Higher prescription opioid exposure among neighboring counties is associated with greater treatment admissions involving prescription opioids. This research indicates clear geographical differences in the distribution of prescription opioids across the US that persisted from 2006 to 2014. Further research into the geography of prescription opioid distribution is necessary given the continued availability of prescription opioids. Part of this manuscript was presented at the American Association of Geographers Annual Meeting 2022 as “Using Spatial Analysis to Model the Geographic Distribution of Prescription Opioids and its Relationship to Opioid-Related Health Outcomes in the United States”.

3.1 Introduction

Pain of known and unknown sources remains a substantial societal burden. Opioid-based analgesics in readily accessible forms like tablets, pills, patches, and more are considered a significant medical achievement (Booth 1999). Yet accessibility and new levels of potency have wrought serious challenges. The rate of prescription opioid sales, deaths, and treatment admissions in the US increased several times over from 1999 to 2008 (Centers for Disease Control and Prevention (CDC) 2011), and prescription opioids were the largest contributor to opioid-related deaths until the mid-2010s (Mattson et al. 2021b). Since then, public attention and research efforts have focused on the rapid rise in heroin and synthetic (e.g., illicit, non-medical fentanyl) drug overdose deaths, which now outpace deaths from prescription opioids (Mattson et al. 2021b). However, prescription opioid dispensing and health outcomes have shown only marginal improvements since 2010. The prescription opioid-involved death rate was 4.4 per 100,000 in 2013 and has decreased less than 5% to 4.2 per 100,000 in 2019 (Mattson et al. 2021b). These rates remain significantly higher than the 1999 prescription opioid-involved death rate of 1.4 per 100,000 (Center for Health Statistics 1999a). Although the rate of opioid prescribing in the US has decreased from peak levels of 81.3 per 100 persons in 2012, the average annual percent change from 2006 to 2018 has been only -3.0% from 72.4 per 100 persons in 2006 to 51.4 per 100 persons in 2018 (Centers for Disease Control and Prevention and National Center for Injury Prevention and Control 2019). These dispensing levels are exceptionally high – international estimates for 2014 through 2018 from the International Narcotics Control Board show that the US consistently has the highest licit narcotic consumption levels in the world (see tables XIV.1.a of International Narcotics Control Board (INCB) 2020). Further research into how the enduring prescription opioid supply is linked to opioid-related health outcomes is a pressing public health issue, especially as the US OOC continues to evolve.

Studies conducted at the individual-level indicate a relationship between exposure to prescription opioids and negative opioid-related health outcomes, such as eventually transitioning from prescription opioids to illicit opioid use (Compton, Jones, and Baldwin 2016;

Mars et al. 2014). For example, data from the National Survey on Drug Use and Health (NSDUH) found the recent heroin incidence rate to be 19 times higher for people who had previously used prescription opioids (Muhuri, Gfroerer, and Davies 2013). In addition to the risk of transitioning to illicit opioids, the use of prescription opioids themselves pose a risk of addiction and fatal overdose. Evidence from the Veterans Health Administration demonstrated that individuals who received higher prescription opioid doses (100 milligrams or more) had an increased risk of opioid overdose death across several health outcomes (Bohnert, Valenstein, et al. 2011). Additional analyses of NSDUH data estimated the prevalence of prescription opioid use disorders among nonmedical prescription opioid users to be as high as 16.9% in 2013 (Han et al. 2015). Several reviews are available that summarize the evidence on the relationship between prescription opioid use and heroin use (Compton, Jones, and Baldwin 2016) as well as prescription opioid use and risk of addition and overdose when prescribed for common conditions like chronic pain and lower back pain (Martell et al. 2007; Chou et al. 2015).

Although the relationship between exposure to prescription opioids and related health outcomes are increasingly substantiated at the individual-level, what remains less clear is how geographic exposure to prescription opioids, such as the supply of prescription opioids in an area, might also shape opioid-related health outcomes. One area of research beyond the individual-level are evaluations of prescription drug monitoring programs (PDMP) (Puac-Polanco et al. 2020). The expectation behind these programs is that monitoring or limiting the distribution of prescription opioids would result in a reduction of the prescription opioid supply and, subsequently, a reduction of prescription opioid-related health outcomes like addiction treatment and overdose. PDMP evaluation has demarcated a sizable area of research, although analyses tend to be organized at the state-level and do not consider variation in local patterns of substance use demonstrable at sub-state units like the county or ZIP Code (Chaney and Rojas-Guyler 2015; Mazumdar et al. 2015). Beyond PDMP evaluation, the discipline of geospatial information science (GIScience) and spatial analysis has produced ample research on sub-state and local patterns of prescription opioid supply and opioid-related health outcomes. GIScience and spatial analysis offer important methodologies that allow researchers to integrate space into questions of prescription opioid supply, demand, and associated harms (Mazumdar et al. 2015). Sub-state patterns are especially important as local geographic units are often logistically and politically meaningful for the current US opioid overdose crisis (Volkow and Collins 2017). Studies have used GIScience techniques to identify sub-state patterns of prescription opioid misuse at the county-level in states like New Mexico and North Carolina (Brownstein et al. 2010; Modarai et al. 2013). More broadly, descriptive maps of prescription opioid availability at the county-level suggest geographic variation in the distribution of prescription opioids across the US (Griffith et al. 2021; Guy Jr. et al. 2017). Other research has examined prescription opioid health phenomenon at smaller sub-state units like the ZIP or ZIP Code Tabulation Area (ZCTA)-level. Hester et al. examined fatal prescription opioid poisoning in New Hampshire at the ZCTA-level, highlighting the relationship between median household income and employment-related disability in opioid mortality variation (Hester, Shi, and Morden 2012). Stopka et al. combined 16 opioid-related datasets available in Massachusetts from 2000 to 2016 and found that more than half the adult population had been prescribed opioids and that nearly all ZIP codes demonstrated increases in the rate of opioid-related overdose (Stopka et al. 2019).

The present research leverages a special, one-time data release from the Drug Enforcement Administration’s Automated Reports and Consolidated Orders System (ARCOS). For the first time, more than 230 million ARCOS shipment records describing prescription opioid distribution across the US from 2006 to 2014 are publicly available. Enhanced detail in the data allows for the calculation of local prescription opioid exposure measurements that can be standardized by both dose and population. Geographic exposure to prescription opioids was measured as per capita morphine milligram equivalents (MME) of oxycodone and hydrocodone shipments. Spatial patterns of prescription opioids are evaluated using geofacet visualization at the state-level and Getis Ord G_i^* statistics at the county-level. In addition, the present analysis estimates the county-level relationship between prescription opioid exposure, per capita MME, and admissions to publicly funded treatment facilities involving prescription opioids. This relationship was considered in terms of prescription opioid exposure in each county and the prescription opioid exposure in adjacent counties using nonspatial and spatial lag of X (SLX) Poisson regression models, respectively. Models are first fit on national data disaggregated from the Substance Abuse and Mental Health Services Administration Treatment Episode Data Set - Admissions. An additional set of models are fit using data from the University of Washington Addictions, Drug & Alcohol Institute, which provides county-level treatment admissions data for the entire state of Washington as an external validity check. Results indicate clear geographical differences in the distribution of prescription opioids across the US using descriptive statistics at state-level and inferential spatial statistics at county-level. In addition, spatial regression models contribute new evidence on the geographic relationship between prescription opioid supply and treatment admissions involving a prescription opioid.

3.2 Theory on Local Prescription Opioid Exposure via the Prescription Opioid Supply

The present study builds on previous theoretical models as to how prescription opioid shipments impact relevant health outcomes like treatment admissions involving a prescription opioid. Previous theoretical models focus on how more shipments of prescription opioids to a state lead to higher availability of prescription opioids as well as additional opportunities of diversion for illicit use (Inciardi, Surratt, Cicero, Kurtz, et al. 2009; Reisman et al. 2009). Both a heightened availability and diversion have been associated with an increase in health outcomes like treatment admissions for opioid use disorder and drug related mortality, although research is limited (Reisman et al. 2009; Monnat 2019). Figure 11 expands on the theory of supply to hypothesize how sub-state patterns in prescription opioid shipments might impact opioid-related health outcomes.

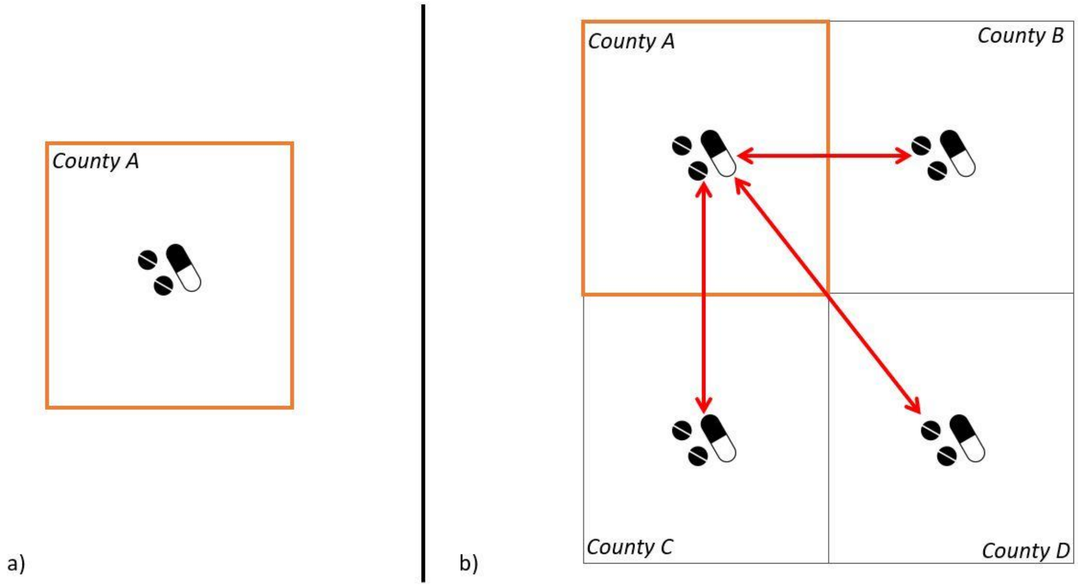

Figure 11. Prescription opioids available within a) a focal geographic unit, and b) neighboring geographic units that may provide additional exposure to prescription opioids. Modeling focal and neighboring measurements of prescription opioid supply motivates the present spatial analysis.

The simplified supply of prescription opioids available in a sub-state geographical area, County A (Figure 11a), is based on multiple individuals and medical facilities receiving shipments of prescription opioids. This supply is further modified by social and structural factors in County A, such as the size of the population, demographic composition, whether the county is subject to PDMP laws, and more. However, geographic areas like County A are rarely isolated in space. While a prescription opioid shipment is received at or dispensed a fixed location, the related activity space for the prescription opioids may be spread across several geographic units (Figure 11b). In addition, each neighboring county to County A maintains its own prescription opioid supply. Spatial analysis can evaluate these focal-neighbor relationships for sub-state geographies to provide information as to how the neighboring prescription opioid supply relates to health outcomes in focal areas. Understanding these focal-neighbor relationships helps to address problems relating to spatial misclassification where measuring the exposure in only the focal unit may ignore nearby exposure opportunities (Duncan et al. 2014). Modeling these focal-neighbor relationships is a primary topic of study in the present research.

3.3 Materials and Methods

3.3.1 Data on treatment admissions involving a prescription opioid

The outcome of interest is county-level counts of treatment admissions to publicly funded drug rehabilitation facilities involving a prescription opioid. Outcome data was gathered from two sources, one describing treatment admissions for major metropolitan areas across the US and one describing treatment admissions for all counties across the state of Washington.

National data for major metropolitan areas comes from the Treatment Episode Data Set - Admissions (TEDS-A) maintained by the Substance Abuse and Mental Health Service Administration (SAMHSA). This ongoing data collection effort records all admissions to publicly funded substance rehabilitation facilities for major metropolitan areas of the US (Martin, Longinaker, and Terplan 2015). Public TEDS-A data files were gathered for the years 2006 to 2014. The data was filtered to include all treatment admissions involving a prescription opioid as identified by the primary, secondary, or tertiary substance problem codes for ‘other opiates and synthetics’ or ‘non-prescription methadone.’ The data also includes geographic information on the patient’s reported Core Based Statistical Area (CBSA), which describe large metropolitan areas across the US. A small area estimation technique - the broad area ratio estimator - was used to disaggregate the TEDS-A data from the CBSA-level to the county-level (Asian Development Bank 2020). This was accomplished by first aggregating the individual-level TEDS-A admission records to the CBSA-level. The CBSA-level admission totals were then multiplied by the population proportion of each county belonging to the CBSA. The results are estimated county-level counts of treatment admissions involving a prescription opioid for major metropolitan areas of the US.

Because the SAMHSA national treatment admissions data is disaggregated from the CBSA-level to the county-level, there exists a possibility that the outcome data might not accurately represent county-level counts of treatment admissions involving prescription opioids. A second dataset describing treatment admissions for all counties across the state of Washington was collected from the University of Washington Addictions, Drug & Alcohol Institute (ADAI). ADAI organizes data from the government of Washington to provide comprehensive county-level estimates of publicly funded treatment admissions for substance-related health outcomes. Annual county-level counts of treatment admissions where the primary problem substance is a prescription-type opioid were gathered from the ADAI website for the years 2006 to 2014. These treatment admissions are identified by substance problem codes for ‘other opiates’ (e.g., not heroin or fentanyl), ‘Non-Rx Methadone’, or ‘Oxy/Hydro Codone’. Comparison of the outcome measures reveals that ADAI treatment admissions strongly resemble those captured in the

SAMHSA TEDS-A (see Appendix E), with the added advantage of having county-level coverage across the entire state of Washington.

3.3.2 Creating geographic estimates of prescription opioid exposure

The geographic prescription opioid exposure data comes from a recently released portion of the Automated Reports and Consolidated Ordering System (ARCOS) maintained by the Drug Enforcement Administration. Until as recent as 2019, access to detailed ARCOS data was normally restricted due to concerns over patient privacy and protecting trade secrets. For example, existing public ARCOS data is aggregated to the ZIP Code-level and reports only the total active ingredient of a substance (“ARCOS Retail Drug Summary Reports” n.d.), which obfuscates shipment types, the number of doses, and the strength of the doses. However, recent litigation efforts have led to the public release of a large portion ARCOS data. This newly released data represents a detailed accounting of all prescription opioids shipped within the US from 2006 to 2014. Each record describes a shipment of prescription opioids from a manufacturer (e.g., Purdue Pharmaceuticals) to a distributing location (e.g., a local retail pharmacy). The analysis is limited to ARCOS shipments containing oxycodone or hydrocodone as these prescription opioids represent both the majority of national prescription opioid shipments (approximately three quarters of all prescription opioid shipments) (*The Washington Post* 2020) and prescription opioid diversion (a combined mention in more than 60% of drug diversion cases) (Inciardi et al. 2007). This ARCOS data is publicly available via twin R and Python packages (Rich et al. 2020).

The actual measurement of geographic exposure to prescription opioids can be considered in a number of ways, commonly in the form of total opioid amount in morphine milligram equivalents (MME) (Puac-Polanco et al. 2020). MME describes the quantity of any opioid as compared to an equivalent amount of controlled morphine administration, allowing for relative comparison across substances (Von Korff et al. 2008). Annual total MME was calculated at the state- and county-level for each year in the study period (Modarai et al. 2013; Bunker 2020). Annual total MME was then standardized per capita to account for differences in population (details in Appendix F).

3.3.3 Model Adjustment variables

Literature on treatment admissions involving prescription opioids, prescription opioid abuse, and prescription opioid distribution were reviewed to identify relevant confounding variables to include in the regression models. These variables included county-level measures of gender (% male), race (% white), education (% high school graduates), employment (% unemployed), head of household status (% female head of household), income (median income), age (median age), and a white-black segregation dissimilarity index (Kallan 1998; Reisman et al. 2009; Goedel et al. 2020). These variables were gathered from the American Community Survey (ACS) 5-year estimates. ACS 5-year estimates for 2005-2009 were used for the 2006 models as 2005-2009 was the earliest 5-year ACS data product available. A variable indicating county rurality was included from the National Center for Health Statistics (Cerdá et al. 2017; Center for Health Statistics 2013). In addition to adjusting for these social and economic factors, the fully adjusted models also included state fixed effects to account for state-level differences in prescription opioid control legislation.

3.3.4 Exploratory analysis of prescription opioid exposure at the state-level

Geofacet visualization and summary statistics were used to assess changes in the prescription opioid exposure at the state-level over time. Geofacet visualization organizes per a sequence of data plots representing the geographical arrangement of contiguous states. Each plot shows the per capita MME for a state from 2006 to 2014. The geofacet visualization is rendered using the geofacet package in R (Hafen 2020).

3.3.5 Exploratory analysis of prescription opioid exposure at the county-level

The extent to which spatial autocorrelation was present in prescription opioid distribution across the US for the period 2006 to 2014 was examined. The study is interested in determining what areas of the US exhibit clustering of high and low amounts of prescription opioids at different time points in the study period. The Getis Ord G_i^* statistic considers prescription opioid volume in a focal county and its immediate neighbors relative to the national average (Getis and Ord 1992). Local spatial analysis was applied to per capita MME at county-level for 2006, 2010, and 2014 using a 1st order queen contiguity spatial weights matrix (presentation of results is adapated from Grieve and Jurgens 2019).

3.3.6 Estimating the relationship between prescription opioid exposure and treatment admissions involving prescription opioids

The final component of the analysis models the relationship between prescription opioid exposure and treatment admissions involving prescription opioids. This modeling had two objectives. The first objective was to estimate the county-level relationship between a measure of prescription opioid exposure and treatment admissions to publicly funded treatment programs involving prescription opioids. The second objective seeks to investigate and estimate the relationship of neighboring prescription opioid exposure on treatment admissions in a focal area. As elaborated in the previous section on opioid diversion theory (Section 3.2), these focal-neighbor relationships may have additional explanatory value in the local dynamics between prescription opioid exposure and related health outcomes. More specifically, the present research is interested in how prescription opioid availability in neighboring units may ultimately impact the prescription opioid supply and exposure in a focal county.

These objectives were accomplished with a series of evolving Poisson regression models. A baseline model estimated the county-level relationship between the measure of prescription opioid exposure, MME per capita, and the primary outcome of interest, counts of treatment admissions involving a prescription opioid. The models were then adjusted for previously described socioeconomic confounders and state-level fixed effects. The fully specified form of this model is presented in Eq 1 as:

$$\ln\big(E(y_i)\big) = \ln(\lambda_i t_i) = \beta_1 O_i + \beta_2 x_i + \gamma_S + \ln(t_i) \tag{1}$$

where y_i is a count of county-level admissions to publicly funded treatment programs involving a prescription opioid, $\beta_1 O_i$ is county-level opioid exposure as MME per capita, $\beta_2 x_i$ is a vector of county-level controls, γ_S is a state fixed effect, and $ln(t_i)$ is the population offset.

The next stage of modeling incorporated a parameter to estimate the effect of prescription opioid exposure in neighboring counties. This model is typically referred to as the spatial lag of X (SLX) model (Halleck Vega and Elhorst 2015). It incorporates an additional spatial lag term that captures the average per capita MME in neighboring counties for each focal area. A 1st order queen contiguity spatial weight matrix was used when calculating the spatial lag. SLX models were fit both with and without confounders and state-level fixed effects. The fully specified SLX model can be seen in Eq 2 as:

$$\ln\big(E(y_i)\big) = \ln(\lambda_i t_i) = \beta_1 O_i + W\beta_1 O_i + \beta_2 x_i + \gamma_S + \ln(t_i) \tag{2}$$

where $W\beta_1 O_i$ represents the spatial lag of county-level opioid exposure in MME per capita and all other terms retain the previous meaning. $W\beta_1 O_i$ estimates the effect of increasing (or decreasing) the opioid volume of neighboring units on the focal unit's treatment admissions involving a prescription opioid.

The modeling strategy was carried out on both the national SAMHSA TEDS-A data as well as the University of Washington ADAI data for the state of Washington. Executing the strategy on both datasets provides an external validity assessment to determine how the models compare when using disaggregated treatment admission counts from a national survey compared to observed treatment admission counts from a comprehensive statewide health system database. The study was determined not Human Subjects Research by the University of Maryland College Park Institutional Review Board (project reference number 1763621-1).

3.4 Results

3.4.1 Characterizing the distribution of prescription opioids at the state-level

Geofacet visualization of per capita MME showed substantial state-level variation from 2006 to 2014 (Figure 12). The states with the highest state per capita MME were Florida (1160.9 per capita MME in 2010), Delaware (1086.5 per capita MME in 2011), Tennessee (965.2 per capita MME in 2012), and Nevada (918.4 per capita MME in 2011). States in the southeast and mid-Appalachia tended to have the highest levels of per capita MME, such as West Virginia

(891.3 per capita MME in 2012), Kentucky (853.7 per capita MME in 2011), and South Carolina (798.9 per capita MME in 2012). Other states that demonstrated high levels included Oklahoma and Alabama.

States with the lowest overall per capita MME were located primarily in the Great Plains and Midwest. For example, both Dakotas had low per capita MME across the study period, with North Dakota reaching as low as 167.6 in 2006 and South Dakota reaching 179.2 in 2006. Illinois had the lowest per capita MME of any state across the study period at 156.4 in 2006. These states also had the lowest per capita MME at the end of the study period, although their per capita MME had increased. For example, the states with the lowest overall per capita MME in 2014 were Illinois (261.1 per capita MME), North Dakota (270.2 per capita MME), Minnesota (278.7 per capita MME), and Nebraska 281.3 per capita MME).

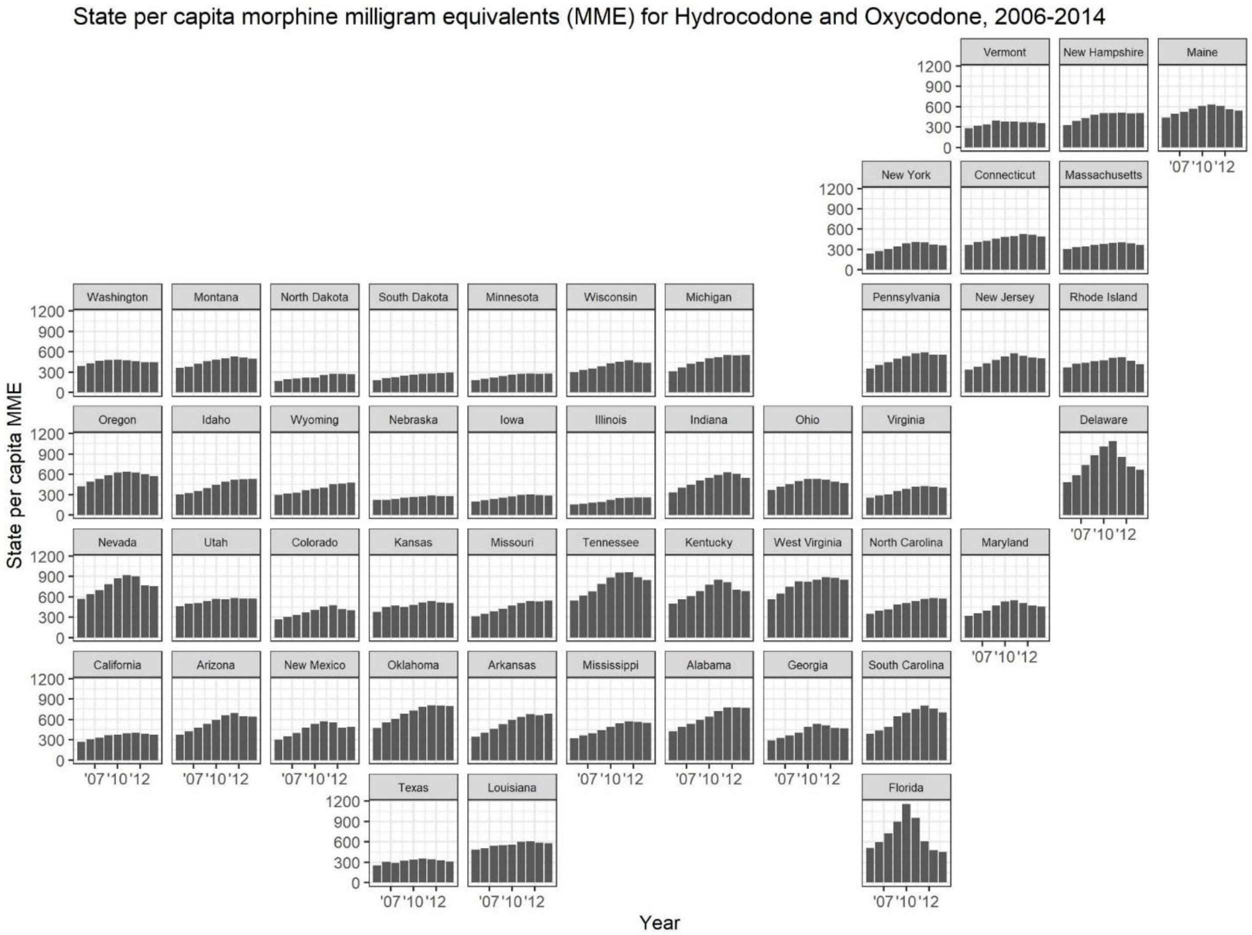

Figure 12. Geofacet visualization of state per capita morphine milligram equivalents (MME) for oxycodone and hydrocodone across the United States from 2006 to 2014. Underlying prescription opioid shipment data comes from the Automated Reports and Consolidated Ordering System (ARCOS).

3.4.2 County-level spatial patterns in prescription opioid exposure

Getis Ord G_i^* analysis on county-level per capita MME identified several clusters of both high and low prescription opioid exposure over the study period. In 2006, there was a large cluster of high county-level per capita MME that extended from northeast Tennessee to West Virginia along the shared border of Kentucky-Virginia, reaching into the southern tip of Ohio (Figure 13a). In addition, counties in northern California demonstrated positive spatial autocorrelation of county-level per capita MME, although the magnitude of these z-scores were lower compared to the previously described cluster in mid-Appalachia.

Clusters of low county-level per capita MME were also observed throughout the country over the study period. Counties with large negative z-scores were located primarily in the Great Plains and Midwest, such as the Dakotas, southern Minnesota, northwestern and eastern Iowa, Nebraska, and Illinois. In addition, there was a consistent set of counties along the Texas-Mexico border that exhibited clustering of low per capita MME. Unlike the positive z-score observed for the counties in northern California, the counties of central and southern California exhibited negative z-scores.

Getis Ord G_i^* results for 2010 and 2014 largely reflect the patterns observed for 2006 with a few notable exceptions. In 2010, western counties of the Florida panhandle exhibited clustering of high county-level per capita MME that was mostly absent in 2006 and entirely gone by 2014 (Figure 13b). In addition, the large, multistate cluster of high county-level per capita MME extending from Tennessee to Ohio shifted southward such that by 2014 much of the cluster was contained in southeastern Kentucky, southern West Virginia, and Tennessee, completely disjoint from Ohio (Figure 13c).

The Getis Ord G_i^* results also highlight within-state differences in the direction and intensity of per capita MME clustering. For example, Tennessee demonstrated an east-west split wherein its eastern counties had negative clustering of per capita MME compared to the western counties that had positive clustering of per capita MME (Figure 13a). Additional examples of within-state differences in per capita MME clustering can be observed in states like California, Michigan, and Alabama (Figure 13c). Taken as a whole, these Getis Ord G_i^* analyses identify areas of both high and low per capita MME, as well as within-state differences in the intensity and direction of per capita MME clustering.

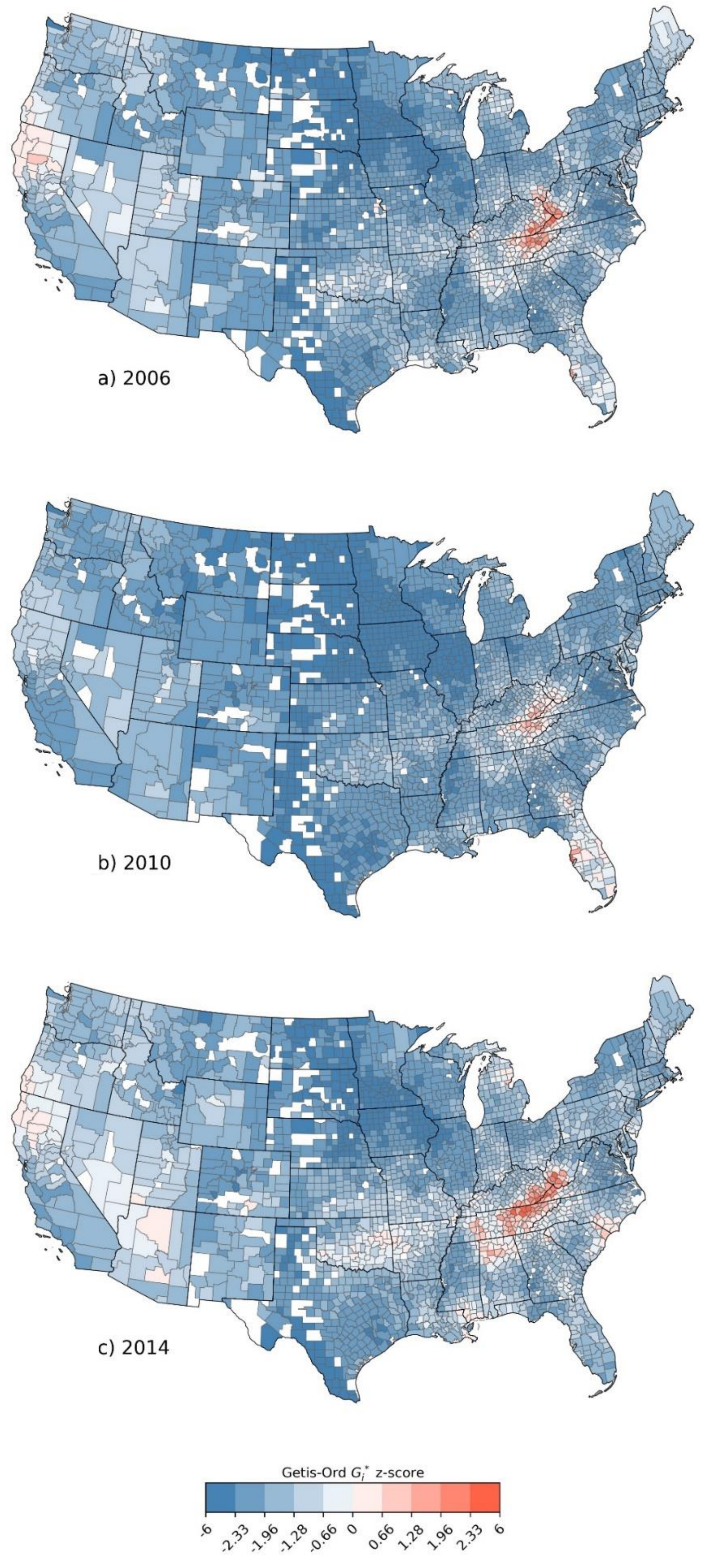

Figure 13. Getis Ord G_i^* analysis of county-level per capita morphine milligram equivalents (MME) across the United States in a) 2006, b) 2010, and c) 2014. Underlying prescription opioid shipment data comes from the Automated Reports and Consolidated Ordering System (ARCOS).

3.4.3 Prescription opioid exposure and treatment admissions for prescription opioids

The estimated relationship between county-level per capita MME and admissions involving prescription opioids are presented for nationwide SAMHSA TEDS-A data (Table 8) and Washington ADAI data (Table 9). Per capita MME and its spatial lag are presented as these are the primary coefficients of interest. Results for all coefficients included in the fully adjusted models are available for the nationwide SAMHSA TEDS-A models in Appendix G and the Washington ADAI models in Appendix H. Each point estimate represents the expected multiplicative increase in the rate of admissions involving prescription opioids for a one unit increase in per capita MME. Because the US witnessed a dramatic increase in per capita MME over the study period, interpreting the model results in terms of a one unit change is unlikely to reflect the actual changes in per capita MME. Thus, the models are interpreted in terms of both a one unit change as well as a 50 unit change, as this is a conservative estimate of the average change in per capita MME across all counties from 2006 to 2014. Multicollinearity was assessed among adjustment variables before modeling using cross correlations and after modeling using generalized variance inflation factors (GVIF). Median income and race (% white) demonstrated high cross correlation with other variables as well as a high GVIF values (GVIF>5), so these covariates were withheld from the final models.

Results from the national models indicated a strong, positive relationship between per capita MME and admissions involving prescription opioids. In the uncontrolled models with no spatial lag (Table 8 Row 1), this multiplicative relationship for a one unit change in per capita MME was estimated at 1.00132 (95% confidence interval, CI, 1.00129-1.00134) in 2006 and 1.00130 (95% CI 1.00128-1.00132) in 2014. A 50 unit increase in per capita MME would increase the rate of admissions involving prescription opioids 6.8% in 2006 and increase 6.7% in

2014. Similar results were observed for the controlled models with no spatial lag (Table 8 Row 2). National estimates for the spatial lag of per capita MME also demonstrated a positive relationship with admissions involving prescription opioids. In the controlled models that contained a spatial lag term (Table 8 Rows 5 and 6), the multiplicative relationship for a one unit change in per capita MME in all neighboring counties was estimated at 1.00171 (95% CI, 1.00163-1.00178) in 2006 and 1.00098 (95% CI 1.00092-1.00104) in 2014. A 50 unit increase in per capita MME in all the neighboring counties would increase the rate of admissions involving prescription opioids in focal counties 8.9% in 2006, which persisted as a 5.0% increase nearly a decade later in 2014. This relationship emerged after adjusting for socioeconomic factors and state-level fixed effects. Inclusion of adjustment variables, spatial lag terms, and state fixed effects greatly improved model fit as assessed using the Akaike Information Criterion (AIC). For example, the uncontrolled model with no spatial lag term had an AIC value of 88339 when fit on 2006 data, whereas the fully adjusted model had an AIC of 42328 when fit on the same data. Results were consistent when considering only those treatment admissions where prescription opioids are listed in the primary reason for treatment admission.

Table 8. Nationwide cross-sectional regression results examining per capita MME in relation to disaggregated SAMHSA treatment admissions involving a prescription opioid (coefficient, 95% confidence interval)

	Year		
Model	2006	2010	2014
Uncontrolled, no W			
Per Capita MME	1.00132***	1.00052***	1.00130***
	[1.00129, 1.00134]	[1.00050, 1.00053]	[1.00128, 1.00132]
Controlled, no W			
Per Capita MME	1.00150***	1.00070***	1.00112***
	[1.00145, 1.00154]	[1.00068, 1.00072]	[1.00108, 1.00116]
Uncontrolled, W			
Per Capita MME	1.00107***	1.00051***	1.00161***
	[1.00103, 1.00110]	[1.00049, 1.00053]	[1.00158, 1.00164]
W x Per Capita MME	1.00084***	1.00002	0.99939***
	[1.00079, 1.00090]	[0.99999, 1.00004]	[0.99935, 0.99944]
Controlled, W			
Per Capita MME	1.00116***	1.00057***	1.00084***
	[1.00112, 1.00121]	[1.00055, 1.00059]	[1.00080, 1.00088]
W x Per Capita MME	1.00171***	1.00065***	1.00098***
	[1.00163, 1.00178]	[1.00062, 1.00068]	[1.00092, 1.00104]
N counties	928	883	825

Notes: W stands for spatial lag. Unadjusted models include only the per capita MME and/or its spatially lagged version. Adjusted models include state fixed effects and county-level measures of % male, % high school graduated, % unemployment, % female head of household, median age, and a dissimilarity index measuring white-black segregation.

+ $p < 0.1$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Models run on data from Washington were largely consistent in direction and magnitude with results from the nationwide data. Uncontrolled estimates on the relationship between per capita MME and treatment admissions in Washington (Table 9 Row 1) had similar point estimates and overlapping confidence intervals to estimates from the nationwide data. The controlled models containing a spatial lag term (Table 9 Rows 5 and 6) estimated the multiplicative change in per capita MME at 1.00121 (95%CI 1.00069-1.00173) in 2006 and 1.00107 (95%CI 1.00070-1.00144) in 2014. A 50 unit increase in per capita MME would expect treatment admissions to increase 6.2% in 2006 and 5.5% in 2014 across the state of Washington. Similarly, estimates regarding the spatial lag of per capita MME in Washington aligned with the nationwide models. Controlled models containing a spatial lag term (Table 9 Row 6) estimated the multiplicative relationship for a one unit change in per capita MME in all neighboring counties at 1.00117 (95% CI, 0.99996 -1.00239) in 2006 and 1.00303 (95% CI 1.00233-1.00374) in 2014. These estimates indicate that a 50 unit increase in per capita MME in neighboring counties would increase the rate of admissions involving prescription opioids in focal counties 5.9% in 2006 and 16.4% in 2014 for the state of Washington. Like the national models, the Washington models saw a strong improvement in AIC when including adjustment variables. For example, the uncontrolled model with no spatial lag term had an AIC value of 702 for 2006 data, whereas the fully adjusted model had an AIC of 543 for the same data.

Table 9. Washington cross-sectional regression results examining per capita MME in relation to treatment admissions where the primary problem substance is a prescription-type opioid (coefficient, 95% confidence interval)

	Year		
Model	2006	2010	2014
Uncontrolled, no W			
Per Capita MME	1.00138***	1.00156***	1.00231***
	[1.00090, 1.00184]	[1.00134, 1.00177]	[1.00207, 1.00254]
Controlled, no W			
Per Capita MME	1.00131***	1.00126***	1.00132***
	[1.00078, 1.00183]	[1.00098, 1.00154]	[1.00095, 1.00170]
Uncontrolled, W			
Per Capita MME	1.00109***	1.00158***	1.00201***
	[1.00062, 1.00157]	[1.00136, 1.00180]	[1.00176, 1.00225]
W x Per Capita MME	1.00301***	1.00138***	1.00268***
	[1.00205, 1.00399]	[1.00099, 1.00177]	[1.00206, 1.00330]
Controlled, W			
Per Capita MME	1.00121***	1.00134***	1.00107***
	[1.00069, 1.00173]	[1.00106, 1.00163]	[1.00070, 1.00144]
W x Per Capita MME	1.00117+	1.00091***	1.00303***
	[0.99996, 1.00239]	[1.00035, 1.00147]	[1.00233, 1.00374]
N counties	39	39	39

Notes: W stands for spatial lag. Spatial lag of per capita MME is not available for the island county of San Juan (no neighbors). Unadjusted models include only the per capita MME and/or its spatially lagged version. Adjusted models include state fixed effects and county-level measures of % male, % high school graduated, % unemployment, % female head of household, median age, and a dissimilarity index measuring white-black segregation.

+ $p < 0.1$, * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

3.5 Discussion

In the study of geographic exposure to substance use, the amount of substance in an area is often an uncertain quantity. For example, estimating the global supply of substances like heroin relies upon measures derived from agricultural yields of poppy or reported seizures (United Nations 2020). Comparatively, mandatory reporting systems like ARCOS present a unique opportunity to examine the supply of prescription opioids with higher precision. Understanding the geographic relationships between prescription supply and substance-related health outcomes remains important even as focus of the US opioid crisis shifts to pressing questions about the role of illicit fentanyl in drug-related mortality (Daniel Ciccarone 2017; Mars, Ondocsin, and Ciccarone 2018; Stewart et al. 2017).

The present study provides a rigorous spatial analysis that advances the understanding of the geographic distribution of prescription opioids across the US. Geofacet visualization displayed space-time trends from 2006 to 2014, highlighting how states like Florida, Delaware, and Nevada, as well as states in mid-Appalachia, had the highest overall levels of per capita MME. Some of these states, namely Florida and Delaware, showed medium levels of per capita MME at the start of the study period, which quickly increased to high levels of per capita MME around 2010, and then sharply declined in 2011 and 2012. The timing in these patterns may reflect changes in PDMP legislation in these states. Florida enacted PDMP legislation midway through 2009, whereas Delaware enacted PDMP legislation midway through 2010 (Prescription Drug Monitoring Program Training and Technical Assistance Center 2020b; 2020a). The state-level calculations are presented here are consistent with research using commercial prescription opioid databases like the IQVIA Xponent database (Schieber et al. 2019).

The county-level Getis Ord G_i^* analysis repeated for 2006, 2010, and 2014 highlighted a large, multi-state cluster of high per capita MME counties extending from northeast Tennessee to West Virginia along the Kentucky-Virginia border. This finding is consistent with previous descriptive mapping results in Kentucky that show the eastern border counties to have the highest prescription opioid dispensing rates in the state (Luu et al. 2019). Many of these areas of high prescription opioid distribution persist past the 2006 to 2014 period considered in the present study. For example, Guy Jr. et al. presents descriptive maps of county-level per capita MME in 2015, showing areas like northern California, southern Nevada, mid-Appalachia, and others highlighted here as having extremely high levels of per capita MME (Guy Jr. et al. 2017). Existing research as to why the Appalachian Region has experienced such high levels of opioid-related morbidity and mortality generally points to the diseases of despair hypothesis, wherein long-term economic downturn and a loss of opportunity drives substance use behaviors and health outcomes (Meit et al. 2017; Holtkamp and Weaver 2018; Dean and Kimmel 2019). However, more recent research challenges the diseases of despair hypothesis and frames substance use in Appalachia as primarily a public health issue. Ruhm demonstrates that changes in economic conditions explains only a small amount of the increase in opioid-related death rates and instead argues for a public health framework focusing on the availability and cost of substances across different population subgroups (C. Ruhm 2018).

Previous spatial studies on geographic exposure to substance use have indicated a relationship between prescription opioid availability and opioid-related health outcomes. For example, quarterly rates of emergency department treatment for opioid overdoses were strongly correlated with prescription opioid sales at the 3-digit ZIP code-level in North Carolina (Modarai et al. 2013). The present research used quantitative measures to estimate the relationship between prescription opioid availability and opioid-related health outcomes across the US at the county-level. There was evidence of a strong, positive relationship between per capita MME and admissions to publicly funded treatment facilities involving prescription opioids. The magnitude and direction of this relationship was consistent when estimated using both SAMHSA TEDS-A data and Washington ADAI data. Existing studies that support the present results linking prescription opioid availability and possible health outcomes are examined in the context of PDMP effectiveness (Grecu, Dave, and Saffer 2019; Reisman et al. 2009; Puac-Polanco et al. 2020). The present research offers a complementary perspective by estimating the relationship between prescription opioid availability and treatment admissions involving prescription opioids during the 2000s and early 2010s, a watershed period in PDMP legislation across the US (Prescription Drug Monitoring Program Training and Technical Assistance Center 2018).

Spatial lag of X (SLX) models can be used to evaluate how patterns of prescription opioid availability might impact opioid-related health outcomes between focal-neighbor units. There was evidence of a positive relationship between neighboring levels of prescription opioid exposure on focal treatment admissions involving prescription opioids as indicated by the size and direction of the spatial lag coefficients. To the best of my knowledge, these SLX estimates on the impact of neighboring prescription opioid availability on treatment admissions involving a prescription opioid are novel. Previous research using SLX models on opioid-related health outcomes and exposures are limited. Monnat examined the average rate of opioid prescribing among neighboring counties as one of many socioeconomic and opioid supply factors relating to US drug mortality rates and found a significant positive association, although the prescription opioid data source was limited to retail pharmacies, excluded high-volume prescribers, and did not consider prescription dosage (Monnat 2019). In addition, recent research has used extensions of SLX, namely the Spatial Durbin Model (SDM) and Spatial Durbin Error Model (SDEM), to examine the potential spillover effects of Naloxone access laws on opioid overdose deaths (Erfanian, Collins, and Grossman 2019a). Other research used a Spatial Error Model (SEM) to examine the association between racial segregation and treatment capacity for opioid use disorder in the presence of spatially autocorrelated residuals (Goedel et al. 2020). The SLX model, as well as its natural extensions into SDM and SDEM, offers an analytical framework to investigate the impact of prescription opioid supply in neighboring areas and may prove useful to other studies where supply-side information is available.

3.5.1 Limitations

Both the outcome and exposure data have limitations. Only those treatment programs receiving public funds are required to report admissions to SAMHSA. Treatment facilities not receiving public funds, such as private treatment facilities, are underrepresented in the TEDS-A data. Nevertheless, SAMHSA TEDS-A data is estimated to capture more than 80% of all treatment admissions in the United States (Martin, Longinaker, and Terplan 2015). In addition, the present study disaggregated SAMHSA TEDS-A data to the county-level based solely on population. Although the disaggregated counts of SAMHSA TEDS-A data showed strong agreement with the external Washington ADAI dataset, this disaggregation method may not produce reliable estimates for other areas of the US.

Geographic prescription opioid exposure was considered as the per capita MME of all shipments of prescription opioids involving oxycodone and hydrocodone. However, the ARCOS data contains information on 12 other prescription opioids like licit fentanyl, morphine, meperidine, buprenorphine, levorphanol, and more. These opioid ingredients are shipped in lower quantities and are often used to treat specific types of pain (e.g., tapentadol is used to treat pain from diabetic neuropathy). These 12 other prescription opioids were excluded as they are not considered regular targets for diversion; nevertheless, their exclusion underestimates MME calculations.

Lastly, there were certain control variables omitted from the models that may be important confounding factors. Two such variables include prescription opioid diversion and the availability of alternative (e.g., non-admission) treatment services. Existing research has used numerous survey methodologies to estimate drug diversion (Inciardi et al. 2007; Inciardi, Surratt, Cicero, and Beard 2009; Cicero et al. 2011), although publicly available, nationwide estimates are not available at this time. Measures of alternative treatment services are available in various formats from SAMHSA. For example, the National Survey of Substance Abuse Treatment Service provides state-level data on non-admission treatment services. Related research approximates local availability of treatment by scraping data from the SAMSHA Treatment Service Locator tool or SAMHSA National Directory of Drug and Alcohol Abuse Treatment Programs reports (Guerrero and Kao 2013; Langabeer et al. 2020; Yarbrough, Abraham, and Adams 2020), although archives of such data could not be located.

3.6 Conclusion

This research provides a spatial analysis of prescription opioid distribution across the US from 2006 to 2014. Prescription opioids records from a recently released portion of the Drug Enforcement Administration’s Automated Reports and Consolidated Ordering System (ARCOS) database were converted to state- and county-level measures of per capita morphine milligram equivalents (MME). Although several Appalachian states enacted prescription drug monitoring programs in the early 2000s, these states consistently experienced the highest levels of per capita MME into the early 2010s. Other states, such as Florida and Delaware, saw steep inclines and declines in per capita MME during the same study period. Getis Ord G_i^* statistics calculated at the county-level for 2006, 2010, and 2014 showed a large, multi-state cluster of high per capita MME that extended from northeast Tennessee to West Virginia. These counties are notable as they had very high z-scores in a context of already elevated prescription opioid distribution. Cross-sectional regressions demonstrated a strong, positive relationship between county-level per capita MME and admissions involving a prescription opioid to publicly funded treatment facilities. This relationship emerged when using both national and state datasets describing treatment admissions, and the effects persisted after adjusting for numerous socioeconomic factors. In addition, spatial lag of X (SLX) models indicated that increases of prescription opioids in adjacent neighboring counties was associated with an increase in treatment admissions of the focal county. These increases were estimated to be 8.9% in 2006 and 5.0% in 2014 when using nationwide data, and 5.9% in 2006 and 16.4% in 2014 when using data for the state of Washington. Results from the SLX models enhance existing theories on the focal-neighbor relationships of prescription opioid exposure and opioid-related health outcomes. The immense detail contained in the recently released ARCOS data allows for several avenues of future research, especially as ARCOS data can be combined with other datasets describing opioid-related health measures. ARCOS data can be used to address spatial questions related to diversion, availability, and potentially inappropriate prescribing practices, all of which are pertinent as prescription opioids remain widely available in the US.

Chapter 4: Geographic information science (GIScience) and the United States Opioid Overdose Crisis: a scoping review of methods, scales, and application areas from 1999 to 2021

Abstract

The OOC continues to generate large amounts of morbidity and mortality in the US, outpacing other prominent accident-related outcomes like vehicle crashes and firearm injury. Multiple disciplines have applied geographic information science (GIScience) to understand geographical patterns in opioid-related health measures. However, there are limited reviews that assess how GIScience generates evidence for opioid-related health measures. The overarching objective of the present scoping review seeks to understand how GIScience has been used to conduct research on the OOC. Specific sub-objectives relate to bibliometric trends in publishing, the location and scale of studies, details of the underlying GIScience methodologies, and what direction future research can take to address existing gaps. The review was pre-registered with the Open Science Framework (protocol url: https://osf.io/h3mfx/). Using the PRISMA Scoping Review Protocol as guiding methodology, scholarly research was gathered from the Web of Science Core Collection, PubMed, IEEE Xplore, and ACM Digital Library. Inclusion criteria was defined as having a publication date between January 1999 and August 2021, using GIScience as a large or central part of the research, and investigating an opioid-related health measure. Descriptive analysis was conducted on data extracted from included studies, with an emphasis on characteristics of publication, GIScience methodologies, units of analysis, and data sources. Two-hundred and thirty-one studies met the inclusion criteria. Most studies have been published from 2017 onward, although the temporal coverage of study years span the 2000s.

While many (41.6%) of studies were conducted using nationwide data, the majority (58.4%) occurred sub-nationally. California, New York, Ohio, and Appalachian states were most frequently studied, while Midwest, Rocky Mountains, and non-contiguous lacked studies using GIScience. The most common GIScience methodology was descriptive mapping, and county-level data was the most common unit of analysis across methodologies. Future research on GIScience on the OOC should focus on developing machine learning applications, executing analyses on geographic units below the county-level, pursue meta-analyses in sub-domains, and address research questions pertaining to illicit fentanyl. These advancements would allow for targeted, location-sensitive interventions. Research using GIScience is likely to continue increasing, and multidisciplinary research efforts amongst GIScientists, epidemiologists, and health professionals can help ensure that methodological innovation meets public health needs.

4.1 Introduction

Over the period of 1999 to 2022 it is estimated that more than one million individuals died from a drug-related overdose in the United States (US), with opioids being the largest contributor to these deaths (Ahmad, FB, Rossen, and Sutton 2022). Although all opioid-related deaths rose steadily in the early 2000s, recognition as a public health issue under the moniker ‘the opioid overdose crisis’ (OOC, sometimes referred to as the ‘the opioid epidemic’) would not coalesce until the early- to mid-2010s (M. R. Jones et al. 2018). Attention was brought to the rising nature of the crisis in the early 2000s (Meier 2003), but it was not until 2017 that the US Federal government officially declared the OOC a public health emergency and committed significant resources (U.S. Department of Health & Human Services 2017).

Translating scientific, bureaucratic, and community efforts into reductions of opioid-related harms has proven challenging. Opioid-related health outcomes and exposures have shown few signs of improvement since the late 1990s. For example, the age-adjusted rate of any opioid-involved death has increased every year on record between 1999 to 2017, from 2.9 deaths per 100,000 in 1999 to 14.9 deaths per 100,000 in 2017 (Center for Health Statistics 1999b). Although there was a brief plateau in the death rates between 2017 and 2018, the death rates increased again in 2019 to 15.5 per 100,000 (Center for Health Statistics 1999b). Provisional counts for 2021 indicate that there were 100,306 drug overdose deaths in 2021, a substantial increase from just over 78,000 deaths in 2020 ("Drug Overdose Deaths in the U.S. Top 100,000 Annually" n.d.). Similarly, nonfatal health outcomes, such as hospitalizations for opioid use disorder and treatment admissions, have continued to increase since the early 2000s (Singh and Cleveland 2020; Substance Abuse and Mental Health Services Administration - Center for Behavioral Health Statistics and Quality 2019). Early data from 2021 indicate that these trends have continued to worsen during the COVID-19 pandemic (Friedman and Akre 2021).

Numerous academic disciplines have studied the OOC, with the repeated observation that opioid-related health outcomes and exposures vary geographically across the US. Geographical variation has been observed along location (e.g., northwest vs southeast), place (e.g., urban vs rural), and scale (e.g., census tracts, counties, and states) (D. J. Peters et al. 2020; C. J. Ruhm 2017). A key discipline underlying the geographic study of health phenomenon, such as opioid-related health outcomes, is geographic information science (GIScience). GIScience broadly refers to the "…branch of information science that deals with the geographical domain, or as the set of fundamental scientific questions raised by geographical information and the technologies that collect, manipulate and communicate [geographical information]" (Goodchild 2011).

GIScience allows researchers to investigate geographic patterns and relationships in health phenomenon using a variety of methods ranging from descriptive mapping to spatial statistics, and GIScience can be integrated into other forms of modeling like simulation and machine learning. GIScience methodologies are increasingly used across disciplines concerned with the OOC, with each discipline developing its own standards of application (Blaschke and Merschdorf 2014). From the perspective of technological development, tracking the multidisciplinary use of GIScience and geographic information systems (GIS) is important as GIScience researchers and software developers must be able to respond to needs and outline best practices for a broadening set of users (N. Smith 1992). In addition, GIScientists should be able to critically examine how GIScience is used to advance the public understanding of the OOC and push for innovations that benefit communities, especially as the crisis continues to worsen (Pickles 1995). One way to approach the breadth of available research applying GIScience on the OOC is through a systematic literature review.

Literature reviews are a form of secondary research wherein the extant knowledge on a topic or field is evaluated to identify publishing trends, synthesize available evidence, point out knowledge gaps, and help outline future research agendas. With the advent of advanced communication technologies, the production of scientific knowledge has increased enormously. A global report on academic publishing from 1968 to 2018 found the number of both articles and journals to be increasing, and estimates from 2018 indicate that the compound annual journal growth rate exceeds 6% (Johnson, Watkinson, and Mabe 2018). With more than 28,000 English-language, peer-reviewed journals estimated to exist, each year yields tens of thousands of articles (Johnson, Watkinson, and Mabe 2018). Increases across all of science are mirrored in publishing in the geosciences. From 2003 to 2019, the total number of geoscience journals increased from

128 to 200 and the total number of articles from 12,500 per year to 26,845 per (information retrieved from Clarivate InCites Journal Citation Reports, jcr.clarivate.com). Given this immense amount of knowledge production, researchers are increasingly turning to meta-science methodologies like bibliometrics and systematic literature reviews to collect, evaluate, and summarize the immense amount of evidence that may be available on a given topic (Snyder 2019). One specific type of systematic literature review is the scoping review, which is meant to "determine the scope or coverage of a body of literature on a given topic and give clear indication of the volume of literature and studies available as well as an overview (broad or detailed) of its focus" (Munn et al. 2018). This type of review is well-suited to the discipline of GIScience as the field frequently uses a variety of study designs, methods, technologies, and datasets, ultimately offering a great diversity of evidence on a given topic. However, this variety makes the exact study-to-study comparison demanded by systematic reviews and meta-analyses challenging (Munn et al. 2018).

As of this writing there are a limited number of reviews offering evidence synthesis on GIScience and the OOC. One example is a review article authored by Wangia and Shireman that focuses on the geographical analysis of health outcomes related to prescription opioids (Wangia and Shireman 2013). Published in 2013, Wangia and Shireman's review understandably focuses on prescription opioids as these were the primary driver of opioid-related mortality at the time. Since 2013, knowledge production on the OOC has increased substantially. Replicating Wangia and Shireman's baseline keyword search strategy in PubMed in 2020 returned more than 22,000 articles, more than a double the 8860 articles initially identified in their 2013 search.[2] Another

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[2] Note this baseline keyword search strategy reflects only *potentially* relevant articles. It does not indicate a need to review more than 22,000 articles.

article by Dijkstra et al. similarly focuses on spatial analytic methods for pharmacoepidemiology and was also published in 2013 in the *Annals of Epidemiology* (Dijkstra, Hak, and Janssen 2013). A third piece by Mazumdar et al. offers a broad discussion as to how geographical methods can be used to address the OOC (Mazumdar et al. 2015). While not a formal review, Mazumdar et al. identifies several trends in the application of geographical analyses to prescription opioid misuse and critically asks how GIScience can be best used to respond to the growing OOC. Crucially, each of these articles focused on GIScience in relation to prescription opioid health outcomes and did not consider GIScience studies on measures relating to heroin, illicit fentanyl, among other non-prescription opioid measures.

Given the evolving nature of the OOC, there exists a need for an updated review that considers more broadly the role of GIScience on the OOC. Such a review can elucidate trends in publication output, the use of GIScience methods, and GIScience application areas on the OOC, as well as identify what unanswered questions or issues persist in the literature. Thus, the present scoping review seeks to understand how GIScience has been used to study the US OOC. From this overarching objective I formulate the following specific research questions: (1) What are the characteristics of publication output for studies on GIScience and opioids in the US since 1999? (2) What are the primary GIScience methodologies as they are applied to different questions of the OOC? (3) At what geographic scale do these geospatial analyses occur? (4) Are certain locations studied more frequently than others and what is the potential impact of this coverage? In addition to these questions, this scoping review acts as a guidepost to define existing research domains and help outline future research agendas for GIScience on the OOC. Results from the present scoping review enables substance use researchers, GIScientists, and external actors to easily review the available GIScience evidence for an ongoing sociomedical crisis.

4.2 Methods

The present review followed best practice guidelines laid out by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR), a multidisciplinary scholarly collaboration seeking to standardize reporting for systematic reviews (Tricco, Lillie, Zarin, O, et al. 2018). A scoping review protocol following the PRISMA-ScR checklist was pre-registered with the Open Science Foundation (OSF) for public viewing on September 8th, 2021, before any data collection or screening occurred (protocol url: https://osf.io/h3mfx/).

The underlying methodology for this analysis follows the classic scoping review methodology laid out by Arksey and O'Malley as well as more recent guidelines suggested by the Joanna Briggs Institute, an international research organization promoting evidence synthesis in healthcare (Arksey and O'Malley 2005; M. Peters et al. 2015). This scoping review follows several sequential steps including identifying an overarching research question and specific sub-questions, building a comprehensive search strategy to identify relevant studies, selecting appropriate studies for the review, charting data extracted from included studies, and, lastly, analyzing and reporting the data (Arksey and O'Malley 2005; M. Peters et al. 2015).

4.2.1 Search strategy

Relevant academic studies (also referred to as documents) needed to be retrieved from online information search engines. Initial search terms for these repositories were iteratively drafted, tested, and edited to ensure that a wide variety of documents were captured whilst avoiding the creation of an insurmountably large number of potentially relevant documents. Search terms for GIScience techniques were acquired by reviewing conference topics offered at

GIScience 2021, a leading academic conference on the study of geographic information science. Search terms for opioid-related exposures and outcomes were built from available literature and bibliographic indexing ontologies, specifically the Medical Subject Headings (MeSH). The resulting search terms were organized into three topic groups relating to GIScience, opioid-related exposures, and opioid-related outcomes, all of which were combined into a single multi-part search string passed to various information search engines (Table 10). The complete multi-part search string was applied to four large electronic academic repositories: Web of Science (WoS) Core Collection, PubMed, and IEEE Xplore, and ACM Digital Library. The exact multi-part search string applied to each repository required slight modification given differences in the technical limitations of each search engine (see Appendix I for the exact search parameters used when querying each repository).

Table 10. Search terms relating to GIScience, opioid-related exposures, and opioid-related outcomes built from *GIScience 2021* as well as Medical Subject Headings (MeSH). Search terms were by topic groupings.

GIS	Opioid-related exposures	Opioid-related outcomes
spatial*	opioid*	addict*
geograph*	heroin	overdose
geostat*	fentanyl	visit
gis	oxycodone	event
cluster	hydrocodone	admission
"geographic information science"	"illicit opioid"	discharge
"space-time"	"prescription opioid"	mortality
"spatio-temporal"	"drug market"	morbidity
"agent-based model"	"street market"	"substance use"
"geovisualization"		"substance abuse"
"multiscale"		"substance misuse"
"multi-scale"		"treatment"
"geo-simulation"		"drug rehabilitation"
"local-scale"		"drug treatment"
"mobility"		"drug use"
"trajectory"		"drug abuse"
"movement"		"drug misuse"
"distance"		"chemical dependence"
"proximity"		"habituation"
"spatial bias"		

Notes: Terms that appear in each column (e.g., GIS, opioid-related exposures, opioid-related outcomes) were considered using the OR operator. Columns were then considered together using the AND operator. The asterisk (*) is wildcard operator that captures multiple forms of a given word (e.g., geostat* could be geostatistics or geostatistical). Quotes ("") are used to specify exact phrases.

4.2.2 Eligibility criteria and screening

In addition to using specific search terms, document eligibility was further refined by date, document type and language. Given the rise of the OOC in the post-2000s, only documents from January 1, 1999, to August 31, 2021, were considered. Peer-reviewed articles and conference proceedings were the only permissible document types. Lastly, considered documents were limited to those written in English as it is the primary scientific communication language of the US.

Eligibility screening applied several selection criteria. The first criteria ensured that key parts of the document clearly communicated GIScience as a large, if not central, focus of the research. For example, a study that used a single map to situate the location of sample sites would not meet this criterion and GIScience is likely to be absent in key descriptors of the study like title, abstract, and keywords. The second criteria checked to ensure that the study investigated an opioid-related health measure. This criterion was made intentionally broad as to capture the many ways in which different disciplines approach the study of opioid use. The final selection criteria confirmed that the study occurred in the US. This geographic criterion was applied as the present scoping review is concerned with the US OOC.

These selection criteria were applied in two phases to determine if a document was to be included in the review. During the first phase the selection criteria were applied to the title, abstract, and keywords to determine if the document clearly met the selection criteria, clearly did not meet the selection criteria, or needed further inspection. Articles that clearly met the selection criteria or needed further inspection were considered potentially relevant and their full text was retrieved. During the second stage, the full text of all potentially relevant articles was screened and the selection criteria re-applied. I conducted all screening, with any uncertainties discussed collaboratively with Dr. Kathleen Stewart. The final list of included documents was reviewed by Dr. Kathleen Stewart.

4.2.3 Data charting and analysis

A data extraction template was created from relevant data items described by the Cochrane Collaboration’s guide for data extraction in a systematic review (“Data Collection Form for Interview Reviews: RCTs and Non-RCTs” 2014). Given the focus on GIScience, I created several new items that captured geographic elements of the study design and analytic methods for each document included in the scoping review. The data extraction template was pre-tested and refined across documents to determine what items needed to be added, removed, or adjusted. The final data extraction template collected bibliographic information on the study (author, title, publication year, information source), objectives and settings (stated objectives, primary geographic scale of study setting, and specific areas of US), study sample (data collection methods, primary opioid-related data source, GIS data type presented, and temporal coverage of study), description of study design (study design, opioid-related health outcome and exposure measures, proxy opioid measure), geospatial data analysis (geospatial method, geographic unit, and opioid-related measure), and discussion (key geographic results, future research questions or problems identified, consideration of spatial autocorrelation, framing of research as hypothesis, and theme of study). Following the PRISMA-ScR guidelines there was no critical appraisal of individual sources, calculation of summary measures, nor assessment the risk of bias across studies (Tricco, Lillie, Zarin, O’Brien, et al. 2018).

I acted as the independent data extractor. The entire data collection, screening, extraction, cleaning, and analysis process occurred from August 2021 and February 2022 (7 months). Data was extracted into and managed in Google Sheets (Google 2021). Additional exploratory data analysis and visualization were completed in R (R Core Team 2021).

4.3 Results

4.3.1 Selection of relevant evidence

The search strategy initially resulted in 3,957 documents across WoS, PubMed, ACM, and IEEE Explore, with most documents originating from PubMed and WoS (Figure 14). Once all documents were combined across information sources, 765 duplicates were removed. The first round of screening removed an additional 2,717 (85.1% of 3194) documents whose title, abstract, and keyword did not meet the eligibility criteria. Full-text review was conducted on the remaining 477 documents. Full-text review excluded an additional 246 (51.6% of 477) documents with reasons, the most common reason being that the study did not use GIScience methods in a significant and scientific way, the study did not consider an opioid-related measure, or the study was not situated in the US. No documents originally sourced from IEEE Explore were retained after the screening processes. Data extraction occurred on the remaining 231 documents. A complete list documents included in the review is available in Appendix J.

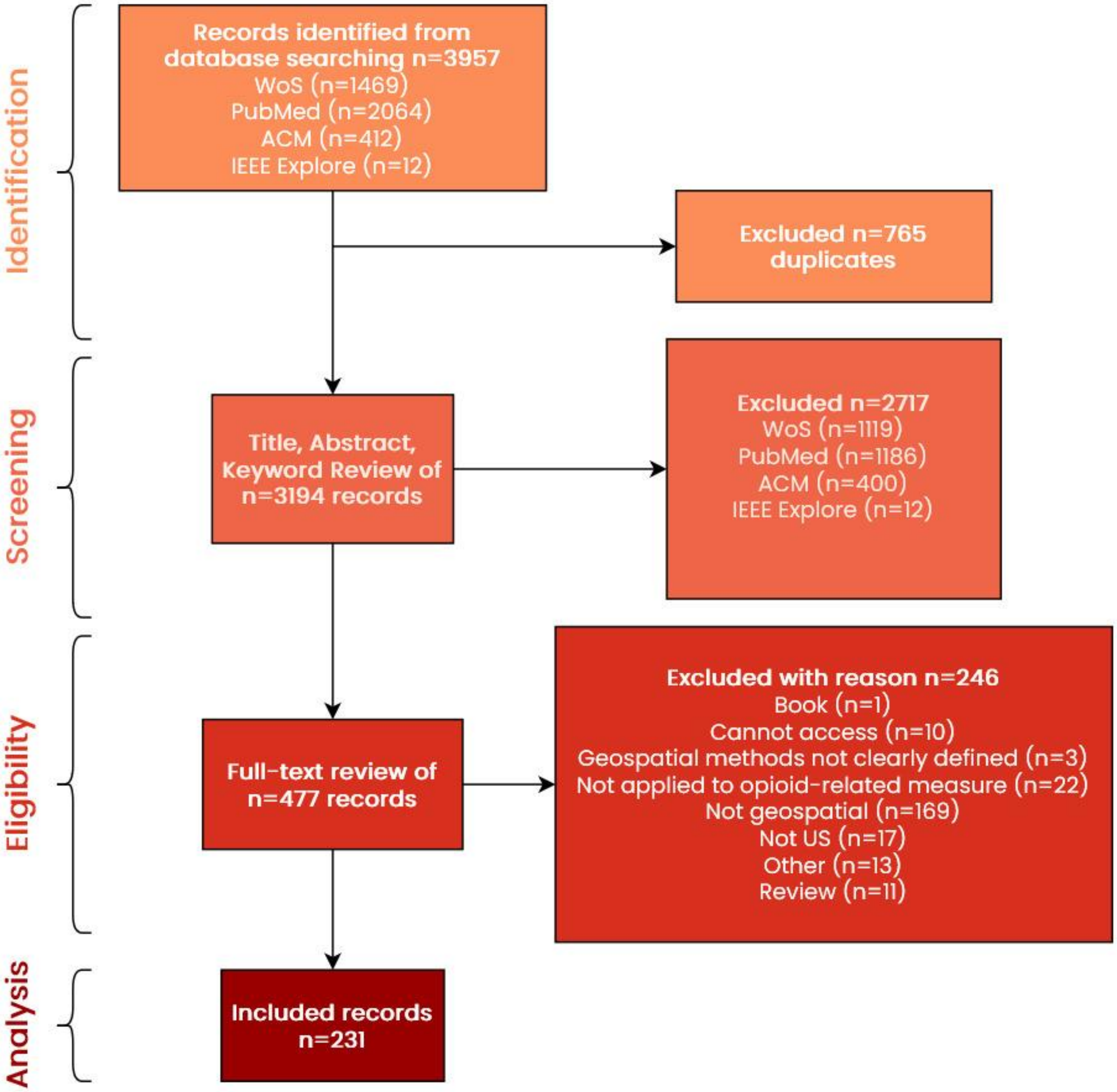


Figure 14. Scoping review flowchart describing the document identification, screening, eligibility, and analysis phases of the present review. Of the 3957 articles originally identified, 231 (5.8%) were included in the final review.

4.3.2 Bibliographic trends and temporal coverage of GIScience on the OOC

The earliest document included in the review was published in 2003. This study used a descriptive map to compare the predominant heroin type to the HIV percent positivity among injection drug users and men who have sex with men for 20 cities monitored by the US Drug Enforcement Agency Domestic Monitoring Program (D. Ciccarone and Bourgois 2003). Between 2003 and 2016 there were 50 publications utilizing GIScience to study the OOC (Figure 15a). Yet from 2017 through 2021 the total number and yearly publication rate dramatically increased, with a total of 181 publications observed between 2017 and 2021. These five years yielded more than triple the number of documents published in the preceding sixteen years.

Considering only the publication year can mask the temporal coverage of the underlying studies. Analysis of the temporal coverage reveals that studies make use of data going as far back as 1979 (Jalal et al. 2018), and the median number of studies including a year between 1979 to 2021 is 14 (Fig 15b). Although the distribution is left skewed, with more study years in the early- and mid-2010s compared to other periods, there is relatively strong temporal coverage of study years from 2000 onwards. This indicates a general availability of GIScience evidence across temporal span of the OOC.

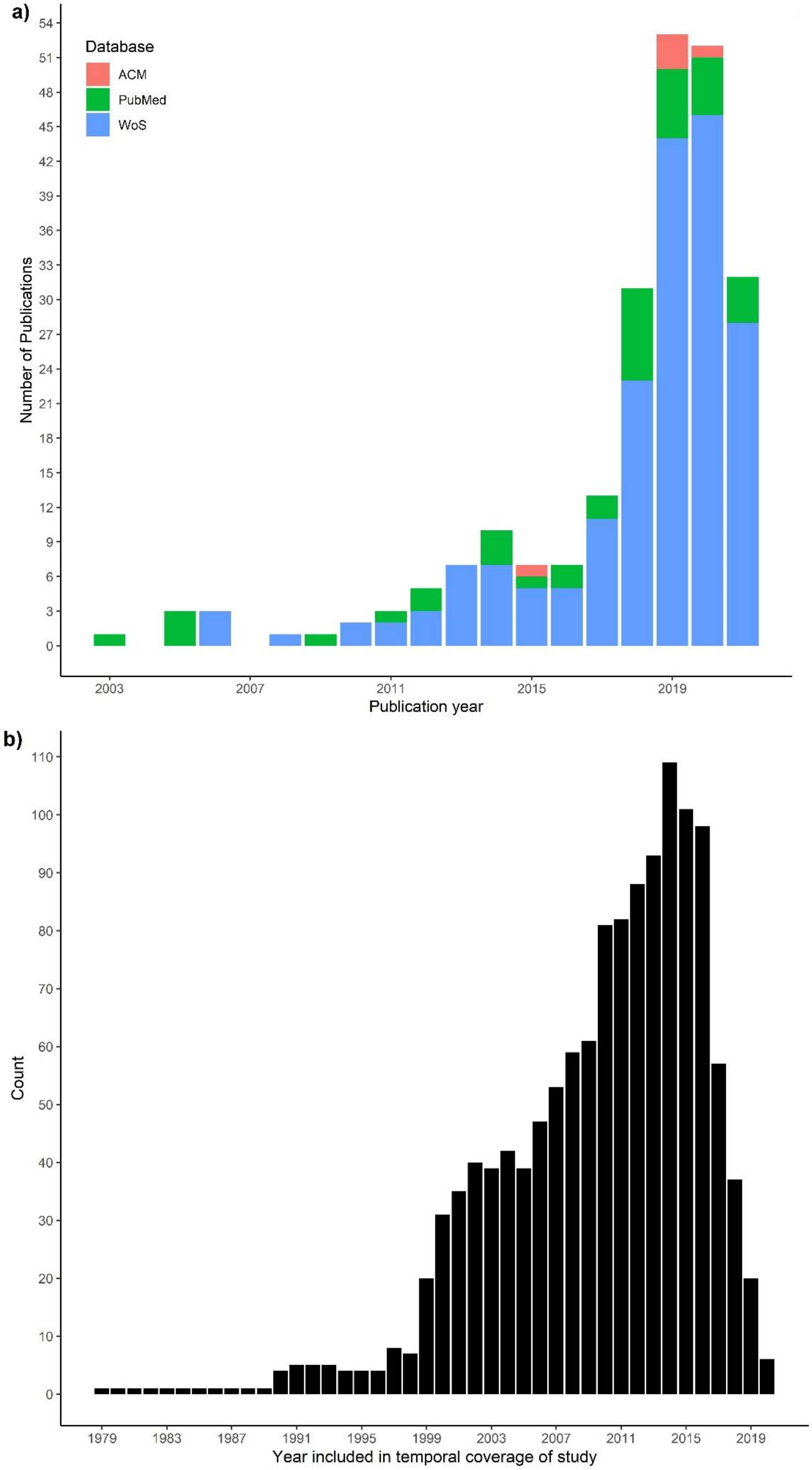


Figure 15. Bar charts describing the a) frequency of publications using GIScience to study the Opioid Overdose Crisis and b) the temporal coverage of included GIScience studies.

4.3.3 The geographic scales and methods underlying GIScience analysis of the OOC

The geographic scales and methods of each study included in the review were extracted. There exists substantial debate as to what scale can mean in geographic research (Manson 2008), so tabulations were limited to the clearly identifiable categories of studies executed at a national, state, or city scale. The geographic units of analysis used at each scale were tabulated, and combinations observed at least five times were visualized (Figure 16). For nationwide studies, county (n=64) and state (n=47) units of analysis were most common. While counties were again the most used unit of analysis for studies conducted at the state scale (n=40), nearly the same number of studies used ZIP or ZCTA (n=39). As the scale of studies decreased from nationwide to city, point data was used more frequently. Point data was the most frequently used unit of analysis for studies conducted at city scale (n=25). Census tracts and block groups, which are some of the smallest geographic units of analysis where health and socioeconomic data is available in the US, were used in relatively similar amounts across all scales, although their frequency of use increased slightly at the scales of state and city.

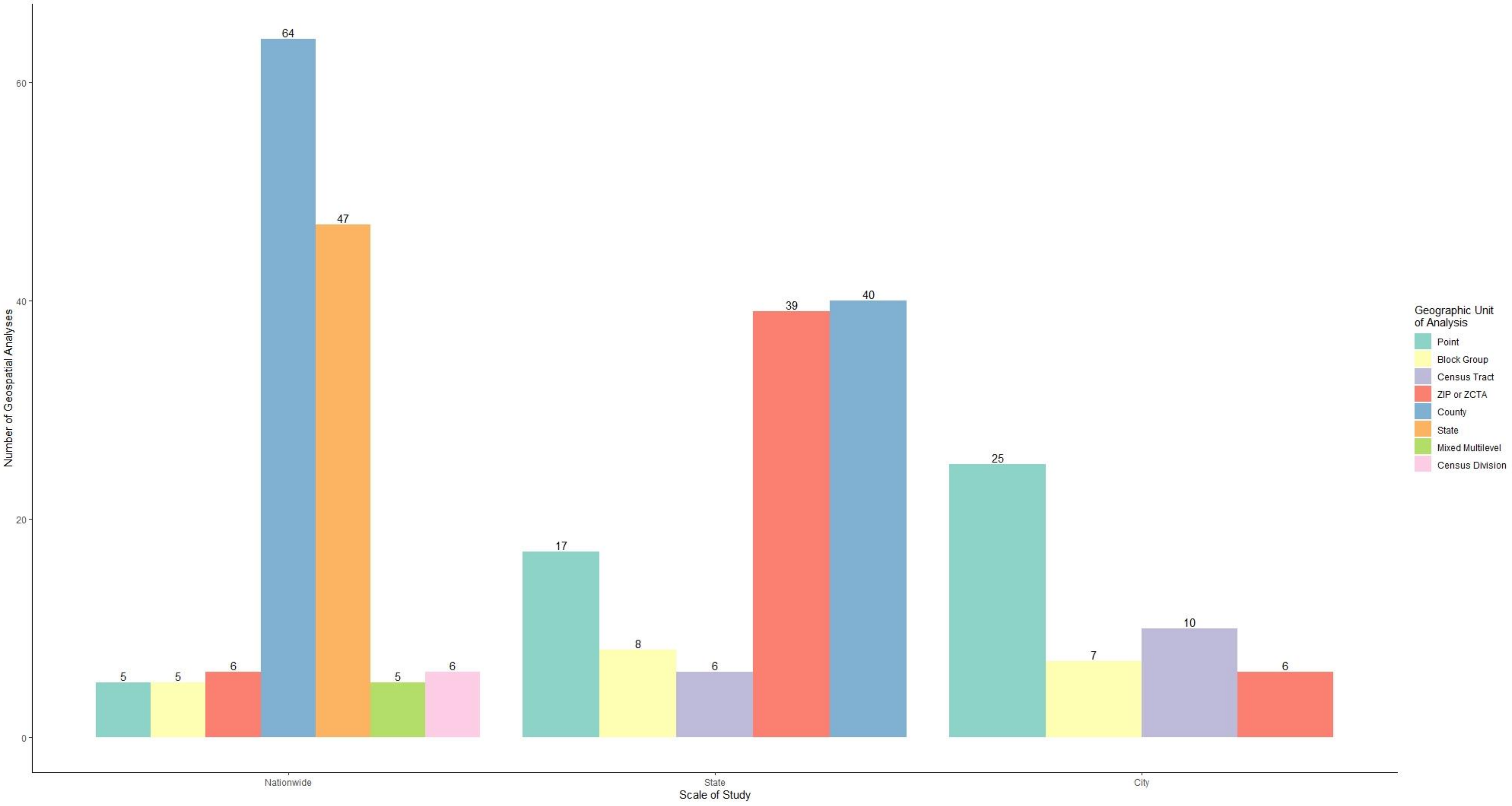


Figure 16. Tabulations of geographic units of analysis by study scale for GIScience studies examining opioid-related health outcomes and exposures. Other units of analysis observed less than five times at a given scale are excluded.

Additional trends were identified by tabulating the specific methods applied on different geographic units of analysis. A heatmap crosstabulation between geospatial methods and units of analysis (Figure 17), focusing on only those methods that were observed at least five times, showed the most common GIScience method to be descriptive mapping (n=157). Descriptive mapping involves displaying an opioid-related measure across geographic units. County- (n=50) and state-level (n=37) descriptive maps were most common, followed by point (n=28) and ZIP or ZCTA (n=25) descriptive maps.

The application of statistical modeling techniques to geographic units using both non-spatial regression on geographic units and spatial regression specifications contributed a large number of analyses using GIScience. Of these regression techniques, both non-spatial regression on geographic units (n=38) and spatio- and spatio-temporal Bayesian approaches were most common (n=36). These regression techniques were applied to county and ZIP/ZCTA-level data most frequently. Other spatial regression techniques, such as traditional econometric specifications like the spatial lag model or emergent methods around (multiscale) geographically weighted regression were used less frequently.

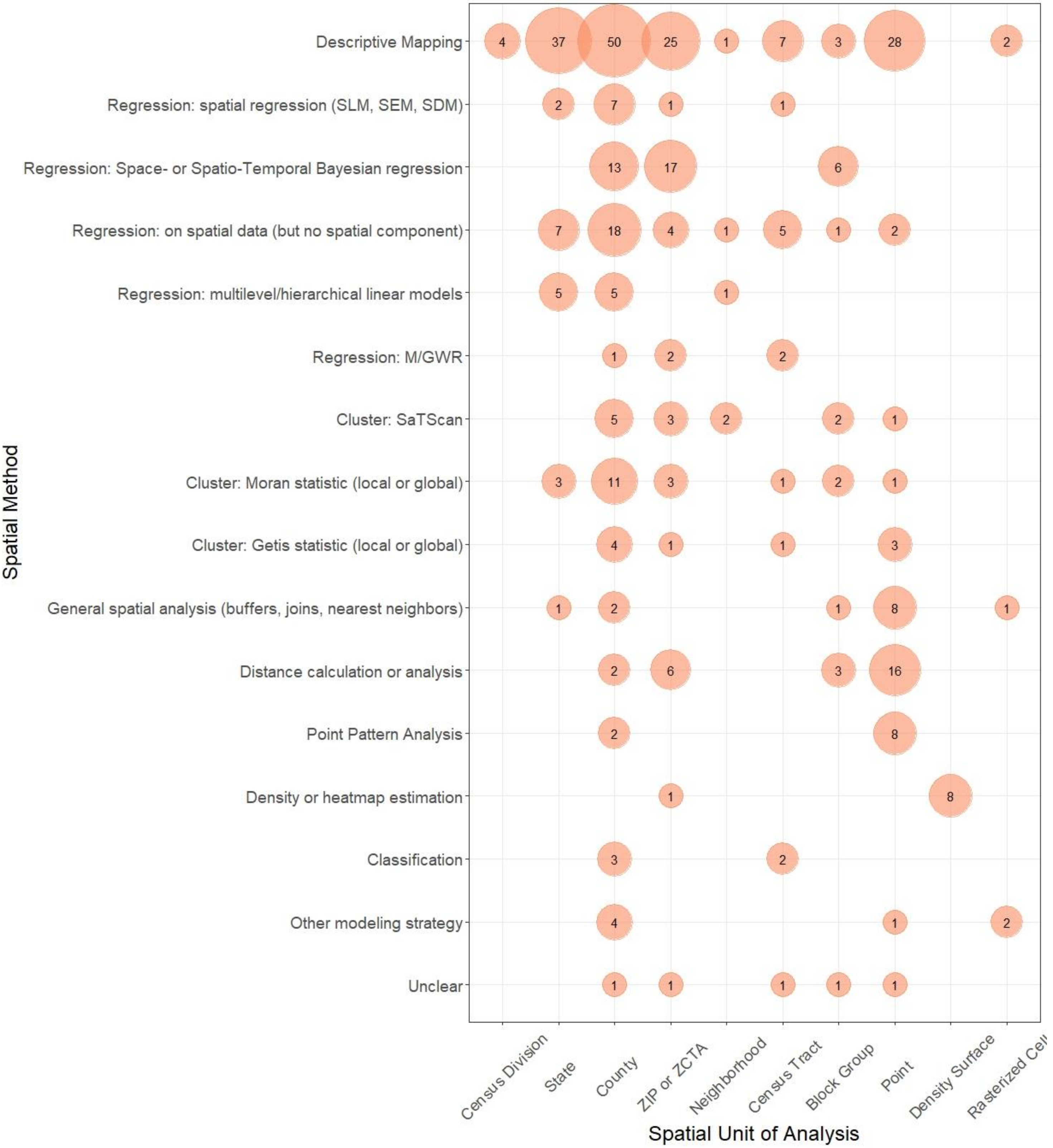


Figure 17. Heatmap crosstabulation of methods by unit of analysis. Larger circles represent a greater number of that method-unit used in combination, whereas smaller circles indicate fewer. Absence of a circle indicates no method-unit used in combination. Only methods observed more than 5 times across all data were included in the crosstab.

Clustering techniques were categorized by the underlying methods, including Moran, Getis, and Kulldorff's Spatial Scan Statistic (SaTScan) statistics (Anselin 1995; Kulldorff and Nagarwalla 1995). Of these clustering techniques, local and global Moran statistics were used most frequently (n=21), with the most common unit of analysis being the county (n=11). SaTScan (n=13) and Getis (n=9) were used less frequently, although these clustering methodologies also used county-level data most commonly.

Another set of GIScience methods relied extensively on point data (n=73). Beyond descriptive mapping, point data was most frequently applied in distance calculations, point pattern analyses, and general spatial analytic techniques (e.g., buffers, joins, nearest neighbor). The underlying point data represented a variety of opioid-related features including the location of medical facilities, location of treatment providers, location and price of illicit substance sales, location of narcotics calls for service, location of overdose events, point-to-point or point-to-other distance calculations, among other features (Meadowcroft and Whitacre 2020; Langabeer et al. 2020; Hswen, Zhang, and Brownstein 2020; Wooditch, Lawton, and Taxman 2013; Dworkis et al. 2018; Kao et al. 2014; Rudolph, Young, and Havens 2017). Additionally, point data was a common format for geo-tagged social media data or user-contributed information relating to substance use (Hswen et al. 2020; Buntain and Golbeck 2015; Cooper et al. 2019). Lastly, there were a limited number of studies where the GIScience method or unit of analysis was unable to be clearly determined. Unclear was defined as when a figure or result was presented without any additional explanation or citation that might identify the method (see for example Hudson, Klekamp, and Matthews 2017).

4.3.4 The geography of GIScience on the OOC in the US

Of the 231 studies included in the present review, 95 (41.6%) were conducted using nationwide data. These studies typically make use of large administrative datasets or surveys, with common data sources including the National Vital Statistics System, Centers for Disease Control and Prevention, Veterans Health Administration, Medicare Services, Substance Abuse and Mental Health Administration, and pharmaceutical recordkeeping datasets (e.g., Quintiles IMS, Optum Datamart). These studies usually offer average effect estimates for an opioid-related health measure or situate geographic clusters across the nation (see for example Langabeer et al. 2020 or Stewart et al. 2017).

Beyond nationwide studies, the remaining 136 (58.4%) GIScience studies were conducted at the sub-national level. These subnational studies offer evidence on opioid-related health measures most frequently for a state (n=64), city (n=31), or county (n=15), with the remaining studies carried out for unique geographies like multiple counties, regions within states, a single clinic, or a local area of interest. The location of these sub-national GIScience studies were extracted and their locations tabulated and mapped by state (Figure 18). Areas with large population centers (e.g., New York, Philadelphia, Baltimore-DC), as well as areas carrying a higher burden of the prescription opioid crisis (e.g., Appalachia) have the highest number of GIScience studies. For example, n=19 sub-national studies were observed for New York, n=17 for Ohio and Pennsylvania, and n=15 for California. However, there were also numerous states where no or few GIScience studies on opioid-related health measures were observed. There were no subnational studies applying GIScience to opioid-related measures in Alaska, Hawaii, Idaho, Kansas, Minnesota, Mississippi, Montana, Nevada, North Dakota, Louisiana, and Wyoming. Maine, New Mexico, and Utah had only one study.

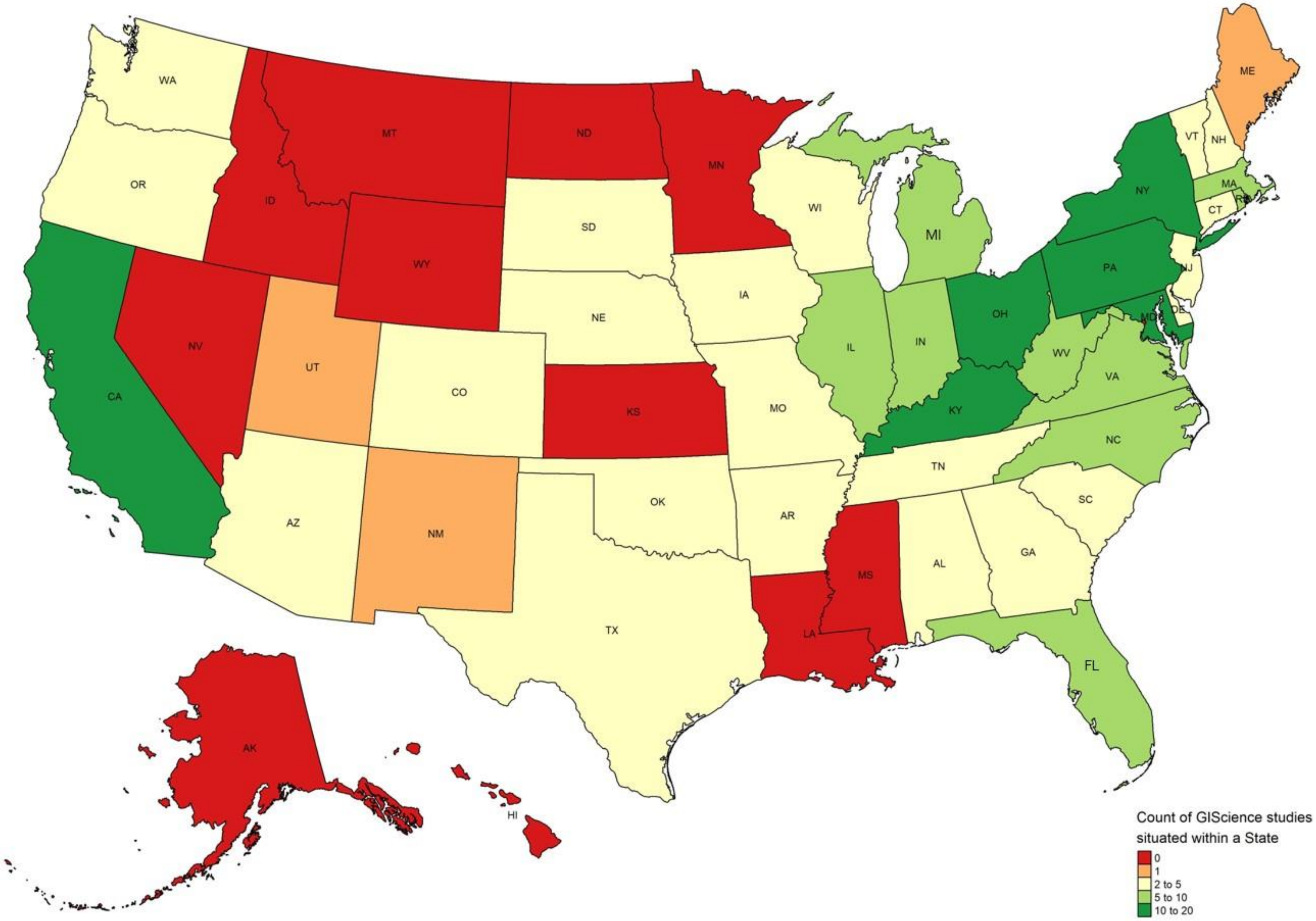


Figure 18. Counts of GIScience articles applied to opioid-related health outcomes and exposures within a given State. Counts exclude GIScience studies conducting nationwide analyses. Reds indicate lower numbers of GIScience studies, whereas greens indicate higher numbers of GIScience studies.

4.3.5 Outlining GIScience research practices on opioid-related phenomena

This study also demarcates the primary GIScience methodologies as they are applied to different questions of the OOC (Munn et al. 2018). GIScience research practices were identified based on trends observed across study objectives and geospatial methods. A definition and explanation of the primary GIScience research practices used to study the OOC are provided, including a brief description of exemplars included in the present review.

Descriptive mapping and geovisualization

Descriptive mapping is the most common GIScience technique applied to opioid-related health measures. Descriptive mapping involves mapping health outcomes, exposures, and proximal measures at differing levels of geography, primarily to highlight geographic variation (K. Jones and Moon 1987). Descriptive mapping features prominently in the OOC as it is often among the first techniques used to situate federal reports on opioid-related data (Mattson et al. 2021a; Hedegaard, Minino, and Warner 2020) or open an exploratory spatial data analysis (X. Chen et al. 2017). These maps most commonly display disease severity via areal data or point locations of opioid-related phenomenon. Descriptive maps of line data were notably absent from the review. Beyond descriptive mapping, this scoping review observed several applications of contemporary cartographic approaches often separately identified as geovisualization. Geovisualization involves digital, interactive, or non-traditional mapping techniques that shift from descriptive communication of data to an emphasis on visual exploration (MacEachren and Taylor 1994). In the context of GIScience on the OOC, the scoping review observed several geovisualization techniques including Dorling cartograms, geofacets, and spatially-embedded rose charts (Zoorob 2019; Barboza and Angulski 2020; Svider et al. 2018).

Distance and proximity-based analysis

GIScience analyses concerned with distance or proximity exploit location information associated with opioid-related data to provide a variety of distance measures. These distance measures most commonly describe the distance between an opioid-related health event to the nearest treatment facility (Hyder et al. 2021; Rudolph, Young, and Havens 2017) or from an administrative unit to the nearest treatment facility (Joudrey et al. 2020; Rosenblum et al. 2011; Green et al. 2005). When possible, analyses can be improved by using road networks or traffic models that account for different timing depending on the mode of travel (e.g., public transit, personal car, or walking) (Rudolph, Young, and Havens 2017; Joudrey et al. 2020). Simpler distance calculations typically use Euclidean (straight line) or Great-Circle approaches (Kleinman 2020). Researchers commonly use centroid or mean population center to approximate location when specific origin-destination data is unavailable (Joudrey et al. 2020; C. Drake et al. 2020; Kleinman 2020; Brady et al. 2021). Distance measures are often considered in subsequent analyses, such as regression modeling, to examine what factors explain differences in distances between opioid-related health phenomenon (C. Drake et al. 2020; Amiri et al. 2018; 2020). Distance is generally interpreted as a measure of accessibility to opioid-related health services.

Closely related to distance calculations as a measure of accessibility are GIScience methodologies that consider the location of health care facilities. In the context of the OOC, the two most relevant types of facility analysis are catchment areas and location-allocation models. Catchment areas define the geographical area and local populations served by health facilities. In comparison, location-allocation analyses suggest optimal placement of health facilities within a study area based on geographic and socioeconomic characteristics. Both methodologies are fundamentally concerned with addressing spatial access to health care services (Guagliardo

2004). The present review observed the frequent use of traditional and enhanced two-step floating catchment area techniques (E/2SFCA) to generate catchment areas for and examine accessibility to facilities offering buprenorphine-waivered prescribers, opioid treatment programs, and emergency medical services (Coleman Drake et al. 2021; Cao et al. 2019; Amiri et al. 2021; Bozorgi et al. 2021). Analyses applying location-allocation techniques focused on the optimal placement of treatment services offering naloxone in both urban and rural areas (Dodson et al. 2018; Banerjee 2020). Both E/2SFCA and location-allocation techniques can be modified to consider additional covariates that may be relevant to the study setting.

Lastly, many GIScience analyses use a distance-based heuristic to determine how many phenomena occur around a location of interest. In GIScience, such determinations are usually made implicitly or explicitly via buffer analyses. Buffer analyses generate zones of a specified size around locations of interest, and these newly generated zones can be used for a variety of purposes such as counting phenomenon that fall within the buffer or analyzing the location of buffers in relation to other geometry (M. J. de Smith, Goodchild, and Longley 2021). Closely related operations that may involve a buffer include overlays (Bates et al. 2019) and spatial joins (Nesoff, Branas, and Martins 2020). For GIScience on the OOC, buffers have been used to examine the distribution of discarded needles in urban settings (Bearnot, Pearson, and Rodriguez 2018), the amount of land area disqualified for hosting syringe exchange programs (Allen et al. 2016), the population residing within different service ranges of treatment centers (Langabeer et al. 2020), among others (Moyer and Ridgeway 2020). An exemplar study combined buffer analyses and a case-control design to compare the frequency of crime around methadone maintenance treatment centers compared to other locations, finding, finding no association between crime counts and treatment centers at several buffer distances (S. J. Boyd et al. 2012). S.

J. Boyd et al. 2020 demonstrates how buffer analyses can be used to both offer a spatial measurement and complement a classic epidemiological study designs to address pertinent questions relating to the OOC.

Spatial autocorrelation and cluster analyses for areal data

Researchers have repeatedly observed that opioid-related health phenomenon do not occur randomly across space (see for example Rookey 2018; Kim, Shoff, and Yang 2021; Dworkis et al. 2017; Des Jarlais et al. 2018). Going beyond this observation requires describing spatial autocorrelation, which is the systematic spatial variation observed for a phenomenon of interest (Haining 2001). Numerous statistical approaches exist to describe spatial autocorrelation and identify groups of areas with similar values (e.g., clusters). Consistent with other reviews of spatial methods used in epidemiology, the present scoping review observed that Moran, Getis, and SaTScan statistics were the most commonly used approaches to characterize spatial autocorrelation and test for spatial clustering in opioid-related health phenomenon (Auchincloss et al. 2012). Both the Moran and Getis approaches offer global and local versions of the statistic that provide an overall measure of spatial autocorrelation or local identification of clusters, respectively. Comparatively, SaTScan uses a spatial or spatio-temporal scanning window to identify local clusters. Moran, Getis, and SaTScan approaches were most commonly applied to opioid-related mortality data (Marshall et al. 2017; Cerdá, Ransome, Keyes, Koenen, Tardiff, et al. 2013; C. W. Jones et al. 2018; Stewart et al. 2017; Cerdá, Ransome, Keyes, Koenen, Tracy, et al. 2013; Palumbo et al. 2020; Erfanian, Collins, and Grossman 2019b), with fewer instances applied to service and accessibility (Ghertner 2019; C. Drake et al. 2020; Pesarsick et al. 2019) or other measures like discarded needles (Bearnot, Pearson, and Rodriguez 2018) and prescription opioid sales (Modarai et al. 2013). In addition to applying these statistics to opioid-related health phenomenon, the Moran statistic was applied to regression residuals to test for the presence of residual spatial autocorrelation (Romeiser, Labriola, and Meliker 2019). While these statistics share commonalities and can all be applied to the same data, such as area counts of opioid overdoses, it is worth emphasizing that each of these methods addresses slightly different conceptualizations of spatial autocorrelation and methods of inference, such as whether or not the local value is included or excluded during calculations and whether analytical or permutation-based methods of inference are available (see Waller and Gotway 2004 and R. S. Bivand and Wong 2018 for a detailed comparison between cluster methodologies).

Point pattern analysis (PPA)

Point pattern analysis (PPA, sometimes referred to as point process modeling), refers to a set of techniques concerned with the exploration and modeling of spatial and spatio-temporal point data (Gatrell et al. 1996). The general objective of these methods is to understand whether the distribution of point data exhibits a random or structured pattern, with data closer than random considered clustered and farther apart than random as dispersed (Gatrell et al. 1996). Point data can be analyzed solely in terms of the intensity of event locations across space (first-order properties) as well as between groups of points at different distances (second-order properties). Researchers have commonly used kernel density estimation on point data to create heat maps that describe, for example, the intensity of opioid-related phenomenon. Examples include heatmaps of opioid overdose deaths (Liu et al. 2021), drug-related keywords associated with locations (A. Curtis et al. 2018), injection drug use around pharmacies offering different harm-reduction tools (Stopka et al. 2012), user-contributed feelings of drug craving (Epstein et al. 2014), and opioid-involved fatal traffic crashes (Rookey 2018). When investigating the relative clustering of point data, researchers often applied Ripley’s *K*-function to determine whether the opioid-related point pattern deviated from complete spatial randomness (Dworkis et al. 2018; Barboza 2020; Nesoff, Branas, and Martins 2020). An exemplar study by Barboza (2020) applied Ripley's *K*-function to heroin-related calls for medical services in Boston, finding that calls clustered independently and demonstrated further clustering around health care centers (Barboza 2020). Other point-based approaches observed in the present review include Knox and Hawkes point processes that attempt to account for space-time clustering of later events that may be triggered by a previous event (e.g., self-excitation). A modified two-step Knox text was applied to law enforcement opioid seizures and opioid-related overdoses, showing excess non-fatal overdoses were triggered in small areas after a seizure event (Mohler et al. 2021). Lastly, researchers also used PPA approaches to generate new polygonal data based on the distribution of underlying points. Examples include generating fishnet polygons from locations of fentanyl related deaths across Maryland (Alexander et al. 2016), as well as Voronoi polygons in the previously described Barboza (2020) to suggest new locations for health care centers (Barboza 2020). Given the rich application of PPA across disciplines, there exist a number of foundational (Gatrell et al. 1996) and contemporary resources (R. S. Bivand, Pebesma, and Gómez-Rubio 2013) for researchers interested in applying PPA to opioid-related health measures.

Spatial regression specifications

One of the most expansive areas of GIScience research on the OOC is the use of spatial regression specifications. Spatial regression specifications are most useful to researchers seeking to either investigate a spatialized version of a dependent or independent variable, or account for spatial autocorrelation observed in data that would violate traditional regression assumptions (Anselin 2011). The first and largest group of spatial regression specifications are spatial and spatio-temporal Bayesian models. These specifications typically incorporate spatial autocorrelation into a multilevel model via a conditionally autoregressive (CAR) random effect, wherein spatial autocorrelation is added in the variance (J Besag, York, and Mollié 1991). These models were observed frequently in studies that were investigating a range of relationships between opioid-related comorbidities and diagnoses (Sumetsky, Burke, and Mair 2019; 2020; Ponicki et al. 2018; Cerdá et al. 2020; Sumetsky et al. 2020; Castillo-Carniglia et al. 2019; Morris et al. 2019). Specific examples include examining the association between deprivation indices and drug-related admissions (Cobert et al. 2020), measures of economic stress and hospital discharges for prescription opioids (Cerdá et al. 2017), arrest rates and opioid overdose rates (Bohnert, Nandi, et al. 2011), child and partner violence in relation to opioids (Wolf et al. 2016; Morris et al. 2019; Sumetsky, Burke, and Mair 2020), among others. An exemplar study by Cerda et al. (2020) used a spatio-temporal Bayesian model to assess the relationship between PDMP implementation and changes in opioid overdose deaths, finding that the years following electronic PDMP access was associated with a 9% decrease in opioid overdose deaths (Cerdá et al. 2020). A variety of spatio-temporal Bayesian approaches exist, and researchers can look at software implementations in R for spatio- (D. Lee 2016) and spatio-temporal models (D. Lee, Rushworth, and Napier 2018), as well as accompanying detailed modeling tutorials by software authors (D. Lee 2020).

Another group of spatial regression specifications is generally associated with the field of spatial econometrics and includes foundational model types such as the spatial lag model (SLM), spatial lag of X (SLX), and spatial error model (SEM). These models introduce spatial autocorrelation into the dependent, independent, or error terms, respectively. Unlike Bayesian approaches, these models are typically single-level and parameters are reached using Maximum Likelihood estimation (Rey et al. 2011). SLM has been applied to opioid mortality (Grigoras et al. 2018; Marotta et al. 2019; Cordes 2018), heroin-related calls for service (Barboza 2020), and treatment admissions for opioid use (Wright et al. 2014), and spatial error has been used several times to account for observed autocorrelation in regression residuals (Goedel et al. 2020; Haffajee et al. 2019; Haley et al. 2019). A few studies combined SLM and SEM models to produce Spatial Durbin Models (SDM), which were used to examine the spillover effects of naloxone laws (Erfanian, Collins, and Grossman 2019b) and drug overdose mortality (Marotta et al. 2019). SLX models were used less frequently, for example, in the analysis of county-level rates of opioid prescriptions in Indiana (Wright et al. 2014). Researchers interested in these econometric approaches can refer to textbook chapters (Rey et al. 2011) and modeling tutorials (Golgher and Voss 2016). These resources explain how to use a Lagrange Multiplier test to choose between spatial specification.

The final group of spatial regression specifications present in the reviewed studies are techniques relating to geographically weighted regression (GWR). The primary purpose behind GWR is to explore how the relationship between an outcome and exposure may vary in intensity across space (Brunsdon, Fotheringham, and Charlton 1998). GWR models are interpreted in terms of both the resulting coefficient surfaces of each independent variable as well as the corresponding numeric coefficient. GWR has been extended to consider both temporal (geographical and temporal weighted regression, GTWR) and multiscale patterns (multiscale geographically weighted regression MGWR). At least one of each approach was observed in the present review. GWR was used to examine the relationship between household income on the opioid poisoning incidence rate (X. Chen et al. 2017), socioeconomic measures on fatal drug poisoning death rates (Kerry et al. 2016), and health and demographic factors on the opioid prescribing rate nationwide (Kim, Shoff, and Yang 2021). Cao et al. used a GTWR model to examine the association between drug-related tweets and adjusted rates of emergency department visits in the greater Baltimore-Maryland region (Cao et al. 2020). Lastly, Forati et al. used an MGWR approach to examine spatially varying relationships between EMS calls for services and prescription opioid distribution in relation to opioid overdose deaths at the census tract-level across Milwaukee (Forati, Ghose, and Mantsch 2021). GWR approaches are useful to researchers seeking to determine whether an opioid-related health measure under consideration is best modeled using global specifications or spatially non-stationary specifications (Brunsdon, Fotheringham, and Charlton 1998). Updated GWR modeling guides are recently available (R. Bivand 2020).

Digital epidemiology using socially sensed data

Several studies included in this review relied on opioid-related data gathered from online sources. Online data is generally gathered as user-provided volunteered geographic information (VGI) or passively collected as socially sensed data (Goodchild 2007). A similar strain of research in the health sciences is referred to as digital epidemiology (Salathé 2018). Twitter was the most frequently used source of digital epidemiological data observed in the present review (Buntain and Golbeck 2015; Cai et al. 2020; Cao et al. 2020; Sarker et al. 2019; Graves et al. 2018; Chary et al. 2017). Researchers parsed the text content of tweets to search for mentions of opioids, and then examined the relationship between the frequency of opioid-related tweets to opioid-related health outcomes. Advanced analysis of tweets involves the application of topic modeling, which attempts to segment large amounts of texts into clearly distinguishable discussion topics that may be of empirical interest to researchers (Cai et al. 2020; Cao et al. 2020; Graves et al. 2018). Other sources of digital epidemiological data include the opioid-related discussion boards of Reddit (Balsamo, Bajardi, and Panisson 2019), the streetRx online database of anonymously submitted local drug prices (Hswen, Zhang, and Brownstein 2020), and the opioid-related news aggregator DrugMap (Hswen et al. 2020). Data that does not explicitly identify user location can be searched using geoparsers and gazetteers to extract place names that can then be geocoded (Sarker et al. 2019; Hswen et al. 2020). Many of these digital epidemiological data sources require that the research team be familiar with online data collection, natural language processing, and geoparsing to convert variously structured digital information into analysis ready data. Digital data is subject to several common criticisms - lack of data consistency, validation challenges, nonrepresentative demographic composition of userbases, and changing platform policies that impact longitudinal data collection - that should be considered by substance use researchers (Hu and Wang 2020).

Geodemographic classification

A small subset of studies conducted geodemographic classification (sometimes referred to as regionalization), which uses spatially explicit classification techniques to identify groups of data with similar characteristics. Although geodemographic classification techniques were most prominently used in the United Kingdom for commercial segmentation (Singleton and Spielman 2014), scholars have since applied the techniques to public health problems to discover co-location and cluster patterns among health phenomenon of interest (Li and Chuang 2009; Lamnisos et al. 2019). In the context of the OOC, geodemographic classification techniques, specifically max-*p* regionalization, were used to identify rural communities with similar risk profiles for opioid-related overdose and infectious diseases (Kolak et al. 2020). A separate geodemographic classification study used a modified *k*-nearest neighbor approach at the county level to identify risk factors related to overdose death rates in Delaware (Wagner et al. 2019). These techniques are closely related or often directly extend from other unsupervised data classification techniques like principal components analysis (PCA), factor analysis, and *k*-clustering. Applying geodemographic classification techniques can help researchers during exploratory spatial data analysis, especially when dealing with high dimensional data (Monnat et al. 2019).

Geospatially enabled technologies

The final application area of GIScience to OOC concerns geospatially enabled technologies and how these technologies could be applied to the collection and presentation of opioid-related data. Examples of relevant geospatially enabled technologies include location sensors, video supplements to interviews, and environmental collection systems. Lai et al. used low-energy Bluetooth real-time location systems (RTLS) to investigate how naloxone kits were used once removed from emergency departments (Lai et al. 2020). Another study used time-stamped location data and randomly prompted participant responses to assess the relationship between neighborhood characteristics and drug craving (Epstein et al. 2014). A separate effort sought to enhance data collected during traditional interviews by having participants record geospatially-tracked audio and video - also known spatial video geonarratives - which allowed researchers to extract highly granular information within spaces of drug activity (A. Curtis et al. 2018). Lastly, a wastewater-based epidemiological (WBE) study conducted in a major metropolitan area of North Carolina deployed a geospatially-tracked robotic sampling device to test public wastewater for opioid metabolites (Endo et al. 2020). Substance use researchers seeking to engage with existing and emergent geospatially enabled technologies may look to interdisciplinary discussions on topics like the Internet of Things (IoT) for guidance on the variety of devices and sensors that could be applied to gather novel opioid-related data and improve public understanding of the OOC (Kamilaris and Ostermann 2018). Another geospatially enabled technology highlighted for its potential in assessing the built environment is Google Street View (GSV) imagery (Rzotkiewicz et al. 2018), although no studies using GSV were observed in the current review.

4.4 Discussion

As the 2020s progress there will be more than 20 years of scholarship available providing information on the OOC. This vast amount of evidence needs to be summarized, synthesized, and critically examined in relation to existing efforts given a lack of improvement in opioid-related health outcomes. Revisiting the evidence is especially important for methodologies that are applied across several disciplines, such as GIScience, to understand the range of research activity, guide future efforts, and avoid duplication. This study presented a systematic scoping review to investigate and provide a framework as to how GIScience has generated knowledge on the OOC from 1999 to 2021.

Researchers approaching the interdisciplinary crossroad of GIScience and the OOC must contend with a large amount of scholarly evidence. I developed a systematic search strategy that reliably identified relevant articles from leading electronic academic repositories. Bibliometric findings indicate that GIScience on the OOC follows broader trends observed in GIScience publishing. Biljecki conducted a scientometric analysis of 20 select English-language GIScience journals from 2000 to 2014 and demonstrated that publication output had more than doubled over the study period (Biljecki 2016). The current scoping review observed a similar dramatic increase in GIScience publishing on the OOC, with few publications before 2005 compared to repeated instances of more than 30 publications per year after 2015. This average growth rate exceeds 20% and, if continued unabated, we could expect GIScience publications on the OOC to exceed 100 publications per year by the late 2020s. The growth in GIScience literature on the OOC presents an important opportunity for GIScientists to develop analysis workflows that allow for continued innovation while also meeting the fundamental epidemiological objectives of describing spatial heterogeneity in health data (Eberth et al. 2021). In particular, there remains ample room for GIScientists to contribute to recent advances in theories on health sciences such as health inequalities, place-based analyses, environmental exposure, health care provision and utilization, and community well-being.

In regard to previous reviews, the current scoping review observed a far greater number of relevant publications compared to a thematically similar review by Wangia and Shireman (Wangia and Shireman 2013). However, the greater number of relevant publications observed here is at least partially explained by the timing of their review (e.g., 2013) and focus solely on only prescription opioids (Wangia and Shireman 2013). Whereas Wangia and Shireman observed that “formal statistical modeling capitalizing on geospatial techniques was rare”, the current research observes an abundance of applied spatial regression techniques to opioid-related measures (Wangia and Shireman 2013). A likely reason for this difference in results may be the omission of terms like ‘spatial’ and ‘spatio-temporal’ in Wangia and Shireman’s search strategy, whereas these phrases were included in the present search strategy. Moreover, the systematic search strategy presented here is amenable to more specific GIScience methodologies or opioid-related measures for future literature reviews. Article metadata provided by specific repositories like WoS allows for further scientometric and bibliometric analyses relating to research impact, authorship networks, and knowledge mapping (C. Chen, Ibekwe-SanJuan, and Hou 2010).

While the amount of GIScience scholarship on the OOC is extensive, trends in specific methodologies, study scales, and units of analysis have been unavailable. These study characteristics are important as they shape the strength and granularity of evidence provided. To understand extant trends in GIScience on the OOC, the current scoping review provided a tabulation and examination of these crucial study characteristics. Although the methods adopted by researchers working on OOC topics can incorporate space-time and confounding factors, important issues around the presentation of area-level disease estimates, such as how spatial variation in a phenomenon may be more closely related to spatial variation in small sample sizes, are generally unaddressed (Gelman and Price 1999). Concerns around cluster analyses have been raised on both epistemological, such as what constitutes a cluster (Lessler et al. 2017), and methodological grounds, addressing technical issues with popular software implementations of cluster methodologies (R. S. Bivand and Wong 2018; Sauer et al. 2021). Across methodologies there exists a common need to improve the spatial resolution of the underlying data and move beyond purely ecological study designs. Coarse spatial resolution is at risk of spatial misclassification, which may alter the measurements under analysis (Duncan et al. 2014). Additionally, scholars at the intersection of GIScience and epidemiology have noted for some time the opportunity to adapt existing epidemiological designs for use with exposure-outcome relationships that are plausibly experienced across space (Elliott and Wartenberg 2004). Study designs like case-control and case-cohort are well-suited to GIScience techniques, yet these designs were observed infrequently in the present scoping review. Future research could look to the work of Cerda et al., Boyd et al., and Pesarsick et al. as exemplars (Cerdá, Ransome, Keyes, Koenen, Tardiff, et al. 2013; S. J. Boyd et al. 2012; Pesarsick et al. 2019). Further opportunities to improve GIScience scholarship on the OOC could be found in the increasing availability of open geospatial data (J. G. Lee and Kang 2015), especially for opioid-related health measures available at sub-county metropolitan scales. Such opportunities dovetail with broader pushes for open and reproducible science, especially within the discipline of Geography (Goodchild et al. 2020). Addressing these concerns will demonstrate the utility of GIScience for geographic questions of the OOC and related fields like spatial epidemiology more broadly.

A separate contribution of the present scoping review describes the location of available GIScience evidence on the OOC. More than half (58.4%) of the GIScience studies included in the present scoping review were conducted at sub-national scales yet mapping the location of these studies revealed geographic disparities in terms of what areas comprise the evidence. The North Mountain and West North Central States, as well as the Louisiana-Mississippi area of the South, have extremely limited or entirely lacking sub-state studies using GIScience on opioid-related measures. To determine what might explain these geographic differences, the rank-order of the number of GIScience studies on the OOC were compared to several common opioid-related health outcomes for each state (Table 11). Understandably, states with the highest number of GIScience studies on the OOC tend to have the worst health outcomes, likely reflecting a reaction to pressing public health needs in places like New York, Pennsylvania, and Ohio. However, many states with the least amount of GIScience studies on the OOC also ranked highly for drug overdose death rates (e.g., Nevada, Alaska, Idaho) and opioid prescribing (e.g., Mississippi, Kansas, Idaho). Going beyond a needs-based explanation, literature on health disparities points to several complex and intersecting reasons that may also explain the observed locational disparity in study availability. These reasons are often centered around rural health disparities, wherein populations located in rural areas generally rank lower on population health behaviors, have more difficulty accessing primary care, and receive less financing towards the health care system (Hartley 2011). Rural health disparities are also a focus for several studies of the OOC, from geographic heterogeneity in opioid-related mortality (Rigg, Monnat, and Chavez

2018) to rural-urban differences in prescription opioid use (Keyes et al. 2014). Mapping the location of GIScience studies on the OOC may reflect an additional consequence of rural health disparities wherein the lack of existing research attention stymies future research efforts. A final and important consideration of the locational disparity in study availability is the impact on rural populations, more specifically Indigenous Peoples of North America. This is especially important as many rural states, and states identified as lacking GIScience studies, contain some of the largest Indigenous populations within the US. Indigenous populations have also experienced the OOC and, in places like Minnesota, are the population group with the highest rate of opioid-related overdose (Minnesota Department of Human Services, n.d.) and receive treatment for opioid use disorder at very high rates (T. Boyd et al. 2021). The lack of GIScience evidence available towards the OOC in presents a clear opportunity for future researchers that can be strengthened by developing partnerships with Indigenous Peoples and scholars (Stanley et al. 2020).

Table 11. Rank-order comparison of opioid-related health measures to the number of GIScience studies on the OOC at the state-level. Ranks range from 1 (lowest) to 50 (highest). A rank may appear more than once due to a tie between states.

State	**GIScience studies on the OOC**	**Drug overdose death rate**[a]	**Opioid prescribing**[b]	**Facility operation**[c]
States with the lowest number of GIScience studies on the OOC				
Alaska	1	21	9	9
Hawaii	1	11	1	19
Idaho	1	12	34	14
Kansas	1	7	41	20
Minnesota	1	10	3	34
Mississippi	1	8	43	11
Montana	1	6	26	8
Nevada	1	24	28	10
North Dakota	1	3	8	7
Wyoming	1	8	29	4
States with the highest number of GIScience studies on the OOC				
Massachusetts	9	39	5	37
Virginia	9	17	14	26
North Carolina	10	29	35	43
West Virginia	11	47	39	12
Maryland	12	41	16	36
Kentucky	13	43	44	39
California	14	6	2	49
Ohio	15	46	31	44
Pennsylvania	15	45	25	45
New York	16	19	4	48

a: Data from the CDC Annual Surveillance Report of Drug-Related Risks and Outcomes, 2019, Figure 2D: Age-adjusted rates per 100,000 population of drug overdose deaths by state. https://www.cdc.gov/drugoverdose/pdf/pubs/2019-cdc-drug-surveillance-report.pdf

b: Data from CDC U.S. State Opioid Dispensing Rate per 100 Maps. https://www.cdc.gov/drugoverdose/rxrate-maps/state2019.html

c: Data from the SAMHSA N-SSATS Report, 2019, Table 6.4a, Number of Treatment Facilities Operational in each state.

By considering the extent and scope of research on GIScience and the OOC, the present review identifies at least four key gaps in the existing literature that can be addressed in future research efforts. Firstly, there is a notable absence of research applying or developing machine learning (ML) techniques to geographic questions of the OOC. The primary instances of ML techniques observed were unsupervised topic modeling applied to social media data to discover patterns in drug-related tweets. There exists immense opportunity to apply ML techniques to non-text data of the OOC, especially in the context of population health (Mhasawade, Zhao, and Chunara 2021). For example, ML techniques could be applied to forecast area-level opioid-related health measures at different geographic scales, which could be useful for health planning and resource allocation. In addition, GIScientists have begun to incorporate space and time into ML algorithms to improve the geographical prediction of drug-related hotspots, which should be translatable for drug-related health outcomes (Xia, Stewart, and Fan 2021).

Secondly, current GIScience approaches to the OOC rely largely on coarse data available at the state- or county-level. While the use of such coarse data is often a result of the need to protect individual privacy, studies commonly note the issue of the ecological fallacy and inability to make causal claims (Marotta et al. 2019; Ponicki et al. 2018; Cordes 2018). In the absence of access to microdata, future GIScience efforts should prioritize study design and data collection efforts specifically at higher resolution units (e.g., ZIP Code, Census Tract, Census Block, or Point) or, borrowing from related disciplines of Small Area Estimation and Remote Sensing, explore the potential of downscaling data. Such efforts would increase the amount of data available to researchers, increase the strength of claims made between exposures and outcomes, and provide new scales of comparison to address concerns over issues like the modifiable area unit problem (MAUP) (Duncan et al. 2014).

Third, the present review identified several areas of GIScience research that may be suitable for full systematic reviews. These include spatio- and spatio-temporal Bayesian models, cluster analyses, and distance-based analyses of the OOC. These reviews will be strengthened if the included studies can be situated in the same geographic area, which is already be possible for areas with a large amount of GIScience research such as New York, Ohio, and California. A particular novelty for systematic reviews of GIScience could be both numeric and locational synthesis of evidence. These types of comparisons would examine whether clusters or areas of differential risk appear in the same geographic units across studies. Companion to these systematic reviews could be the development of digital evidence synthesis platforms wherein the spatial results of several studies are mapped simultaneously in a dashboard to allow for interactive evidence comparison in real-time.

Fourth and lastly, few studies in the review used GIScience to analyze the synthetic opioid fentanyl (n=3) (Alexander et al. 2016; Nesoff, Branas, and Martins 2020; Mohler et al. 2021). Recent increases in overall opioid-related mortality have been driven by synthetic opioid overdose deaths (Mattson et al. 2021a), and additional research suggests an influx of illicit fentanyl into the domestic drug supply sometime in the early 2010s (Zoorob 2019). Exactly how and why fentanyl has entered the US drug landscape remains a pressing public health and national security question (Daniel Ciccarone 2017). This review demonstrates that there is a paucity of GIScience studies offering evidence on illicit fentanyl-related measures. Given a lack of nationwide data due to nonstandard fentanyl testing, future GIScience studies of the OOC are most likely to succeed via local partnerships that can obtain high-quality, high-resolution health data with accompanying location information (Z. Dezman et al. 2020). GIScience methodologies like descriptive mapping, origin-destination modeling, and cluster analyses can provide basic yet important information on the geographic characteristics of illicit fentanyl-related measures.

4.4.1 Limitations

This scoping review may be subject to the commonly reported issue of omitting relevant studies (Pham et al. 2014). Four leading academic databases – WoS, PubMed, IEEE Xplore, and ACM Digital Library – were searched to retrieve potentially relevant studies, although searching additional databases may have revealed relevant studies. For example, the original scoping review protocol suggested the inclusion of GEOBASE, which is a recently developed repository for publications in the field of geosciences ("GEOBASE | Geoscience Literature Research Database" n.d.). GEOBASE was ultimately not included in the search strategy as it has significant overlap with Web of Science – a journal overlap analysis from 2020 indicated that 34% of titles included in GEOBASE were also indexed in Web of Science (Kimball 2020) and it leans more to earth science, geology, and physical geography. Unlike a systematic review, scoping reviews are not meant to provide an exhaustive accounting of the literature (Tricco, Lillie, Zarin, O, et al. 2018). Providing an exhaustive account for GIScience is especially challenging given the use of GIScience across multiple disciplines. The results of the present scoping review should be interpreted through August of 2021. Given observed increases in publication output for GIScience on the OOC, and GIScience more broadly (Biljecki 2016), I expect a large number of relevant studies to be published through the 2020s. An updated review later in the 2020s would provide a useful point of comparison and help to continue to track the use of GIScience in the OOC.

Another possible limitation of the present scoping review relates to the fact that one researcher conducted the data extraction and coding, preventing the calculation of commonly used inter-rater reliability metrics such as Cohen's Kappa statistic (McHugh 2012). The potential consequence of a single data extractor is inaccurate data extraction, which may have a downstream impact on the tabulation of study characteristics. To avoid these problems and researcher fatigue, as well as promote accurate data extraction, I created and followed a data extraction schedule to spread the task over an extended period of time (Rousson, Gasser, and Seifert 2002). In addition, the present scoping review focused on extracting discrete features of each study (e.g., study setting, units of analysis, statistical methods) that limited the need to infer underlying details.

The review does not provide a systematic comparison of evidence offered by included studies. Quality appraisals are not an objective of scoping reviews as outlined by the PRISMA-ScR (Tricco, Lillie, Zarin, O, et al. 2018), and different authors have both praised (Njelesani, Couto, and Cameron 2011) and criticized (Feehan et al. 2011) this commonly noted characteristic of scoping review methodology (Pham et al. 2014). Future reviews of GIScience studies on the OOC could adapt the strategy presented here to target specific geographies and methodologies compatible with a systematic review. One example could be a systematic review on the use of spatio- and spatio-temporal Bayesian models for opioid-related health measures.

4.5 Conclusions

This research sought to summarize the expanding literature on geographic information science (GIScience) and the ongoing United States Opioid Overdose Crisis (OOC). A systematic scoping review framework was applied to leading academic research repositories and successfully retrieved more than two-hundred thirty peer-reviewed publications that applied GIScience to questions of the OOC. This review demonstrates a rapid increase in GIScience publishing on the OOC, especially since the late 2010s. Additionally, this review identifies eight core GIScience methodologies applied to questions of the OOC, citing exemplar studies. This review found geographic disparities in terms of where GIScience research on the OOC occurs, namely that few studies were in rural states of the North Mountain and West North Central regions. I also highlight four important avenues for future research, specifically the application of machine learning techniques, analyses at geographic units below the county-level, the execution of systemic reviews in specific sub-domains of GIScience research on the OOC, and the application of GIScience to questions regarding fentanyl. Given the range of the OOC across opioid types, fatal and nonfatal health measures, and complex geographies of the United States, future reviews will need to contend with enduring questions of managing depth versus breadth. Yet the challenge of numerous methodologies, study designs, and units of analysis should not act as an excuse to preclude future reviews. Reviews remain an essential tool to provide clear, digestible summaries the evidence available on a given topic and capabilities of a technology-driven discipline like GIScience. Having accessible summaries of the evidence and tools available to anticipate public health needs should the US OOC develop in another setting.

Chapter 5: Conclusions and future work

5.1 Review of dissertation

The US OOC continues to worsen in the early years of the 2020s. Opioid-related deaths and nonfatal treatment admissions have increased. Opioid prescribing, although declining, remains exceptionally high compared to similar countries. This dissertation combined two rigorous academic frameworks from geography, health geography and GIScience, to provide interdisciplinary evidence addressing pertinent research questions of the ongoing crisis. Health geography provided the outcome-exposure disease model that was the conceptual focus of Chapters 2 and 3, and GIScience motivated a systematic collection of evidence that was critically reviewed in Chapter 4. Underlying these chapters is an immense amount of data describing different facets of the US OOC. These data include electronic health records from urban emergency departments in one of the largest metropolitan areas of the US, prescription opioid distribution records from a nationwide monitoring program, and a novel collection of scientific articles that apply GIScience to opioid-related health measures.

The first study of the dissertation (Chapter 2) examined more than 8,000 electronic health records for emergency department visits involving heroin-, cocaine-, or methadone-related at four emergency departments in the greater Baltimore-Maryland region. This study calculated ZCTA-level SMR for several opioid-related health outcomes. Exploratory spatial data analysis revealed changes over time in the spatial autocorrelation for both univariate and bivariate SMR for the opioid-related health outcomes, and spatio-temporal models produced unique spatial risk surfaces for each drug-related health outcome. The spatial risk surfaces were posterior median risk and posterior exceedance probabilities, the latter of which, to the best of my knowledge, have not previously been generated for drug-related health outcomes. Covariates included in the spatio-temporal models were also evaluated to identify what area-level factors were associated with a higher or lower risk of drug-related health outcomes. Areas with a higher score in a multivariate deprivation index and areas adjacent to the sampling hospitals had an elevated risk of presenting with drug-related health problems to the sampled ED. For example, a one standard deviation change in the deprivation index increased risk 45% (credible interval, CI, 18-79%) for total heroin visits. Conversely, covariates relating to the propensity for a drug issue in an area, which are routinely used in the literature, showed no association with the drug-related outcomes.

The second study of the dissertation (Chapter 3) made use of a newly released portion of data from ARCOS. This release provided unprecedented access to exhaustive prescription opioid distribution records across the US. ARCOS records were transformed to create standardized measures of area-level prescription opioid exposure, specifically per capita MME. A conceptual model of prescription opioid risk - wherein a greater availability of prescription opioids leads to a greater opportunity for diversion and abuse - guided the modeling procedure. I estimated the county-level relationship between area-level prescription opioid exposure and nonfatal treatment admissions involving a prescription opioid using both the nationwide SAMHSA TEDS-A dataset as well as a comprehensive statewide dataset from the University of Washington ADAI. Results from nonspatial and spatial lag of X models indicated that conservative increases in per capita MME were associated with a 5% to 7% increase in nonfatal treatment admissions involving a prescription opioid, depending on the year, even after accounting for numerous socioeconomic factors and state-level differences. A similar effect was observed for the spatial lag of per capita MME, providing evidence that treatment admissions in a county are impacted by the neighboring prescription opioid supply. Results were consistent when using nationwide and statewide data.

The third and final study of the dissertation (Chapter 4) implemented a systematic scoping literature review. Peer-reviewed studies using GIScience to address questions of the US OOC since 1999 were gathered. Review studies are increasingly important and prevalent given massive increases in scholarly publishing. In total, 231 articles were included in the review. I extracted data on the study objectives, design, geographic unit of analysis, geographic method, core findings, limitations, and more from each study. The review found that the majority of GIScience evidence on the US opioid crisis was produced after 2015 and the rate of publishing has continued to increase year-over-year. Most GIScience analyses use an ecological study design at the state- or county-level, highlighting a need to both expand the types of study designs used and make use of higher resolution spatial data. In addition, mapping the sub-national location of studies indicated a lack of research in the North Mountain, West North Central, and Southern areas like Louisiana and Mississippi. The systematic scoping review framework presented in Chapter 4 is flexible for future reviews that may want to focus on a specific opioid of interest or GIScience methodology.

As with all research there are certain limitations worth noting. Extended discussions of the limitations of each Chapter are described in Sections 2.4.1, 3.4.1, and 4.4.1. All Chapters can be related to the to the broadly applicable issue of the ecological fallacy. The ecological fallacy is when a population-level trend is inappropriately assumed to be true for every individual in the population. Both Chapters 2 and 3 are empirically subject to the ecological fallacy in that the associations observed across areal units may not hold for everyone in each areal unit. In Chapter 2, for example, the area-level factors associated with higher risk of presenting to an emergency department (e.g., deprivation index, adjacency to hospitals, and CMS claims) may not have been the specific risk factors prompting a drug-related ED visit each individual residing in an area.

Similarly, the observed association in Chapter 3 between excess opioid prescribing and treatment admissions was estimated at county-level, which indicates a population-level effect but not necessarily the individual reasons for entering treatment. Chapter 4 noted that numerous studies describe challenges with the ecological fallacy and caveat results with statements about the inability to make individual-level claims. While cautions around the ecological fallacy are valid, there exist numerous reasons where ecological design may be desirable, such as monitoring population-level health measures for public health planning, or when it is the only design feasible, such as with scarce health measures that must be aggregated for statistical analysis. Adaptation of ecological data to mixed designs involving case-control, cohort, and matching designs can help strengthen future GIScience studies evaluating opioid-related health measures.

5.2 Significant contributions

The present dissertation offers several significant contributions at the intersection of health geography and GIScience for the US OOC. Each significant contribution is expanded upon to draw out the implications for the broader scientific study of opioid-related health measures.

Significant Contribution 1: Chapter 2 investigated spatio-temporal patterns of emergency department visits for several drug-related health outcomes in the greater Baltimore metropolitan area from 2016 to 2019. Several ZCTA-level covariates were found to be associated with an elevated risk of heroin-, methadone- and cocaine-involved ED visits, specifically a multidimensional deprivation index, ZCTA adjacency to a sample ED, and the total share of CMS claims. In particular, the deprivation index is a useful composite measure of socioeconomic status that can reduce model dimensionality in future studies. Null results for other ZCTA-level covariates used in modeling literature - such as a measure of rural-urban classification, propensity for drug issues in an area, and the number of SAMHSA-listed treatment facilities - provides complicated but important counterevidence that speaks to the potential sensitivity of such measures depending on the study location and unit of analysis. Lastly, the unique risk spatial risk surfaces estimated for each drug-related health outcome should also be used as evidence of the importance of modeling drug outcomes separately in future research.

Significant Contribution 2: An additional contribution of Chapter 2 was to demonstrate the versatility and viability of a recently proposed spatio-temporal Bayesian model originally developed for an environmental outcome-exposure disease relationship (Rushworth, Lee, and Mitchell 2014). Using a limited number of sample emergency departments, Chapter 2 produced area-level estimates of the standardized morbidity ratio for heroin-, methadone- and cocaine-involved ED visits across numerous sex and age demographic strata. Type III error analysis indicated that model estimates were consistent in direction in 99.4% of ZCTA for total heroin-related ED visits, 93.4% of ZCTA for total cocaine-related visits, and 96.5% of ZCTA for total methadone-related visits. This chapter demonstrates the utility of the spatio-temporal Bayesian model even in data constrained scenarios.

Significant Contribution 3: Chapter 3 leveraged a special, one-time release of the DEA ARCOS dataset that includes complete distribution records for prescription opioids across the US from 2006 to 2014. Shipment records were converted to a standardized area-level measure of prescription opioid exposure, per capita morphine milligram equivalents, which was previously unavailable to researchers using public ARCOS data. Geofacet visualization identified several states with elevated levels of prescription opioid exposure not often discussed in the literature (Delaware, Nevada, Tennessee, Oklahoma, South Carolina). Getis-Ord G_i^* analysis identified a large, multistate cluster of elevated opioid prescribing in Appalachia that shifted southward over time. These descriptive and inferential analyses provide a detailed characterization of the space-time patterns in prescription opioid distribution across the US for nearly 10 years of the OOC.

Significant Contribution 4: The nonspatial and spatial lag of X models deployed in Chapter 3 estimated the county-level relationship between per capita MME and nonfatal treatment admissions. These novel estimates indicated a strong, positive relationship between prescription opioid exposure and a directly relevant health outcome that persisted after accounting for numerous socioeconomic, demographic, and state-level factors. Associations demonstrated a similar strength and direction in an external validity analysis using a comprehensive statewide dataset. The models also demonstrated evidence of the neighboring effects of prescription opioid exposure on local treatment admissions. This effect can be interpreted as further evidence for the theory that large supplies of prescription opioids may translate into additional opportunities for diversion and inappropriate use, ultimately resulting in a greater number of treatment admissions.

Significant Contribution 5: The third and final study (Chapter 4) developed a systematic review strategy to gather the available evidence of GIScience applied to opioid-related health measures in the US OOC. Examination as to where the evidence was situated across the US revealed clear locational research inequalities, with some states having an abundance of GIScience studies (e.g., New York, Pennsylvania, Ohio, Maryland, Kentucky, and California) and other states entirely lacking (e.g., Minnesota, North Dakota, Montana, Idaho, Wyoming, Nevada, among others). State-level opioid-related health measures like mortality, prescribing, and treatment capacity did not clearly explain why some states had more studies than others, and I argue that locational research gaps are more likely attributable to a lack of research resources for rural areas. These research gaps likely exacerbate health inequalities among historically disenfranchised populations, particularly Indigenous Peoples and rural populations.

Significant Contribution 6: Examination of methodologies and units of analysis present in studies using GIScience revealed both changes and consistencies in evidence generated over the past 20 years. While descriptive mapping is the most used methodology, studies are increasingly using spatio- and spatio-temporal modeling techniques to identify factors associated with opioid-related health outcomes and exposures. However, the most common unit of analysis for these methodologies is the state- and county-level, which is a coarse unit of analysis. Taken together these trends indicate a clear need to move beyond purely ecological study designs in future research. Overall, the review provides an accounting of the GIScience evidence available on the OOC and identifies several gaps that can be addressed by future researchers.

5.3 Future work

As the US opioid crisis continues unabated there are several open questions for future researchers. Important in the pursuit of future research is balancing between immediate public health needs and larger gaps in the body of evidence. The following paragraphs expand upon possibilities for future research noted in each chapter.

Chapter 1 addressed the opioid-related health outcomes of heroin-, cocaine-, and methadone-involved ED visits. Absent from these outcomes are illicit fentanyl-involved ED visits, which have since been identified as common and frequently missed in ED patients (Z. D. W. Dezman et al. 2020). This outcome was not considered in Chapter 1 as data on fentanyl-involved ED visits was only available for 2019, but future studies of the EDDS data could apply the modeling strategy to generate disease risk surfaces for other drug-related health outcomes, some of which may also suffer from small area issues. In addition, polydrug outcomes have been a longstanding research interest in terms of both individuals purposefully using multiple substances or unknowingly consuming mixed substances (Leri, Bruneau, and Stewart 2003; Mars, Ondocsin, and Ciccarone 2018). Polydrug combinations can be identified in Chapter 1 data, although, as previously discussed, researchers should recognize that disease risk surfaces may be unique to each substance of interest and grouping multiple drugs together could obfuscate interpretation.

The wealth of information contained in the ARCOS data featured in Chapter 2 opens several pathways for future research. For example, information on local prescription opioid availability could be linked to other opioid-related health outcome data, especially mortality data on heroin and illicit fentanyl. This data linkage would be most useful to further explore the pathway from prescription opioids to other substances (Mars et al. 2014; Evans, Lieber, and Power 2019), and future analyses could examine the relationship between high prescription opioid exposure and excess heroin-related mortality using temporally lagged data. From a geospatial perspective, location information on recipient health facilities could enable analysis of the ARCOS data as a marked point process. Considering ARCOS data as points would also enable aggregation to higher spatial resolutions such as census blocks, tracts, and ZIP Codes.

Lastly, a main research question of Chapter 3 was identifying research gaps in GIScience research on the US opioid crisis. Beyond those identified in the chapter - namely developing and applying machine learning techniques, using higher resolution spatial data, undertaking systematic reviews, applying GIScience methodologies to fentanyl-related health measures - there are several additional avenues for future research. Firstly, the amount of actual text contained in the articles retrieved by the scoping review is well-suited to exploratory topic modeling (Blei and Lafferty 2007). Topic modeling could reveal additional patterns in the gathered evidence or offer a point of comparison to the manually extracted data. Topic modeling's primary application area has been on mining patterns from text data that is too large to manually process, and this application will be especially important as the body of scientific literature continues to grow. Secondly, future research seeking to synthesize GIScience evidence could construct interactive data platforms that would allow for seamless comparison of spatial results across studies. This hypothetical data platform would allow users to visually inspect spatial results situated in similar locations and help to centralize research findings for policymakers and planners. Such platforms have been identified as important in terms of dissemination research findings, engaging in integrated knowledge translation, and promoting open science practices (Pike et al. 2017; Huston, Edge, and Bernier 2019).

5.4 Concluding remarks

In conclusion, this dissertation advances how geographical sciences can be applied to a complex, multi-decade health issue. While robust in its own right, GIScience excels when paired with related concepts and sub-disciplines, such as the outcome-exposure disease model of health geography. As demonstrated in this dissertation, GIScience methodologies can model nonfatal opioid-related outcomes in data constrained scenarios, opioid-related exposures in nationwide monitoring systems, and reveal what type of evidence is needed to advance population health for opioid-related measures. The findings offered across these chapters can be used by health system managers interested in enhancing the delivery of emergency department care at metropolitan scales (Chapter 2). In addition, policymakers seeking to ebb the flow of prescription opioids now have updated, granular evidence on the baseline association between prescription opioid availability and negative opioid related-health outcomes (Chapter 3). Lastly, future researchers should prepare for a need to synthetize an ever-growing body of evidence, which may require the development of new methodologies to compare results across disparate locations and measures (Chapter 4). GIScience can be used to enable a more rapid deployment of solutions targeting overdose prevention, predict where elevated levels of substance use or related health risks may emerge, as well as help identify areas in need of assistance for treatment initiation and retention. The United States Opioid Overdose Crisis is the current chapter of a longer history wherein humans interact with substances to manage complex and often immeasurable pain. Researchers cannot not forget this pain, and empathy towards individuals who are suffering from pain must ground future scholarship.

Appendices

Appendix A

Coefficient estimates and 95% confidence interval for nonspatial Poisson models used to estimate the SMR of ED visits for a heroin-involved health issue in four ED of the UMMS health system, 2016 to 2019.

Model. Coefficient value and 95% confidence interval (CI).

Covariate	**Total**	**Male**	**Female**	**Age 25-34**	**Age 35-44**	**Age 45-54**	**Age 55-64**
Race (% white)	0.90 (0.71-1.13)	0.65 (0.49-0.86)	1.70 (1.09-2.64)	5.08 (3.03-8.54)	2.01 (1.09-3.7)	0.48 (0.30-0.76)	0.19 (0.11-0.33)
CMS Total Share	1.59 (1.55-1.63)	1.60 (1.56-1.65)	1.58 (1.51-1.65)	1.53 (1.46-1.6)	1.51 (1.42-1.6)	1.60 (1.52-1.68)	1.58 (1.49-1.67)
ZCTA neighboring hospital location	2.35 (2.13-2.62)	2.25 (2.00-2.54)	2.49 (2.07-2.99)	2.48 (2.01-3.07)	2.55 (1.96-3.32)	1.75 (1.43-2.14)	2.81 (2.26-3.5)
RUCA Classification	0.93 (0.87-1.01)	0.95 (0.86-1.05)	0.9 (0.78-1.05)	0.99 (0.88-1.12)	1.05 (0.91-1.21)	0.80 (0.61-1.04)	0.96 (0.77-1.19)
Opioid Prescribing rate	1.02 (1.01-1.03)	1.02 (1.01-1.03)	1.02 (1.00-1.04)	1.00 (0.98-1.02)	1.02 (0.99-1.04)	1.02 (1.00-1.04)	1.05 (1.03-1.07)
Number of SAMHSA-listed treatment facilities	1.02 (1.01-1.02)	1.02 (1.02-1.02)	1.02 (1.01-1.02)	1.01 (1.00-1.01)	1.02 (1.02-1.02)	1.02 (1.02-1.03)	1.02 (1.02-1.02)
Deprivation index	1.76 (1.65-1.86)	1.69 (1.57-1.82)	1.93 (1.72-2.16)	1.26 (1.09-1.46)	1.79 (1.53-2.1)	2.18 (1.95-2.45)	1.78 (1.56-2.02)
WAIC: Null model (no adjustment variables)	13585	9864	4642	3652	2490	4561	3897
WAIC: Covariate model (adjustment variables)	3758	2974	1725	1699	1220	1390	1215

Appendix B

Coefficient estimates and 95% confidence interval for nonspatial Poisson models used to estimate the SMR of ED visits for a cocaine-involved health issue in four ED of the UMMS health system, 2016 to 2019.

Model. Coefficient value and 95% confidence interval (CI).

Covariate	**Total**	**Male**	**Female**	**Age 25-34**	**Age 35-44**	**Age 45-54**	**Age 55-64**
Race (% white)	0.98 (0.69-1.39)	0.81 (0.53-1.24)	1.29 (0.70-2.37)	5.00 (2.27-11.03)	2.39 (1.11-5.15)	0.40 (0.19-0.74)	0.26 (0.11-0.60)
CMS Total Share	1.54 (1.49-1.60)	1.55 (1.48-1.62)	1.54 (1.45-1.64)	1.54 (1.43-1.65)	1.50 (1.39-1.63)	1.49 (1.38-1.60)	1.58 (1.44-1.74)
ZCTA neighboring hospital location	2.37 (2.05-2.75)	2.12 (1.77-2.55)	2.84 (2.20-3.68)	2.18 (1.58-3.01)	2.86 (2.06-3.99)	2.14 (1.63-2.90)	2.31 (1.62-3.28)
RUCA Classification	0.88 (0.76-1.01)	0.85 (0.69-1.03)	0.93 (0.76-1.15)	1.03 (0.87-1.22)	0.77 (0.51-1.17)	0.52 (0.28-0.98)	0.88 (0.57-1.36)
Opioid Prescribing rate	1.04 (1.02-1.05)	1.04 (1.02-1.05)	1.04 (1.01-1.06)	1.02 (0.99-1.05)	1.04 (1.01-1.07)	1.04 (1.02-1.07)	1.06 (1.03-1.09)
Number of SAMHSA-listed treatment facilities	1.02 (1.02-1.02)	1.02 (1.02-1.02)	1.02 (1.01-1.02)	1.02 (1.01-1.02)	1.02 (1.01-1.02)	1.02 (1.02-1.03)	1.02 (1.02-1.03)
Deprivation index	2.06 (1.89-2.25)	1.95 (1.75-2.17)	2.25 (1.93-2.63)	1.61 (1.30-2.00)	2.47 (2.04-2.99)	2.21 (1.89-2.57)	2.02 (1.64-2.48)
WAIC: Null model (no adjustment variables)	7206	4904	2859	1786	1783	2750	1767
WAIC: Covariate model (adjustment variables)	2104	1643	1028	901	773	950	640

Appendix C

Coefficient estimates and 95% confidence interval for nonspatial Poisson models used to estimate the SMR of ED visits for a methadone-involved health issue in four ED of the UMMS health system, 2016 to 2019.

	Model. Coefficient value and 95% confidence interval (CI).						
Covariate	**Total**	**Male**	**Female**	**Age 25-34**	**Age 35-44**	**Age 45-54**	**Age 55-64**
Race (% white)	0.85 (0.5-1.44)	0.75 (0.37-1.51)	0.94 (0.42-2.1)	4.91 (1.44-16.76)	2.26 (0.83-6.16)	0.12 (0.04-0.33)	0.61 (0.2-1.88)
CMS Total Share	1.60 (1.52-1.69)	1.62 (1.51-1.74)	1.59 (1.46-1.72)	1.63 (1.47-1.81)	1.63 (1.46-1.81)	1.57 (1.39-1.77)	1.57 (1.39-1.78)
ZCTA neighboring hospital location	2.48 (2-3.08)	2.36 (1.76-3.15)	2.62 (1.89-3.63)	1.43 (0.86-2.38)	2.51 (1.64-3.86)	3.22 (2.10-4.94)	2.33 (1.44-3.77)
RUCA Classification	0.80 (0.6-1.07)	0.81 (0.56-1.18)	0.78 (0.49-1.25)	0.81 (0.5-1.32)	0.83 (0.49-1.39)	0.75 (0.3-1.85)	0.67 (0.29-1.58)
Opioid Prescribing rate	1.06 (1.04-1.07)	1.05 (1.02-1.07)	1.07 (1.04-1.09)	1.01 (0.96-1.07)	1.09 (1.06-1.12)	1.07 (1.04-1.1)	1.03 (0.97-1.08)
Number of SAMHSA-listed treatment facilities	1.02 (1.02-1.02)	1.02 (1.01-1.02)	1.02 (1.02-1.02)	1.01 (1.01-1.02)	1.02 (1.02-1.03)	1.02 (1.02-1.03)	1.02 (1.02-1.03)
Deprivation index	2.15 (1.88-2.45)	2.12 (1.78-2.53)	2.18 (1.79-2.66)	1.72 (1.22-2.43)	2.79 (2.16-3.59)	1.77 (1.4-2.25)	2.29 (1.74-3.02)
WAIC: Null model (no adjustment variables)	3711	2213	1841	806	1127	1358	1030
WAIC: Covariate model (adjustment variables)	1178	841	692	493	490	520	454

Appendix D

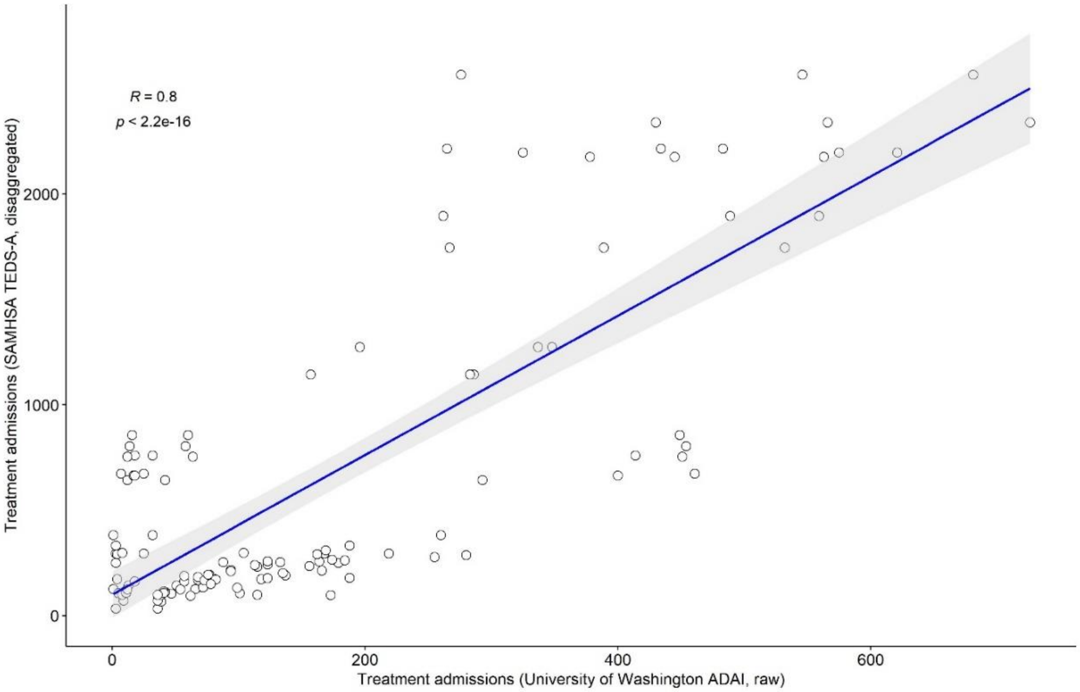
Global Moran's *I* value among residuals of nonspatial covariate Poisson models fit for drug-demographic stratum.

Drug-related ED Visit	**Total**	**Male**	**Female**	**25-34**	**35-44**	**45-54**	**55-64**
Heroin	0.367	0.325	0.206	0.189	0.103	0.245	0.198
Cocaine	0.289	0.253	0.127	0.057	0.101	0.209	0.137
Methadone	0.190	0.123	0.128	0.084	0.025	0.101	0.046

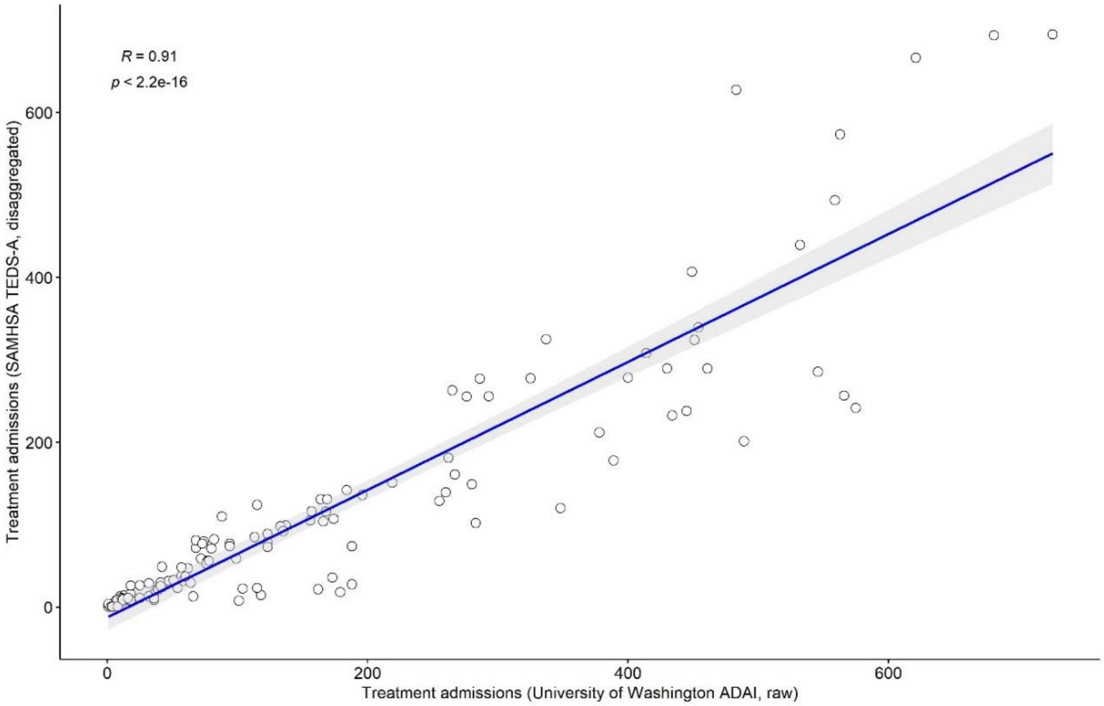
Appendix E

Comparison of SAMHSA TEDS-A and Washington ADAI treatment admissions

As the SAMHSA TEDS-A data is disaggregated from the CBSA-level to the county-level using a broad area ratio estimator, there exists the possibility that the disaggregated admission counts do not resemble actual county-level admission counts. Agreement between the disaggregated SAMHSA TEDS-A data to actual treatment admissions described in the Washington ADAI data was checked using scatterplot visualization and Pearson's correlation coefficient. A scatterplot visualization of SAMHSA TEDS-A data and Washington ADAI data are presented in the figures on the following pages. Appendix E Figure 1 is for SAMHSA TEDS-A data for treatment admissions involving a prescription opioid identified in the primary, secondary, or tertiary substance problem codes. Comparatively, Appendix E Figure 2 is for SAMHSA TEDS-A data limited to treatment admissions involving a prescription opioid in only the primary substance problem code. Both show strong alignment between the disaggregated SAMHSA TEDS-A data and Washington ADAI data (Pearson's correlation coefficient $R = 0.8$ when considering prescription opioids in any substance problem code, $R = 0.91$ when considering prescription opioids in only the primary substance problem code).



Appendix E Figure 1. Scatterplot visualization comparing SAMHSA TEDS-A treatment admissions involving a prescription opioid in any substance problem code and University of Washington ADAI treatment admissions for a primary problem substance for prescription-type opioids. Unit of analysis is county-level treatment admission counts for the state of Washington, 2006-2014 (n=351).



Appendix E Figure 2. Scatterplot visualization comparing SAMHSA TEDS-A treatment admissions involving a prescription opioid in only the primary substance problem code and University of Washington ADAI treatment admissions for a primary problem substance for prescription-type opioids. Unit of analysis is county-level treatment admission counts for the state of Washington, 2006-2014 (n=351).

Appendix F

Calculating Morphine Milligram Equivalents (MME)

Each shipment record of the ARCOS data includes information on the total number of actual pills T, the dosage strength of each pill (in milligrams) D, and the MME conversion factor C. Taking into consideration these factors, the total MME for all shipments s for each area i can be calculated as

$$MME_i = \sum_{s}^{i} T_s * D_s * C_s$$

Annual total MME was calculated at the state- and county-level for all shipments where oxycodone or hydrocodone was the active ingredient for each year in the study period (Modarai et al. 2013; Bunker 2020). These prescription opioids were selected because they represent both the majority of prescription opioid volume (approximately three quarters of all prescription opioid shipments) and prescription opioid diversion (mentioned in more than 60% of diversion cases) (Inciardi et al. 2007). MME was then standardized per capita (e.g., $MME_i\ per\ capita = \frac{MME_i}{population_i}$) using the state- or county-level population for each area i in each year to account for differences in population.

Appendix G

Fully adjusted SLX regressions using national-level SAMHSA data

Additional estimates for the fully adjusted model using nationwide cross-sectional data to examine per capita MME in relation to disaggregated SAMHSA treatment admissions involving a prescription opioid (coef., stand. err.)

	2006	2010	2014
Per capita MME	1.00116***	1.00057***	1.00084***
	[1.00112, 1.00121]	[1.00055, 1.00059]	[1.00080, 1.00088]
W x Per capita MME	1.00171***	1.00065***	1.00098***
	[1.00163, 1.00178]	[1.00062, 1.00068]	[1.00092, 1.00104]
% Male	15.23848***	126.82519***	542.23227***
	[6.12089, 37.33108]	[61.93297, 257.44333]	[255.02846, 1142.09931]
Median age	1.04438***	1.04327***	1.04287***
	[1.04129, 1.04747]	[1.04093, 1.04561]	[1.04052, 1.04523]
% High school grad	1.70803***	7.65044***	3.26592***
	[1.41960, 2.05522]	[6.62044, 8.84115]	[2.78558, 3.82924]
% Unemployment	0.00002***	0.00002***	0.00006***
	[0.00001, 0.00005]	[0.00001, 0.00003]	[0.00003, 0.00009]
% Female head of household	26.89618***	23.10504***	19.15061***
	[23.44833, 30.83441]	[20.94479, 25.48380]	[17.18340, 21.33798]
Rurality score	1.28320***	1.30164***	1.22851***
	[1.27285, 1.29362]	[1.29308, 1.31025]	[1.22030, 1.23677]
Dissimilarity	0.44219***	0.65223***	0.62409***
	[0.40766, 0.47965]	[0.61383, 0.69306]	[0.58471, 0.66614]

Notes: W stands for spatial lag. Adjusted models also include state fixed effects (not shown in consideration of space).

+ $p < 0.1$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix H

Fully adjusted SLX regressions using Washington state ADAI data

Additional estimates for the fully adjusted model using Washington state cross-sectional data to examine per capita MME in relation to treatment admissions where the primary problem substance is a prescription-type opioid (coef., stand. err.)

	2006	2010	2014
Per capita MME	1.00121***	1.00134***	1.00107***
	[1.00069, 1.00173]	[1.00106, 1.00163]	[1.00070, 1.00144]
W x Per capita MME	1.00117+	1.00091**	1.00303***
	[0.99996, 1.00239]	[1.00035, 1.00147]	[1.00233, 1.00374]
% Male	0.00000***	0.04529	69.03912
	[0.00000, 0.00000]	[0.00004, 50.78502]	[0.08121, 50982.92174]
Median age	0.99488	1.03206***	1.01741**
	[0.97844, 1.01163]	[1.02001, 1.04419]	[1.00463, 1.03036]
% High school grad	34.27744***	1.33803	45.69303***
	[5.97811, 192.15712]	[0.37887, 4.65649]	[9.02586, 226.77344]
% Unemployment	0.00018**	0.05482	0.00002***
	[0.00000, 0.05032]	[0.00122, 2.43432]	[0.00000, 0.00081]
% Female head of household	0.18792	4.10212*	3119.18437***
	[0.01751, 2.00353]	[1.26475, 13.18840]	[558.61707, 17577.18280]
Rurality score	1.13325***	1.05560**	0.93850**
	[1.07912, 1.18925]	[1.01640, 1.09631]	[0.89725, 0.98111]
Dissimilarity	0.11455***	0.16026***	0.96054
	[0.06324, 0.20964]	[0.10455, 0.24693]	[0.51872, 1.78611]

Notes: W stands for spatial lag. Spatial lag of per capita MME is not available for the island county of San Juan (no neighbors).

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

Appendix I

Full details on search parameters used to query academic repositories

Database	Search string and/or search settings	Notes on database query
ACM Digital Library	[[All: opioid*] OR [All: heroin] OR [All: fentanyl] OR [All: oxycodone] OR [All: hydrocodone] OR [All: "illicit opioid"] OR [All: "prescription opioid"] OR [All: "drug market"] OR [All: "street market"]] AND [[All: "space-time"] OR [All: geostat*] OR [All: "gis"] OR [All: cluster] OR [All: "geographic information science"] OR [All: geograph*] OR [All: spatial*] OR [All: "spatio-temporal"] OR [All: "agent-based model"] OR [All: "geovisualization"] OR [All: "multiscale"] OR [All: "geo-simulation"] OR [All: "local-scale"] OR [All: "distance"] OR [All: "proximity"] OR [All: "spatial bias"] OR [All: "mobility"] OR [All: "movement"] OR [All: "trajectory"]] AND [[All: overdose] OR [All: visit] OR [All: event] OR [All: admission] OR [All: discharge] OR [All: mortality] OR [All: morbidity] OR [All: "substance use"] OR [All: "substance abuse"] OR [All: "substance misuse"] OR [All: addict*] OR [All: treatment] OR [All: "drug rehabilitation"] OR [All: "drug use"] OR [All: "drug abuse"] OR [All: "drug misuse"] OR [All: "chemical dependence"] OR [All: "habituation"]] AND [Publication Date: (01/01/1999 TO 08/31/2021)]	None to report.
IEEE Xplore	("spatial analysis" OR “space-time” OR geostat* OR gis OR cluster OR “geographic information science” OR geograph* OR spatial* OR "spatio-temporal" OR "agent-based model" OR "geovisualization" OR "multiscale" OR "multi-scale" OR "geo-simulation" OR "local-scale" OR "mobility" OR "trajectory" OR "movement" OR "distance" OR "proximity" OR "spatial bias") AND (heroin OR opioid* OR fentanyl OR oxycodone OR hydrocodone OR "illicit opioid" OR "prescription opioid" OR "drug market" OR "street market") AND (overdose OR visit OR event OR admission OR discharge OR mortality OR morbidity OR "substance use" OR "substance abuse" OR "substance misuse" OR addict* OR "treatment" OR "drug rehabilitation" OR "drug use" OR "drug abuse" OR "drug misuse" OR "chemical dependence" OR "habituation")	Search string cannot begin with a wildcard term, as this appeared to break the search engine at the time of search. The search engine claims that more than 20 terms cannot be passed, although passing more than 20 terms resulted in retrieving additional articles. Early experiments with very large searches resulted in an inconsistent number of articles retrieved.
PubMed	((spatial* OR "space-time" OR geostat* OR "gis" OR "cluster" OR "geographic information science" OR geograph* OR "spatio-temporal" OR "agent-based model" OR "geovisualization" OR "multiscale" OR "multi-scale" OR "geo-simulation" OR "local-scale" OR "distance" OR "proximity" OR "spatial bias") AND (opioid* OR heroin OR fentanyl OR oxycodone OR hydrocodone OR "illicit opioid" OR "prescription opioid" OR "drug market" OR "street market") AND (overdose OR visit OR event OR admission OR discharge OR mortality OR morbidity OR "substance use" OR "substance abuse" OR "substance misuse" OR addict* OR treatment OR "drug rehabilitation" OR "drug use" OR "drug abuse" OR "drug misuse" OR "chemical dependence" OR "habituation")) AND (english[Filter]) AND (1999:2021[pdat])	The terms ‘mobility’, ‘trajectory’, and ‘movement’ were removed as these more than doubled the PubMed search results. Each of these terms is associated with medical
Web of Science	TS=((“space-time” OR geostat* OR "gis" OR cluster OR “geographic information science” OR geograph* OR spatial* OR "spatio-temporal" OR "agent-based model" OR "geovisualization" OR "multiscale" OR "multi-scale" OR "geo-simulation" OR "local-scale" OR "distance" OR "proximity" OR "spatial bias" OR "mobility" OR "movement" OR "trajectory") AND (opioid* OR heroin* OR fentanyl OR oxycodone OR hydrocodone OR "illicit opioid" OR "prescription opioid" OR "drug market" OR "street market") AND (overdose OR visit OR event OR admission OR discharge OR mortality OR morbidity OR "substance use" OR "substance abuse" OR "substance misuse" OR addict* OR treatment OR "drug rehabilitation" OR "drug use" OR "drug abuse" OR "drug misuse" OR "chemical dependence" OR "habituation")) and Articles or Proceedings Papers (Document Types) and English (Languages) and USA (Countries/Regions)	Executed on Web of Science Core Collection.

Appendix J

Full list of studies included in the scoping review. Studies are ordered alphabetically. Citations are presented in Chicago Author-Date style.

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