PRESCRIPTION OPIOID USE, OPIOID OVERDOSE, AND LINKS TO SYPHILIS DIAGNOSES IN NORTH CAROLINA

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ABSTRACT

Bethany L. DiPrete: Prescription opioid use, opioid overdose, and links to syphilis diagnoses in North Carolina
(Under the direction of Brian W. Pence)

The United States is facing both a devastating opioid epidemic and increasing syphilis incidence. Duration of opioid therapy influences risk of nonmedical opioid use and overdose, and drug use is associated with behaviors that facilitate infectious disease transmission. Therefore, the opioid epidemic may have a role in recent increases in syphilis diagnoses. This dissertation investigates how initial indication and duration of prescription opioid therapy is associated with risk of opioid overdose and uses spatial regression methods to examine spatiotemporal links between opioid overdoses and rising syphilis rates.

We analyzed claims data of 492,983 patients initiating opioid therapy for pain management in North Carolina (NC) from 2006 through 2018. We identified patients exposed to long-term opioid therapy (LTOT) using a conservative definition requiring consistent exposure prescription opioids. In this cohort of opioid-naïve patients initiating opioid therapy, 1.7% of patients went on to have LTOT and 381 opioid overdoses were observed. The three-year risk of opioid overdose was 0.7 percentage points (RD_w= 0.007, 95% CI: 0.001, 0.013) higher in the LTOT group compared to patients with shorter durations of use. Sensitivity analyses revealed a dose-response relationship

between duration of opioid therapy and risk of opioid overdose. We did not find meaningful modification by clinical indication for opioid therapy.

Next, we used surveillance data of diagnosed syphilis cases and emergency department visits for probable opioid overdose in NC from 2008 through 2017. Using spatial regression methods of aggregate zip code-level rate data, we found that recent increases in early syphilis cases in North Carolina may be spatiotemporally associated with the opioid epidemic. This relationship held in an ancillary pseudo-causal analysis that adjusted for relevant population-level confounders.

Future work using rigorous causal inference techniques to further disentangle the key points in clinical decision-making around duration of opioid therapy could provide additional insights on how to mitigate risks of opioid use disorders and opioid overdose in pain patients. Further, future analyses of individual-level data to investigate possible causal mechanisms linking opioid use and syphilis incidence are warranted.

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LIST OF ABBREVIATIONS

ACS	American Community Survey
AIC	Akaike information criterion
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPT	Current Procedural Terminology
DAG	Directed acyclic graph
ED	Emergency Department
HCUP	Healthcare Cost and Utilization Project
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICD-9-CM	International Classification of Diseases, 9th Revision
ICD-10-CM	International Classification of Diseases, 10th Revision
IPCW	Inverse probability of censoring weights
IPTW	Inverse probability of treatment weights
IPW	Inverse probability weights
IQR	Interquartile range
LTOT	Long-term opioid therapy
MME	Morphine milligram equivalent
MSM	Men who have sex with men
MSW	Men who have sex with women
NC	North Carolina

NC DPH	North Carolina Division of Public Health
NC DETECT	NC Disease Event Tracking and Epidemiologic Collection Tool
OLS	Ordinary Least Squares
OUD	Opioid use disorder
PTSD	Post-traumatic Stress Disorder
PWIO	Person who injects opioids
RD	Risk difference
RD_w	Risk difference, weighted
RD_c	Risk difference, crude
SMTOT	Short- to medium-term opioid therapy
SD	Standard deviation
SSRI	Selective serotonin reuptake inhibitor
STI	Sexually transmitted infection
SUD	Substance use disorder
US	United States
ZCTA	ZIP Code Tabulation Areas

CHAPTER I: SPECIFIC AIMS

Opioid overdoses account for >66% of drug-related deaths in the United States (US) (1, 2) and 33% of emergency department (ED) visits for nonfatal drug overdoses (3). Prescription opioid use remains a significant contributor to opioid-related mortality (4), and often precedes initiation of heroin and illicit synthetic opioids (5-12). However, pain diagnoses are common in US adults (13, 14), and prescription opioids maintain an important role in pain management (15). In 2016, the Centers for Disease Control and Prevention (CDC) released prescribing guidelines that include minimizing the duration of opioid therapy in pain patients (16).

Long-term opioid therapy (LTOT) often begins with treatment of acute (17-20) and post-surgical pain for which opioid prescriptions are intended to be time-limited (17, 21-23). LTOT has been shown to be associated with opioid use disorders and opioid overdose (24, 25). The definition of LTOT varies widely across studies (26, 27), with many studies not requiring consistent exposure to prescription opioids (27). Furthermore, few studies have examined the relationship between opioid therapy duration and opioid overdose according to the initial pain management indication (28). Chronic pain patients may initiate opioid therapy with a clinical goal of long-term therapy, but poor pain management can result in withdrawal symptoms or return of pain symptoms (29); patients may then seek treatment through illegitimate sources (7).

Opioid use can also be associated with behaviors that can lead to transmission of infectious diseases (30-32). There is a “converging public health crisis” as a result of the opioid epidemic driving increases in both viral and bacterial infectious diseases (33). US syphilis rates have steadily increased (34, 35). While the majority of diagnosed syphilis infections occur in men who have sex with men (35), recent increases have also surfaced among women and in men who have sex with women (MSW). The CDC has noted recent trends in reporting injection drug use, heroin use, and sex with a person who injects drugs among women and MSW newly diagnosed with syphilis (34, 36). Therefore, the opioid epidemic might have played a role in recent rises in new syphilis diagnoses, particularly in women and MSW. Spatial regression methods may provide insights into potential correlations between the opioid epidemic and rising syphilis rates, since both opioid use (37) and syphilis infections (38-40) can be spatially dependent.

In this study, we used multiple large, diverse datasets to examine associations between duration of opioid therapy, opioid overdose, and diagnosed cases of early syphilis by addressing the following specific aims:

Aim 1: Among privately insured patients with an indication for opioid management for pain, estimate the risk of opioid overdose by duration of opioid therapy.

Among opioid-naïve patients who initiated prescription opioid therapy for pain management, we compared three-year risk of opioid overdose between patients exposed to long-term opioid therapy (LTOT) and patients exposed to short- to medium-term opioid therapy (SMTOT) using a rigorous definition of LTOT. We hypothesized that

exposure to LTOT increased risk of fatal or nonfatal opioid overdose over three years of follow-up.

Aim 1b: Assess potential modification of the association between duration of opioid therapy and opioid overdose by initial derived clinical indication.

We explored potential modification by derived clinical indication at opioid initiation, stratifying by chronic pain versus acute pain or surgery. We hypothesized that the association between duration of opioid therapy and opioid overdose would be increased among patients with an initial chronic pain indication.

Aim 2: Estimate the spatiotemporal association between opioid overdose rates and syphilis diagnosis rates in North Carolina from 2008-2017.

We used spatiotemporal regression methods to analyze potential associations between opioid overdoses, as a proxy for nonmedical opioid use or heroin use, and syphilis diagnoses using surveillance data aggregated by zip code and year. We hypothesized that opioid overdose rates would be spatiotemporally associated with recent rises in syphilis diagnosis rates.

Overall, this dissertation combines causal inference methods in insurance claims data with innovative spatiotemporal regression methods in surveillance data to better understand the contribution of long-term opioid prescribing to the opioid epidemic and subsequent links to rising syphilis rates. Recognizing true long-term opioid use and reducing the risk of opioid use disorders and opioid overdose early in treatment may help curb overdose rates in patients treated for pain. To combat rising rates of new syphilis cases and congenital syphilis, identification of individuals known to misuse prescription opioids or persons who inject opioids (PWIO) for increased syphilis testing

may aid detection of new syphilis cases and allow for initiation of treatment to break the chain of transmission.

CHAPTER II: BACKGROUND

The opioid epidemic has unfolded as a major public health crisis in the United States (US) since the turn of the century due to rapid increases in deaths attributable to opioid overdose, with over 440,000 deaths from 1999 through 2018 (1, 41, 42). Deaths involving an opioid have surpassed deaths due to motor vehicle accidents as the leading cause of death due to unintentional injury. In 2017 and 2018, almost 70% of deaths attributable to drug overdose were found to involve an opioid (1, 41). Opioid-involved overdose deaths in the US peaked in 2017 at 47,600 deaths (15).

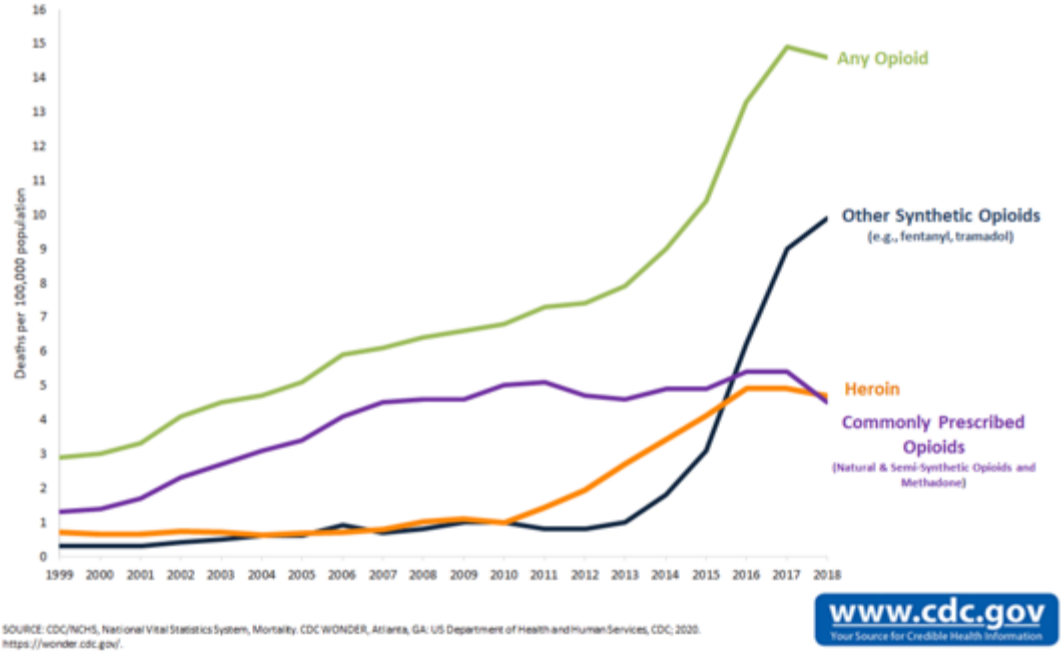
The epidemic has not only resulted in in high mortality rates, but also in high rates of misuse, opioid use disorders, and nonfatal poisonings. More than 11 million people per year in the US were estimated to have misused opioid prescriptions from 2015 through 2018, and over 2.1 million people were estimated to have an opioid use disorder (OUD) in 2017 (15, 41, 43, 44). Almost 200,000 people visited an emergency department for opioid-related poisonings in 2016 (15). In response, the White House declared the opioid epidemic a public health emergency in Fall 2017.

This public health crisis began as an epidemic of overprescribing of opioid analgesics. While the landscape of pain management had been changing for several decades, two key events helped set the course that would result in a flooding of the market with prescription opioids and surging overdose rates (45). First, between 1995 and 2001, pain was adopted as the *fifth vital sign* (26, 45, 46). This placed an emphasis

on quantification and treatment of pain. Second, Purdue Pharma obtained approval from the Food and Drug Administration for their new prescription opioid analgesic, Oxycontin (45). Purdue falsely marketed this long-acting form of oxycodone as a non-addictive analgesic.

The United States has experienced three main waves of the opioid crisis. From 1999 through 2010, prescription opioids, such as Oxycontin, were the main drivers of the opioid epidemic (Figure 2.1) (47). While this trend continued through 2015, the United States also began to experience surging death rates due to heroin overdose starting in 2010, followed by synthetic opioids, such as illicitly manufactured fentanyl, starting in 2014. Since 2015, overdose deaths involving heroin or synthetic opioids have surpassed death rates from prescription opioids (48-50).

Figure 2.1. Overdose death rates involving opioids, by type, United States, 1999-2018



Prescription opioids maintain an important role in pain management (46). A large 2012 survey of American adults found that 55% of US adults reported pain within the past 3 months (13), and the Centers for Disease Control and Prevention (CDC) estimates that more than 20% of US adults experience chronic pain (14). Many of these individuals receive prescription opioids to manage their pain; despite national decreases in annual opioid prescribing since 2012, 15% of the US population filled at least one prescription for an opioid in 2018 (15).

High volumes of written prescriptions, high prescribed doses, and longer prescription durations have been shown to be associated with increased opioid-related morbidity and mortality (28, 37, 51-53). High-volume opioid prescribing is also widely thought to be a major source of diverted opioid prescriptions for nonmedical use (7, 51, 52, 54), since unused opioids are frequently are not disposed of properly and may even be shared with family or friends (55, 56). Specifically, opioids are commonly overprescribed after surgery and go unused, creating opportunities for pill diversion and nonmedical use of prescription opioids (26, 57-59).

Encouragingly, the annual volume of written prescriptions for opioids has declined nationwide since 2012 after years of steady increases (15). However, the number of individuals receiving opioid prescriptions each year remains high and average days of supply of opioids per prescription has increased since 2006. In 2017, the average prescription duration was >18 days (41). The Centers for Disease Control and Prevention (CDC) released guidelines for opioid prescribing in 2016, recommending that providers minimize the duration of opioid therapy in both acute and chronic pain patients (16).

Long-term use of prescription opioids often begins with treatment of acute (17-20) and post-surgical pain (17, 21-23) that then extends past the window of normal healing (20, 60). While the effectiveness in opioid therapy in treating short-term and severe pain is well recognized, the clinical benefit of long-term opioid therapy (LTOT) for chronic non-cancer pain has been disputed (61, 62). Further, LTOT has been shown to be associated with multiple negative outcomes, including opioid use disorders (OUD) and opioid overdose (24, 25). Much work has been done on incidence and risk factors for LTOT in three main contexts: 1) post-surgical settings, 2) chronic pain patients, or 3) any opioid prescription regardless of indication. The definition of LTOT varies widely across studies (26, 27), with many studies not requiring consistent long-term use of prescription opioids following initiation of opioid therapy (27).

Furthermore, little is known about the relationship between opioid therapy duration and opioid overdose according to the initial pain management indication. Specifically, patients initiating opioid therapy for chronic pain may be at increased risk of opioid-related morbidity and mortality. Additionally, poor pain management can result in withdrawal symptoms, relapse, or return of pain symptoms (29), which may lead patients to seek treatment through illegitimate sources (7). Among patients addicted to opioids, a commonly reported precursor to dependency or misuse is inadequately controlled pain (18, 44). While much of opioid epidemic has been fueled in recent years by nonmedical use heroin and illicit synthetic opioids, prescription opioids continue to be a significant contributor to opioid-related morbidity and mortality (4). Prescription opioid-involved deaths accounted for >35% of opioid-involved deaths in 2017 (15).

Individuals exposed to prescription opioids may also transition to using heroin or illicit synthetic opioids; many individuals who use heroin report past nonmedical use of opioids that preceded initiation of heroin use (5-11), and prescription opioid use has been found to be common prior to heroin overdose (12). Increases in heroin overdoses have tracked with increases in prescription opioid overdoses, suggesting an association between opioid overdose and surging death rates from heroin and illicit synthetic opioids (63). Heroin is pharmacologically similar to oxycodone and often is cheaper and easier to find than prescription opioids (7, 8, 52). The availability and low cost of heroin and illicit synthetic opioids coupled with high purity of the drug are associated with increases in rates of heroin and illicit synthetic opioid use (6, 63, 64). In 2016, >900,000 people in the US reported heroin use within the last year (65).

In addition to the risk of overdose and mortality, drug use can also be associated with behaviors that can lead to the transmission of infectious diseases (30-32). A recent report highlighted a “converging public health crisis” as a result of the opioid epidemic driving increases in both viral and bacterial infectious diseases (33). The link between injection drug use and HIV and hepatitis C virus (HCV) infection through needle-sharing behaviors is well documented, with recent attention focused on HIV and HCV outbreaks among persons who inject opioids (PWIO) (66-69). In 2015, Indiana experienced an outbreak of HIV and acute HCV that spread rapidly through a network of injection drug users who injected oxymorphone (66). Drug use can also be associated with condomless sex (31) and exchanging sex for drugs or money (70, 71); these sexual behaviors, in addition to sex with a PWIO, may provide opportunities and efficient routes for sexual transmission of infectious diseases such as syphilis.

Syphilis rates have steadily increased in the US since 2001 (34, 35), increasing 74% from 2012 to 2016. The majority of diagnosed syphilis infections occurring in men who have sex with men (MSM) (35). Since 2013, increases in diagnosed syphilis have also surfaced among women and in men who have sex with women (MSW). From 2015 to 2016 reported cases rose by 36% among women (72). Rising syphilis rates among women have also driven increasing congenital syphilis rates in the US (73). In early 2019, the CDC noted increases since 2013 in reporting of both injection drug use (including heroin use) and sex with a person who injects drugs among women and MSW newly diagnosed with syphilis (34, 36). Therefore, the opioid epidemic might have played a role in the recent rise in new syphilis diagnoses, particularly in women and MSW.

In rural areas and the Southern United States, the opioid epidemic has progressed rapidly, with increases in opioid sales, ED visits for overdose, and opioid-related mortality rates (37, 51, 66, 74, 75). Many rural areas were naïve to IDU before the rise in non-medical opioid use (75). Opioid prescribing rates have been shown to be higher in rural and micropolitan areas (76). North Carolina in particular has a high number of residents with opioid prescriptions (77). High prescribing rates in the state may be fueled in part by the high density of hospitals and physicians across the state. North Carolina experienced many years with dramatic increases in opioid- and heroin-related overdose and deaths (37, 48, 78), From 2011 through 2016 alone, there were over 61,000 naloxone administrations for opioid overdose by emergency medical services in North Carolina (79). Statewide, there was a 73% increase in opioid-related deaths from 2005-2015 (80). Of particular concern, from 2010 through 2012, the

Southern US saw a >180% increase in rates of death due to heroin overdose (81). Heroin and fentanyl are increasingly involved in opioid-related overdoses in North Carolina—the proportion of opioid overdose deaths in North Carolina involving heroin and fentanyl steadily increased from 18% in 2010 to 69% in 2016 (78).

The burden of syphilis is especially high in North Carolina, with the rate of reported primary and secondary syphilis cases in 2016 ranking 8th in the United States (72) and surpassing the national reported case rate. Syphilis, like HIV, is transmitted through sexual contact and may also be associated with risky sexual behaviors among drug users (82, 83). Although syphilis is treatable with penicillin, syphilis infection is associated with additional adverse outcomes. Specifically, syphilis infection increases the risk of HIV co-infection, and women of child-bearing age who contract syphilis are at risk of passing the infection to their infants, resulting in congenital syphilis infection (72, 82).

Significance

Substantial efforts have been focused on curbing opioid prescribing rates, but overdose deaths continue to rise. In response, thousands of lawsuits have been filed against Purdue and other pharmaceutical companies, with millions of dollars in settlements already to date. Numbers of syphilis cases have also been steadily increasing even among populations not normally considered to be at highest risk of syphilis infection. This study provides a unique opportunity to use >10 years of existing data from multiple data sources to provide timely insight on adverse outcomes related to opioid use as the epidemic continues to unfold. The results of this study will inform future intervention research to prevent OUD-related outcomes among pain patients. It

also serves as a hypothesis-generating study for future work investigating links between opioid use and incident syphilis infections.

Innovation

This dissertation made use of multiple large data sources to understand the relationship between opioid prescriptions, overdose, and diagnosed syphilis. By harnessing linked datasets from a large provider of health insurance in North Carolina and public death records, we had access to extensive data on >20% of adult North Carolina residents over 13 years from 2006 through 2018 to analyze individual-level risks of opioid overdose by initial prescribing trajectory and clinical indication. Additionally, by harnessing ZIP code-level linkages between surveillance data on diagnosed cases of early (primary, secondary, and early latent) syphilis from the North Carolina Division of Public Health (NC DPH) Communicable Diseases Branch (CDB) and Emergency Department (ED) records from The North Carolina Disease Event Tracking and Epidemiologic Collection Tool (NC DETECT), we were able to analyze population-level associations between trends in opioid overdoses and newly diagnosed syphilis infections in North Carolina from 2008 through 2017. These data sources provided us with a timely and unique opportunity to take advantage of existing data to answer pertinent questions on the opioid crisis on a large scale as it continues to unfold.

In Aim 1, we used a rigorous approach to overcome past methodological issues in estimating the effect of long-term opioid therapy on the risk of opioid overdose among patients newly initiating opioid therapy for pain management. The literature lacks a consistent definition of long-term opioid therapy. Most studies use approaches that either do not adequately account for consistent exposure to prescription opioids or

require long periods of follow-up to determine long-term opioid therapy, which may introduce selection bias while simultaneously introducing potential measurement error by associating future opioid prescriptions with the initial treatment episode after large gaps in treatment. Additionally, to our knowledge, only few studies have directly assessed overdose risk by the initial clinical indication for initiating opioid treatment.

In Aim 2, we expanded on previous research suggesting potential associations between the opioid epidemic and rising syphilis cases in the United States by using a spatiotemporal regression approach to examine state-wide population-level associations between opioid overdoses and syphilis diagnoses. To our knowledge, this study is the first to examine links between these epidemics in this way. Our approach considers the likely spatially dependent nature of both the opioid epidemic and incident syphilis diagnoses to infer potential associations. To our knowledge, this study is also among the first to examine the recent increases in primary and secondary syphilis diagnoses in the US in the context of the opioid epidemic. Given recent rises in syphilis diagnosis rates, especially among groups that tend to be at lower risk of infection, this is extremely timely. The results of this analysis have the potential to lay the groundwork for future modeling analyses of opioid use disorders and syphilis infections.

CHAPTER III: METHODS

Overview

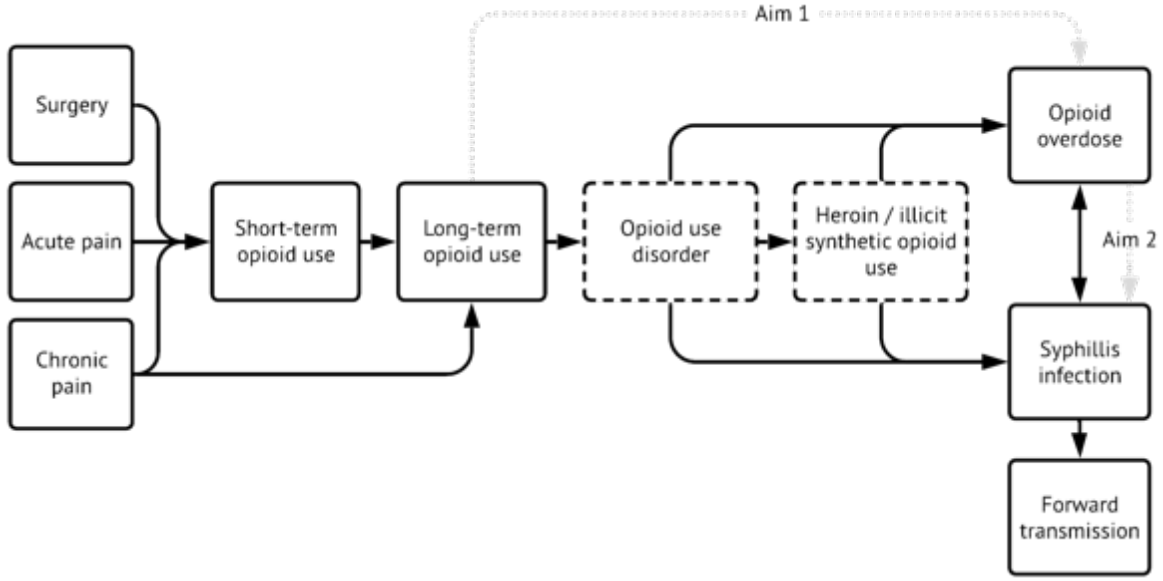
The overall goal of this dissertation is to examine adverse outcomes related to opioid use in North Carolina. Longitudinal insurance claims data were used to estimate the effect of long-term use of prescription opioids on risk of opioid overdose in opioid-naïve individuals initiating opioid therapy for pain management, stratified by clinical indication (Aim 1). Aggregate surveillance data were then used to examine the spatiotemporal association between opioid overdoses, as a proxy for nonmedical opioid use and heroin or illicit synthetic opioid use, and diagnosed cases of early (primary, secondary, and early latent) syphilis in North Carolina (Aim 2).

In the first aim, we examined the association between duration of prescription opioid use and nonfatal and fatal opioid overdose in individual-level data from privately insured patients in North Carolina. Specifically, our purpose was to study the association between long-term use of prescription opioid use and clinically recognized fatal or nonfatal opioid overdose using a rigorous definition of long-term use that makes use of days of supply to better capture true long-term use. Further, we examined whether this association differed by clinical indication at the time of the first opioid prescription, stratifying by acute pain or postsurgical pain versus chronic pain. We hypothesized that long-term use is associated with increased risk of opioid overdose, and that this risk differs by clinical indication at the time of initiation of treatment with

prescription opioids.

In the second aim, we examined the spatiotemporal association between opioid overdose, a proxy for nonmedical use of prescription opioids or heroin and fentanyl use in a given area, and diagnosed early syphilis in North Carolina. We hypothesized that rates of opioid overdose would be positively associated with rates of syphilis diagnoses in space and time. Figure 3.1 depicts the conceptual model for all analyses in this dissertation.

Figure 3.1 Conceptual Model



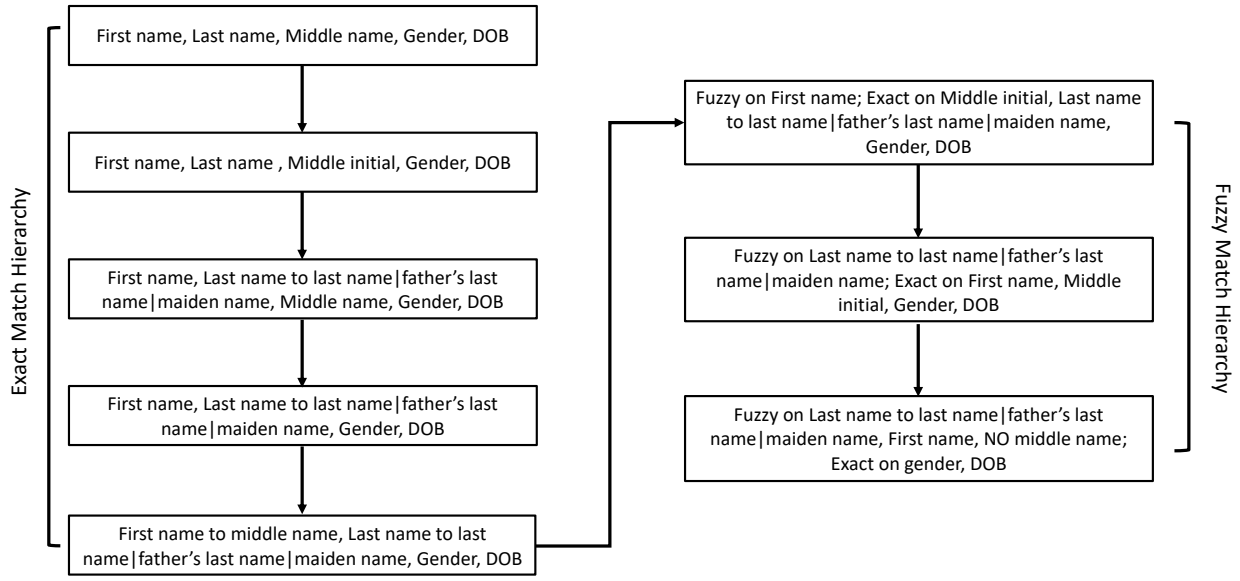
Aim 1

Data Source

In this individual-level analysis, we used 13 years of de-identified claims data from a large provider of private health insurance in North Carolina covering about one-fifth of North Carolina's population, from 2006 through 2018. These longitudinal healthcare data include member demographics, residence, pharmacy claims, and inpatient and outpatient claims with data on dates of service and billed diagnoses and

procedures. Insurance claims were linked to North Carolina death records using a hierarchical matching algorithm, starting with exact matches and moving down the exact match hierarchy and moving onto fuzzy matching in the event that none of the exact match criteria were met (Figure 3.2). Fuzzy matches were visually inspected for accuracy.

Figure 3.2. Matching algorithm



Study Population

We used a new-user design (84), identifying opioid-naïve individuals initiating prescription opioids (Table 3.1) for pain management between July 1, 2006 and July 1, 2018. Eligible patients were aged 18-64, living in NC, and actively insured. Patients were required to have six months (180 days) of continuous insurance enrollment (washout period) prior to their index date.

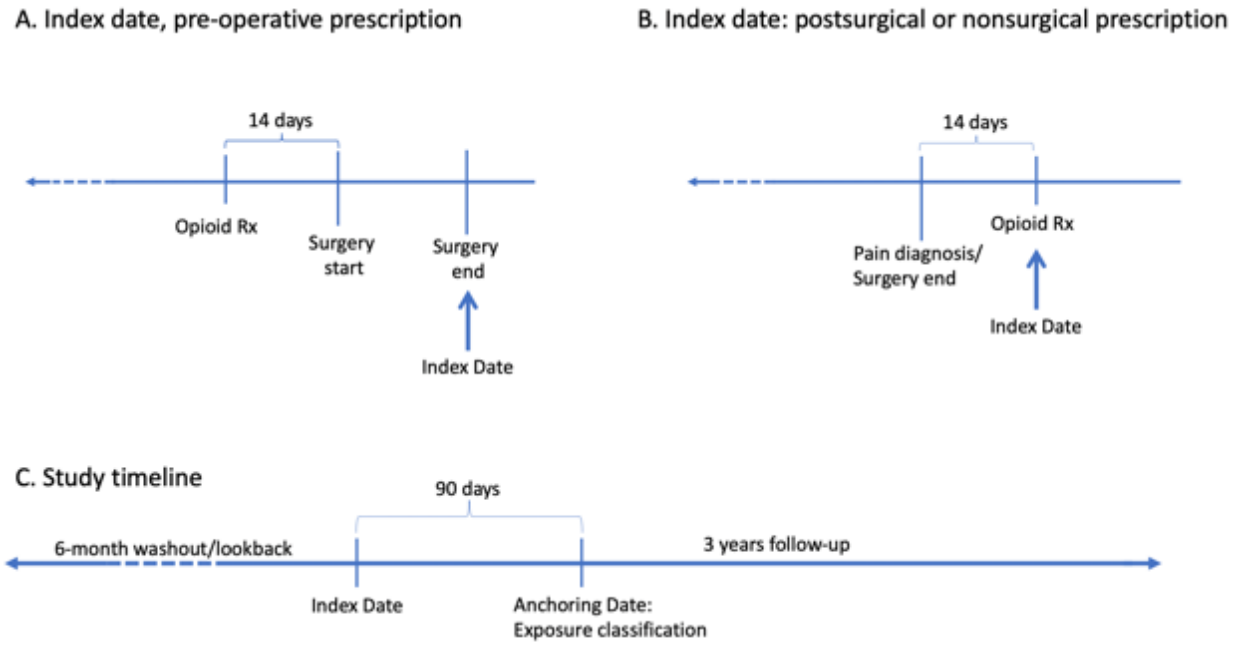
Table 3.1. Prescription opioids

Opioid Ingredient
Codeine
Dihydrocodeine
Fentanyl
Hydrocodone
Hydromorphone
Morphine
Oxycodone
Oxymorphone
Pentazocine
Propoxyphene
Tapentadol
Tramadol

Excluding formulations used to treat cough, cold, and allergies. This include opioids in combination with: chlorpheniramine, gauifenesin, bromodiphenhydramine, pseudoephedrine, brompheniramine, calcium, pryilamine, phenylpropanolamine, phenylephrine, promethazine, dexbrompheniramine, diphenhydramine, chlorcyclizine, terpin, phos/gg, triprolidine, homatropine, carbinoxamine.

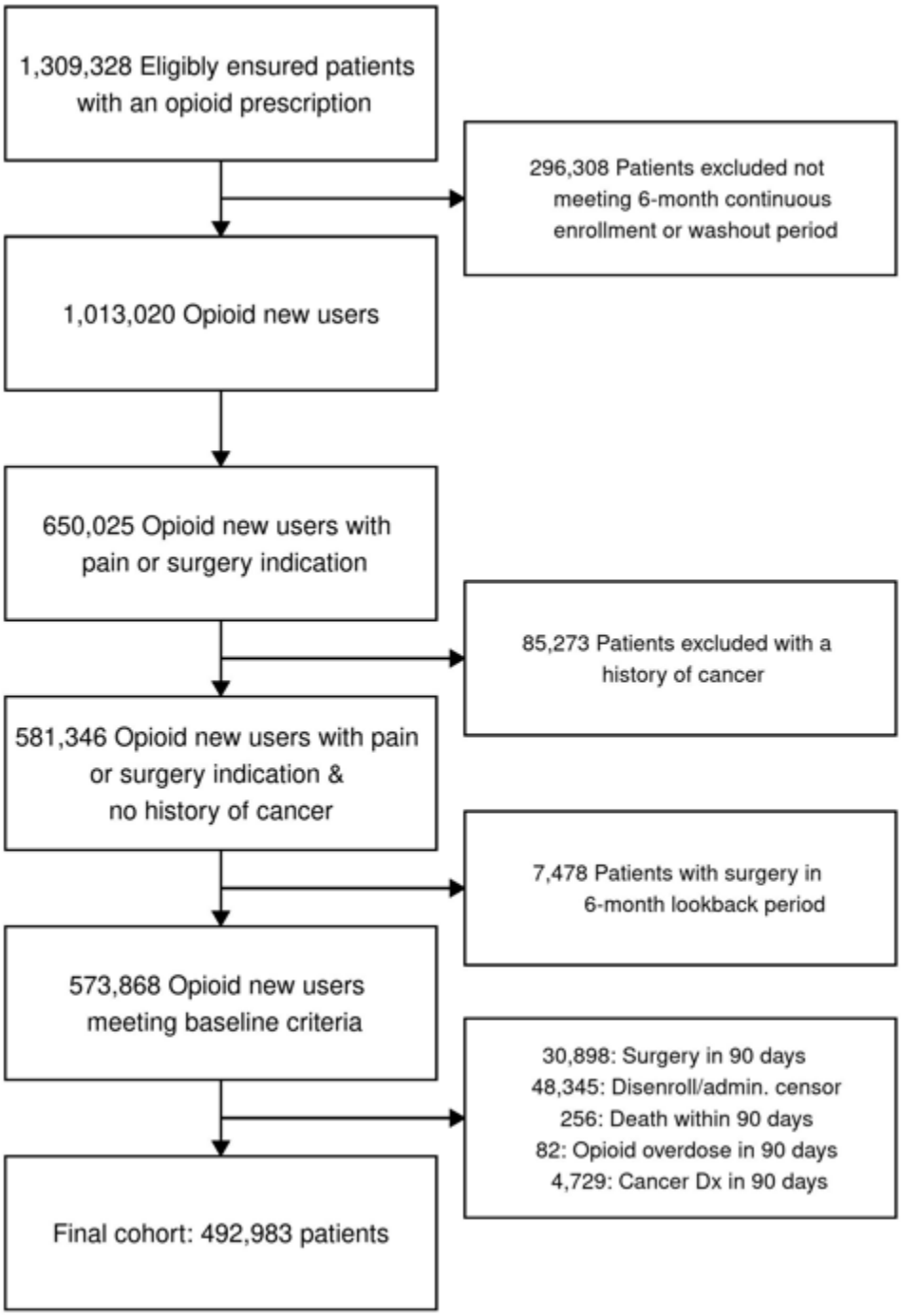
For surgical patients, the index date was defined as (1) the date of outpatient surgery or final day of an inpatient stay for an inpatient surgery event if the first opioid prescription was billed to insurance ≤14 days before the date of outpatient surgery or first day of an inpatient stay for an inpatient surgery event (Figure 3.3A), or (2) the prescription claim date if the first opioid prescription was filled ≤14 days after a surgery event (Figure 3.3B). Among patients without a surgery event, the index date was defined as the date of the first opioid prescription claim ≤14 days after a pain diagnosis (Figure 3.3B).

Figure 3.3. Timelines of: (A) Index date definition for preoperative prescriptions, (B) Index date definition for postsurgical or nonsurgical prescriptions, and (C) Overall study timeline



In order to ensure patients were opioid naïve at their index date, we excluded patients if they had evidence of prescription claims for opioid analgesics, opioid overdose, opioid use disorder (OUD), or medication-assisted treatment for OUD during the 180-day washout period prior to the index date. Patients were also excluded if they had a cancer diagnosis using all-available lookback or a surgery within 180 days prior to the index date. These patients were excluded due to the potential complex nature of their pain conditions and treatment regimens. Patients were followed forward 90 days from the index date for exposure classification and were excluded if they experienced one or more of 1) opioid overdose, 2) death, 3) disenrollment, 4) an invasive surgery, or 5) cancer diagnosis in that 90-day period (Figure 3.4). The impact of excluding overdoses (n=82) in the first 90 days of follow-up was evaluated in a sensitivity analysis.

Figure 3.4 Aim 1 study flowchart



Classification of indication for initial prescription

Our definition of a derived clinical indication of pain management included postsurgical pain, defined as patients undergoing invasive surgery as classified by the Healthcare Cost and Utilization Project (HCUP) (85) using Current Procedural Terminology (CPT) codes, diagnosis of acute pain(22, 86-88) using International Classification of Diseases, 9th Revision (ICD-9-CM) and 10th Revision (ICD-10-CM), Clinical Modification (Table 3.2), or diagnosis of chronic pain (22, 86-88) using ICD-9-CM and ICD-10-CM codes (Table 3.3).

We used a hierarchical algorithm to assign a derived clinical indication, assuming that (1) patients with a surgical indication (Figures 3.3A and 3.3B) received an opioid prescription related to that surgery, (2) patients without an indication of surgery who had a diagnosis of acute pain (Figure 3.3B) received an opioid prescription related to the acute pain diagnosis, and (3) patients without evidence of surgery or acute pain who had a chronic pain diagnosis $\leq$14 days prior to the index prescription received the prescription for the chronic pain condition (Figure 3.3B).

Table 3.2. ICD-9-CM and ICD-10-CM Diagnostic Codes for Acute Pain

Acute Pain			
ICD-9-CM	**Description**	**ICD-10-CM**	**Description**
282.62	Sickle cell anemia	D57	Sickle cell anemia
338.11, 338.12, 338.18, 338.19	Other nervous system disorders	G89.11, G89.12, G89.18	Other nervous system disorders
522.5, 522.7	Disorders of teeth and jaw	K04.6, K04.7	Disorders of teeth and jaw
574	Biliary tract disease	K80, K87	Biliary tract disease
577	Pancreatic disorders (not diabetes)	K85-K86	Pancreatic disorders (not diabetes)
592	Genitourinary	L08.89	Skin and subcutaneous tissue infections
733	Pathological fracture	M48.5	Other spondylopathies
800-804, 850-854	Intracranial injury; skull and face fractures	M80, M84.4	Pathological fracture
805, 807-829	Fractures	M84.75, M99.1, S00-S99, T08, T14-T19, T71, T73, T74.01-T74.02, T75.4, T79	Injury
830-839	Joint disorders and dislocations; trauma-related	T20-T28, T30-T32	Burns**
840-848	Sprains and strains	N13.9, N13.2, N20, N22	Genitourinary**
860-869, 900-904, 925-929	Crushing injury or internal injury	R52	Pain, not elsewhere classified
870-897	Open wounds	V00-V99, W00-W99, X00-X99, Y00-Y38	E codes
910-924	Superficial injury; contusion		
930-939, 951-951, 953-959	Other injuries and conditions due to external causes		
940-949	Burns		
806, 952	Spinal cord injury		
E800-E999	E codes		

Table 3.3. ICD-9-CM and ICD-10-CM Diagnostic Codes for Chronic Pain

Chronic Pain			
ICD-9-CM	**Description**	**ICD-10-CM**	**Description**
307.81	Miscellaneous mental health disorders	A18.01, A18.02	Tuberculosis of other organs
338.21, 338.22, 338.28, 338.29, 338.4	Other nervous system disorders	A52.16	Late syphilis
346.0-346.5, 346.7-346.9	Headache, migraine	E08.610, E08.618, E09.610, E09.618, E10.610, E10.618, E11.610, E11.618	Diabetes mellitus with complications
346.6	Acute cerebrovascular disease	G43, G44.209	Headache, including migraine
710, 725-726, 727-729	Other connective tissue disease	G89.21, G89.22, G89.28, G89.29, R26.2	Other nervous system disorders
711	Infective arthritis and osteomyelitis	M00.00, M01, M02.1, M02.3-M02.9	Infective arthritis and osteomyelitis
712	Gout	M02.0, M02.2, M12.1, M13, M14.6, M14.8, M36.1-M36.4, R29.4	Other non-traumatic joint disorders
713, 716, 718.1-718.9, 719	Other non-traumatic joint disorders	M04.2, M04.8, M04.9	Immunity disorders
714-715, 720.0	Rheumatoid arthritis and osteoarthritis	M05-M08, M12, M14.6, M14.8, M15-M19, M45, M48.8	Rheumatoid arthritis and osteomyelitis
716.1, 717-718	Joint disorders and dislocations, trauma-related	M11	Gout
718.4	Other acquired deformities	M12.5, M22, M23, M24.0-M24.3, M24.6-M24.9, M43.3-M43.5	Joint disorders and dislocations; trauma-related
720.1, 721-724	Spondylosis; intervertebral disc disorders; other back problems	M20.1, M20.6	Acquired foot deformities
727.1	Acquired foot deformities	M24.5, M43.8X9	Other acquired deformities
		M32-M34, M35, M36.0, M36.8, M60-M62, M63.8, M65-M67, M75-M79, R25.2, R29.898	Systemic lupus and connective tissue disorders
		M43.2, M48.0-M48, M49.8, M50, M51, M53, M54, M62.830, M96, M99.2	Spondylosis; intervertebral disc disorders, other back problems
		Q68.6	Other congenital anomalies

Exposure

We defined long-term opioid therapy (LTOT) using the date of fill and days' supply to calculate the total days of supply of prescribed opioids received and timing of receipt. Our definition of LTOT required ≥1 prescription in each of three 30-day periods within the 90-day exposure definition period after the index date (89), with a cumulative days' supply of opioids received totaling ≥60 days. A prescription was determined to occur in a 30-day period if it was dispensed in that period, or if the date of fill plus days' supply fell within that 30-day period. When overlapping prescriptions of the same ingredient occurred, we used a seven-day rule such that if the start date was within seven days of the end date of the previous prescription, this was assumed to reflect an early refill and the start date of that prescription was pushed forward to the end date of the previous prescription (90). If the overlap was greater than seven days, the prescriptions were assumed to truly overlap and treated as such. Patients with <60 days' supply of opioids dispensed and without consistent exposure in each of the 30-day periods were classified as short- to medium-term opioid therapy (SMTOT).

Patients were followed forward 90 days from the index date. On day 90, the anchoring date, patients were classified as exposed to LTOT or SMTOT (Figure 3.3C). We conducted sensitivity analyses (described in "Sensitivity Analyses" below) of our exposure definition to examine the robustness of our findings to varying definitions of LTOT.

Follow-up time

We followed patients forward from the anchoring date (index date plus 90 days) until the first of 1) nonfatal or fatal opioid overdose (outcome), 2) loss of eligible

insurance coverage (censoring event), 3) cancer diagnosis (competing risk) (91, 92), 4) death due to causes other than opioid overdose (competing risk), 5) administrative censoring three years after the anchoring date, or 6) administrative censoring at the end of the study period (September 30, 2018).

Outcome

Our outcome of interest was the first fatal or nonfatal opioid overdose within three years of initiating prescription opioids for pain management. In insurance claims, clinically recognized opioid overdose was defined using ICD-9-CM and ICD-10-CM diagnosis codes in inpatient, outpatient, and emergency department (ED) claims (Table 3.4). In linked death records, fatal opioid overdose was defined using ICD-10 codes and a combination of underlying and contributing cause of death (Table 3.5) (86).

Table 3.4. ICD-9-CM and ICD-10-CM Diagnostic Codes for Opioid Overdose in Claims Data

ICD-9-CM	ICD-10-CM
965.00	T40.1X1A, T40.1X4A
965.01	T40.0X1A, T40.0X4A
965.02	T40.2X1A, T40.2X4A
965.09	T40.3X1A, T40.3X4A
E850.0	T40.4X1A, T40.4X4A
E850.1	T40.601A, T40.604A
E850.2	T40.691A, T40.694A
	F11.12, F11.120, F11.121, F11.122, F11.129
	F11.22, F11.220, F11.221, F11.222, F11.229
	F11.92, F11.920, F11.921, F11.922, F11.929

Table 3.5. ICD-10 Codes for Fatal Opioid Overdose in Death Records

Underlying Cause*	Contributing Cause
X40	T40.0
X41	T40.1
X42	T40.2
X43	T40.3
X44	T40.4
X60	
X61	
X62	
X63	
X64	
X85	
Y10	
Y11	
Y12	
Y13	
Y14	

*The death must have a both an underlying cause code and contributing cause code.

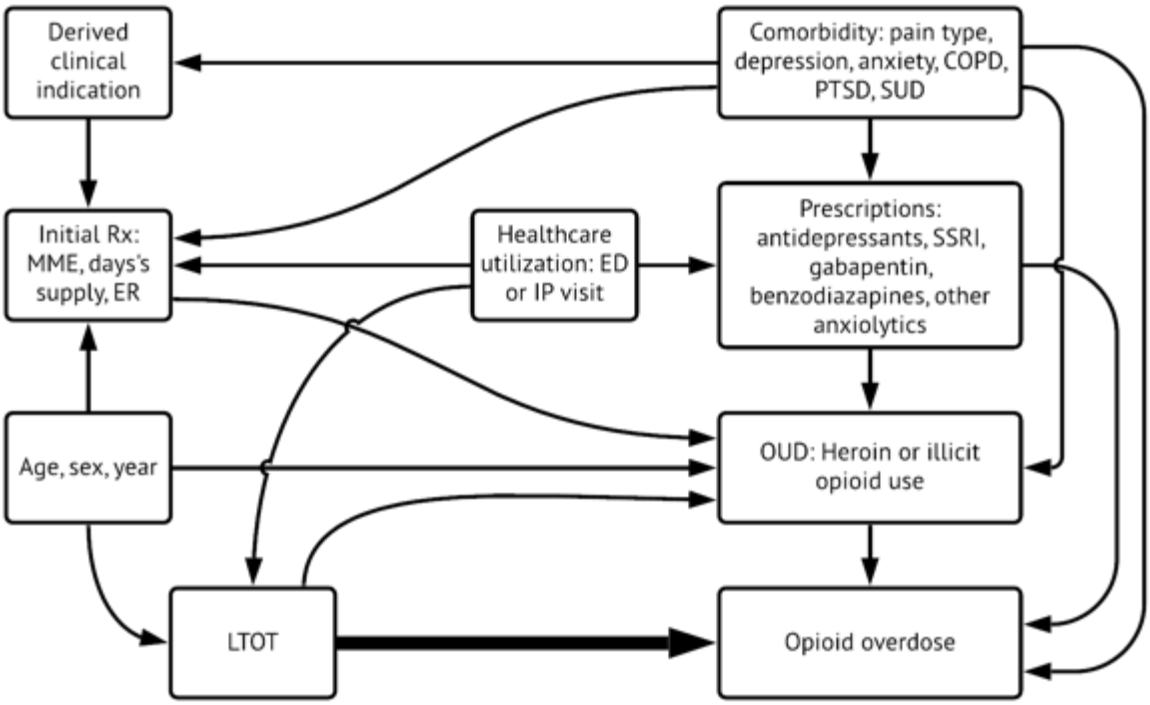
Competing Events

Competing events after the anchoring date were treated as competing risks rather than censoring events in Aim 1 analyses (91, 92). These competing events included death not due to opioid overdose, identified in death records, cancer diagnosis in insurance claims. Censoring competing events infers the assumption that a patient can still experience the outcome of interest following the competing event, which can introduce bias into our effect estimates. By treating death not due to opioid overdose as a competing event, we recognize that a patient who dies due to other causes cannot go on to experience an opioid overdose event. Similarly, once a patient is diagnosed with cancer, they are then no longer part of a population of patients without a history of cancer. In this analysis that uses an all-available lookback to define cancer history, a patient diagnosed with cancer cannot then transition back to a non-cancer state and cannot experience an opioid overdose as a patient without a history of cancer.

Clinical and Demographic Characteristics

Clinical and demographic characteristics were identified *a priori* as potential confounders based on a directed acyclic graph (DAG) (Figure 3.5). Characteristics identified at the time of the index prescription included derived clinical indication (surgery, acute pain, or chronic pain), initial dose of opioids received in morphine milligram equivalents (MMEs), initial days' supply, opioid duration of action (e.g., extended release), demographics (sex, age), and year of initiation. Additional clinical conditions ≤180 days prior to the index opioid prescription included benzodiazepine or other anxiolytics use, selective serotonin reuptake inhibitor (SSRI) or other antidepressant use, gabapentin use, depression, anxiety or post-traumatic stress disorder (PTSD), substance use disorders excluding OUD (e.g. alcohol use disorder), and chronic obstructive pulmonary disease (COPD). We also identified any diagnosed acute or chronic back pain, injury pain, neuropathic pain, arthritic (rheumatoid or osteoarthritis) pain, or other pain within 180 days prior to the index date. Finally, we identified any inpatient or ED visit within 30 days prior to the index date.

Figure 3.5. Directed acyclic graph of hypothesized relationships of key variables in Aim 1



Statistical analyses

We first described the proportion of opioid-naïve patients exposed to LTOT following surgery or pain diagnosis by the above covariates.

Our primary aim was to examine the association between LTOT and risk of clinically recognized nonfatal or fatal opioid overdose. The causal diagram in Figure 3.5 outlines the hypothesized associations between the exposure, outcome, and potential confounders of our association of interest.

We used stabilized inverse probability of treatment weights (IPTW) to account for measured confounding. To create IPTW, propensity scores were derived from a multivariate logistic regression model estimating the probability of LTOT as a function of measured covariates described above. We stabilized the IPTW by dividing the probability of treatment by the propensity score (Formula 1). To improve confounding

(1)

control, we used restricted cubic spline terms for continuous covariates where appropriate, determined using the Akaike information criterion (AIC).

$$IPTW_i = \frac{\hat{P}\ (A_i = a)}{\hat{P}\ (A_i = a|L_i)}$$

To account for informative censoring, we estimated time-varying stabilized inverse probability of censoring weights (IPCW) using pooled logistic regression at 6-month intervals over the duration of follow-up, multiplying weights over time as (1) ו in Formula 2, where D_i is an indicator of whether the patient did not drop out prior to time q and L_i is a vector of covariates as defined above. Total inverse probability weights (IPW) were calculated by multiplying IPTW by IPCW. To minimize the impact of extreme weights, we truncated IPW at the upper and lower 0.02%. We used the Aalen-Johansen estimator of the cumulative incidence function accounting for competing risks of cancer diagnosis or death not due to opioid overdose and weighted by truncated IPW, as shown in Formula 3 (91, 92). Robust variance estimators were used to obtain conservative 95% confidence intervals (CI). We calculated risk differences (RD) at 6 months, 1 year, 2 years, and 3 years.

$$IPCW_i = \prod_{q \le t} \frac{\hat{P}\{D_i(q) = 0\}}{\hat{P}\{D_i(q) = 0|L_i\}} \quad (2)$$

$$\hat{F}(t, j) = \sum_{k \le t} \frac{d_{jk}^{IPW}}{n_k^{IPW}} \prod_{h<k} \left(1 - \frac{d_h^{IPW}}{n_h^{IPW}}\right) \quad (3)$$

Our secondary aim was to examine modification of the association between LTOT and risk of opioid overdose, stratifying by chronic pain versus acute pain or surgery. We re-estimated IPTW and IPCW, including derived indication in the numerator

of the stabilized weights and stratifying the cumulative incidence function by derived indication. We examined magnitude of stratum-specific estimates and confidence interval overlap for evidence of meaningful modification by derived clinical indication.

Sensitivity analyses

We conducted two sensitivity analyses of our exposure definition. First, we relaxed our definition of LTOT to ≥1 prescription in each of the three 30-day periods within the 90-day exposure definition period after the index date, without a requirement for cumulative days of supply. We then re-estimated IPTW and IPCW and repeated the above analyses. Next, we created a multi-category definition of duration of opioid therapy, categorizing patients as short-term (<30 days' supply), medium-term (30-59 days), and long-term (≥60 days). We re-estimated IPTW using multinomial logistic regression and repeated the above analyses.

Next, we investigated the threat of survivor bias due to our 90-day exposure classification window and the resulting exclusion of overdoses experienced in those 90 days. To do so, we included patients with a fatal or nonfatal opioid overdose during the 90-day exposure classification window who met all other inclusion and exclusion criteria. We first characterized the time distribution of opioid overdose events within 90 days of the index date. Next, among patients experiencing an opioid overdose at any point, we examined predictors of experiencing a fatal or nonfatal opioid overdose within those first 90 days of the index date compared to ≥90 days after the index date. For each covariate outlined in "Patient Factors", we examined the distribution of each factor, using Fisher's exact test to test for differences in categorical variables, and the Mann-Whitney U test in the case of continuous variables. Variables with a *p*-value of <0.05

were considered strongly predictive of opioid overdose within the first 90 days following the index date.

Aim 2

Data Sources

In this ecological analysis of aggregate data, we used surveillance data of syphilis diagnoses from the North Carolina Division of Public Health HIV/STD/Hepatitis Surveillance Unit and emergency department (ED) visits from the North Carolina Disease Event Tracking and Epidemiologic Collection Tool (NC DETECT) (93), a syndromic surveillance system that contains data from North Carolina EDs, Poison Control, and emergency medical services. Population characteristics for US Zip Code Tabulation Areas (ZCTA) and counties in North Carolina were obtained from US census data, using American Community Survey (ACS) 5-year estimates from 2012 (94) and 2017 (95).

Syphilis Diagnoses

We examined all diagnoses of early (primary, secondary, and early latent syphilis) reported between January 1, 2008 and December 31, 2017 to the North Carolina Division of Public Health HIV/STD/Hepatitis Surveillance Unit. Cases diagnosed in these early stages represent more recent infections and thus are more proximate measures of incident syphilis infections. Syphilis is a reportable disease; therefore, surveillance data are expected to contain all diagnosed infections. Residential county and 5-digit ZIP code were extracted for each diagnosed person. Cases with a missing or incorrectly entered ZIP code or a residence outside North Carolina were excluded from analysis.

Emergency Department Visits for Opioid Overdose

As a proxy for opioid use, we enumerated emergency department (ED) visits for possible opioid overdose from the North Carolina Disease Event Tracking and Epidemiologic Collection Tool (NC DETECT) (93). For this analysis, we obtained a limited dataset containing visit date, county, 5-digit ZIP code, chief complaint, and International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and 10th Revision (ICD-10-CM) diagnosis and procedure codes for all ED visits from January 1, 2008 to December 31, 2017. NC DETECT collects data from >100 EDs in NC, following a 2005 statewide mandate requiring all civilian EDs to report certain data to the state (96).

Possible cases of opioid overdose were identified using a combination of chief complaint text searches and diagnosis codes. ICD-9-CM codes have been shown to have high specificity, but low sensitivity (97, 98); therefore, this study additionally makes use of chief complaint. Included cases met at least one of the following criteria: (a) “Narcan” or “naloxone” recorded in chief complaint, (b) terms in chief complaint indicating overdose (e.g. poison, overdose, loss of consciousness, etc.) in combination with involvement of an opioid (e.g., heroin, opioid, etc.), (c) ICD-9-CM and ICD-10-CM diagnosis codes for opioid poisoning or intoxication, or (d) chief complaint indicating overdose and diagnosis code for opioid-related disorders (See Table 3.6 for all search terms and ICD codes used) (93). Cases with missing or incorrectly entered ZIP code or a residence outside North Carolina were excluded from this analysis.

Table 3.6. Opioid Overdose Case Definition[a,b]

Criterion #	Chief Complaint	Diagnosis Codes	
		ICD-9-CM	*ICD-10-CM*
1	Narcan OR naloxone		
2	***Any of***: poison*; overdose* OR overdoes*; averdose*; averdoes*; "over dose*"; overose*; nodding; nod; snort*; ingest*; injest*; intoxic*; unresponsiv*; "loss of consciousness"; syncop*; "shortness of breath"; "altered mental status"; od **AND** ***Any of***: heroin; herion; hod; speedball; "speed ball"; dope; opioid; opiod; opoid; opiate; opate; opium; opuim; opum; methadone; suboxone; oxyco*; oxyi*; percoc*; vicod*; fentan*; hydrocod*; morphin*; codeine; codiene; codene; oxymor*; dilaud*; hydromor*; tramad*; suboxin*; buprenorphine		
3		965.00, 965.01, 965.02, 965.09, E850.0, E850.1, E850.2	T40.1X1A, T40.1X4A, T40.0X1A, T40.0X4A, T40.2X1A, T40.2X4A, T40.3X1A, T40.3X4A, T40.4X1A, T40.4X4A, T40.601A, T40.604A, T40.691A, T40.694A, F11.12, F11.120, F11.121, F11.122, F11.129, F11.22, F11.220, F11.221, F11.222, F11.229, F11.92, F11.920, F11.921, F11.922, F11.929
4	***Any of***: poison*; overdose*; overdoes*; averdose*; averdoes*; "over dose*"; overose*; od; nodding; nod; snort*; ingest*; injest*; intoxic*; unresponsiv*; "loss of consciousness"; syncop*; "shortness of breath"; "altered mental status")		**AND** F11.[129]0

[a]To meet the definition of possible opioid overdose, a patient had to meet one of the four criteria. For criteria 1 and 2, designation is made in terms of chief complaint. For criterion 3, the designation is made based on diagnosis code. For criterion 4, the designation is made based on both chief complaint and diagnosis code.

[b]This definition has been adapted from NC DETECT Opioid Overdose/Unintentional – Beta case definition, https://ncdetect.org/case-definitions/

Population Data and Rate Estimation

Characteristics of interest from the ACS for North Carolina ZCTAs and counties included percentage of the population aged 20-24 and 25-34, percent Black or African American, percent Hispanic, unemployment rate, poverty rate, percent completing high school (or equivalent), percent female, and population density.

Annual counts of syphilis diagnoses were converted to incident diagnosis rates by dividing the annual number of diagnosed cases among residents of a given geographic area by the total population estimate from the ACS in that area in a given year. Similarly, the annual overdose rate was calculated as the number of overdose events in EDs among residents of each geographic area in a given year, divided by the total population in that area in that year. We multiplied both quantities by 100,000 to express rates as counts per 100,000 people.

Observation Units

The primary geographic observation unit for this analysis was ZCTA. ZIP codes from NC DETECT and syphilis surveillance data were mapped to ZCTAs (hereafter referred to as ZIP codes), which were then used to join these data to census data and mapping files. As detailed under “Ancillary Analyses” below, we used counties as the geographic observation unit in sensitivity analyses.

Spatial smoothing

Spatial local empirical Bayes estimation (99) was used to smooth both syphilis and overdose rates in order to reduce noise due to mapping rare events in areas with small populations. Such events could lead to extreme differences across boundaries that may be artifacts created by the specific geographic boundaries used and not

representative of the true underlying local diagnosis and overdose rates. This approach shrinks estimators towards a local mean based on neighborhoods defined using contiguity weighting matrices (99).

Regression Analyses

Smoothed syphilis and overdose rates were truncated at the 99th percentile to minimize the impact of extreme outliers and were transformed using a natural log + 1 transformation to correct for overdispersion inherent to rare disease data.

We first used Ordinary Least Squares (OLS) regression models of syphilis rates regressed on overdose rates, using smoothed data for each year. OLS regression assumes independence in model residuals. In order to test for spatial dependence, we ran Moran's I tests on residuals from yearly OLS models, which demonstrated significant spatial autocorrelation of model residuals. We then proceeded with using spatial autoregressive panel data regression models with fixed effects (Formula 4), including a term for spatial lag of the dependent variable (syphilis rates) and a spatially lagged error term (100, 101).

$$y_{nt} = \lambda W y_{nt} + X_{nt}\beta + c_n + u_{nt}$$
$$u_{nt} = \rho W u_{nt} + v_{nt} \qquad t = 1,2,\dots,T \tag{4}$$

where ynt = (y1t, y2t, . . . , ynt) 0 is an n × 1 vector of observations on the dependent variable for time period t;
Xnt is an n × k matrix of nonstochastic time-varying regressors for time period t. Xnt may also contain spatial lag of exogenous covariates; cn is an n × 1 vector of individual effects;
unt is an n × 1 vector of spatially lagged error;
vnt = (v1t, v2t, . . . , vnt) 0 is an n × 1 vector of innovations, and vit is i.i.d. across i and t with variance σ 2 ;
and W is a n × n spatial weighting matrix

Results from these models can be interpreted in three parts: the direct association, indirect association, and total association (102). The direct association is

the association between the independent variable and the dependent variable in a given ZIP code. The indirect association is the spillover impact from neighboring areas. The total association is the sum of the indirect and direct association.

We used a weighting matrix of first-order (queen) contiguity neighbors in our primary analyses (103). Queen neighbors share a common edge or vertex. In order to determine whether any spatial association between overdose rates and syphilis diagnoses varied over time, we included an interaction term between log overdose rate and time (in years). We assessed significance of the spatial lag, spatial error, and interaction terms using a significance threshold of 0.05.

Ancillary Analyses

In an ancillary analysis, we aimed to explore a more causal interpretation of opioid use as a driver of syphilis incidence. While a true causal analysis could not be conducted due to the ecological nature of this study, we recognized that there are factors that may be driving both epidemics. We identified *a priori* population-level characteristics likely to be associated with both overdose rates and syphilis rates (that is, potential confounders for which adjustment would be warranted in a causal analysis). These characteristics included ACS estimates of all covariates listed above except race, which was explored in a modification analysis detailed below (2, 104-106). We modeled covariates using restricted cubic splines and examined variance inflation factors for potentially problematic collinearity, finding none. We repeated the above regression analyses, this time adjusting for these potential confounders. Additionally, we explored possible effect measure modification, including an interaction term between overdose rates and an indicator for whether the percentage of the population identifying as Black

or African American in a given ZIP code was above or below the median percentage across all NC ZIP codes.

To examine the extent to which the opioid epidemic might have played a role in the recent rise in new syphilis diagnoses in women and MSW specifically, we conducted analyses limiting syphilis diagnoses to: (1) women only, and (2) women and MSW, excluding men who report having sex with other men. We used all syphilis diagnoses in primary analyses due to 1) small case counts, and 2) missing data on gender of sexual partners and potential for misclassification of MSW status.

Results of spatial analyses can be highly sensitive to the level of data aggregation, also known as the Modifiable Area Unit Problem (107), as well as the specification of neighbors in weighting matrices (103). Thus, we conducted sensitivity analyses to examine the impact of using: (3) raw rates instead of spatial empirical Bayes smoothed rates, (4) county-level rather than ZIP code-level data aggregation, (5) rook (neighbors that share a common edge) contiguity rather than queen contiguity weighting matrices, and (6) contiguity weighting matrices with both first- and second-order queen neighbors (neighbors of neighbors), with first-order neighbors assigned a weight of 1 and second-order neighbors assigned a weight of 0.5. To address potential sensitivities of results to other design choices, we conducted two further sensitivity analyses in which we: (7) lagged syphilis rates by one year relative to overdose rates in order to account for time from syphilis infection to diagnosis, and (8) used only the first overdose event among people who overdosed multiple times in a year to examine the possible impact of multiple overdose events per person inflating overdose rates relative

to the number of people experiencing an opioid overdose in areas with small population size.

Software

In Aim 1, data management was completed in SAS 9.4 (Cary, NC) and all analyses were conducted in R v3.6.0 (108, 109). In Aim 2, data processing, spatial smoothing, and visualization were completed in R v3.6.1 (108) and spatial regression analyses were done in Stata 16 (College Station, TX) (101). Appendix 1 lists all R packages used.

Ethical Approval

The institutional review board of the University of North Carolina at Chapel Hill approved all analyses in Aim 1 and determined the secondary analysis of existing data in Aim 2 to be exempt from further review.

CHAPTER IV: LONG-TERM OPIOID THERAPY AND RISK OF OPIOID OVERDOSE BY DERIVED CLINICAL INDICATION: AN OBSERVATIONAL COHORT STUDY OF PRIVATELY INSURED PATIENTS IN NORTH CAROLINA

Introduction

Opioid overdoses account for more than two-thirds of drug-related deaths in the United States (US) (1, 2) and one-third of emergency department (ED) visits for nonfatal overdoses involving drugs (3). The US opioid epidemic resulted in >440,000 deaths from 1999 through 2018 (1) and >300,000 ED visits for nonfatal opioid overdose in 2017 alone (3). While much of this epidemic has been driven in recent years by heroin and illicit synthetic opioids, prescription opioids remain a significant contributor to opioid-related morbidity and mortality (4). Prescription opioid use often precedes initiation of heroin and synthetic opioids (5-12).

Prescription opioids have an important role in pain management (110). In a survey of US adults, 55% reported recent pain (13), and the Centers for Disease Control and Prevention (CDC) estimates that >20% of US adults experience chronic pain (14). Many of these individuals receive prescription opioids to manage their pain; 15% of the US population filled at least one opioid prescription in 2018 (15). While the annual volume of written prescriptions for opioids has declined nationwide since 2012 after years of steady increases, the average days of opioid supply per prescription have increased since 2006 (15, 41). In 2016, the CDC released guidelines for opioid

prescribing, recommending that providers minimize the duration of opioid therapy in pain patients (16).

Long-term use of prescription opioids often begins with treatment of acute (17-20) and post-surgical pain (17, 21-23) that then extends past the window of normal healing (20, 60). Long-term opioid therapy (LTOT) has been shown to be associated with opioid use disorders (OUD) and opioid overdose (24, 25). Much work has been done on incidence and risk factors for LTOT in three main contexts: (1) post-surgical settings, (2) chronic, non-cancer pain patients, and (3) any opioid prescription regardless of indication. The definition of LTOT varies widely across studies (26, 27), with many studies not accounting for consistent long-term use of prescription opioids following initiation of opioid therapy (27). Furthermore, few studies have examined the relationship between opioid therapy duration and opioid overdose according to the initial pain management indication (28), Patients with chronic non-cancer pain may initiate opioid therapy with a clinical goal of long-term therapy, and treatment recommendations differ for patients with chronic pain compared to patients treated for acute or post-surgical pain (16).

Our objective was to examine the three-year risk of fatal or nonfatal opioid overdose by duration of opioid therapy while applying a rigorous definition of LTOT requiring consistent exposure to opioid therapy. We further assessed whether the relationship between duration of opioid therapy and opioid overdose differed for patients with a chronic pain indication compared to a surgical or acute pain condition for their initial opioid prescription.

Methods

Data Source

We used 13 years of de-identified claims data from a large provider of private health insurance in North Carolina (NC) covering about one-fifth of NC's population from 2006 to 2018. These longitudinal healthcare data include member demographics, residence, pharmacy claims, and inpatient and outpatient claims with data on dates of service and billed diagnoses and procedures. Insurance claims were linked to NC death records using a hierarchical matching algorithm (Figure 3.2).

Study Population

We used a new-user design (84), identifying opioid-naïve individuals initiating prescription opioids (Table 3.1) for pain management between July 1, 2006 and July 1, 2018. Eligible patients were aged 18-64, living in NC, and actively insured. Patients were required to have six months (180 days) of continuous insurance enrollment (washout period) prior to their index date.

For surgical patients, the index date was defined as (1) the date of outpatient surgery or final day of an inpatient stay for an inpatient surgery if the first opioid prescription was billed to insurance ≤14 days before the date of outpatient surgery or first day of an inpatient stay for an inpatient surgery event (Figure 3.3A), or (2) the prescription claim date if the first opioid prescription was filled ≤14 days after a surgery event (Figure 3.3B). Among patients without a surgery event, the index date was defined as the date of the first opioid prescription claim ≤14 days after a pain diagnosis (Figure 3.3B).

In order to ensure patients were opioid naïve at their index date, we excluded patients if they had evidence of prescription claims for opioid analgesics, opioid overdose, opioid use disorder (OUD), or medication-assisted treatment for OUD during the 180-day washout period prior to the index date. Patients were also excluded if they had a cancer diagnosis using all-available lookback or surgery within 180 days prior to the index date. These patients were excluded due to the potentially complex nature of their pain conditions and treatment regimens. Patients were followed forward 90 days from the index date for exposure classification and were excluded if they experienced one or more of 1) opioid overdose, 2) death, 3) disenrollment, 4) an invasive surgery, or 5) cancer diagnosis in that 90-day period (Figure 3.4). The impact of excluding overdoses (n=82) in the first 90 days of follow-up was evaluated in a sensitivity analysis.

Classification of clinical indication for initial prescription

Our definition of a derived clinical indication of pain management included post-surgical pain, defined as patients undergoing invasive surgery as classified by the Healthcare Cost and Utilization Project (HCUP) (85) using Current Procedural Terminology (CPT) codes, diagnosis of acute pain (22, 86-88) using International Classification of Diseases, 9th Revision (ICD-9-CM) and 10th Revision (ICD-10-CM), Clinical Modification (Table 3.2), or diagnosis of chronic pain (22, 86-88) using ICD-9-CM and ICD-10-CM codes (Table 3.3).

We used a hierarchical algorithm to assign a derived clinical indication, assuming that (1) patients with a surgical indication (Figures 3.3A, 3.3B) received an opioid prescription related to that surgery, (2) patients without an indication of surgery who had a diagnosis of acute pain (Figure 3.3B) received an opioid prescription related to the

acute pain diagnosis, and (3) patients without evidence of surgery or acute pain who had a chronic pain diagnosis ≤14 days prior to the index prescription received the prescription for the chronic pain condition (Figure 3.3B).

Exposure

We defined long-term opioid therapy (LTOT) using the date of fill and days' supply to calculate the total days of supply of prescribed opioids received and timing of receipt. Our definition of LTOT required ≥1 prescription in each of the three 30-day periods within the 90-day exposure definition period after the index date (89), with a cumulative days' supply of opioids received totaling ≥60 days. A prescription was determined to occur in a 30-day period if it was dispensed in that period, or if the date of fill plus days' supply fell within that 30-day period. When overlapping prescriptions of the same ingredient occurred, we used a seven-day rule such that if the start date was within seven days of the end date of the previous prescription, this was assumed to reflect an early refill and the start date of that prescription was pushed forward to the end date of the previous prescription (90). If the overlap was greater than seven days, the prescriptions were assumed to truly overlap and treated as such. Patients with <60 days' supply of opioids dispensed and without consistent exposure in each of the 30-day periods were classified as short- to medium-term opioid therapy (SMTOT).

Patients were followed forward 90 days from the index date. On day 90, the anchoring date, patients were classified as exposed to LTOT or SMTOT (Figure 3.3C). We conducted sensitivity analyses (described in "Sensitivity Analyses" below) of our exposure definition to examine the robustness of our findings to varying definitions of LTOT.

Follow-up time

We followed patients forward from the anchoring date (index date plus 90 days) until the first of 1) nonfatal or fatal opioid overdose (outcome), 2) loss of eligible insurance coverage (censoring event), 3) cancer diagnosis (competing risk) (91, 92), 4) death due to causes other than opioid overdose (competing risk), 5) administrative censoring three years after the anchoring date, or 6) administrative censoring at the end of the study period (September 30, 2018).

Outcome

Our outcome of interest was the first fatal or nonfatal opioid overdose within three years of initiating prescription opioids for pain management. In insurance claims, clinically recognized opioid overdose was defined using ICD-9-CM and ICD-10-CM diagnosis codes in inpatient, outpatient, and emergency department (ED) claims (Table 3.4). In linked death records, fatal opioid overdose was defined using ICD-10 codes and a combination of underlying and contributing cause of death (Table 3.5) (86).

Patient factors

Clinical and demographic characteristics were identified *a priori* as potential confounders based on a directed acyclic graph (DAG). Characteristics identified at the time of the index prescription included derived clinical indication (surgery, acute pain, or chronic pain), initial dose of opioids received in morphine milligram equivalents (MMEs), initial days' supply, opioid duration of action (e.g., extended release), demographics (sex, age), and year of initiation. Additional clinical conditions ≤180 days prior to the index opioid prescription included benzodiazepine or other anxiolytics use, selective serotonin reuptake inhibitor (SSRI) or other antidepressant use, gabapentin use,

depression, anxiety or post-traumatic stress disorder (PTSD), substance use disorders excluding OUD (e.g. alcohol use disorder), and chronic obstructive pulmonary disease (COPD). We also identified any diagnosed acute or chronic back pain, injury pain, neuropathic pain, arthritic (rheumatoid or osteoarthritis) pain, or other pain within 180 days prior to the index date. Finally, we identified whether any inpatient or ED visit occurred within 30 days before the index date.

Statistical analyses

We first described the proportion of opioid-naïve patients exposed to LTOT following surgery or pain diagnosis by the above covariates.

Our primary aim was to examine the association between LTOT and risk of clinically recognized nonfatal or fatal opioid overdose. We used stabilized inverse probability of treatment weights (IPTW) to account for measured confounding. To create IPTW, propensity scores were derived from a multivariable logistic regression model estimating the probability of LTOT as a function of measured covariates described above. To improve confounding control, we used restricted cubic spline terms for continuous covariates where appropriate, determined using the Akaike information criterion (AIC). To account for informative censoring due to disenrollment prior to administrative censoring at three years or end of study period, we estimated time-varying stabilized inverse probability of censoring weights (IPCW) using pooled logistic regression at six-month intervals over the duration of follow-up, multiplying weights over time. Total inverse probability weights (IPW) were calculated by multiplying IPTW by IPCW. To minimize the impact of extreme weights, we truncated IPW at the upper and lower 0.02%. We used the Aalen-Johansen estimator of the cumulative incidence

function accounting for competing risks of cancer diagnosis or death not due to opioid overdose and weighted by truncated IPW (91, 92). Robust variance estimators were used to obtain conservative 95% confidence intervals (CI). We calculated risk differences (RD) at six months, one year, two years, and three years.

Our secondary aim was to examine modification of the association between LTOT and risk of opioid overdose, stratifying by chronic pain versus acute pain or surgery. We re-estimated IPTW and IPCW, including derived indication in the numerator of the stabilized weights and stratifying the cumulative incidence function by derived indication. We examined the magnitude of stratum-specific estimates and confidence interval overlap for evidence of meaningful modification by derived clinical indication.

Sensitivity analyses

We conducted two sensitivity analyses of our exposure definition. First, we relaxed our definition of LTOT to ≥1 prescription in each of the three 30-day periods within the 90-day exposure definition period after the index date, without a requirement for cumulative days of supply. We then re-estimated IPTW and IPCW and repeated the above analyses. Next, we created a multi-category definition of duration of opioid therapy, categorizing patients as short-term (<30 days' supply), medium-term (30-59 days), and long-term (≥60 days). We re-estimated IPTW using multinomial logistic regression and repeated the above analyses.

Next, we investigated the threat of survivor bias due to our 90-day exposure classification window and the resulting exclusion of overdoses experienced in those 90 days. To do so, we included patients with a fatal or nonfatal opioid overdose during the 90-day exposure classification window who met all other inclusion and exclusion

criteria. We first characterized the time distribution of opioid overdose events within 90 days of the index date. Next, among patients experiencing an opioid overdose at any point, we examined predictors of experiencing a fatal or nonfatal opioid overdose within those first 90 days of the index date compared to ≥90 days after the index date. For each covariate outlined in "Patient Factors", we examined the distribution of each factor, using Fisher's exact test to test for differences in categorical variables, and the Mann-Whitney U test in the case of continuous variables. Variables with a *p*-value of <0.05 were considered strongly predictive of opioid overdose within the first 90 days following the index date.

Software

Data management was completed in SAS 9.4 (Cary, NC). All analyses were conducted in R v3.6.0 (see Appendix 1 for packages used) (108, 109).

Ethical Approval

This study was approved by the institutional review board of the University of North Carolina at Chapel Hill.

Results

We identified 492,983 eligible patients initiating prescription opioids for pain management between July 1, 2006 and July 1, 2018 (Figure 3.4). The mean age of patients was 43 years (SD 12 years) and 50% were female (Table 4.1). Most had a derived clinical indication of acute pain (32%) or surgery (35%). Thirteen percent had filled a prescription for benzodiazepines in the six months prior to the index date, 12% had received an SSRI, and 3% had filled a prescription for gabapentin. The majority of patients received an initial opioid dose of 20 to 49 MMEs (56%) and the most common

days' supply of the initial prescription was 4-7 days (45%). Extended-release opioids were not commonly prescribed (<1%).

Long-term Opioid Therapy

Of patients newly initiating prescription opioids for pain management, 8,582 (1.7%) went on to receive long-term opioid therapy (LTOT). Patients exposed to LTOT were more likely to fall into the 45-54 or 55-64 age ranges compared to younger age ranges and were majority male (Table 4.1). Most patients (76%) who went on to receive LTOT had chronic pain as the clinical indication at the time of the first prescription, compared to 32% of patients with short- to medium-term opioid therapy (SMTOT). Counter-intuitively, patients who went on to receive LTOT were less likely than patients exposed to SMTOT to receive an initial dose of 50-89 MMEs (11% vs. 21%) or ≥90 MMEs (8% vs. 10%) but were more likely to receive longer initial days' supply.

Patients who went on to receive LTOT were also more likely than patients with SMTOT to have had prescriptions for benzodiazepines (26% vs. 12%), SSRIs (18% vs. 12%) or other antidepressants (20% vs. 9%), or gabapentin (13% vs. 3%) in the six months prior to their index date. Comorbidities were also more common in those receiving LTOT. Covariates were well balanced after weighting with stabilized IPTW (Figure 4.1).

Follow-up

Median length of follow-up was 792 days (IQR: 318-1095 days) following the anchoring date. Patients with LTOT contributed less follow-up (median 643 days, IQR: 267-1095) than patients with SMTOT (median 795 days, IQR: 319-1095), due to the distribution of those experiencing competing risk of death not due to opioid overdose

(LTOT: n=56 [0.7%]; SMTOT: n=979 [0.2%]) or cancer diagnosis (n=363 [4.2%]; n=19,542 [4.0%]), opioid overdose (n=40 [0.5%]; n=341 [0.1%]), and disenrollment prior to administrative censoring (n=4,550 [53%]; n=245,612 [51%]).

Risk of opioid overdose

We identified 381 opioid overdose events within three years of follow-up after the anchoring date. Seventeen percent (n=64) of opioid overdose events were fatal. The proportion of overdose events that were fatal was higher among patients with LTOT (20%) compared to patients exposed to SMTOT (16%).

The crude overall three-year risk of opioid overdose was 0.1% (95% CI: 0.1-0.1), and the crude cumulative incidence of opioid overdose was consistently higher in patients with LTOT than patients with SMTOT (Figure 4.2). Among patients exposed to LTOT, the crude three-year risk of opioid overdose was 0.7% (95% CI: 0.5-1.0), compared to 0.1% (95% I: 0.0-0.1) among patients exposed to SMTOT.

In weighted analyses to address confounding and informative censoring, the cumulative incidence of opioid overdose in the LTOT group within the first year of follow-up remained consistently higher than the risk of opioid overdose in patients with SMTOT (Figure 4.3). The three-year risk of opioid overdose was 0.7 percentage points (RD_w= 0.007, 95% CI: 0.001,0.013) higher in the LTOT group compared to patients with SMTOT (Table 4.2).

In analyses stratified by derived clinical indication, patients who were exposed to LTOT in each stratum were at increased risk of opioid overdose compared to SMTOT through three years of follow-up (Figure 4.4). Stratified estimates did not differ significantly from each other at any point during follow-up, so we cannot infer

meaningful modification by initial clinical indication (Figure 4.5). These results are imprecise at later points of follow-up due to small case counts and should be interpreted with caution.

Sensitivity Analyses

In our first sensitivity analysis, we examined the impact of using evidence of a prescription each month with no minimum days of supply to define LTOT. Using this definition, 25,423 (5.2%) patients had LTOT. The trend in the risk of opioid overdose among patients with LTOT compared to patients with SMTOT was similar to estimates from the primary analysis, but estimates were attenuated towards the null (Table 4.2, Figure 4.6).

In our second sensitivity analysis we used a categorical exposure of short-term use (<30 days' supply), monthly prescriptions of 30-59 days' supply, or ≥60 total days of prescription opioids received. Using this definition, 474,549 (96%) patients did not receive a prescription each month or filled <30 days of supply, 9,862 (2%) had a prescription each month with cumulative days of supply of 30-59 days of opioids, and 8,582 (1.7%) received ≥60 days of prescription opioids in the 90 days following the index date. The absolute risk differences comparing patients exposed to ≥60 days of prescription opioids to patients prescribed <30 days were comparable to results from the primary analysis (Figure 4.6). The cumulative incidence among patients prescribed 30-59 days of opioids was consistently higher than among patients prescribed <30 days through three years of follow-up, but the magnitude of the absolute risk difference was smaller than the absolute risk difference comparing ≥60 days of prescription opioids to

<30 days (Table 4.2, Figure 4.6). These results suggest a dose-response relationship between duration of opioid therapy in the first 90 days and subsequent overdose risk.

Finally, we examined outcomes occurring <90 days after the index date compared to ≥90 days after the index date. There were 82 opioid overdose events <90 days following the index date, ten (12%) of which were fatal, and the median time to overdose was 36 days (IQR: 16-54 days). Among patients experiencing an opioid overdose at any time after the index date (n=463), the distribution of patient factors was similar between patients overdosing within 90 days and patients overdosing ≥90 days after the index date. Among those with an overdose, only a history of ED visit within 30 days before the index date (p=0.018) was associated with a higher likelihood of that overdose occurring within the first 90 days rather than >90 days after the index date.

Discussion

In this sample of patients with private insurance in North Carolina who initiated prescription opioid therapy for a clinical indication of acute pain, chronic pain, or surgery, the cumulative incidence of opioid overdose among patients receiving long-term opioid therapy (LTOT) in the first 90 days was persistently higher than among patients receiving short- to medium-term opioid therapy (SMTOT). Our estimates of risk of opioid overdose by duration of opioid therapy were robust to varying definitions of opioid therapy. Less conservative definitions of opioid therapy in this study still demonstrated an increased risk of opioid overdose among patients exposed to LTOT, as well as a dose-response relationship between duration of opioid therapy in the first 90 days and subsequent overdose risk when using a categorical exposure definition.

We did not find meaningful modification of the relationship between duration of opioid therapy and risk of opioid overdose by initial derived clinical indication.

Our findings are consistent with existing evidence that long-term opioid use puts patients at higher risk of adverse outcomes, including OUD and overdose (24, 111), and emphasize the importance of the 2016 CDC prescribing guidelines that called on physicians to minimize the duration of opioid therapy for pain management (16). While prescription opioids have an important role in pain management, the clinical benefit of long-term opioid therapy compared to treatment with non-opioid analgesics has been called into question (16).

Within our population of patients initiating prescription opioid therapy for pain management, 1.7% went on to have LTOT. This is lower than many (27, 112), but not all (27, 113), previous estimates of LTOT incidence after surgery or for chronic pain management among opioid-naïve patients. As noted in a recent review of long-term opioid therapy definitions (27), there is no consistent definition of LTOT. Our definition of LTOT is more conservative than has been used in many previous studies (27, 112), requiring consistent monthly exposure to prescription opioids with at least 60 total days of supply of prescribed opioids dispensed in the three months following a pain diagnosis or surgery. This conservative definition focuses on ensuring consistent exposure to opioid therapy following a clinical indication compared to definitions that simply look at whether the patient has an active prescription at some point in the future, which may lead to classification of a later separate prescription of possibly different etiology as related to the initial episode of opioid therapy despite a gap in treatment. Our approach minimized the likelihood that we were evaluating patients exposed to repeated short-

term episodes of opioid therapy, but instead were measuring overdose risk in patients continuously exposed to opioid therapy. Relaxing our definition of LTOT to monthly exposure to prescription opioids with no requirement for days of supply dispensed within the first 90 days resulted in 5.2% of patients transitioning to LTOT in our population, consistent with the range of previous estimates using more relaxed definitions of LTOT in opioid-naïve patients (27, 111, 114).

In our secondary aim, we examined modification of the relationship between LTOT and opioid overdose by the initial derived clinical indication. Presumably unintended long-term use has been noted as a troubling adverse outcome of postsurgical and acute pain management, where opioid therapy continues past the expected window of healing (17, 22, 23, 111, 112, 114, 115). Several challenges in managing chronic non-cancer pain that can increase risk of OUD and opioid overdose have been noted in previous research, including dose escalations and hyperalgesia (116, 117), tapering or stoppage of opioids (16, 118), and use of long-acting opioids instead of short-acting opioids in pain management (119, 120). However, we did not find strong evidence of modification by initial derived clinical indication for treatment with opioid analgesics.

Consistent with previous work, patients exposed to LTOT in our population had higher prevalence of several baseline characteristics that are known risk factors for opioid overdose, including benzodiazepine use, receiving an extended-release formulation (119), diagnosed substance use disorder, depression and anxiety, and COPD (23, 27, 114, 121, 122). These findings suggest that patients who transition to LTOT have several clinical comorbidities and co-medication use at baseline that not

only have been shown to increase risk of LTOT, but also of opioid-related morbidity and mortality. We controlled for these factors using IPTW and still saw increased risk of opioid overdose among patients exposed to LTOT. While our analytic approach was methodologically rigorous, our results may be subject to residual confounding due to the use of insurance claims, which may under-measure important confounders such as substance use disorders and mental health conditions. Insurance claims also do not capture information such as socioeconomic status, which may result in unmeasured confounding.

Our study makes use of a diverse population of privately insured patients representing one-fifth of the population of NC over 13 years during the height of the opioid epidemic. While many previous studies have examined prescription opioid use in specific surgical or chronic pain cohorts, we used a broad population of patients initiating opioid therapy for postsurgical or non-surgical pain management. However, it is important to note that because this study makes use of data from a population of patients with private insurance in NC, our results may not generalize to the broader US population. Our target population was also restricted to patients without a history of cancer; therefore, our results may not generalize to patients who are receiving prescription opioids to manage cancer-related pain.

To measure the long-term risk of opioid overdose by duration of opioid therapy, we restricted our population of patients to those with 90 days of follow-up after their index date. This approach excluded those with acute outcomes occurring within the first 90 days after the index date, which could have led to survivor bias. In sensitivity analyses, we found that history of an ED visit within 30 days prior to the index date was

the only significant difference between those experiencing acute events versus events after 90 days, suggesting that there was likely not a strong measurable selective pressure leading to survivor bias in our primary analyses. We further accounted for selection bias due to missed outcomes after 90 days by applying IPCW to correct for informative censoring.

There are several additional limitations to consider when interpreting these results. This study makes use of insurance claims to measure prescription opioid use and key confounders of the relationship between LTOT and opioid overdose. Pharmacy claims only capture prescriptions that were filled and billed to a patient's insurance but do not capture medications that were paid for out of pocket or illicit opioid use and do not measure what the patient actually consumed, which could lead to exposure misclassification. However, we used a definition of LTOT that we believe more adequately captures true consistent long-term opioid use following an initial prescription in opioid-naïve patients than prior definitions. Opioid overdoses are known to be under-measured in claims data and electronic health records (97). Fatal opioid overdoses are also likely under-measured in mortality records (123), but by taking advantage of linked death records we were able to identify fatal events that may be missed in insurance claims data. Additionally, we do not expect differential sensitivity of outcome classification by duration of opioid therapy and, therefore, do not expect under-measurement of opioid overdoses to be a significant source of bias. Further, diagnostic codes for clinically recognized opioid overdose have high specificity, meaning clinically recognized opioid overdoses are likely true opioid overdoses.

Conclusions

In conclusion, even though a small minority of patients initiating opioid therapy had LTOT, this subset of patients was at notably higher risk of opioid overdose. We found that 1.7% of patients who initiated prescription opioid analgesics following surgery or a pain diagnosis went on to have monthly exposure to prescription opioids with ≥60 total days' supply within 90 days of the index prescription, and there was evidence of a dose-response relationship between duration of opioid therapy and risk of opioid overdose as exposure to opioid therapy increased. The literature lacks a standard definition of LTOT, and this analysis utilized a more conservative definition of LTOT than most previous studies. Future work should examine this definition of LTOT in other patient populations. While opioid therapy has an important role in pain management, these findings confirm the importance of the CDC guidelines to minimize the duration of opioid therapy whenever possible.

Table 4.1. Baseline demographic and clinical characteristics

	Overall (n=492983)	SMTOT (n=484401)	LTOT (n=8582)
Age (mean (SD))	42.87 (12.3)	42.80 (12.3)	46.67 (11.0)
Derived clinical indication (%)			
Surgery	174159 (35.3)	173193 (35.8)	966 (11.3)
Acute pain	157067 (31.9)	155983 (32.2)	1084 (12.6)
Chronic pain	161757 (32.8)	155225 (32.0)	6532 (76.1)
Age category (%)			
18-24	43733 (8.9)	43472 (9.0)	261 (3.0)
25-34	93958 (19.1)	92771 (19.2)	1187 (13.8)
35-44	120077 (24.4)	118205 (24.4)	1872 (21.8)
45-54	131137 (26.6)	128315 (26.5)	2822 (32.9)
55-64	104078 (21.1)	101638 (21.0)	2440 (28.4)
Sex (%)			
Male	245455 (49.8)	240659 (49.7)	4796 (55.9)
Female	247528 (50.2)	243742 (50.3)	3786 (44.1)
Year (%)			
2006	30344 (6.2)	29859 (6.2)	485 (5.7)
2007	59018 (12.0)	58056 (12.0)	962 (11.2)
2008	53586 (10.9)	52719 (10.9)	867 (10.1)
2009	49969 (10.1)	49096 (10.1)	873 (10.2)
2010	44511 (9.0)	43779 (9.0)	732 (8.5)
2011	39017 (7.9)	38334 (7.9)	683 (8.0)
2012	35539 (7.2)	34929 (7.2)	610 (7.1)
2013	34459 (7.0)	33806 (7.0)	653 (7.6)
2014	36249 (7.4)	35492 (7.3)	757 (8.8)
2015	37816 (7.7)	37010 (7.6)	806 (9.4)
2016	30289 (6.1)	29740 (6.1)	549 (6.4)
2017	29474 (6.0)	29010 (6.0)	464 (5.4)
2018	12712 (2.6)	12571 (2.6)	141 (1.6)
Pain: Back or neck (%)	156187 (31.7)	151388 (31.3)	4799 (55.9)
Pain: Arthritis (%)	41677 (8.5)	40068 (8.3)	1609 (18.7)
Pain: Injury (%)	182179 (37.0)	180214 (37.2)	1965 (22.9)
Pain: Neuropathic (%)	39530 (8.0)	37976 (7.8)	1554 (18.1)
Pain: Other pain (%)	316901 (64.3)	310092 (64.0)	6809 (79.3)
Benzodiazepines (%)	62176 (12.6)	59926 (12.4)	2250 (26.2)
Anxiolytics (%)	9034 (1.8)	8751 (1.8)	283 (3.3)
SSRI (%)	58289 (11.8)	56786 (11.7)	1503 (17.5)
Other antidepressants (%)	45592 (9.2)	43917 (9.1)	1675 (19.5)

Table 4.1 Continued	Overall	SMTOT	LTOT
Gabapentin (%)	13338 (2.7)	12233 (2.5)	1105 (12.9)
Depression (%)	35613 (7.2)	34461 (7.1)	1152 (13.4)
Anxiety or PTSD (%)	40604 (8.2)	39320 (8.1)	1284 (15.0)
Substance Use Disorder (%)	6065 (1.2)	5806 (1.2)	259 (3.0)
COPD (%)	11633 (2.4)	11232 (2.3)	401 (4.7)
Initial dose (MME) (%)			
<20MMEs	62484 (12.7)	59310 (12.2)	3174 (37.0)
20-<50MMEs	277687 (56.3)	273888 (56.5)	3799 (44.3)
50-<90MMEs	104029 (21.1)	103107 (21.3)	922 (10.7)
90+MMEs	48783 (9.9)	48096 (9.9)	687 (8.0)
Initial days' supply (%)			
0-3 Days' Supply	160750 (32.6)	160226 (33.1)	524 (6.1)
4-7 Days' Supply	223785 (45.4)	222538 (45.9)	1247 (14.5)
8-14 Days' Supply	65819 (13.4)	64790 (13.4)	1029 (12.0)
15-30 Days' Supply	41898 (8.5)	36413 (7.5)	5485 (63.9)
>30 Days' Supply	731 (0.1)	434 (0.1)	297 (3.5)
Emergency department visit (%)	133040 (27.0)	131752 (27.2)	1288 (15.0)
Inpatient visit (%)	52888 (10.7)	52075 (10.8)	813 (9.5)
Extended-release opioid (%)	3384 (0.7)	2826 (0.6)	558 (6.5)

Table 4.2. Weighted risk differences for opioid overdose through 3 years of follow-up using varying definitions of duration of prescription opioid therapy

Exposure Definition	6 months		1 year		2 years		3 years	
	RD	95% CI	RD	95% CI	RD	95% CI	RD	95% CI
LTOT: 60+ vs. <60 days	0.001	0.000-0.002	0.002	0.000-0.004	0.004	0.001-0.007	0.007	0.001-0.013
LTOT: Monthly vs. short-term	0.001	0.000-0.001	0.001	0.000-0.001	0.002	0.001-0.003	0.002	0.001-0.004
Categorical: 30-59 vs. <30 days	0.000	0.000-0.001	0.001	0.000-0.002	0.001	0.000-0.002	0.002	0.000-0.003
Categorical: 60+ vs. <30 days	0.001	0.000-0.002	0.002	0.000-0.004	0.004	0.001-0.007	0.007	0.013-0.001

Figure 4.1. Covariate balance

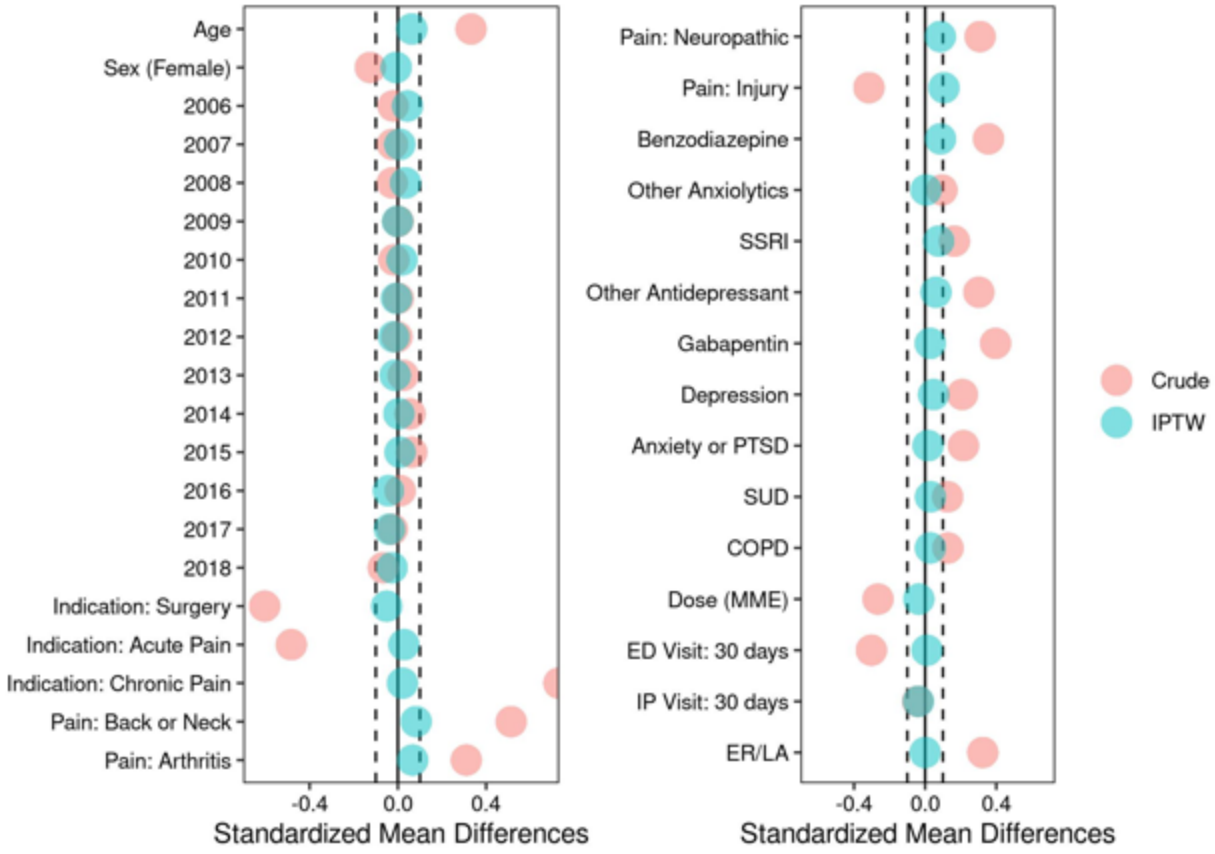


Figure 4.2. Cumulative incidence of opioid overdose by duration of use, crude

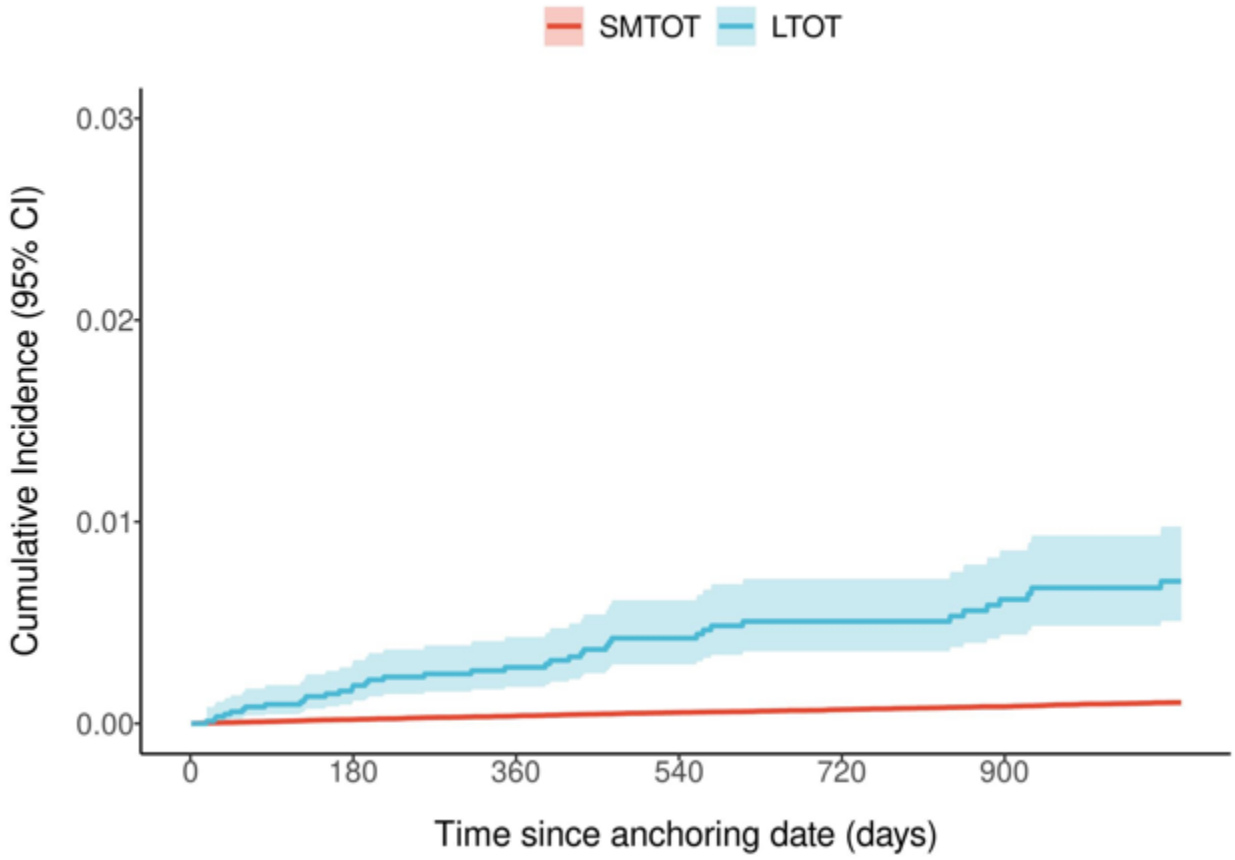


Figure 4.3. Weighted cumulative incidence of opioid overdose by duration of opioid therapy

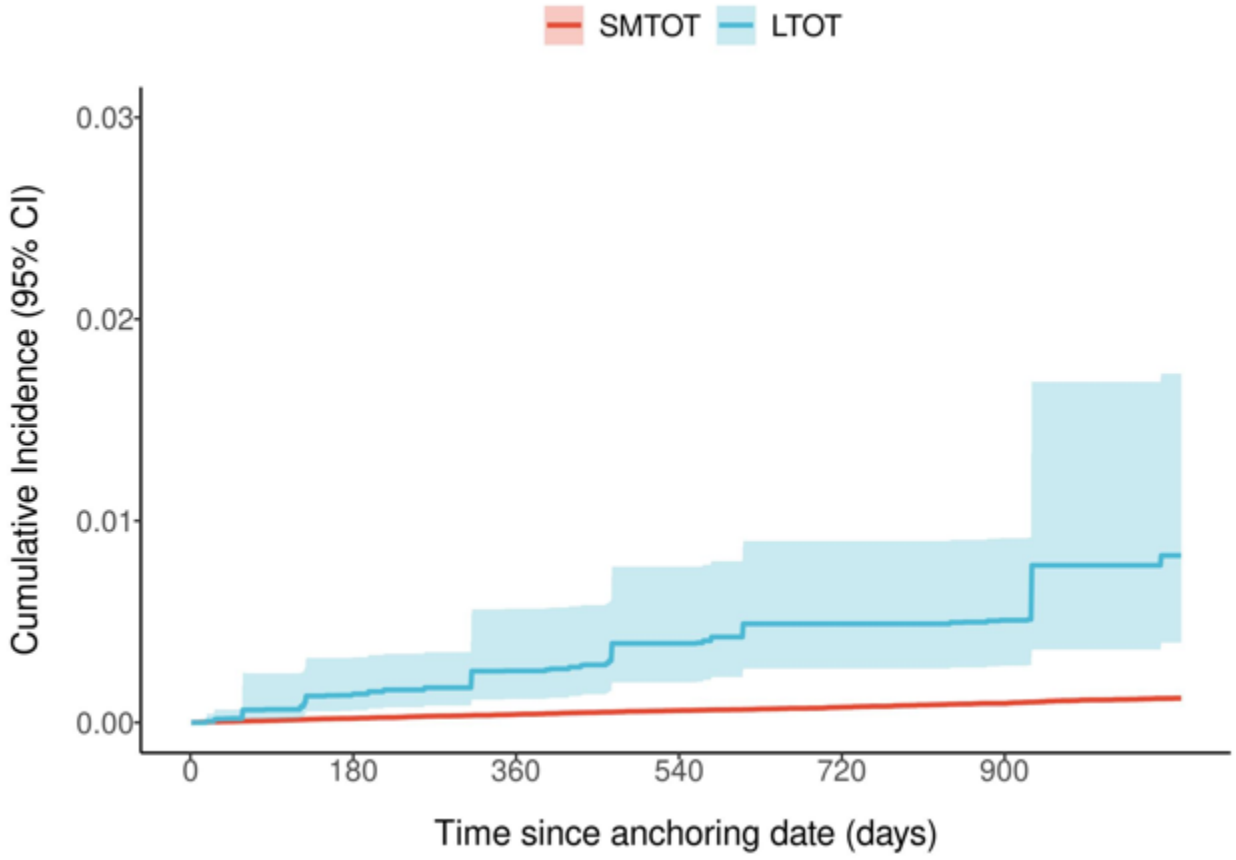


Figure 4.4. Cumulative incidence of opioid overdose by duration of use, stratified by clinical indication

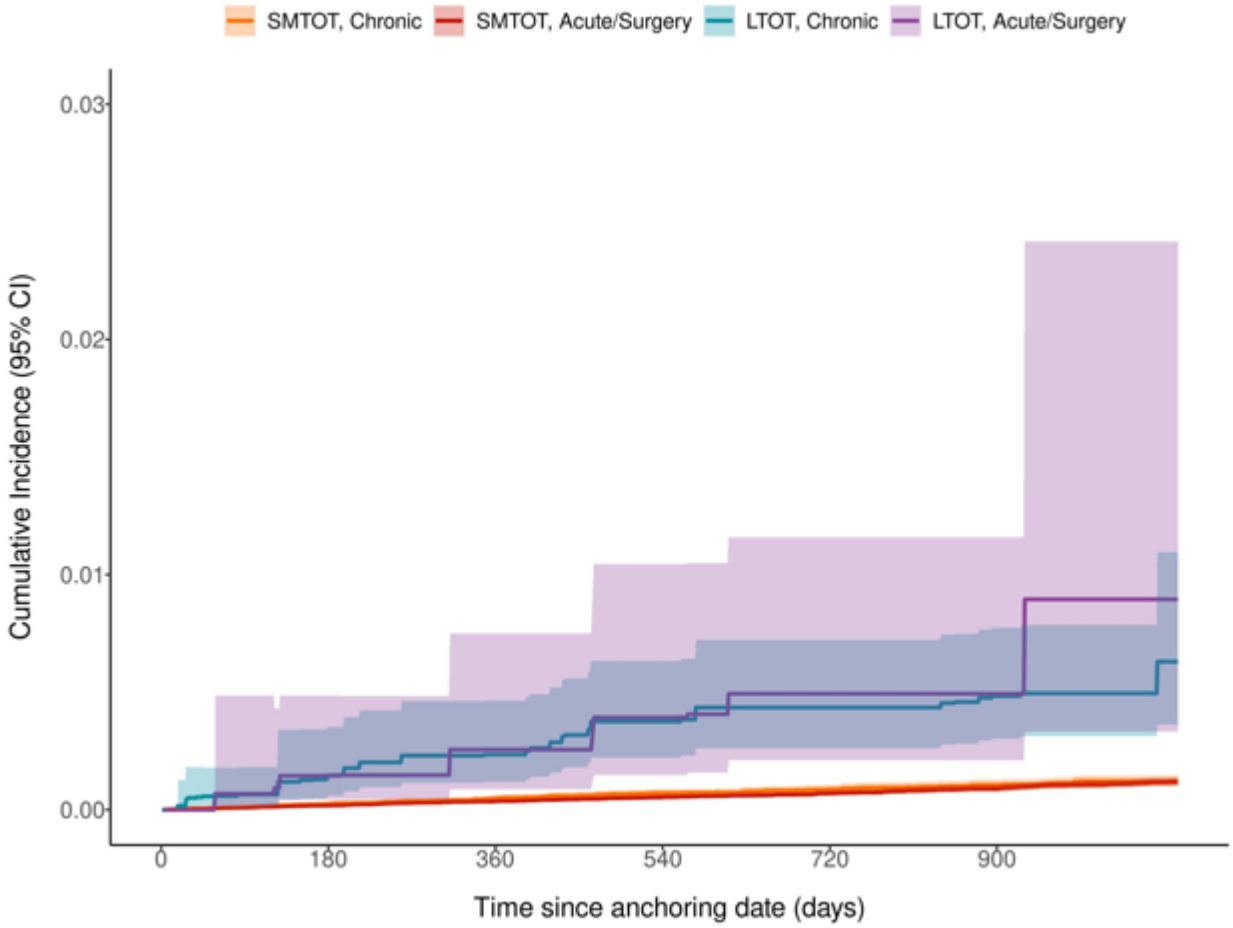


Figure 4.5. Weighted risk difference comparing LTOT to short-term opioid use, stratified by clinical indication

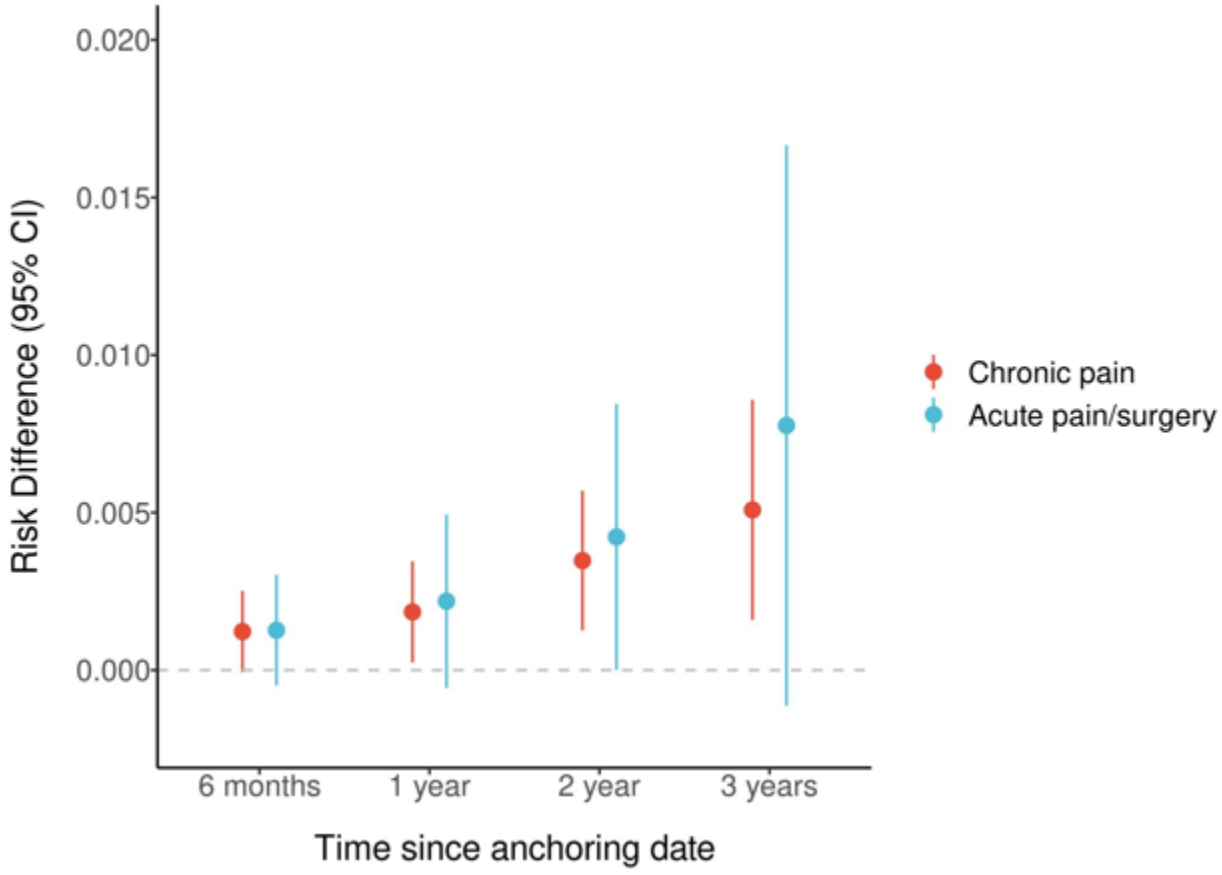
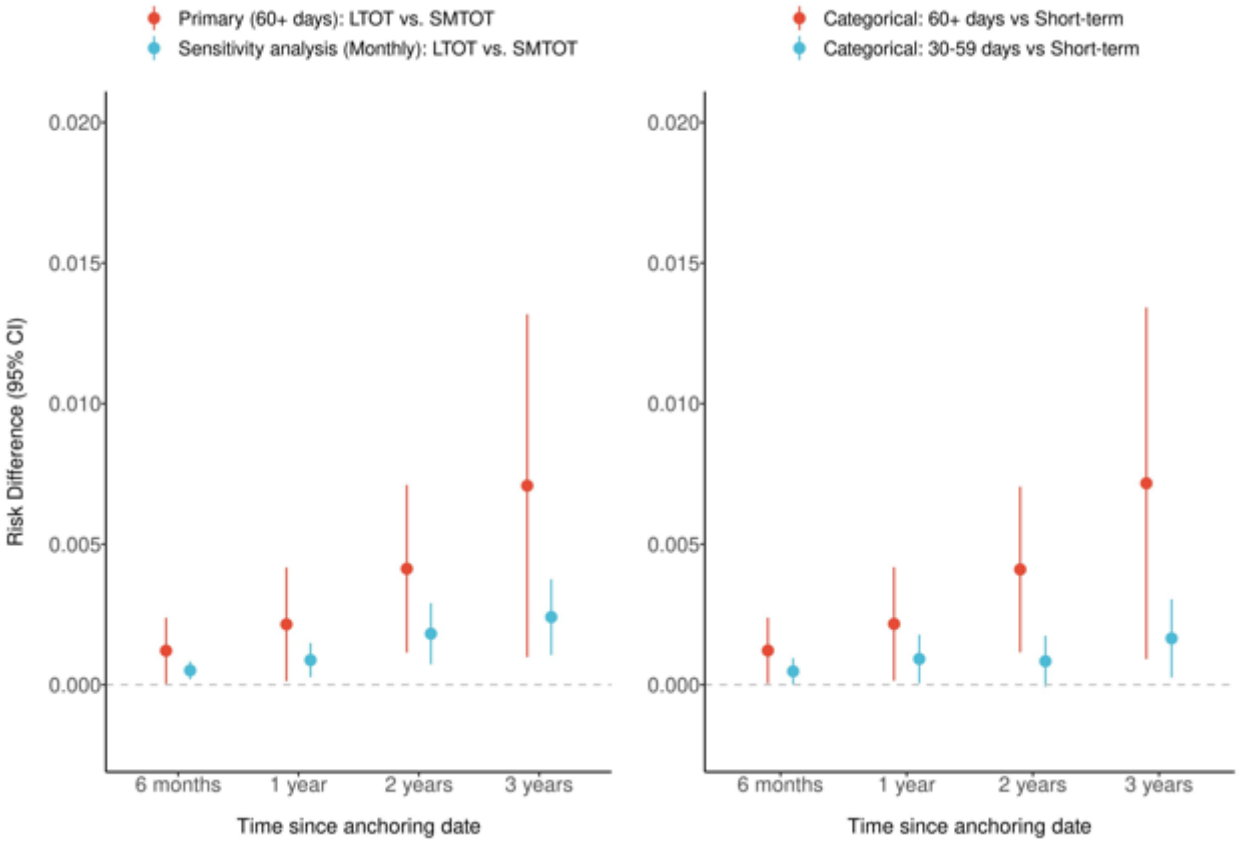


Figure 4.6. Weighted risk difference of opioid overdose comparing longer duration of use to short-term use by varying exposure definitions



CHAPTER V: SYPHILIS IN THE CONTEXT OF THE OPIOID EPIDEMIC: A SPATIOTEMPORAL ANALYSIS USING NORTH CAROLINA SURVEILLANCE DATA, 2008-2017

Introduction

Syphilis rates have steadily increased in the United States (US) since 2001 (35, 124), with the majority of diagnosed syphilis infections occurring in men who have sex with men (MSM) (35). Since 2013, rapid increases in diagnosed syphilis have also surfaced among women and in men who have sex with women (MSW). Rising syphilis rates among women have also driven increasing congenital syphilis rates in the US (125). In early 2019, the Centers for Disease Control and Prevention (CDC) noted increases since 2013 in reporting of both injection drug use (including heroin use) and sex with a person who injects drugs among women and MSW newly diagnosed with syphilis (36, 124).

Alongside increased syphilis rates, the US has experienced a public health crisis of opioid overdoses, driven in early years by nonmedical prescription opioid use and followed closely by a recent upswing in use of heroin and illicit synthetic opioids (48, 63, 126, 127). In 2015 and 2016, nearly two million people in the US were estimated to have an opioid use disorder (OUD) and in 2016, >900,000 people reported heroin use within the last year (43, 44, 126). Opioids accounted for more than 350,000 deaths from 1999 though 2016 (42, 49, 126) and opioid-related poisonings led to >140,000 emergency department (ED) visits in 2015 alone (126).

In addition to risk of overdose and mortality, drug use can also be associated with behaviors that can lead to transmission of infectious diseases (30-32). A recent report highlighted a “converging public health crisis” as a result of the opioid epidemic driving increases in both viral and bacterial infectious diseases (33). The link between injection drug use and HIV and hepatitis C virus (HCV) infection through needle-sharing behaviors is well documented, with recent attention focused on HIV and HCV outbreaks among persons who inject opioids (PWIO) (66-69). Drug use can also be associated with condomless sex (31) and exchanging sex for drugs or money (70, 71); these sexual behaviors, in addition to sex with PWIO, may provide opportunities and efficient routes for sexual transmission of syphilis. Therefore, the opioid epidemic might have played a role in recent rises in new syphilis diagnoses, particularly in women and MSW.

HIV and HCV outbreaks have been shown to spread in networks of PWIO (66, 69) and have been modeled using spatial methods (128). Spatial regression methods may likewise provide insights into potential correlations between the opioid epidemic and rising syphilis rates, since both opioid use (37) and syphilis infections (38-40) can be spatially dependent. In this ecological, hypothesis-generating study, we utilized communicable disease and ED surveillance data to examine whether rates of primary, secondary, and early latent syphilis were spatiotemporally associated with ED visits for opioid overdose (a proxy for nonmedical opioid use) in North Carolina (NC) from 2008 through 2017.

Methods

Syphilis Diagnoses

We examined all diagnoses of early (primary, secondary, and early latent) syphilis reported between January 1, 2008 and December 31, 2017 to the North Carolina Division of Public Health (NC DPH) HIV/STD/Hepatitis Surveillance Unit. Cases diagnosed in these early stages represent more recent infections and thus are more proximate measures of incident syphilis infections. Syphilis is a reportable disease; therefore, surveillance data are expected to contain all diagnosed infections. Residential county and 5-digit ZIP code were extracted for each diagnosed person. Persons with missing or incorrectly entered ZIP codes or residences outside NC were excluded from analysis.

Emergency Department Visits for Opioid Overdose

As a proxy for opioid use, we enumerated emergency department (ED) visits for possible opioid overdose within the North Carolina Disease Event Tracking and Epidemiologic Collection Tool (NC DETECT) (93), a syndromic surveillance system containing data from NC EDs, Poison Control, and emergency medical services. We obtained a limited dataset with visit date, county, 5-digit ZIP code, chief complaint, and International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and 10th Revision (ICD-10-CM) diagnosis and procedure codes for all ED visits from January 1, 2008 through December 31, 2017. NC DETECT collects data from >100 EDs in NC, following a 2005 statewide mandate requiring all civilian EDs to report certain data to the state (129).

Possible cases of opioid overdose were identified using a combination of chief complaint text searches and diagnosis codes. ICD-9-CM codes have been shown to have high specificity, but low sensitivity (97, 98); therefore, this study additionally makes use of chief complaint (See Table 3.6 for all search terms and ICD codes used) (93). Cases with missing or incorrectly entered ZIP codes or residence outside NC were excluded from analysis.

Population Data and Rate Estimation

Population characteristics for US ZIP Code Tabulation Areas (ZCTA) and counties in NC were obtained from US census data, using American Community Survey (ACS) 5-year estimates from 2012 (94) and 2017 (95). Characteristics of interest included percentage of the population aged 20-24 and 25-34, percent Black or African American, percent Hispanic, unemployment rate, poverty rate, percent completing high school (or equivalent), percent female, and population density.

Annual counts of syphilis diagnoses were converted to incident diagnosis rates by dividing the annual number of diagnosed cases among residents of a given geographic area by the total population estimate from the ACS in that area in a given year. Similarly, annual overdose rates were calculated as the number of overdose events in EDs among residents of each geographic area in a given year, divided by the total population in that area in that year. We multiplied both quantities by 100,000 to express rates as counts per 100,000 people.

Observation Units

The primary geographic observation unit for this analysis was ZCTA. ZIP codes from NC DETECT and syphilis surveillance data were mapped to ZCTAs (hereafter

referred to as ZIP codes), which were then used to join these data to census data and mapping files. As detailed under “Ancillary Analyses” below, we used counties as the geographic observation unit in sensitivity analyses.

Spatial smoothing

Spatial local empirical Bayes estimation (99) was used to smooth both syphilis and overdose rates in order to reduce noise due to mapping rare events in areas with small populations. Such events could lead to extreme differences across boundaries that may be artifacts created by specific geographic boundaries used and not representative of the true underlying local diagnosis and overdose rates.

Regression Analyses

Smoothed syphilis and overdose rates were truncated at the 99th percentile to minimize the impact of extreme outliers and transformed using a natural log + 1 transformation to correct for overdispersion inherent to rare disease data.

To descriptively assess associations between syphilis diagnosis and opioid overdose rates, we first used Ordinary Least Squares (OLS) regression models of syphilis rates regressed on overdose rates, using smoothed data for each year. However, because Moran’s I tests on residuals from yearly OLS models demonstrated significant spatial autocorrelation of model residuals, we then used spatial autoregressive panel data regression models with fixed effects, including a term for spatial lag of the dependent variable (syphilis rates) and a spatially lagged error term (100). Results from these models can be interpreted in three parts: the direct association, indirect association, and total association (102). The direct association is the association between the independent variable and the dependent variable in a given

ZIP code. The indirect association is the spillover impact from neighboring areas. The total association is the sum of the indirect and direct association.

We used a weighting matrix of first-order (queen) contiguity neighbors in our primary analyses (103). Queen neighbors share a common edge or vertex. To determine whether any spatial association between overdose rates and syphilis diagnoses varied over time, we included an interaction term between log overdose rate and time (in years). We assessed significance of the spatial lag, spatial error, and interaction terms using a significance threshold of 0.05.

Ancillary Analyses

In an ancillary analysis, we aimed to explore a more causal interpretation of opioid use as a driver of syphilis incidence. While a true causal analysis could not be conducted due to the ecological nature of this study, we recognized that there are factors that may be driving both epidemics. We identified *a priori* population-level characteristics likely to be associated with both overdose rates and syphilis rates (that is, potential confounders for which adjustment would be warranted in a causal analysis). These characteristics included ACS estimates of all covariates listed above except race, which was explored in a modification analysis detailed below (2, 104-106). We modeled covariates using restricted cubic splines and examined variance inflation factors for potentially problematic collinearity, finding none. We repeated the above regression analyses, this time adjusting for these potential confounders. Additionally, we explored possible effect measure modification, including an interaction term between overdose rates and an indicator for whether the percentage of the population identifying as Black

or African American in a given ZIP code was above or below the median percentage across all NC ZIP codes.

To examine the extent to which the opioid epidemic might have played a role in the recent rise in new syphilis diagnoses in women and MSW specifically, we conducted analyses limiting syphilis diagnoses to: (1) women only, and (2) women and MSW, excluding men who report having sex with other men. We used all syphilis diagnoses in primary analyses due to 1) small case counts, and 2) missing data on gender of sexual partners and potential for misclassification of MSW status.

Results of spatial analyses can be highly sensitive to the level of data aggregation, also known as the Modifiable Area Unit Problem (107), as well as the specification of neighbors in weighting matrices (103). Thus, we conducted sensitivity analyses to examine the impact of using: (3) raw rates instead of spatial empirical Bayes smoothed rates, (4) county-level rather than ZIP code-level data aggregation, (5) rook (neighbors that share a common edge) contiguity rather than queen contiguity weighting matrices, and (6) contiguity weighting matrices with both first- and second-order queen neighbors (neighbors of neighbors), with first-order neighbors assigned a weight of 1 and second-order neighbors assigned a weight of 0.5. To address potential sensitivities of results to other design choices, we conducted two further sensitivity analyses in which we: (7) lagged syphilis rates by one year relative to overdose rates in order to account for time from syphilis infection to diagnosis, and (8) used only the first overdose event among people who overdosed multiple times in a year to examine the possible impact of multiple overdose events per person inflating overdose rates relative

to the number of people experiencing an opioid overdose in areas with small population size.

Ethics Statement

The Institutional Review Board at the University of North Carolina at Chapel Hill determined this secondary analysis of existing data to be exempt from further review.

Software

Data processing, spatial smoothing, and visualization were completed in R 3.6.1 (108) (Appendix 1 lists R packages). Spatial regression analyses were completed in Stata 16 (College Station, TX) (101).

Results

Diagnoses of early (primary, secondary, or early latent) syphilis reported to NC DPH with verifiable NC ZIP codes increased from 518 (5.4 per 100,000 population) in 2008 to 1,889 (18.8 per 100,000 population) in 2017 (Figure 5.1). Over the same period, the number of ED visits for possible opioid overdose increased from 2,792 (29.3 per 100,000 population) in 2008 to 9,231 (91.8 per 100,000 population) in 2017. These trends mirror those in official reports (130, 131), with minor differences likely attributable to restriction here to individuals reporting an NC ZIP code and the inclusion of chief complaint in the definition of opioid overdose. Prior to 2013, high case rates of both opioid overdoses and syphilis diagnoses were limited to smaller geographic areas but became much more widespread by 2017 (Figure 5.2).

There was an early weak inverse association between opioid overdoses and incident diagnoses of early syphilis at the ZIP code level from 2008 through 2013, which then reversed to a significant positive association from 2015 through 2017 (Figure 5.3).

This positive association from 2015 through 2017 occurred during the three years with the highest syphilis rates in NC (Figure 5.1). In 2017, a one percent increase in the ZIP-code-level log overdose rate corresponded to a 0.18 percent increase in the mean log syphilis rate (95% CI: 0.14, 0.21). Most of the observed relationship was due to the direct association (0.15 percent) between the rate of people visiting EDs for possible opioid overdose and the rate of newly diagnosed syphilis cases in an area (Figure 5.3).

In the ancillary analysis with adjustment for potential confounders, we found a similar trend to that seen in unadjusted analyses (Figure 5.4a). A modification analysis demonstrated meaningful modification by the percentage of the population in a given ZIP code identifying as Black or African American, using the median across NC ZIP codes as a cut-point (Figure 5.4b). Trends over time were similar in both strata, but the magnitude of the association differed. Specifically, areas where the percentage of the population identifying as Black or African American was below the median had a weakly negative-to-null association between opioid overdose rates and syphilis rates before 2014, followed by a strong positive association after 2014. Areas above the median demonstrated a negative association prior to 2014, followed by a weaker positive association from 2015 through 2017.

When restricting our population to (1) women, and (2) women and MSW, the overall trend remained consistent with that seen in primary analyses, although overdose-syphilis associations were attenuated toward the null in most years (Figure 5.5). Sensitivity analyses showed similar relationships between aggregate opioid overdose rates and syphilis rates when using different weighting matrices (Figure 5.6), county-level data instead of ZIP code data (Figure 5.7), and raw rates instead of

smoothed rates (Figure 5.8). Using all overdose events instead of the first overdose event per person per year produced similar results (Figure 5.9), as did the analysis using lagged syphilis rates (Figure 5.10).

Discussion

To our knowledge, this ecological study is among the first to analyze syphilis diagnosis rates in the context of the opioid epidemic using spatial regression methods. Recent US surveillance reports have noted increases in self-reported injection drug use, heroin use, or sex with a person who injects drugs among women and MSW diagnosed with early syphilis (36, 124). We sought to identify possible population-level associations between rates of ED visits for opioid overdose, a proxy for opioid use in a ZIP code, and rates of early syphilis diagnoses, accounting for the spatial nature of these epidemics. We found a weak inverse relationship prior to 2014 and a strong positive association from 2015 through 2017, when rates of early syphilis and ED visits for opioid overdose both increased substantially.

Our results suggest that recent rises in early syphilis cases may be spatiotemporally associated with the opioid epidemic, consistent with recent CDC reports that prevalence of self-reported heroin use, injection drug use, or sex with a person who injects drugs among women and MSW diagnosed with early syphilis more than doubled from 2013 through 2017 (36). These factors were reported by a notable proportion of women and MSW diagnosed with early syphilis in 2017, ranging from 3% of MSW reporting heroin use to 12% of women reporting sex with a person who injects drugs (36). Individuals who use opioids nonmedically and PWIO have been shown to be at higher risk of engaging in condomless sex, having sex with a person who injects

drugs, and exchanging sex for drugs or money (30-32, 132). These factors could provide opportunities for efficient transmission of syphilis in sexual networks of persons who use opioids. Previous outbreaks of syphilis have been similarly hypothesized to be a consequence of trends in drug use; a resurgence of syphilis among MSW in the 1980s and 1990s was associated with crack-cocaine use (133, 134).

While opioid use may be related to syphilis diagnoses in women and MSW, it is important to note that the majority of the syphilis epidemic remains concentrated among MSM (35, 105, 135); 63% of newly diagnosed cases of early syphilis in NC in 2017 occurred in men reporting sex with men (135), and MSM still make up much of the recent increase in syphilis diagnoses nationwide (125). Recent data have shown that while syphilis diagnoses continue to rise among MSM, a positive trend in reported opioid use and injection drug use among MSM diagnosed with syphilis has not been observed in individual-level surveillance data (124). When we restricted syphilis diagnoses to women and MSW, we found a similar overall trend to what was seen in primary analyses utilizing all syphilis diagnoses in NC. While these results should be interpreted with caution due to small case counts, they do suggest that opioid use is associated with rising syphilis rates in women and MSW specifically in recent years.

The majority of syphilis diagnoses in NC in 2017 were made in Black/African American men (105), whereas the national rate of opioid overdoses is highest among white individuals (126). When stratifying by the percentage of the population identifying as Black or African American falling above or below the state median, our results suggest that any positive association between opioid use and syphilis diagnoses in

recent years may be most pronounced in areas where smaller percentages of the population identify as Black or African American.

This study benefits from the use of state surveillance data on syphilis diagnoses and ED visits. Surveillance data are expected to contain all diagnosed syphilis infections, and NC DETECT collects data from over 100 EDs in NC. Our opioid overdose case definition makes use of chief complaint in addition to diagnosis codes, which likely improves sensitivity by including cases that could have been missed if only diagnosis codes were used to identify opioid overdoses (97). However, it is worth noting that inclusion of chief complaint may also increase the likelihood of false positives. Finally, this study uses spatial models to account for spatial dependency in the potential relationship between opioid use and syphilis rates. Our finding that spatial autoregressive models are more appropriate than OLS regression when modelling sexually transmitted infections is consistent with findings from spatial regression analyses of sexually transmitted infections in Texas (136) and nationally (104, 106).

We cannot establish individual-level causal mechanisms in this ecological study, so while our results demonstrate a significant positive association between opioid overdose rates and syphilis rates since 2015, these results are only correlational. Rising syphilis rates may be attributable to methamphetamine (36) or other drug use in women and MSW (70), or to other societal factors contributing to the opioid epidemic. The opioid crisis has also become intertwined with decreased labor force participation (137), and opioid sales and overdoses are correlated with poverty and unemployment (138). In NC, persons living in high-poverty areas are also more likely to be diagnosed with syphilis (135). Our ancillary pseudo-causal analysis demonstrated a trend consistent

with that seen in our primary analysis after adjustment for relevant population-level confounders of the relationship between opioid use and syphilis transmission; however, these results should be interpreted with caution.

There are several additional limitations to consider when interpreting the results of this study. We used ED visits for opioid overdose as a proxy for nonmedical prescription opioid use, heroin use, and illicit synthetic opioid use in a geographical area. This is likely an imperfect measure that underestimates not only all opioid overdoses (since many do not reach the ED and not all EDs report to the state), but also the drug use for which it serves as a proxy. However, nonmedical opioid use and heroin use in an area are hard to measure directly, and ED visits for opioid overdose likely capture a portion of overall trends. We also note that rising opioid overdose rates may be due in part not only to increasing prevalence of nonmedical opioid use and injection use, but also increased potency of illicit opioids (2, 139). Additionally, while syphilis surveillance records are expected to capture all diagnosed infections, these data cannot inform us about the true incidence of syphilis infection, as a portion of incident infections are not diagnosed (105). Finally, there could be a non-trivial role of spatial patterns in healthcare seeking behaviors such that areas where people are more likely to present for syphilis testing are also areas where people are more likely to present to the ED for opioid overdose, rather than being treated in the field. Model results showed that a spatially lagged error term contributed significantly, suggesting there are important spatially dependent explanatory variables omitted from our adjusted models.

Conclusions

As the US has struggled to curb the opioid epidemic, syphilis diagnoses have also surged. Future analyses should further investigate possible causal links between opioid use and syphilis diagnoses with individual-level data, accounting for spatiotemporal clustering of these epidemics. Screening for OUD among persons newly diagnosed with syphilis could be indicated in order to improve linkage to OUD treatment services. Similarly, to combat rising rates of new syphilis cases and congenital syphilis, identification of individuals known to misuse prescription opioids or PWIO for increased syphilis testing may aid detection of new syphilis cases and allow for initiation of treatment to break the chain of transmission.

Figure 5.1. Early syphilis and opioid overdose case counts in North Carolina, 2008-2017

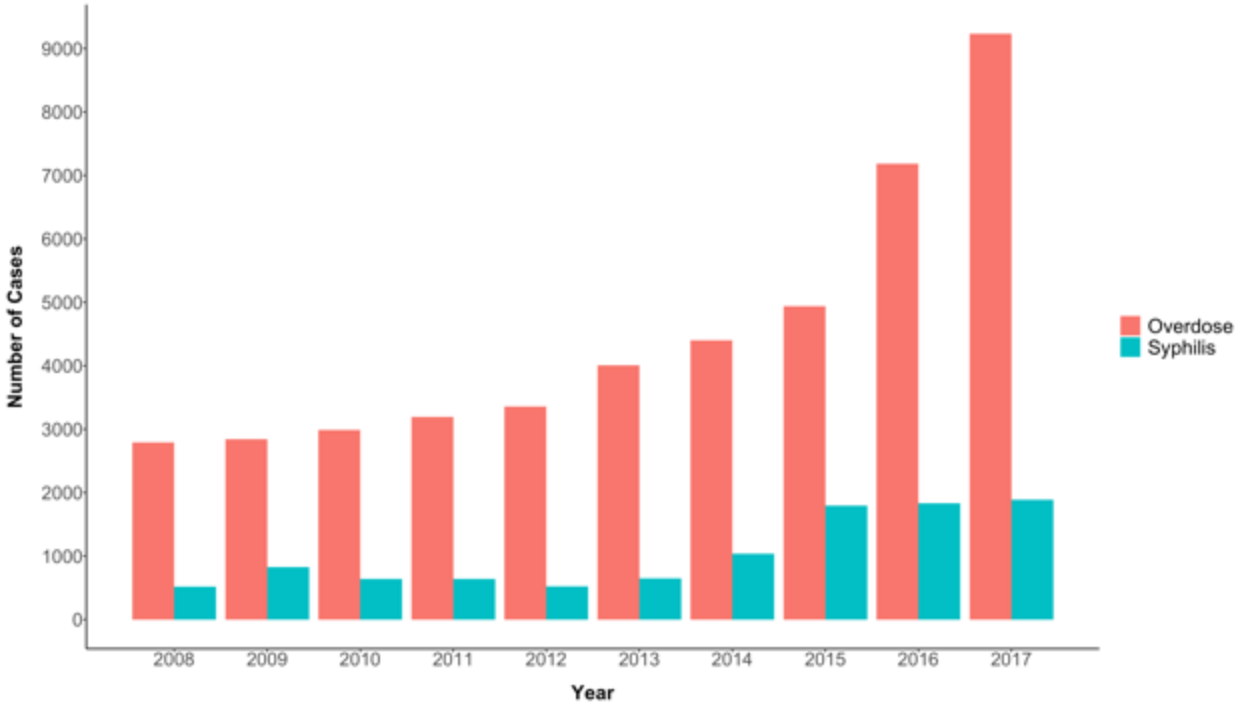


Figure 5.2. Rates of (A) early syphilis diagnoses and (B) ED visits for opioid overdose, 2008-2017, using local empirical Bayes smoothing estimators

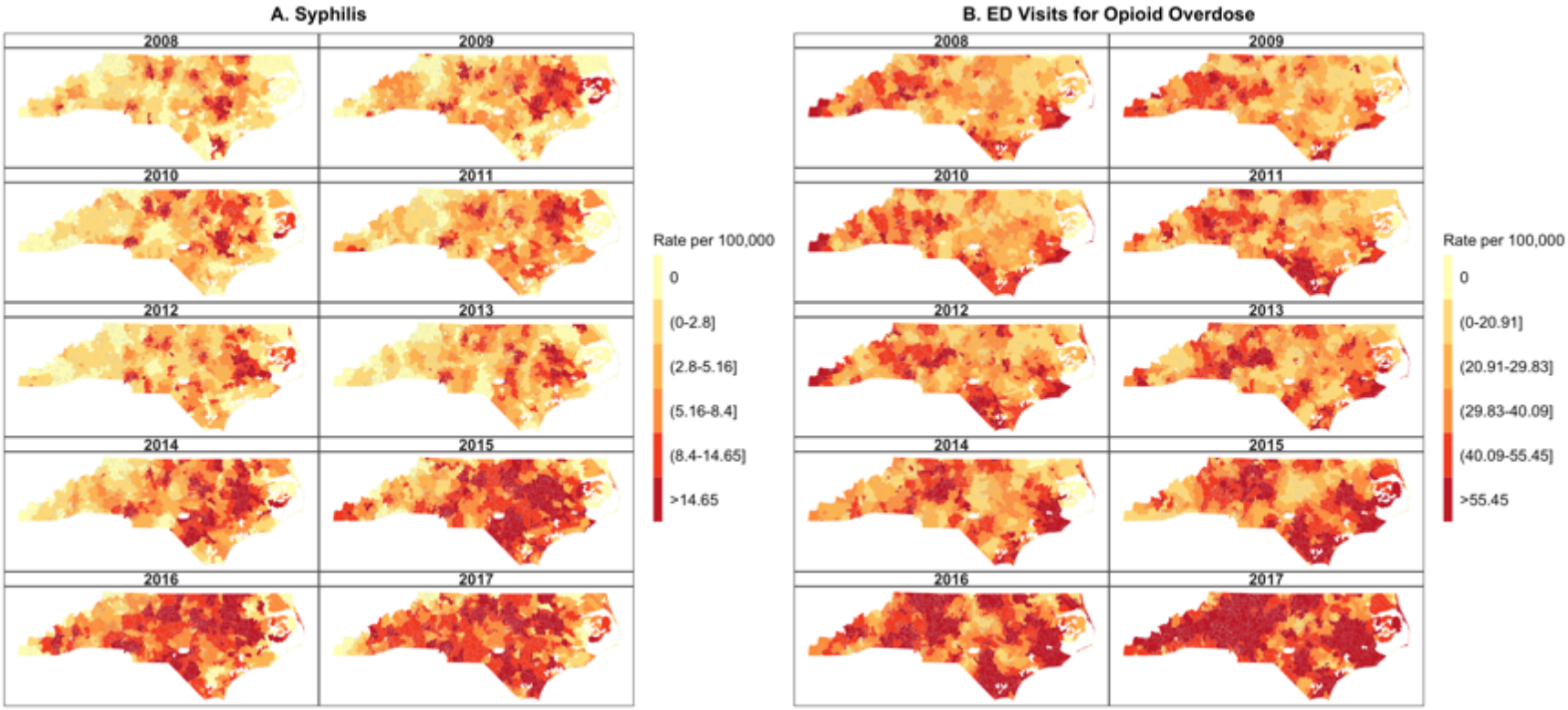
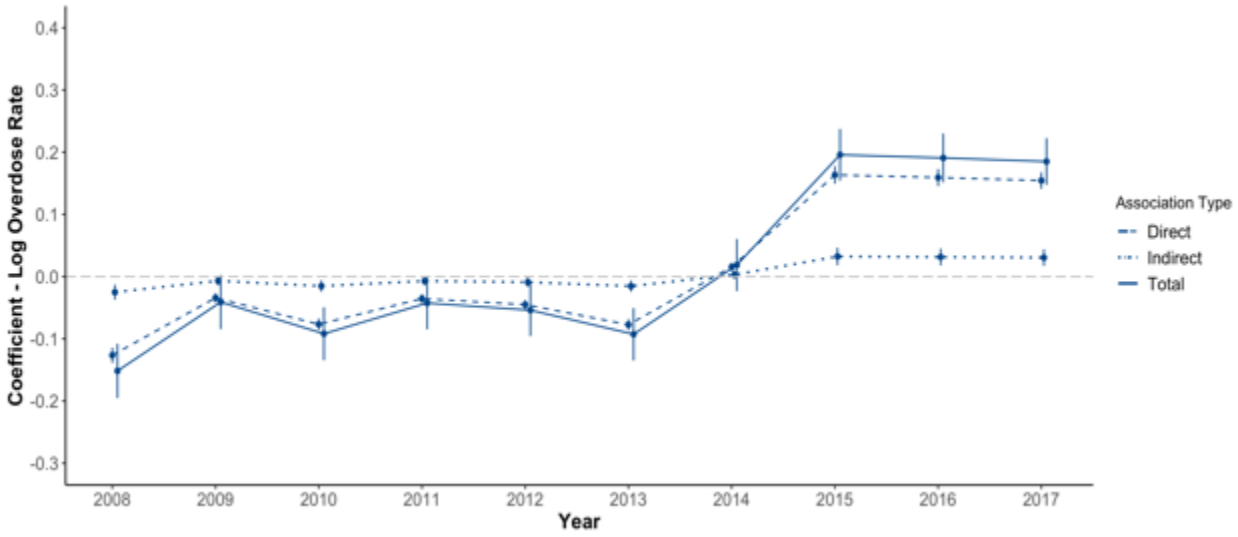


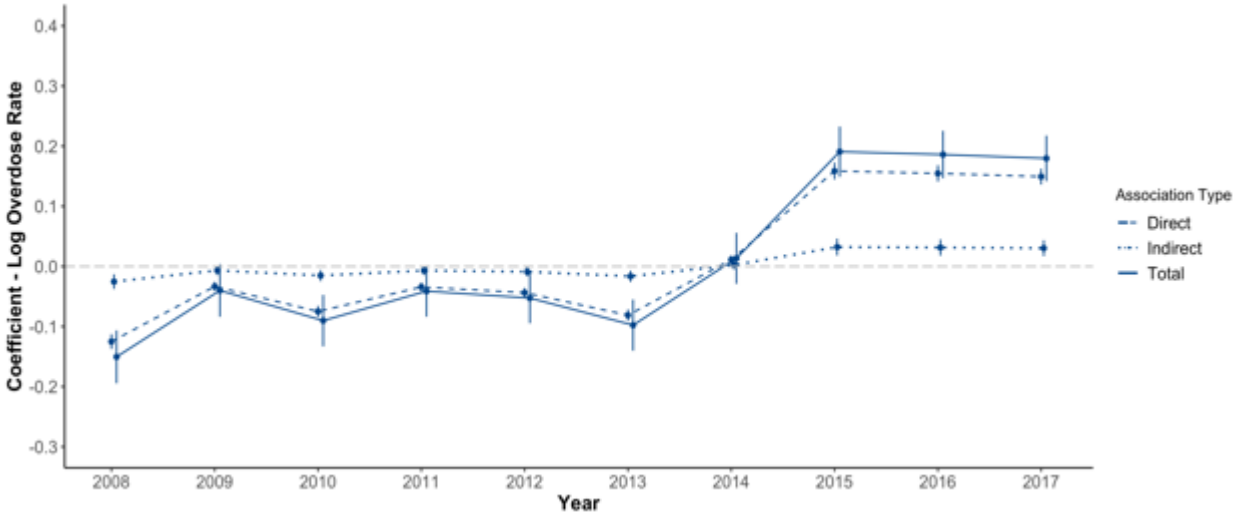
Figure 5.3. Unadjusted association between opioid overdose and early syphilis rates[a]



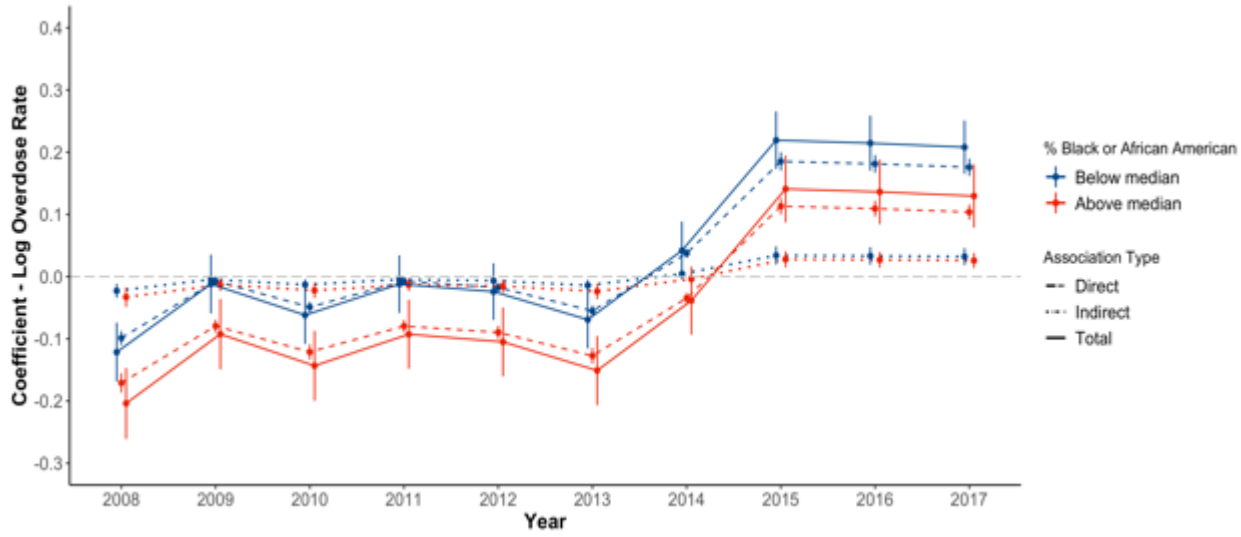
[a]Zip code aggregation of spatial Empirical Bayes smoothed rates, first order (Queen) weights matrix, spatial lag of syphilis rate and error, rates transformed using log(rate+1) transformation

Figure 5.4. A. Adjusted[a] association between opioid overdose and early syphilis rates,[b] B. Adjusted[c] association between opioid overdose and early syphilis rates,[b] accounting for modification by percentage of the population identifying as Black or African American falling above or below the state median

A.



B.

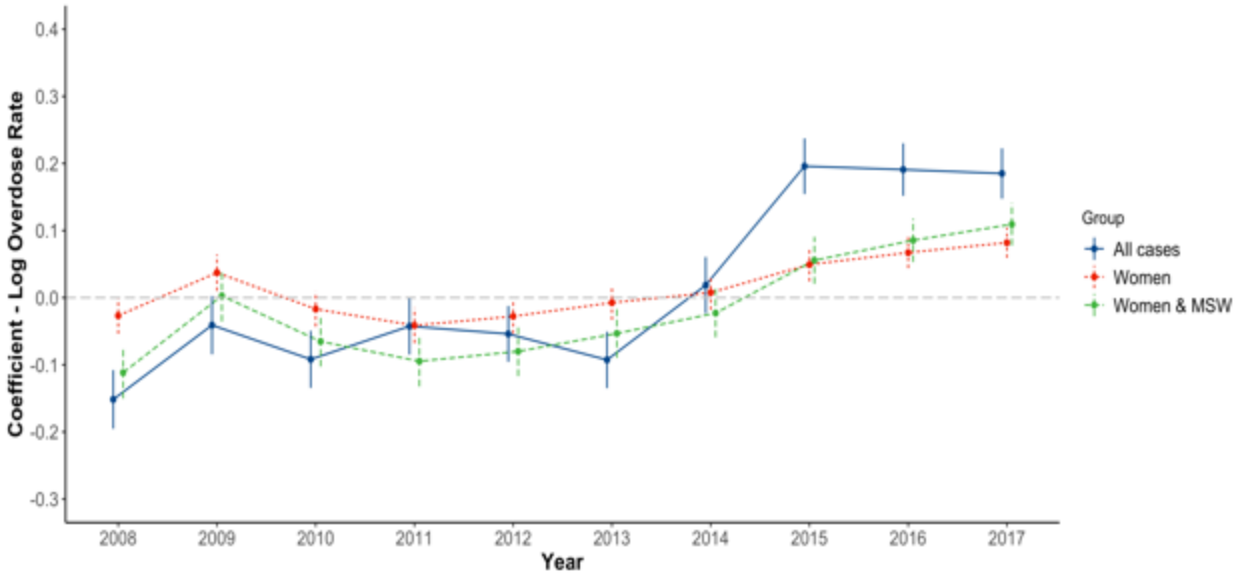


[a]Adjusted for percentage of the population age 20 to 24 and age 25 to 34, percent Hispanic, unemployment rate, poverty rate, percent completing high school (or equivalent), percent female, and population density

[b]Zip code aggregation of spatial Empirical Bayes smoothed rates, first order (Queen) weights matrix, spatial lag of syphilis rate and error, rates transformed using log(rate+1) transformation

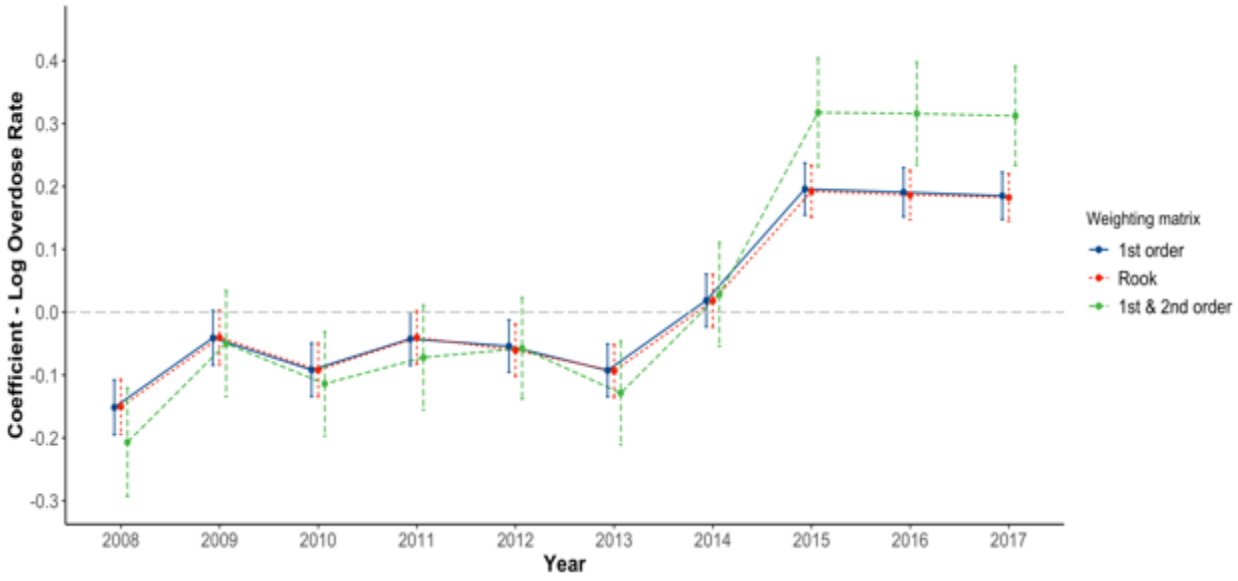
[c]Adjusted for percentage of the population age 20 to 24 and age 25 to 34, percent Hispanic, unemployment rate, poverty rate, percent completing high school (or equivalent), percent female, and population density

Figure 5.5. Unadjusted total association between opioid overdose and early syphilis rates[a] using early syphilis case rates among 1) all diagnosed early syphilis cases, 2) women only, or 3) women and MSW



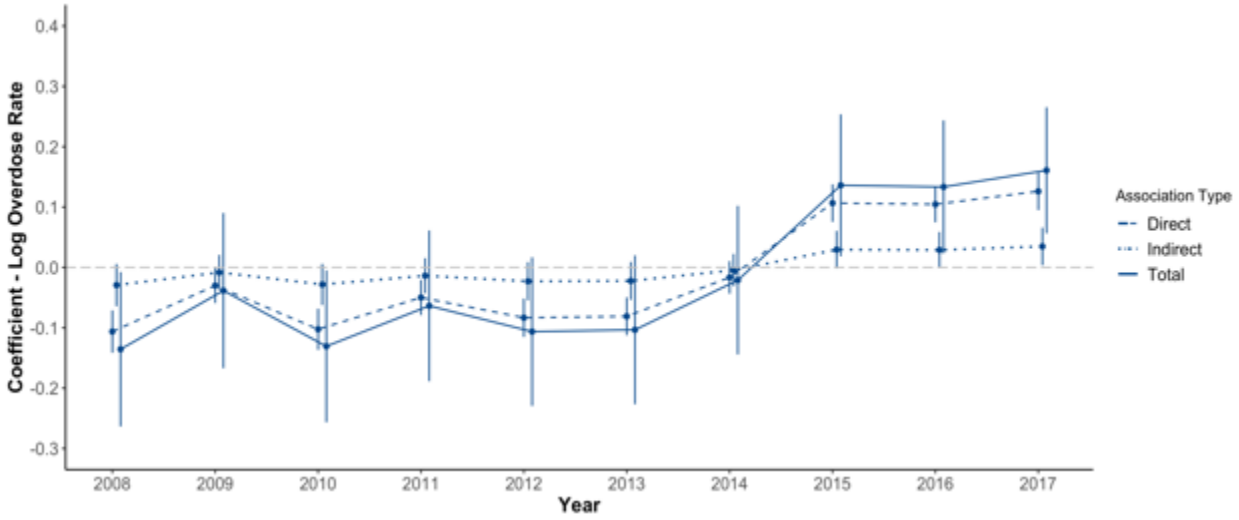
[a]Zip code aggregation of spatial Empirical Bayes smoothed rates, first order (Queen) weights matrix, spatial lag of syphilis rate and error, rates transformed using log(rate+1) transformation

Figure 5.6. Unadjusted total association between opioid overdose and early syphilis rates,[a] comparing weighting matrices



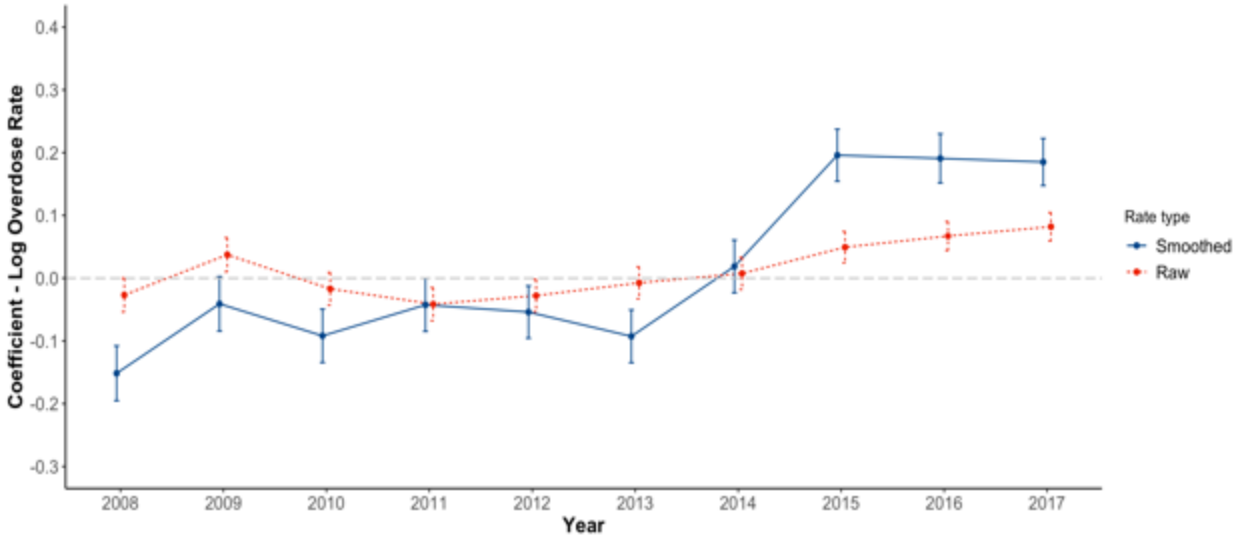
[a]Zip code aggregation of spatial Empirical Bayes smoothed rates, spatial lag of syphilis rate and error, rates transformed using log(rate+1) transformation

Figure 5.7. Unadjusted association between opioid overdose and early syphilis rates,[a] county-level aggregation



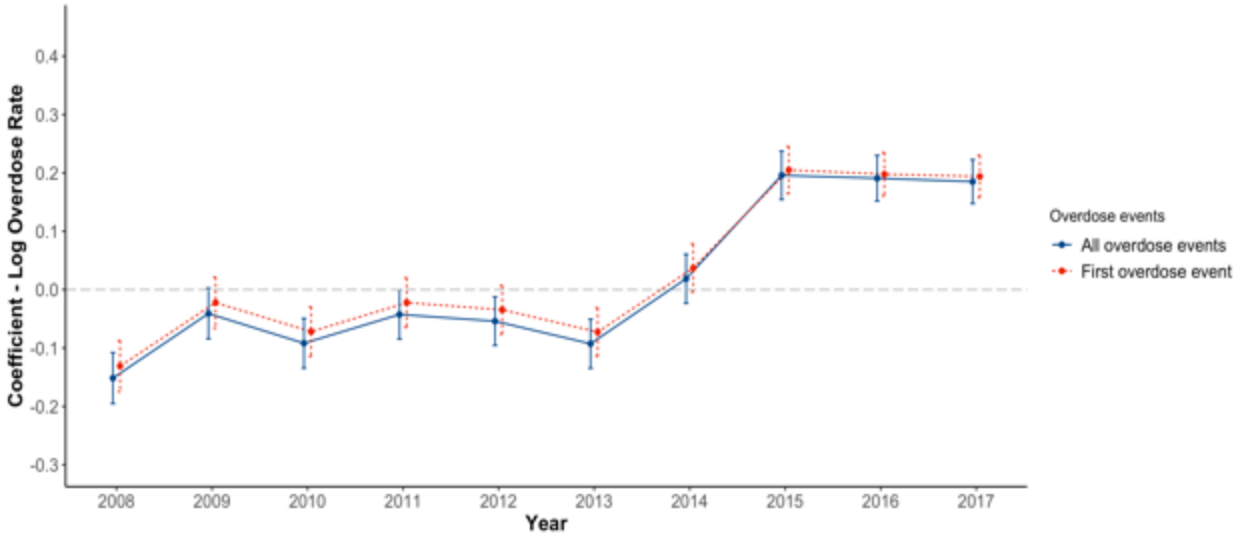
[a]County aggregation of spatial Empirical Bayes smoothed rates, first order (Queen) weights matrix, spatial lag of syphilis rate and error, rates transformed using log(rate+1) transformation

Figure 5.8. Unadjusted total association between opioid overdose and early syphilis rates,[a] comparing smoothed and raw rates



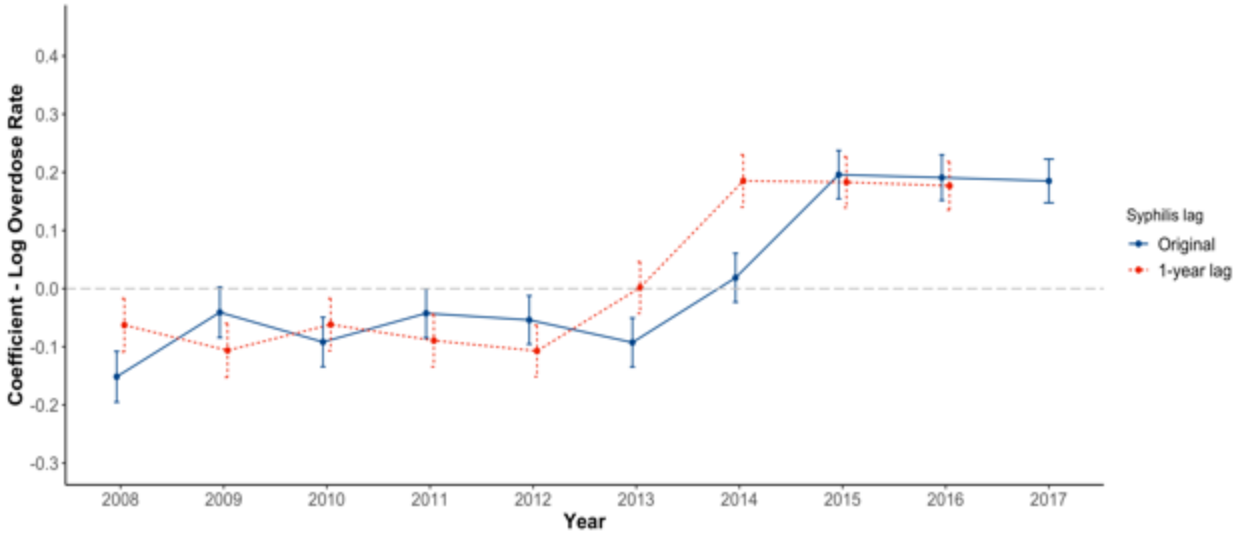
[a]Zip code aggregation of rates, spatial lag of syphilis rate and error, rates transformed using log(rate+1) transformation

Figure 5.9. Unadjusted total association between opioid overdose and early syphilis rates,[a] comparing all overdose events to first overdose event per person per year



[a]Zip code aggregation of spatial Empirical Bayes smoothed rates, spatial lag of syphilis rate and error, rates transformed using log(rate+1) transformation

Figure 5.10. Unadjusted total association between opioid overdose and early syphilis rates,[a] examining a one-year lag of early syphilis diagnosis rates



[a]Zip code aggregation of spatial Empirical Bayes smoothed rates, spatial lag of syphilis rate and error, rates transformed using log(rate+1) transformation

CHAPTER VI: CONCLUSIONS

Summary of Findings

This dissertation study was motivated by two public health challenges currently facing the United States: (1) a devastating epidemic of opioid-related morbidity and mortality, and (2) marked increases in syphilis incidence, including in women and in men who have sex with women (MSW). Prescription opioid use often precedes initiation of heroin and illicit synthetic opioids and remains a significant contributor to opioid-related morbidity and mortality. Given this, as well as recent increases among women and MSW newly diagnosed with syphilis in reporting of both injection drug use, heroin use, and sex with a person who injects drugs, it is important to understand how initial exposure to prescription opioids can place people at higher risk of opioid-related adverse outcomes including opioid overdose, and how nonmedical use of opioids may be linked to rising syphilis rates.

In order to better understand opioid overdose risk among privately insured patients initiating opioid therapy in North Carolina, we first sought to examine the relationship between prescribing trajectory and risk of opioid overdose by initial clinical indication using causal inference methods. We then explored population-level spatiotemporal relationships between the opioid epidemic and syphilis infections in North Carolina using spatial regression methods to analyze aggregate surveillance data

of emergency department visits for suspected opioid overdose and diagnosed cases of early (primary, secondary, and early latent) syphilis in North Carolina.

The first aim of this dissertation study used longitudinal insurance claims data from a large, private health insurance company in North Carolina from 2006 through 2018. We identified 492,983 patients initiating opioid therapy for pain management, of whom 1.7% went on to have long-term opioid therapy (LTOT) using a more rigorous definition of LTOT than has been used in many previous studies. In this patient cohort, we found that exposure to LTOT significantly increased three-year risk of opioid overdose after accounting for relevant baseline confounders and informative censoring. Additionally, we found a dose-response relationship between duration of use and risk of opioid overdose, confirming the importance of the CDC guidelines to reduce the duration of opioid therapy. Finally, we did not find meaningful modification of the relationship between duration of opioid therapy and overdose risk by initial derived clinical indication.

The second aim made use of surveillance data of diagnosed cases of early syphilis and suspected emergency department visits for opioid overdose in North Carolina from 2008 through 2017. Using spatial regression methods of aggregate rate data, we found that recent increases in early syphilis cases in North Carolina may be associated with the opioid epidemic in space and time, both in the full study population and when we restricted syphilis diagnoses to women and MSW. This relationship held in an ancillary pseudo-causal analysis that adjusted for relevant population-level confounders.

Taken together, the results of this dissertation demonstrate that patients exposed to long-term opioid therapy are at higher risk of opioid overdose, and that, since 2015, opioid overdoses (as a proxy for nonmedical opioid use) are associated with early syphilis diagnoses in space and time. These findings confirm the importance of the CDC recommendation to reduce duration of opioid therapy in patients initiating prescription opioid therapy for pain management and lend support for state legislation in North Carolina to limit prescription durations for treatment of acute and post-surgical pain with opioid analgesics (140). They also are consistent with recent findings from the CDC of increased prevalence of drug use or sex with a person who uses drugs among women and MSW receiving syphilis diagnoses (36).

Strengths and Limitations

The strengths and limitations of this dissertation will be considered in the context of the main threats to internal and external validity in epidemiologic research.

Confounding

Uncontrolled confounding is one of the key threats to internal validity in observational studies. In the first aim of this dissertation study, the assumption of no unmeasured confounding implies that patients exposed to long-term opioid therapy are exchangeable with patients exposed to short- to medium-term opioid therapy. A small minority of patients in this analysis were exposed to long-term opioid therapy; however, we found important differences between patients in each exposure group by key confounders that had been identified *a priori* based on a directed acyclic graph (DAG) (e.g., sex, prevalence of painful conditions, benzodiazepine use, depression). We used a rigorous methodological approach of inverse probability of treatment weighting (92) to

address potential confounding by indication (141). However, our results may be subject to residual confounding due to the use of insurance claims, which may undermeasure important confounders such as substance use disorders and mental health conditions. Insurance claims also do not include all potential confounders (e.g., socioeconomic status), which may result in unmeasured confounding.

In Aim 2, we conducted an ecological analysis to identify population-level associations between opioid overdoses, a proxy for nonmedical opioid use, and early syphilis diagnoses. Our approach could not infer causation and, therefore, we did not consider potential confounding of our hypothesized exposure-outcome relationship in primary analyses. However, we recognized that there are factors that may be driving both epidemics. In a pseudo-causal ancillary analysis, we identified *a priori* population-level characteristics likely to be associated with both overdose rates and syphilis rates (that is, potential confounders for which adjustment would be warranted in a causal analysis). There is also particular concern regarding population density in spatial analyses (142), which was accounted for in adjusted analyses in combination with the potential population-level confounders discussed above.

Measurement

There were several key variables used in this dissertation study that may have been subject to bias from measurement error. In Aim 1, we used insurance claims to capture our exposure and key confounder variables. We relied on insurance claims and linked mortality records to measure outcomes of fatal or nonfatal opioid overdose. As mentioned in “Confounding” above, insurance claims may under-measure key covariates (e.g. substance use disorders or depression). This may occur because these

conditions are inconsistently diagnosed or treated by providers who bill their services to a patient's private insurance.

Our exposure of long-term opioid therapy may also be subject to measurement error. Patients may pay for some opioid prescriptions out of pocket, which may make them appear as though they are not continuing to receive prescription opioids. Similarly, patients classified as exposed to long-term opioid therapy may have filled prescriptions that they did not consume. In order to assess potential bias arising from exposure misclassification, we conducted several sensitivity analyses of our definition of long-term opioid therapy and found that our results were robust to varying exposure definitions. Additionally, we used a primary definition of long-term opioid therapy that we believe more adequately identifies true long-term use of prescription opioids than what has been used in many previous studies of long-term opioid therapy.

Insurance claims and mortality records likely undermeasure our outcome of opioid overdoses (97). However, by linking insurance claims to mortality records, we were able to identify fatal overdoses that may have been missed in claims data. We also do not expect differential misclassification of opioid overdose by exposure status. Therefore, we believe that the threat of bias due to outcome misclassification is minimal. Further, outcomes captured in our datasets are likely true opioid overdoses due to documented high specificity of diagnostic codes in detecting opioid overdose (97).

In Aim 2, we used emergency department visits for opioid overdose as a proxy for nonmedical prescription opioid use, heroin use, and illicit synthetic opioid use in a geographical area. As described above, diagnostic codes have low sensitivity and may miss many cases of opioid overdose. To improve our detection of opioid overdoses, we

additionally made use of chief complaint in our definition of probable opioid overdose in emergency department surveillance data. While this approach may have increased the threat of false positives, we believe this threat is minimal and that the addition of chief complaint to our case definition improved our ability to capture a portion of overall trends in opioid overdose as a proxy for nonmedical opioid use, heroin use, and illicit synthetic opioid use in a geographical area. Our definition of syphilis cases utilized cases diagnosed in primary, secondary, and early latent stages, which are indicative of recent infection and thus a suitable measure of incidence of syphilis within a given year. We assessed potential measurement error of incident syphilis infections by incorporating a time lag in sensitivity analyses. While surveillance records are expected to contain all diagnosed infections, undiagnosed cases in the early stages of infection (primary, secondary, and early latent) are missed in this data source. Early syphilis infections accounted for only 65% of all reported newly diagnosed syphilis cases in NC in 2017 (105).

Spatial rate data may be subject to additional sources of measurement error. Mapping rare events in areas with small populations could lead to extreme differences across boundaries that may be artifacts created by specific geographic boundaries used and not representative of the true underlying local diagnosis and overdose rates. To account for this, we used spatial local empirical Bayes estimation (99) to smooth both syphilis and overdose rates and compared results of smoothing to results using raw rate data. Results of spatial analyses can also be highly sensitive to the level of data aggregation, also known as the Modifiable Area Unit Problem (107), as well as the specification of neighbors in weighting matrices (103). To assess these threats, we

conducted multiple sensitivity analyses using different levels of data aggregation and weighting matrices and found that our results were robust.

Selection

In Aim 1, entry into the risk set required both the presence of an insurance claim for a filled opioid prescription as well as an accompanying insurance claim indicating a pain diagnosis or surgery. Insurance claims may miss individuals who are prescribed opioids for pain management and pay for their prescriptions out of pocket, as well as patients who are prescribed opioids for pain without rigorous documentation of the pain condition. Additionally, we were unable to measure outcomes in patients who disenrolled prior to administrative censoring. Informative censoring may occur if patients who are more likely to experience an opioid overdose are also be more likely to disenroll from their private insurance plan. We applied time-varying inverse probability of censoring weights to account for selection bias stemming from informative censoring based on measured covariates.

In Aim 2, we used aggregate data of all diagnosed cases of early syphilis and emergency department visits for opioid overdose. These data sources cannot capture patients who do not present to the emergency department for possible opioid overdose, or patients who do not present for syphilis testing. However, our data are expected to contain all diagnosed cases of syphilis, and NC DETECT contains data from >100 emergency departments in North Carolina.

Survivor Bias and Temporality

Pharmacoepidemiologic research using insurance claims data may be subject to issues of immortal time bias (143, 144) and temporality (84). This may occur if patients

are followed from a defined start of study follow-up without consideration of prevalent users of the drug of interest versus patients newly initiating treatment. We accounted for this possibility by implementing a new-user design (84, 145) that required patients to meet a six-month washout period during which they could have no documented use of prescription opioids or evidence of opioid use disorders. However, as discussed above, pharmaceutical claims may under-measure conditions such as opioid use disorders and prescriptions paid for out of pocket are not captured in claims data. An additional potential source of immortal time bias can arise during the window of exposure classification, since our definition of long-term opioid therapy required 90 days of follow-up for exposure differentiation. In order to reduce the threat of immortal time bias during these 90 days, we restricted analyses to patients with at least 90 days of continuous enrollment following entry into the study cohort. Further, we assessed the threat of survival bias by examining potential selective pressure by baseline covariates that may lead patients to overdose in the first 90 days of follow-up as opposed to after our 90-day exposure definition window. We did not find evidence of strong selective pressure, with the exception of a recent emergency department visit.

Generalizability

The data source used in Aim 1 includes individuals insured by a large provider of private health insurance that insures a diverse population of patients. However, this dataset does not include uninsured individuals or those on Medicare/Medicaid and is restricted to a single state in the southeastern United States. Therefore, primary study findings may not be generalizable to the broader population of patients prescribed opioid therapy for pain management in the United States. Similarly, Aim 2 utilized data

from North Carolina surveillance systems and the results from this spatiotemporal analysis may not generalize to the broader United States population.

Public Health Implications and Future Directions

Future research building on our analyses of risk of opioid overdose among patients exposed to long-term opioid therapy are warranted, as are analyses further probing observed associations between the opioid epidemic and rising syphilis rates.

To further explore the risks of opioid use disorders and opioid overdose among pain patients treated with prescription opioids, methodologically rigorous causal inference methods accounting for the time-varying nature of exposure to long-term opioid therapy and time-varying confounding should be employed to disentangle crucial points in clinical decision-making that impact risk adverse outcomes related to nonmedical use of opioids. First, analyses should investigate the time-varying nature of the relationship between initial duration of opioid therapy and risk of opioid use disorders including opioid overdose. Our analyses in this dissertation restricted patients to those with at least 90 days of continuous enrollment in order to define exposure to long-term opioid therapy. Consequently, we removed overdose events within those first 90 days. A rigorous time-varying approach may be able to more thoroughly scrutinize a dose-response effect of cumulative opioid exposure on overdose risk. Additionally, time-varying approaches that analyze the impact that treatment decisions surrounding continuation versus discontinuation of opioid therapy may have on subsequent risk of opioid overdose could inform clinical decision-making for physicians treating patients receiving opioid therapy for pain management.

As noted in the limitations section, while pharmaceutical claims contain rich patient data, there are analytical challenges that come with analyzing insurance claims data. Future work integrating big data linkages between insurance claims and electronic health records could aid in investigations of the impact of measurement error and selection bias in opioid research using claims data. These linkages could also provide insight on questions of external validity by including a population of patients treated regardless of insurance status.

Finally, future analyses investigating possible causal links between opioid use and syphilis diagnoses with individual-level data, accounting for spatiotemporal clustering of these epidemics, are warranted. Linkages between insurance claims, electronic health records, and surveillance records of diagnosed cases of early syphilis will inform future studies making use of causal inference methods to examine possible causal links between the opioid epidemic and syphilis.

In conclusion, this dissertation confirmed that patients exposed to long-term opioid therapy are at increased risk of opioid overdose compared to patients exposed to shorter durations of opioid therapy, and that this association likely follows a dose-response relationship. Further, we found evidence of spatiotemporal associations between the opioid epidemic and recent increases in diagnosed syphilis rates in North Carolina. These results support prescribing guidelines that clinicians minimize opioid therapy duration when opioid treatment is deemed clinically necessary for pain management. Additionally, screening for opioid use disorders among persons newly diagnosed with syphilis may be useful in improving linkage to treatment services for opioid use disorders. Similarly, to combat rising rates of new syphilis cases and

congenital syphilis, identification of individuals known to misuse prescription opioids or persons who inject opioids for increased syphilis testing may aid in detection of new syphilis cases and enable treatment initiation to break the chain of transmission.

APPENDIX 1: R PACKAGES USED IN ANALYSES

Source: CRAN package repository https://cran.r-project.org/

Package	Version
broom	0.5.5
cobalt	4.1.0
cowplot	1.0.0
dplyr	1.0.0
forcats	0.5.0
foreign	0.8-72
gganimate	1.4.5
ggplot2	3.3.1
ggsci	2.9
glue	1.4.1
haven	2.3.1
here	0.1
knitr	1.28
labelled	2.2.2
lubridate	1.7.9
magrittr	1.5
maps	3.3.0
nnet	
purrr	0.3.4
RColorBrewer	1.1-2
readr	1.3.1
rlang	0.4.6
rmarkdown	2.2
rms	
sf	0.9-3
spData	0.3.5
spdep	1.1-3
stringr	1.4.0
survival	3.1-11
survminer	0.4.6
tableone	0.11.1
tibble	0.3.1
tidyr	1.1.0
tidyverse(109)	1.3.0
viridis	0.5.1

APPENDIX 2: DISCLAIMERS

The NC Department of Health and Human Services (DPH) does not take responsibility for the scientific validity or accuracy of methodology, results, statistical analyses, or conclusions presented.

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The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

1. Wilson N, Kariisa M, Seth P, et al. Drug and Opioid-Involved Overdose Deaths - United States, 2017-2018. *MMWR Morb Mortal Wkly Rep* 2020;69(11):290-7.

2. Scholl L, Seth P, Kariisa M, et al. Drug and Opioid-Involved Overdose Deaths - United States, 2013-2017. *MMWR Morb Mortal Wkly Rep* 2018;67(5152):1419-27.

3. Vivolo-Kantor AM, Hoots BE, Scholl L, et al. Nonfatal Drug Overdoses Treated in Emergency Departments - United States, 2016-2017. *MMWR Morb Mortal Wkly Rep* 2020;69(13):371-6.

4. Jones CM, Einstein EB, Compton WM. Changes in Synthetic Opioid Involvement in Drug Overdose Deaths in the United States, 2010-2016. *JAMA* 2018;319(17):1819-21.

5. Jones CM. Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers - United States, 2002-2004 and 2008-2010. *Drug Alcohol Depend* 2013;132(1-2):95-100.

6. Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. *N Engl J Med* 2016;374(2):154-63.

7. Unick GJ, Rosenblum D, Mars S, et al. Intertwined epidemics: national demographic trends in hospitalizations for heroin- and opioid-related overdoses, 1993-2009. *PLoS One* 2013;8(2):e54496.

8. Cicero TJ, Ellis MS, Surratt HL, et al. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. *JAMA Psychiatry* 2014;71(7):821-6.

9. Olsen Y. The CDC Guideline on Opioid Prescribing: Rising to the Challenge. *JAMA* 2016;315(15):1577-9.

10. Mars SG, Bourgois P, Karandinos G, et al. "Every 'never' I ever said came true": transitions from opioid pills to heroin injecting. *Int J Drug Policy* 2014;25(2):257-66.

11. Al-Tayyib AA, Koester S, Riggs P. Prescription opioids prior to injection drug use: Comparisons and public health implications. *Addict Behav* 2017;65:224-8.

12. Lagisetty P, Zhang K, Haffajee RL, et al. Opioid prescribing history prior to heroin overdose among commercially insured adults. *Drug Alcohol Depend* 2020;212:108061.

13. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. *J Pain* 2015;16(8):769-80.

14. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. *MMWR Morb Mortal Wkly Rep* 2018;67(36):1001-6.

15. Centers for Disease Control and Prevention. Annual Surveillance Report of Drug-Related Risks and Outcomes — United States, 2019. *Surveillance Special Report*: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services., 2019.

16. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. *JAMA* 2016;315(15):1624-45.

17. Callinan CE, Neuman MD, Lacy KE, et al. The Initiation of Chronic Opioids: A Survey of Chronic Pain Patients. *J Pain* 2017;18(4):360-5.

18. Stumbo SP, Yarborough BJ, McCarty D, et al. Patient-reported pathways to opioid use disorders and pain-related barriers to treatment engagement. *J Subst Abuse Treat* 2017;73:47-54.

19. Strayer RJ, Motov SM, Nelson LS. Something for pain: Responsible opioid use in emergency medicine. *Am J Emerg Med* 2017;35(2):337-41.

20. Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use - United States, 2006-2015. *MMWR Morb Mortal Wkly Rep* 2017;66(10):265-9.

21. Hah JM, Bateman BT, Ratliff J, et al. Chronic Opioid Use After Surgery: Implications for Perioperative Management in the Face of the Opioid Epidemic. *Anesth Analg* 2017;125(5):1733-40.

22. Brummett CM, Waljee JF, Goesling J, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. *JAMA surgery* 2017;152(6):e170504.

23. Sun EC, Darnall BD, Baker LC, et al. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. *JAMA Intern Med* 2016;176(9):1286-93.

24. Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. *Bmj* 2018;360:j5790.

25. Edlund MJ, Martin BC, Russo JE, et al. The Role of Opioid Prescription in Incident Opioid Abuse and Dependence Among Individuals with Chronic Non-Cancer Pain: The Role of Opioid Prescription. *Clin J Pain* 2014;30(7):557-64.

26. Neuman MD, Bateman BT, Wunsch H. Inappropriate opioid prescription after surgery. *Lancet* 2019;393(10180):1547-57.

27. Karmali RN, Bush C, Raman SR, et al. Long-term opioid therapy definitions and predictors: A systematic review. *Pharmacoepidemiol Drug Saf* 2020;29(3):252-69.

28. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *Jama* 2011;305(13):1315-21.

29. Berna C, Kulich RJ, Rathmell JP. Tapering Long-term Opioid Therapy in Chronic Noncancer Pain: Evidence and Recommendations for Everyday Practice. *Mayo Clin Proc* 2015;90(6):828-42.

30. Mateu-Gelabert P, Guarino H, Jessell L, et al. Injection and sexual HIV/HCV risk behaviors associated with nonmedical use of prescription opioids among young adults in New York City. *J Subst Abuse Treat* 2015;48(1):13-20.

31. Zule WA, Oramasionwu C, Evon D, et al. Event-level analyses of sex-risk and injection-risk behaviors among nonmedical prescription opioid users. *Am J Drug Alcohol Abuse* 2016;42(6):689-97.

32. Brookmeyer KA, Haderxhanaj LT, Hogben M, et al. Sexual risk behaviors and STDs among persons who inject drugs: A national study. *Prev Med* 2019;126:105779.

33. Schwetz TA, Calder T, Rosenthal E, et al. Opioids and Infectious Diseases: A Converging Public Health Crisis. *J Infect Dis* 2019;220(3):346-9.

34. Centers for Disease Control and Prevention. Syphilis Surveillance Supplement 2013-2017. Atlanta: U.S.: Department of Health and Human Services, 2019.

35. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2018. Atlanta, GA: U.S. Department of Health and Human Services, 2019.

36. Kidd SE, Grey JA, Torrone EA, et al. Increased Methamphetamine, Injection Drug, and Heroin Use Among Women and Heterosexual Men with Primary and Secondary Syphilis - United States, 2013-2017. *MMWR Morb Mortal Wkly Rep* 2019;68(6):144-8.

37. Modarai F, Mack K, Hicks P, et al. Relationship of opioid prescription sales and overdoses, North Carolina. *Drug Alcohol Depend* 2013;132(1-2):81-6.

38. Escamilla V, Hampton KH, Gesink DC, et al. Influence of Detection Method and Study Area Scale on Syphilis Cluster Identification in North Carolina. *Sex Transm Dis* 2016;43(4):216-21.

39. Gesink DC, Sullivan AB, Miller WC, et al. Sexually transmitted disease core theory: roles of person, place, and time. *Am J Epidemiol* 2011;174(1):81-9.

40. Gesink DC, Sullivan AB, Norwood TA, et al. Does core area theory apply to sexually transmitted diseases in rural environments? *Sex Transm Dis* 2013;40(1):32-40.

41. Centers for Disease Control and Prevention. 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes — United States. *Surveillance Special Report*: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services., 2018.

42. Seth P, Scholl L, Rudd RA, et al. Overdose Deaths Involving Opioids, Cocaine, and Psychostimulants - United States, 2015-2016. *MMWR Morb Mortal Wkly Rep* 2018;67(12):349-58.

43. Center for Behavioral Health Statistics and Quality. 2016 National Survey on Drug Use and Health: Detailed Tables. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2017.

44. Han B, Compton WM, Blanco C, et al. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Ann Intern Med* 2017;167(5):293-301.

45. Bernard SA, Chelminski PR, Ives TJ, et al. Management of Pain in the United States-A Brief History and Implications for the Opioid Epidemic. *Health services insights* 2018;11:1178632918819440.

46. Jones MR, Viswanath O, Peck J, et al. A Brief History of the Opioid Epidemic and Strategies for Pain Medicine. *Pain and therapy* 2018;7(1):13-21.

47. CDC/NCHS NVSS, Mortality,. Overdose Death Rates Involving Opioids, by Type, United States, 1999-2018. Atlanta, GA, 2020.

48. Dasgupta N, Creppage K, Austin A, et al. Observed transition from opioid analgesic deaths toward heroin. *Drug Alcohol Depend* 2014;145:238-41.

49. Rudd RA, Seth P, David F, et al. Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. *MMWR Morb Mortal Wkly Rep* 2016;65(5051):1445-52.

50. Hedegaard H, Chen LH, Warner M. Drug-poisoning deaths involving heroin: United States, 2000-2013. *NCHS Data Brief* 2015(190):1-8.

51. King NB, Fraser V, Boikos C, et al. Determinants of increased opioid-related mortality in the United States and Canada, 1990-2013: a systematic review. *Am J Public Health* 2014;104(8):e32-42.

52. Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain--Misconceptions and Mitigation Strategies. *N Engl J Med* 2016;374(13):1253-63.

53. Beaudoin FL, Banerjee GN, Mello MJ. State-level and system-level opioid prescribing policies: The impact on provider practices and overdose deaths, a systematic review. *J Opioid Manag* 2016;12(2):109-18.

54. Webster LR. Chronic Pain and the Opioid Conundrum. *Anesthesiol Clin* 2016;34(2):341-55.

55. Lipari RN, Hughes A. How People Obtain the Prescription Pain Relievers They Misuse. *The CBHSQ Report*. Rockville (MD), 2013:1-7.

56. Lewis ET, Cucciare MA, Trafton JA. What do patients do with unused opioid medications? *Clin J Pain* 2014;30(8):654-62.

57. Bicket MC, Long JJ, Pronovost PJ, et al. Prescription Opioid Analgesics Commonly Unused After Surgery: A Systematic Review. *JAMA surgery* 2017;152(11):1066-71.

58. Feinberg AE, Chesney TR, Srikandarajah S, et al. Opioid Use After Discharge in Postoperative Patients: A Systematic Review. *Ann Surg* 2018;267(6):1056-62.

59. Schirle L, Stone AL, Morris MC, et al. Leftover opioids following adult surgical procedures: a systematic review and meta-analysis. *Syst Rev*, 2020.

60. Shah A, Hayes CJ, Martin BC. Factors Influencing Long-Term Opioid Use Among Opioid Naive Patients: An Examination of Initial Prescription Characteristics and Pain Etiologies. *J Pain* 2017;18(11):1374-83.

61. Trescot AM, Helm S, Hansen H, et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. *Pain Physician* 2008;11(2 Suppl):S5-S62.

62. Von Korff M, Kolodny A, Deyo RA, et al. Long-Term Opioid Therapy Reconsidered. *Ann Intern Med* 2011;155(5):325-8.

63. Jones CM, Logan J, Gladden RM, et al. Vital Signs: Demographic and Substance Use Trends Among Heroin Users - United States, 2002-2013. *MMWR Morb Mortal Wkly Rep* 2015;64(26):719-25.

64. Unick G, Rosenblum D, Mars S, et al. The relationship between US heroin market dynamics and heroin-related overdose, 1992-2008. *Addiction* 2014;109(11):1889-98.

65. Billock RM, Samoff E, Cope AB, et al. Repeat HIV Testing by Transmission Risk Group and Rurality of Residence in North Carolina. *Sex Transm Dis* 2018.

66. Conrad C, Bradley HM, Broz D, et al. Community Outbreak of HIV Infection Linked to Injection Drug Use of Oxymorphone--Indiana, 2015. *MMWR Morb Mortal Wkly Rep* 2015;64(16):443-4.

67. Zibbell JE, Iqbal K, Patel RC, et al. Increases in hepatitis C virus infection related to injection drug use among persons aged <=30 years - Kentucky, Tennessee, Virginia, and West Virginia, 2006-2012. *MMWR Morb Mortal Wkly Rep* 2015;64(17):453-8.

68. Suryaprasad AG, White JZ, Xu F, et al. Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006-2012. *Clin Infect Dis* 2014;59(10):1411-9.

69. Peters PJ, Pontones P, Hoover KW, et al. HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014-2015. *N Engl J Med* 2016;375(3):229-39.

70. Schmidt R, Carson PJ, Jansen RJ. Resurgence of Syphilis in the United States: An Assessment of Contributing Factors. *Infect Dis (Auckl)*, 2019.

71. Sena AC, Muth SQ, Heffelfinger JD, et al. Factors and the sociosexual network associated with a syphilis outbreak in rural North Carolina. *Sex Transm Dis* 2007;34(5):280-7.

72. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance, 2016. Atlanta, GA: Department of Health and Human Services, 2017.

73. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance, 2017. Atlanta, GA: Department of Health and Human Services, 2018.

74. Dunn KE, Barrett FS, Yepez-Laubach C, et al. Opioid Overdose Experience, Risk Behaviors, and Knowledge in Drug Users from a Rural versus an Urban Setting. *J Subst Abuse Treat* 2016;71:1-7.

75. Havens JR, Walker R, Leukefeld CG. Prevalence of opioid analgesic injection among rural nonmedical opioid analgesic users. *Drug Alcohol Depend* 2007;87(1):98-102.

76. Guy GP, Jr., Zhang K, Bohm MK, et al. Vital Signs: Changes in Opioid Prescribing in the United States, 2006-2015. *MMWR Morb Mortal Wkly Rep* 2017;66(26):697-704.

77. CDC. Prescribing Data. CDC, 2012.

78. Division of Public Health- Injury and Violence Prevention Branch. N.C. Overdose Data: Trends and Surveillance. . 2017.

79. North Carolina Department of Health & Human Services. Opioid-related Overdoses. . 2017.

80. Porter F. County-by-County Figures: The Opioid Crisis in North Carolina. Raleigh, NC, 2017.

81. Rudd RA, Paulozzi LJ, Bauer MJ, et al. Increases in heroin overdose deaths - 28 States, 2010 to 2012. *MMWR Morb Mortal Wkly Rep* 2014;63(39):849-54.

82. Stamm LV. Syphilis: Re-emergence of an old foe. *Microb Cell* 2016;3(9):363-70.

83. Hoffman J. Hunting a Killer: Sex, Drugs and the Return of Syphilis. *New York Times*, 2017.

84. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003;158(9):915-20.

85. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). HCUP Tools and Software. Rockville, MD; May 2019. (www.hcup-us.ahrq.gov/tools_software.jsp.). (Accessed).

86. Centers for Disease Control and Prevention. Prescription Drug Overdose Data & Statistics: Guide to ICD-9-CM and ICD-10 Codes Related to Poisoning and Pain. Atlanta, GA, 2013.

87. Calcaterra SL, Scarbro S, Hull ML, et al. Prediction of Future Chronic Opioid Use Among Hospitalized Patients. *J Gen Intern Med* 2018;33(6):898-905.

88. Mundkur ML, Rough K, Huybrechts KF, et al. Patterns of opioid initiation at first visits for pain in United States primary care settings. *Pharmacoepidemiol Drug Saf* 2018;27(5):495-503.

89. Glanz JM, Narwaney KJ, Mueller SR, et al. Prediction Model for Two-Year Risk of Opioid Overdose Among Patients Prescribed Chronic Opioid Therapy. *J Gen Intern Med* 2018;33(10):1646-53.

90. Ray GT, Bahorik AL, VanVeldhuisen PC, et al. Prescription Opioid Registry Protocol in an Integrated Health System. *Am J Manag Care* 2017;23(5):e146-55.

91. Cole SR, Hudgens MG, Brookhart MA, et al. Risk. *Am J Epidemiol* 2015;181(4):246-50.

92. Cole SR, Lau B, Eron JJ, et al. Estimation of the standardized risk difference and ratio in a competing risks framework: application to injection drug use and progression to AIDS after initiation of antiretroviral therapy. *Am J Epidemiol* 2015;181(4):238-45.

93. University of North Carolina. North Carolina Disease Event Tracking Epidemiologic Collection Tool (NC DETECT). (https://ncdetect.org/). (Accessed).

94. American FactFinder. 2008-2012 American Community Survey. United States Census Bureau's American Community Survey Office.; 2019. (Accessed).

95. American FactFinder. 2013-2017 American Community Survey. United States Census Bureau's American Community Survey Office.; 2019. (Accessed).

96. Emergency department data reporting. *NCGS* 2018.

97. Rowe C, Vittinghoff E, Santos GM, et al. Performance Measures of Diagnostic Codes for Detecting Opioid Overdose in the Emergency Department. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine* 2017;24(4):475-83.

98. Reardon JM, Harmon KJ, Schult GC, et al. Use of diagnosis codes for detection of clinically significant opioid poisoning in the emergency department: A retrospective analysis of a surveillance case definition. *BMC Emerg Med* 2016;16:11.

99. Marshall RJ. Mapping disease and mortality rates using empirical Bayes estimators. *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 1991;40(2):283-94.

100. Lee L-f, Yu J. Estimation of spatial autoregressive panel data models with fixed effects. *Journal of Econometrics* 2010;154(2):165-85.

101. StataCorp. Stata: Release 16. College Station, TX: StataCorp LLC, 2019:Statistical Software.

102. LeSage JP, Pace RK. *Introduction to Spatial Econometrics*. Boca Raton: CRC Press; 2009.

103. Dubin R. Spatial Weights. In: A. Stewart Fotheringham PAR, ed. *The SAGE Handbook of Spatial Analysis*. London, England: SAGE Publications, LTD, 2009:124-58.

104. Owusu-Edusei K, Jr., Gift TL, Leichliter JS, et al. The Spatial Association Between Federally Qualified Health Centers and County-Level Reported Sexually Transmitted Infections: A Spatial Regression Approach. *Sex Transm Dis* 2018;45(2):81-6.

105. North Carolina HIV/STD/Hepatitis Surveillance Unit. 2017 North Carolina HIV/STD/Hepatitis Surveillance Report. Raleigh, NC: North Carolina Department of Health and Human Services, Division of Public Health, Communicable Disease Branch, 2018.

106. Chang BA, Pearson WS, Owusu-Edusei K, Jr. Correlates of county-level nonviral sexually transmitted infection hot spots in the US: application of hot spot analysis and spatial logistic regression. *Annals of epidemiology* 2017;27(4):231-7.

107. Fotheringham AS, Wong DW. The modifiable areal unit problem in multivariate statistical analysis. *Environment and planning A* 1991;23(7):1025-44.

108. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2019.

109. Wickham H, Averick M, Bryan J, et al. Welcome to the tidyverse. *Journal of Open Source Software* 2019;4(43):1686.

110. Volkow N, Benveniste H, McLellan AT. Use and Misuse of Opioids in Chronic Pain. *Annu Rev Med* 2018;69:451-65.

111. Deyo RA, Hallvik SE, Hildebran C, et al. Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naive Patients: A Statewide Retrospective Cohort Study. *J Gen Intern Med* 2017;32(1):21-7.

112. Young JC, Dasgupta N, Chidgey BA, et al. Postsurgical Opioid Prescriptions and Risk of Long-term Use: An Observational Cohort Study Across the United States. *Ann Surg* 2019.

113. Young JC, Wu JM, Willis-Gray M, et al. Persistent Opioid Use After Hysterectomy in the United States, 2005-2015. *Obstetrics and gynecology* 2020;135(1):123-32.

114. Clarke H, Soneji N, Ko DT, et al. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *BMJ* 2014;348:g1251.

115. Thiels CA, Habermann EB, Hooten WM, et al. Chronic use of tramadol after acute pain episode: cohort study. *BMJ* 2019;365:l1849.

116. Henry SG, Wilsey BL, Melnikow J, et al. Dose escalation during the first year of long-term opioid therapy for chronic pain. *Pain Med* 2015;16(4):733-44.

117. Hayes CJ, Krebs EE, Hudson T, et al. Impact of opioid dose escalation on pain intensity: a retrospective cohort study. *Pain* 2020;161(5):979-88.

118. Perez HR, Buonora M, Cunningham CO, et al. Opioid Taper Is Associated with Subsequent Termination of Care: a Retrospective Cohort Study. *J Gen Intern Med* 2020;35(1):36-42.

119. Miller M, Barber CW, Leatherman S, et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. *JAMA Intern Med* 2015;175(4):608-15.

120. Young JC, Lund JL, Dasgupta N, et al. Opioid tolerance and clinically recognized opioid poisoning among patients prescribed extended-release long-acting opioids. *Pharmacoepidemiol Drug Saf* 2019;28(1):39-47.

121. Sun EC, Dixit A, Humphreys K, et al. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. *BMJ* 2017;356:j760.

122. Dasgupta N, Funk MJ, Proescholdbell S, et al. Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality. *Pain Med* 2016;17(1):85-98.

123. Ruhm CJ. Corrected US opioid-involved drug poisoning deaths and mortality rates, 1999-2015. *Addiction* 2018;113(7):1339-44.

124. Centers for Disease Control and Prevention. Syphilis Surveillance Supplement 2013-2017. Atlanta: U.S.: Department of Health and Human Services, 2019.

125. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance, 2017. Atlanta, GA: Department of Health and Human Services, 2018.

126. Centers for Disease Control and Prevention. 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes — United States. *Surveillance Special Report* Centers for Disease Control and Prevention, U.S. Department of Health and Human Services., 2018.

127. Jones CM, Christensen A, Gladden RM. Increases in prescription opioid injection abuse among treatment admissions in the United States, 2004-2013. *Drug Alcohol Depend* 2017;176:89-95.

128. Heimer R, Barbour R, Shaboltas AV, et al. Spatial distribution of HIV prevalence and incidence among injection drugs users in St Petersburg: implications for HIV transmission. *AIDS* 2008;22(1):123-30.

129. Emergency department data reporting. *NCGS*, 2018.

130. North Carolina HIV/STD/Hepatitis Surveillance Unit. Syphilis Epidemiology in North Carolina 2018. Raleigh, NC: North Carolina Department of Health and Human Services, Division of Public Health, Communicable Disease Branch, 2019.

131. North Carolina Injury & Violence Prevention Branch. North Carolina Emergency Department (ED) Visits for Opioid Overdose: November 2019. Raleigh, NC: North Carolina Department of Health and Human Services, 2019.

132. Johnson KM, Fibbi M, Langer D, et al. Prescription drug misuse and risk behaviors among young injection drug users. *J Psychoactive Drugs* 2013;45(2):112-21.

133. Hook EW, 3rd. Syphilis. *Lancet* 2017;389(10078):1550-7.

134. Centers for Disease Control and Prevention. Current Trends Primary and Secondary Syphilis --- United States, 1981 - 1990. Atlanta, GA, 1991:314, 21-23.

135. North Carolina HIV/STD/Hepatitis Surveillance Unit. 2018 North Carolina STD Surveillance Report. Raleigh, North Carolina: North Carolina Department of Health and Human Services, Division of Public Health, Communicable Disease Branch, 2019.

136. Owusu-Edusei K, Jr., Chesson HW. Using spatial regression methods to examine the association between county-level racial/ethnic composition and reported cases of Chlamydia and gonorrhea: an illustration with data from the state of Texas. *Sex Transm Dis* 2009;36(10):657-64.

137. Krueger AB. Where Have All the Workers Gone? An Inquiry into the Decline of the U.S. Labor Force Participation Rate. In: Institute B, ed. *Brookings Papers on Economic Activity*. Washington, D.C., 2017.

138. Ghertner R GL. The opioid crisis and economic opportunity: geographic and economic trends. *ASPE Research Brief*: U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, 2018.

139. Kansagra SM, Cohen MK. The Opioid Epidemic in NC: Progress, Challenges, and Opportunities. *N C Med J* 2018;79(3):157-62.

140. The Strengthen Opioid Misuse Prevention (STOP) Act of 2017. 2017.

141. Walker AM. Confounding by indication. *Epidemiology* 1996;7(4):335-6.

142. Sabel C, Loytonen M. *GIS in Public Health Practice. Chapter 4- Clustering of Disease*. Boca Raton: CRC Press; 2004.

143. Suissa S. Effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease: immortal time bias in observational studies. *Am J Respir Crit Care Med* 2003;168(1):49-53.

144. Suissa S. Immeasurable time bias in observational studies of drug effects on mortality. *Am J Epidemiol* 2008;168(3):329-35.

145. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep* 2015;2(4):221-8.