INFECTIONS AND MORTALITY AMONG PEOPLE WHO USE DRUGS

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A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2023

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ABSTRACT

Mary C. Figgatt: Infections and Mortality Among People Who Use Drugs
(Under the direction of Yvonne M. Golightly)

Bacterial and fungal infections associated with injection drug use are increasing substantially alongside trends in drug overdose deaths. Methadone and buprenorphine are two medications (MOUD) known to reduce opioid use disorder symptoms and modify underlying behaviors such as injection drug use, which are a driver of bacterial infections including skin and soft tissue infections (SSTI).

The overall objective of this proposal is to expand the knowledge base concerning infection-related mortality and the potential effects of medications for opioid use disorder (MOUD) on infection-related outcomes. The project utilized an extensive dataset of public and private healthcare insurance claims linked with death certificate data for North Carolina residents during 2007 through 2018. The specific aims were to 1) examine the incidence and risk factors of bacterial and fungal infection-related mortality and drug overdose among people who use drugs, and 2) estimate the association between MOUD mortality among people with opioid use-associated skin and soft tissue infections.

Bacterial and fungal infections and overdose were contributors to mortality among people with drug use diagnoses. Specifically, within the first year of follow up, overdose mortality incidence was 36 per 10,000 people (95% confidence interval: 33-40). Bacterial and fungal infection-associated mortality incidence was 16 per 10,000 people (95% confidence interval: 14-

18). Bacterial and fungal infection-associated mortality was higher as age increased. In contrast, overdose mortality was higher among younger adults.

People with opioid use-related skin or infections had a high risk of mortality, with 12 per every 100 people dying within the first 3 years after their initial SSI diagnosis. However, MOUD was associated with reductions in both mortality and hospitalization: for every 100 people on MOUD, there were 4 fewer deaths (95% confidence interval: 2 to 6) compared to what it would have been, had they not been on MOUD. However, few people were on MOUD (16% among the total population) following their infection diagnosis. While bacterial and fungal infections are contributors to mortality among people who use drugs, MOUD are one approach to improve the wellbeing among people who develop these infections.

ACKNOWLEDGEMENTS

Thank you to my chair, Yvonne Golightly, for providing guidance and support throughout the dissertation progress and my doctoral training as a whole. I would also like to thank my committee members: Steve for encouraging me to pursue new methodologic and grant opportunities, Nab for the the time on the ground and providing a space to learn outside of the classroom, Asher for bringing research back to practice and support in career development, and Juan for career guidance and positive encouragement throughout. I would also like to thank Chris Baggett and Bradford Jackson at the Cancer Information and Population Health Resource for providing the data and support to accomplish this project. Thanks to Louise, Zach, and Don at North Carolina Survivors Union for keeping the purpose grounded in health and teaching what research can look like in the future. I would also like to thank Josie Caves-Sivaraman, Anna Austin, Becky Naumann, Jessie Edwards, and Michele Jonsson-Funk for methodologic guidance and resources that has informed a lot of this work.

Thank you to my husband, Ricky, who has been the constant support behind the scenes. You have always encouraged me to go above and beyond, even at times when you have way more faith in me than I do. Thank you for everything.

Research reported in this publication was supported by the National Institute On Drug Abuse of the National Institutes of Health under Award Number F31DA055345. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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LIST OF ABBREVIATIONS

ART	antiretroviral therapy
CI	confidence interval
CLR	confidence limit ratio
CMS	Centers for Medicare and Medicaid Services
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FDA	Federal Drug Administration
HCPCS	Healthcare Common Procedure Coding System
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
ICD	International Classification of Diseases
IQR	interquartile range
IRR	incidence rate ratio
MOUD	medications for opioid use disorder
NC	North Carolina
OAT	opioid agonist treatment
OR	odds ratio
OTP	opioid treatment programs
OUD	opioid use disorder
PPV	positive predictive value
RCT	randomized control trials

SSTI	skin and soft tissue infections
US	United States
WHO	World Health Organizations

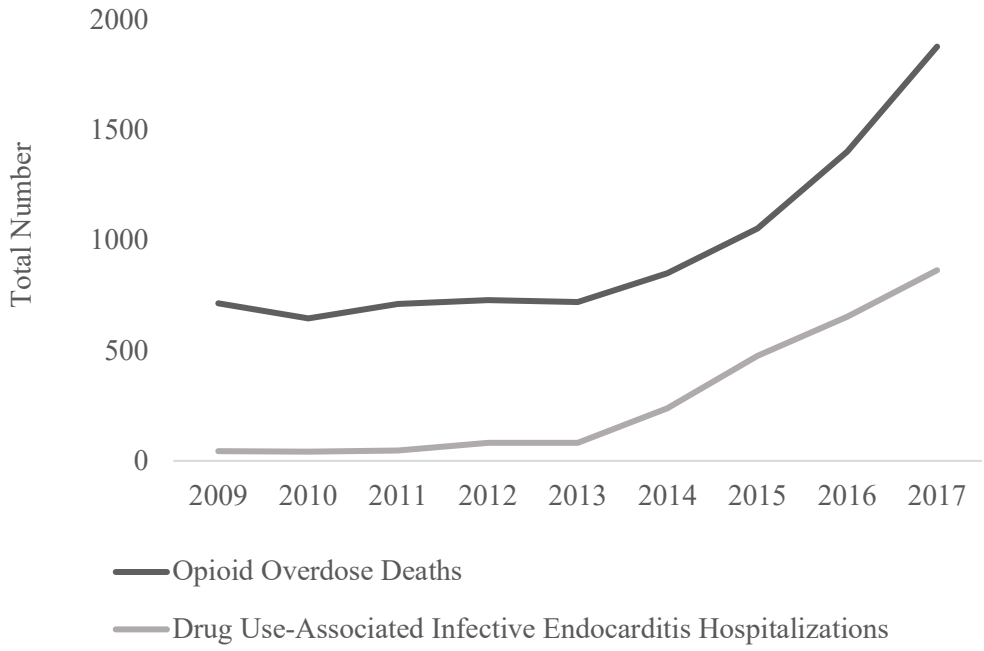
CHAPTER 1: BACKGROUND

Severe infections and drug overdose are increasing rapidly and in tandem. Since 2013, infections related to injection drug use have increased substantially in the United States.[1–3] In one US state, the number of drug use-related serious infections from 2008 to 2018 increased by 18 times.[4] Two such infections, skin and soft tissue infections (SSTI) and infective endocarditis, occur from the introduction of bacteria or fungi past the skin via contaminated drug injection and preparation equipment. SSTI are a common reason why people who use drugs seek healthcare. As many as 65% of people who inject drugs have a lifetime history of SSTI.[5–7] In their mildest form, SSTI manifest as abscesses and cellulitis. Endocarditis is a serious infection of the inner lining of heart chambers and valves that can result in death in their most severe form.[8–12] endocarditis is also associated with prolonged hospital stays. While less common than minor skin infections,[1] severe SSTI and endocarditis require inpatient hospitalization, surgery, prolonged intravenous antibiotics and long-term hospitalization.

1.1. Drug overdose and other causes of mortality among people who use drugs

Drug overdose, SSTIs, and endocarditis are closely intertwined. Fatal opioid overdose and drug use-associated endocarditis are increasing in parallel (Figure 1.1).[3,13] Drug overdose is a leading cause of death in the United States, accounting for nearly 70,000 lives lost in 2018.[14] While overdose mortality is well-documented in the United States, mortality resulting from infections among people who use drugs has not been described to our knowledge. Yet, there is an urgent public health need to understand to what extent these infections contribute to mortality among people who use drugs.

Figure 1.1. Opioid Overdose Deaths[13] and Drug Use-Associated Infective Endocarditis Hospitalizations[3] in North Carolina.



1.2. Preventing drug use-related morbidity and mortality

Overdose, SSTIs, and endocarditis are preventable. Prevention comes in a variety of forms, from community-level to individual-level interventions. Strategies to reduce drug use-related harms can involve a combination of factors that work best for an individual's needs: medications (such as opioid agonist treatments), psychotherapy, harm reduction services (such as community distributed naloxone), and evidence-based drug and alcohol treatment programs.

When people seek care for drug use-associated infections, these interactions with the healthcare system present an opportunity to link individuals to comprehensive treatment and community-based services (e.g., syringe service programs, peer support specialists and organizations). Medications for opioid use disorder (MOUD) may reduce infection-related outcomes due to decreases in occurrence and frequency of drug use itself, particularly injection drug use, which are causative factors of SSTI. While important, this is just one approach to reduce the harms of serious infections.

1.3. Defining the population of interest

Throughout this document, the use of stigmatizing language is avoided to the best of our knowledge. Over time, these words will adapt as new ones become more respectful or relevant. We purposefully use people-first language, such as "people who use drugs." While this term may seem ambiguous, it is purposefully ambiguous to recognize the diverse experiences among this population.

Drug use patterns may differ among each person and over time. For the purposes of this dissertation, the population will include people who have specific drug use events, documented in healthcare claims data, to which there is a stronger indication of injection drug use. We are interested in injection drug use specifically because it is most commonly the cause of bacterial and fungal infections among people who use drugs. However, injection drug use is not directly observable in insurance claims data. Thus, we will focus on drug-related diagnoses and medications that are more commonly associated with injection. We call the population "people who use drugs" and not "people who *inject* drugs" because we acknowledge that not everyone will take their drugs via injection. These approaches used in these analyses are imperfect in measuring the population, and more importantly, contextualizing the circumstances surrounding someone's health encounters. Healthcare data are limited in understanding of circumstances surround an individual's interactions with the healthcare system, and the social and economic conditions that impact their health and outcomes. While healthcare data provide an opportunity to quantify the burden of these diseases, they are inherently limited in information and provide one facet to the larger study area.

CHAPTER 2: LITERATURE REVIEW

2.1. Epidemiology of bacterial and fungal infections

2.1.1. Drug use-associated bacterial and fungal infections among the general population

The burden of drug use-associated bacterial and fungal infections is high. In 2011, it was estimated that anywhere from 155,000 to 540,000 Americans had a drug use-associated SSTI in the previous year.[15] Overall, it is estimated that the national burden of hospital visits in 2017 was 98,000 for drug use-associated SSTI hospital visits and between 9,700 to 11,500 drug use-associated endocarditis hospital visits.[15] However, these estimates were loosely defined projections and dependent on a variety of data sources, of which the generalizability to the US population likely varies.

Beyond the overall burden at one point in time, there is a growing recognition that drug use-associated SSTI and endocarditis are increasing among the general population.[4,15,16] In Oregon, the percent of drug use-associated bacteria and sepsis hospitalizations increased by over 1,700% from 2008 (n=189) to 2018 (n=3,345).[4] During the same time period, drug use-associated endocarditis hospitalization increased by over 800% from 112 to 929 people who use drugs hospitalized with endocarditis. Drug use-associated SSTI hospitalizations also increased substantially (from 620 to 1,620 during the time period, representing a 230% increase).

Epidemiologic analyses of SSTI and endocarditis have been largely descriptive in nature, particularly in healthcare database studies.[1–3,15,17] Additionally, estimates of the burden of SSTI and endocarditis are mainly among the general population as opposed to among people who use drugs, specifically. Obtaining a denominator of people who use drugs is typically challenging to

define and estimate, particularly within administrative data. Still, obtaining a people who use drugs specific denominator is needed in future research, as this denominator will provide stronger estimates that account for changes to people who use drugs population size over time.

2.1.2. SSTI and endocarditis among people who use drugs

SSTI are common among people who use drugs, specifically among those who inject. endocarditis appears to be less common, but its' incidence may be increasing. In a systematic review of studies of injection-related injuries and diseases, the lifetime prevalence of SSTI ranged from 6-69%, endocarditis from 0.5-23%, and sepsis from 2-10%.[5] The past 6- to 12-month history of SSTI ranged from 7% to 37%. The estimates of point prevalence (infection at the time of survey) to 1-month history of SSTI ranged from 6% to 32%. The studies evaluated in the systematic review were published dating back to 2000 through 2015 in many regions worldwide, but mainly in the United States, Canada, Australia, and the United Kingdom.

Notably, one study[18] confirmed the presence of infections by clinical evaluation at the time of the survey. This survey was conducted among 152 participants of a Baltimore-based syringe service program during 2012-2013. The point prevalence estimates include 35% with any active wounds, 20% with chronic wounds, and 18% with abscesses.

A recent survey[7] conducted among syringe service program participants in North Carolina during 2020 collected self-reported data on SSTI and endocarditis history. 46% of participants had a history of SSTI in the past 12 months and 64% had a lifetime history. Ten percent of participants reported a history of endocarditis in the past 12 months and 17% had a lifetime history.

Estimates of SSTI and endocarditis occurrence among people who use drugs have largely been limited to prevalence estimates, drawn from community-based cross-sectional surveys. Many of these surveys rely on self-reported infection data by participants. Even with these

limitations, the burden of severe SSTI and endocarditis among people who use drugs is concerning. More research specific to people who use drugs is needed to estimate infection incidence and obtain clinical information to understand infection severity. Larger sample sizes with more comprehensive data on predictors, including drug use behaviors, factors relating to socioeconomic position, and protective behaviors is needed

2.1.3. Predictors and causes

While current incidence estimates of SSTI and endocarditis among people who use drugs are not well established, specific predictors and causes of these infections have been explored in detail over the past several decades. At the biological level, a common pathogen that causes these infections is *Staphylococcus aureus.*[1,8] Other bacteria and fungi are also known pathogenic causes.[15,19] At the individual behavioral and social level, individual characteristics and drug use behaviors have been explored through cross-sectional surveys. Many studies have taken place within community-based settings, such as syringe service programs.

A 2017 systematic review[5] found the following predictors were associated with an increased occurrence of a lifetime history of SSTI: being female, injecting more frequently, injecting intramuscularly or subcutaneously. The authors note that inconsistent definitions for SSTI are used across studies, resulting in difficulties comparing results. Though not explicitly identified in this systematic review, stimulant injection is another well-documented predictor of increased SSTI occurence.[7,20–22]

Similar predictors have been identified in other studies, such as in a 2015 cross-sectional study examining current abscesses and chronic wounds as an outcome.[18] A strength of this study was that the outcome was confirmed by clinical examination. In contrast, many other studies collected outcome data via self-report. While self-report is valuable, particularly for

understanding the person's past history, clinical confirmation can provide additional information on the infection's severity.

In terms of factors associated with decreased occurrence of SSTI, cleaning the injection site before use had been demonstrated to be a protective factor.[5] In a 2020 cross-sectional survey of North Carolina syringe service program participants[7], having access to a trusted doctor was a protective predictor of recent SSTIs. Public health messaging on SSTI prevention for people who use drugs often cites the following: using new and sterile injection equipment, avoiding equipment sharing, washing hands and injection site before use, and preparing drugs on a clean surface when possible.[23]

To date, there is limited research on predictors of endocarditis among people who use drugs. One Denmark-based study[24] found a longer history of injection drug use was associated with increased prevalence of endocarditis history. The sample size consisted of only 14 people with an endocarditis history. Thus, more research with larger samples is needed on individual predictors of endocarditis.

2.1.4. Trends in North Carolina

North Carolina has also seen a dramatic increase in drug use-associated bacterial and fungal infections among the general population. From 2010 to 2018, hospitalizations for drug use-associated invasive infections increased from 1.2 to 15.1 hospitalizations per 100,000 North Carolina residents.[25] These infections included endocarditis, septic arthritis, central nervous system/spine infections, and osteomyelitis. Endocarditis hospitalizations associated with drug use increased from 1.2 to 15.1 per 100,000 North Carolina residents from 2007 to 2017.[3]

One recent cross-sectional survey about injection-related skin infections[7] was conducted 105 participants recruited from 5 syringe service programs in North Carolina. The study found that nearly half of participants had a skin or soft tissue infection within the previous 12 months.

For those with a recent history of infections, 71% had visited an emergency room to received treatment of their infection. Many people had delayed care for their infections due a variety of reasons, with the most common being: concerns about judgment or mistreatment by medical staff (54%), they initially treated the infections themselves (52%), and the visit taking too much time (37%). However, the study also found the prevalence of infection was lower among people who had access to a trusted doctor compared to those who did not, after adjusting for health insurance coverage and gender (prevalence difference: -27 per 100 people, 95% confidence interval: -52, -2).

2.2. Healthcare utilization and costs of care for people with drug use-associated infections

Healthcare utilization is often necessary and extremely expensive for people with endocarditis. Inpatient hospitalization often costs more than $60,000 per hospitalization.[8,3,26] Endocarditis requires cardiac surgery in more than 25% of cases, adding to medical expenses.[27] Many people with endocarditis require long term antibiotic therapy, in which some hospitals may require an individual to be hospitalized for up to 6 weeks.[28] Though, outpatient antibiotic therapy may be an approach that improves both patient experiences while reducing costs.[29] Other costs due to time away from work and caretaker responsibilities are difficult to directly quantify but are likely quite costly to individuals and their families.

Healthcare utilization is also common for people who use drugs with SSTI. A recent survey found 71% of people who use drugs with recent SSTI in North Carolina received emergency care and 24% had surgery for the infection.[7] Medical costs for people who use drugs with SSTI, are estimated to be less expensive than endocarditis, but are still costly. One study estimated a mean cost of drug use-associated SSTI hospitalizations to be slightly over $10,000.[30] Longer-term economic costs for SSTI are unknown, but likely differ by SSTI severity. For both SSTI and endocarditis, the social and emotional costs of these infections are not well understood.

Yet, these infections likely have a much larger societal impact beyond their medical expenses, particularly for more severe infections.

2.3. Outcomes of people with drug use-associated infections

Among people who use drugs in the United States, the extent of infection-related mortality is not well described. However, one Baltimore-based study quantified the burden of human immunodeficiency virus (HIV) and other infection-related mortality among a cohort of over 5,500 people who inject drugs.[31] Individuals were recruited into the cohort beginning in 1988 and ending in 2018. Overall, 44% of participants had died at the end of follow up. The largest group of cause specific mortality had HIV and infection-related death, representing 31% of all deaths. Of those who died from HIV and infection-related causes, 73% were attributed to HIV/AIDS (22% of all deaths) and 8.3% were attributed to sepsis (2.5% of all deaths). However, the trends in causes of deaths differed substantially over the study period, with a large surge in HIV and infection-related deaths in the early 1990s, and an increase in drug and violence-related death after 2014. Two issues arise with this study's estimates of infection-related mortality. First, trends in sepsis-related mortality were not presented as separate estimates nor presented temporally, making their relevance to the current landscape of infection-related mortality difficult to assess. Additionally, even though the study was an open cohort design which allowed new participant entry as late as 2018, it did not appear the authors used uniform risk periods for the parameter estimate calculations. Thus, those who were newer entries would have contributed a much smaller amount of time under observation compared with those entered the cohort several decades prior. If the hazard of infection-related mortality varies over time (a highly probable assumption), then these non-uniform risk periods may bias the parameter estimates.

Recently, several studies have examined all-cause mortality among people who use drugs following their endocarditis diagnosis. Table 2.1 presents an overview of these estimates by

study and risk period. Overall all-cause mortality estimates (as an incidence proportion) range from 6-11% for in-hospital mortality[2,3,8,32,33], 6-15% for 30-day mortality[9,11], and 16-25% for 1-year mortality[8,9,11]. The study designs, target populations, data sources, and samples sizes vary among these studies. Notably, the index date for their risk periods appears to vary between studies, with some beginning at the time of hospitalization and others beginning after hospital discharge (excluding those who died in the hospital). Many studies were largely limited to inpatient mortality or small samples with low statistical power.[10,11]

Additionally, many studies examine drug use as a predictor of mortality among the general patient population.[2–4,8,11,30,32] While informative of the changing epidemiology of a given disease, this approach does not advance our understanding of what factors are associated with mortality among people who use drugs, who have specific health needs.

While mortality has been explored in the context of people with drug use-associated endocarditis, mortality associated with drug use-associated SSTI remains unknown.

Table 2.1. All-cause mortality estimates among people with drug use-associated endocarditis by risk period.

					Incidence Proportion				
Author, Year	**Design**	**Time**	**Location**	**Sample Size**	**In-hospital**	**30-day**	**90-day**	**6-month**	**1-year**
Kadri et al, 2019[2]	Hospitalized patients with endocarditis	2002 - 2016	United States (weighted)	94,350 people with drug use-associated endocarditis (weighted)	6.4%	--	--	--	--
Leahey et al, 2019[8]	Hospitalized patients with endocarditis	2007 - 2015	Mass.	103 people with drug use-associated endocarditis	6%	--	--	--	16%[a]
Schranz et al, 2019[3]	Endocarditis hospitalizations	2007 - 2017	North Carolina	2,602 hospitalizations for drug use-associated endocarditis	8%	--	--	--	--
Thakarar et al, 2019[32]	Patients admitted to a medical center with endocarditis	2013 - 2016	Maine	42 people with drug use-associated endocarditis	10%	--	19%	--	--
Pericas et al, 2021[33]	Registry of PWID with endocarditis	2000 - 2006, 2008 - 2012	Worldwide	591 people with drug use-associated endocarditis	11%	--	--	14%, 25%[a]	--
Goodman-Meza et al, 2019[11]	Meta-analysis of 19 studies of PWID with endocarditis who underwent surgery	1972 - 2014	North America and Europe	648 PWID with endocarditis who had surgery	--	5.7%[b]	--	--	19%[b]
Straw et al, 2020[9]	Registry of PWID with endocarditis	2006 - 2016	United Kingdom	92 PWID with endocarditis	--	15%[b]	--	--	26%[b]

[a]Includes in-hospital mortality.
[b]Unclear if in-hospital mortality is included.

2.4. Medications to treat opioid use disorder (MOUD)

Opioid use disorder (OUD) is a diagnosis defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as "a problematic pattern of opioid use leading to clinically significant impairment or distress […] occurring within a 12-month period."[34] A list of symptoms are used to classify whether the individual meets criteria for OUD diagnosis and the severity (mild, moderate, severe).

Currently, there are several FDA-approved medications for the treatment of OUD, including methadone, buprenorphine, and naltrexone (specifically in its extended-release formulation). Table 2.2 presents a briefly overview of each medication, their psychological activity, forms for OUD treatment, prescribers, and non-long-term OUD treatment indications.[35]

Table 2.2. Current FDA-approved medications for the treatment of OUD symptoms.[35]

Medication	Psychological Activity	Forms for OUD Treatment	Prescribers	Non-OUD Treatment Indications
Buprenorphine	Partial opioid agonists	• Tablet or film taken daily • Injection administered monthly • Implant replaced after 6 months	• Office-based treatment where prescriber has a waiver • Opioid Treatment Programs (OTP)	• Medically supervised withdrawal • Pain management
Methadone	Full opioid agonist	• Liquid oral doses taken daily	• Opioid Treatment Programs (OTP)	• Medically supervised withdrawal • Pain management
Naltrexone	Opioid antagonist	• Injection administered monthly • Pill taken daily	• Office-based treatment	• Alcohol use disorder

Information presented is repurposed from the Substance Abuse and Mental Health Service Administration's 2021 manual on MOUD.

Overall, these medications are effective treatments in minimizing symptoms among people experiences symptoms included in an OUD diagnosis.[36–41] Methadone and buprenorphine have been rigorously evaluated in terms of their effectiveness on all-cause mortality and other outcomes. Study results consistently show an association between methadone and buprenorphine on improved individual outcomes.[35,42] Several recent studies have shown potential benefits of methadone and buprenorphine, as compared with naltrexone.[43,44] Methadone was not covered by Medicare or private insurers in North Carolina during the study period. Due to the currently available FDA-approved medications and data availability in insurance claims, this proposal will primarily focus on buprenorphine and methadone among Medicaid enrollees in Aims 2.

A 2021 systematic review and meta-analysis assessed association between MOUD and all-cause and cause-specific mortality.[45] This review included 15 randomized control trials (RCT) and 36 cohort studies conducted worldwide during 1964 through 2018. Opioid agonist treatment (OAT) was the specific treatment examined which included buprenorphine and methadone. The unadjusted pooled incidence rate ratio (IRR) of all-cause mortality was 0.47 (95% CI = 0.42-0.53, CLR = 1.3) when comparing time on OAT versus time not on OAT. Both methadone and buprenorphine had strong protective effects on all-cause mortality when examined separately. For drug-related death (including poisoning/overdose), the unadjusted IRR comparing OAT time with non-OAT time was 0.41 (95% CI = 0.33 - 0.52, CLR = 1.6). However, the definition for drug-related death included those with any cause of death both those with any code for drug overdoses or substance use disorders. Thus, drug overdose death was not reported as a standalone cause of death.

Notably, this review included studies where mortality measurements included injection-related injuries and infections (n=13 studies covering 168,705 people), subset by endocarditis

(n=13 studies covering 168,705 people), bacteremia or sepsis (n=14 studies covering 169,002 people), and skin or soft tissue infections (n=13 studies covering 168,705 people).[45] None of these studies were conducted among populations in the United States. These studies had a wide range of target populations, study designs (such as inclusion criteria and follow-up periods), and analytic methods. Additionally, the definition used for injection-related injuries were based on disease *morbidity*, not *mortality*.

For all injection-related injury deaths, the unadjusted IRR comparing OAT use with no OAT use was 0.90 (95% CI = 0.72 – 1.12, CLR = 1.5).[45] For specific injection-related injuries deaths, the unadjusted IRR was 0.80 (95% CI = 0.59 – 1.08, CLR = 1.8) for endocarditis-related death, 0.93 (95% CI = 0.62 – 1.40, CLR = 2.3) for bacteremia/sepsis-related death, and 1.17 (95% CI = 0.65 – 2.09, CLR = 3.2) for skin/soft tissue infection-related death.

Medications used for OUD treatment have also been proven effective in reducing overdose.[45,46] Using a unique population-based dataset linked across healthcare record, prescription, behavioral health, and medical examiner data, a 2018 study examined outcomes among Massachusetts residents who had survived a nonfatal overdose during 2012-2014. The authors found a strong protective association between methadone and buprenorphine use on all-cause mortality.[46] Notably, they accounted for time-varying medication use and discontinuation of medication during each discrete time unit.

MOUD has also shown promising results on HIV outcomes among people diagnosed with OUD.[47] A systematic review and meta-analysis including 6 studies examining the association between MOUD (being on MOUD compared to not on MOUD) on HIV viral suppression had an odds ratio of 2.19 (95% CI = 1.88, 2.59).[47] Beneficial results were also

identified for the association between MOUD and the outcomes of antiretroviral therapy (ART) adherence and hepatitis C viral suppression.

While some non-fatal outcomes have been explored, the impact of medication for OUD on mortality among people who use drugs with OUD and SSTIs has not been explored in large populations in the United States (Table 2.3). While some studies have assessed the effectiveness of medication for OUD on mortality outcomes among people who use drugs with endocarditis, these studies have been limited to examinations of all-cause mortality, among small scale[48–50] or selective[51–53] populations, such as privately-insured individuals. In addition, studies to date have not distinguished between prevalent users (continuous use over a period of time) versus new users (initiators) of medication for OUD, a study design error that can induce substantial bias and lead to false negative results.[54–56] Given socioeconomic root causes of the overdose crisis,[57] and with Medicaid and Medicare being the most common payers for drug use-associated endocarditis hospitalizations,[3,25] additional research is needed to examine outcomes of medication for OUD among diverse populations of people who use drugs with SSTI.

Table 2.3. Studies examining the association between MOUD and outcomes among people with drug use-associated SSTI.

Author, Year	Population and Setting	Study Design	Exposure	Exposure Prevalence	Main Outcome(s)	Measure of Association Estimate
Marks et al, 2020[50]	220 people admitted to tertiary care for OUD invasive infections in St Louis, MO	Cohort study	Exposure: Methadone, buprenorphine, methadone taper for detox during hospitalization Comparator: No medication	46.8%	90-day readmission	Odds ratios 90-day readmission Buprenorphine vs no treatment: OR = 0.38 (95% CI = 0.17-0.85) Methadone maintenance vs no treatment: OR = 0.43 (95% CI = 0.20 - 0.94) Methadone taper vs no treatment: 1.87 (95% CI = 0.62, 5.10)
Barocas et al, 2020[52]	6,538 commercially insured adults with hospitalized with an OUD-related SSTI during 2010-2017	Cohort study	Exposure: Prescription claims for buprenorphine or naltrexone (injectable or oral) within 30 days of discharge Comparator: No MOUD claim	5.5%	30-day and 1-year rehospitalization and recurrent SSTI	Hazard ratio (HR) using Cox models adjusted for sex, age, region, type of coverage, co-existing SUD, surgery 30-day rehospitalization: 1.29 (95% CI = 1.05-1.59) 1-year Recurrent SSTI: 0.62 (95% CI = 0.42, 0.91)
Brothers et al, 2022[58]	8,943 people who had injection-related infection hospitalizations who had accessed any OAT treatment during 2001-2018 in New South Wales, Australia	Cohort study similar to per-protocol	Time-varying, time on and off OAT Exposure: methadone or buprenorphine Comparator: No MOUD	48% had OAT rx at discharge	All-cause mortality Rehospitalization	HR using Cox models adjusted for age, sex, ethnicity, comorbidities, prior opioid-related hospitalization, prior alcohol use hospitalization, prior incarceration history, year, length of stay, discharge against medical advice Mortality HR = 0.63 (95% CI = 0.57, 0.70) Rehospitalization HR = 0.89 (95% CI = 0.84 – 0.96)

2.5. Health inequities in medication access

Racism- and sexism perpetuate health inequities related medication access and use.[59] Even though it is established within the scientific community that race is a social construct and structural racism is the source of racial disparities[60], some healthcare providers continue to hold false biologic beliefs that cause a multitude of harm.[61] Racism is a persistent component of the United States' "War on Drugs"[62], and thus, racial inequities are intensified among people of color who use drugs through law enforcement, societal stigma, and policies. The recent increases in fatal drug overdose among Black and Latino populations[63,64] shows the pervasiveness of this issue.

Women also face discrimination when facing healthcare, particular for those with chronic pain[65] in which opioids may be a treatment. Still, intersectionality of race and gender[66] is a critical, yet historically overlooked detail in public health research and drug use research.

Inequities in MOUD treatment access impede progress to prevent drug-related mortality. Understanding race, ethnicity, and gender inequity in OUD treatment is fundamental to ensuring an equitable approach to mitigate the overdose crisis. Racial and gender inequities are well documented in healthcare experiences[67,68] and likely persist among people who use drugs with SSTIs and endocarditis seeking OUD treatment.[69–73]

To date, some research has examined access and utilization of medications for OUD by race. In terms of geography, access to OUD treatment is associated with neighborhood race and ethnicity.[74,75] Specifically, an ecologic study on neighborhood buprenorphine access found greater access in neighborhoods with more white residents compared to neighborhoods with more Black or Hispanic residents.[76]

At the individual level, Black patients are less likely to receive medication for OUD than white patients.[71,72,77] Additionally, women may more commonly face worse treatment outcomes, such as retention in care, than men.[78,79] Some studies on drug use-associated SSTI and endocarditis have provided basic descriptive statistics on demographic characteristics. However, racial and gender inequities in medications for OUD use have not been evaluated in the context of people with drug use-associated infections. To our knowledge, research on medication use and access for OUD has not yet been conducted with an intersectionality lens.

2.6. Drug use-algorithms in healthcare record data

There is no standard definition to identify or flag people who use drugs in healthcare data.[80] While most coding schema, like the International Classification of Diseases (ICD), have codes for substance use disorders, there is no single indicator of drug use. Further, these codes do not differentiate between specific routes of administration, such as injection or snorting. Owing to the original purpose of financial billing, substance use disorders with well-established pharmacological treatments, like buprenorphine for OUD, are more likely to be coded for than substances where treatment options are limited or non-existent, such as stimulant and cannabis use disorders. Thus, combinations of proxy diagnosis codes are often used to identify cohorts in research studies.

Some drug use-related algorithms are more specific than others. For example, the Centers for Medicare and Medicaid Services (CMS) developed an algorithm for drug use disorders[81]. However, this algorithm contains a wide range of diagnosis and procedure codes, including people with nicotine use disorders, infants receiving care for prenatal substance exposure, and the family members receiving psychotherapy for another person's substance use. To our knowledge, no validation studies have assessed the performance of this algorithm.

While several validation studies have been published recently[82–84], many drug use-related algorithms remain unvalidated. Additionally, the existing validation studies are either focused solely on drug use-associated endocarditis cases[83,84] or were based in Canada[82], which may have a slightly different codes and coding practices than in the United States. A systematic review by McGrew et al. underscored the need for additional validation studies of illicit drug use algorithms.[85] The authors also found issues in interpretability of these algorithms due to inconsistent reporting.

In the absence of validated algorithms, healthcare record data have been successfully used to study health outcomes among people who use drugs.[3,82,86] Algorithms based on combinations of substance use disorders, hepatitis C virus (HCV) infection, and previous overdoses diagnosis[3,83,87] provide a robust and reproducible means of identifying people who use drugs in healthcare record data.

CHAPTER 3: SPECIFIC AIMS

Bacterial and fungal infections are increasing among people who use drugs.[2,3,30] These infections occur due to the introduction of bacteria or fungi past the skin surface via contaminations in drugs and preparation/injection equipment. Skin and soft tissue infections, including abscesses and cellulitis, are the most common infections among people who use drugs, with up to 65% reporting skin and soft tissue infections in the past year.[5,7,88,89] Some skin and soft tissue infections can be serious, leading to more invasive infections (e.g., endocarditis), surgery, or prolonged antibiotic treatment.[7] Some of these invasive infections can be particularly severe[3,8,26,27]; therefore, early prevention is an important public health strategy. Among those with OUD, medication for OUD is an effective treatment[90,91]; yet, its effect has not been rigorously evaluated in terms of infection-related mortality. Increases in serious infections closely mirror trends in drug overdose death in the United States. These two health concerns are closely intertwined, requiring careful consideration of both in the overall burden of disease among people who use drugs.

Overall, there is scant information examining outcomes associated with skin and soft tissue infections in people who use drugs. Existing research surrounding severe infections among people who use drugs is focused on diagnosis, management, and outcomes following diagnosis,[2,3,8,92] and limited research has examined the effectiveness of clinical interventions in reducing morbidity and mortality among people who use drugs undergoing care for these serious infections. The impact of MOUD on mortality among people with skin and soft tissue infections has also not previously been studied in large populations in the United States.

The primary objective of this study was to systematically evaluate the burden of infection-related mortality and the prevention of adverse infection-related outcomes among people who use drugs. The study analyzed healthcare records representing over half of North Carolinians from 2007 through 2018. We examined both publicly (Medicaid and Medicare) and privately insured patient data linked with statewide cause-specific mortality records. Time-to-event models assessed drug use-related morbidity and mortality and quantified the impact of MOUD on these outcomes among people with opioid use disorder. To accomplish these objectives, the specific aims included:

Aim 1: Examine the incidence and risk factors of bacterial and fungal infection-related mortality and drug overdose among people who use drugs. We estimated the cumulative incidence of infection-related mortality and overdose among a cohort of people who use drugs following their initial drug use-related healthcare visits.

Aim 2: Estimate the association between MOUD mortality among people with opioid use-associated skin and soft tissue infections. Among people with opioid use-associated skin and soft tissue infections, we quantified the association between two MOUD (methadone and buprenorphine) on incidence of 3-year all-cause mortality and 1-year hospitalization. We hypothesized that use of MOUD is associated with decreased mortality and hospitalization incidence.

This study offered an exceptional opportunity to examine the burden of serious infections on mortality and drug overdose, two complex and urgent health threats facing people who use drugs. Results from this study enhanced our understanding of outcomes following serious infections, while beginning to explore racial and gender disparities that impede progress. In turn, these results informed public health efforts to improve the health of people who use drugs.

CHAPTER 4: METHODS

4.1. Study objectives

The objective of this cohort study is to examine the burden of, and health outcomes associated with, bacterial and fungal infections among people who use drugs. Particular attention will be paid to buprenorphine and methadone, medications used to treat symptoms associated with OUD.

We will accomplish the study objectives by applying robust epidemiologic methods to existing healthcare data from North Carolina. Aims 1 and 2 will be addressed in a retrospective cohort study design using administrative healthcare claims data. Healthcare claims are cost-effective and a proven strategy to longitudinally study health outcomes among people who use drugs.[82,86] These data provide a comprehensive picture of drug use-related health events over a long period of time among a large population size, something rarely achievable via primary data collection.

4.2. Study population

The study population includes North Carolinian adults (≥18 years) with documented drug use-related diagnoses. The study population will include all adults residing in NC during a 12-year period from January 1, 2007 to December 31, 2018 who were enrolled in one or more of the three largest health insurance providers in the state: NC Medicaid, Medicare, and a private insurance company in NC (name suppressed due to data use agreement conditions). Collectively, these insurers cover over 5 million lives (55% of the total state population, 48% of those aged

<65 years). This population allows examination of outcomes among a wide range of younger to older adults. All of NC's 100 counties are represented.

Data from people represented in these data were linked deterministically and probabilistically using person-level identifiers (name, gender, birthdate)[93] with NC vital statistics death certificate data, a data set that is readily accessible to researchers at no cost. This large cohort will facilitate a comprehensive population-based assessment, encompassing the elderly, those with no or low incomes, and a large middle-class population that includes all state employees, teachers, and their families. Medical elements of the analytic dataset include inpatient visits, outpatient visits, outpatient prescriptions, underlying and contributing causes of death, and toxicological classifications.

4.3. Cohort definitions

The validity of a cohort algorithm is assessed via the algorithm's positive predictive value (PPV). PPV depends on the population's prevalence of the condition.[95] The validity of a cohort algorithm is assessed via the algorithm's positive predictive value (PPV) and algorithms to identify these two populations demonstrate excellent PPV. For instance, an algorithm to identify people with OUD has a PPV of 95% with an overall prevalence of 0.5%.[86] We estimate that there was a similar prevalence in this study.

Healthcare record data have been successfully used to study health outcomes among people who use drugs using comprehensive algorithms based on diagnosis codes.[3,82,86] Taking advantage of these new developments, we constructed cohort definitions that will minimize potential misclassification biases. Algorithms based on diagnosis of substance use disorders, hepatitis C virus (HCV) infection, and previous overdoses[3,83,87] provide a robust and reproducible means of identifying people who use drugs in healthcare record data.

A cohort of people with drug use-related healthcare visits will be constructed for Aim 1. For substance use disorders, opioids, stimulants, and sedatives will be included due to associations with drug-related harm in previous studies using similar databases.[25,46,96,97] We will examine outcomes among those individuals from their initial drug use-related diagnosis date that meets inclusion criteria through a maximum of 1 year of follow up. For Aim 2, the cohort of interest will include people with opioid use-associated skin and soft tissue infection healthcare visits. We will assess their MOUD use following this diagnosis and examine their outcomes through a maximum of 3 years.

4.4. Aim 1: Examine the incidence and risk factors of bacterial and fungal infection-related mortality and drug overdose among people who use drugs.

4.4.1. Data sources and linkage

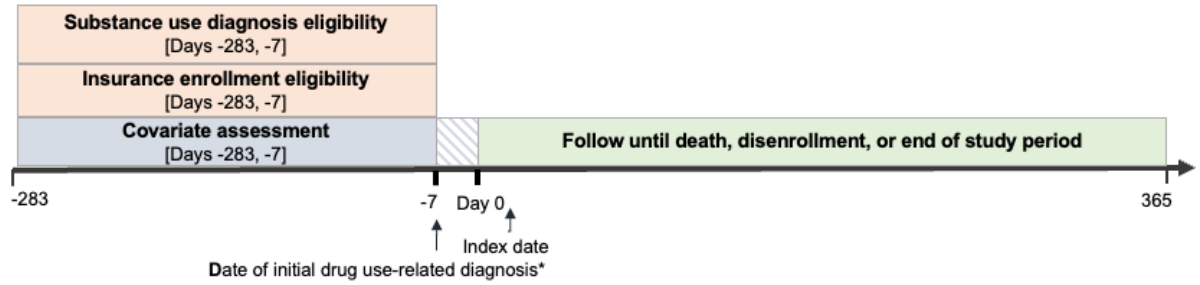
Our study used administrative data for health insurance claims and death certificates in North Carolina.[98] Healthcare claims included those for Medicaid, Medicare, and private plans were available for all adults in North Carolina with coverage from January 1, 2007 through December 31, 2018. These claims sources account for approximately 70% of the insured population of NC. Claims included date, diagnoses, procedures, and prescriptions for inpatient and non-inpatient encounters and services. Claims data also included information about the enrollees, such as their months of coverage and basic demographic information (date of birth, sex). Death certificate data was available for all North Carolina residents who died during January 1, 2007 through December 31, 2018. Death certificate data included causes and dates of death. We linked death certificate data to our cohort data using a combination of probabilistic and deterministic methods[93] based on individual identifiers including name, date of birth, and gender.

4.4.2. Study design, setting, and participants

We conducted a longitudinal cohort study among publicly and privately insured North Carolina adults (18 years and older) who had an initial drug use-associated healthcare visit that occurred from January 1, 2007 through December 31, 2018.

The target population was adults with drug use-associated healthcare visits in North Carolina. Our study population included people aged 18-99 years who had ³1 inpatient visit or ³2 outpatient visits occurring within a 12-month period with drug use-associated conditions. Specific drug use-associated diagnoses included OUD, stimulant use disorder, sedative/hypnotic use disorder, and hepatitis C virus for those born after 1965 based on prior studies and substance-specific drivers of overdose.[82,99,100] To allow times to establish clinical history, we included people who had insurance coverage for at least 6 of the 9 months prior to their index date. We also excluded those who had a death date before index date due to false positive matches. To reduce issues with reverse temporality between the index date and death (e.g., the index visit was coded as drug use-associated due to the subsequent cause of death), we excluded those who died within the first 7 days immediately following the drug use diagnosis date. Of the 132,429 people who met initial criteria, we excluded: 191 for having a date of death prior to index date and 717 for dying within the first 7 days.

Figure 4.1. Study design, eligibility assessment, and covariate assessment.



We sought to estimate the cumulative incidences of all-cause and cause-specific mortality. The index date was 7 days after an individual's first drug use-associated diagnosis date (i.e., the first date of either of the following: the date of the first inpatient discharge or the date of the second outpatient visit) (Supplemental Figure A.1). For each individual, we calculated the days from their index date until death, disenrollment, or end of study period at 1 year (whichever occurred first).

4.4.3. Outcomes

In the absence of a standardized definition, bacterial and infection-associated mortality was defined as death records ascertained from death certificate data that were preceded by any hospitalizations for invasive bacterial and fungal infections in the 30 days prior (Supplemental Table A.5).

Prior issues with the sensitivity and specificity of sepsis codes[101] led us to choose the 30-day hospitalization lookback as the primary definition. We also explored two additional infection-associated mortality definitions in sensitivity analyses that were derived from underlying and contributing causes of death on death certificates. On the (the "second definition") was sepsis-associated mortality using the World Health Organizations (WHO) definition.[102] The other ("third definition") included the WHO definition for sepsis-associated mortality, as well as deaths in which other invasive infections associated with injection drug use were indicated (Supplemental Table A.5).[25]

All-cause mortality was defined as any individual who had a linked death certificate during follow up. Cause-specific mortality was defined using the underlying and contributing causes of death ICD-10 codes listed on the death certificates. Overdose mortality included any individuals with an underlying cause of death of drug overdose (Supplemental Table A.5).[99]

4.4.4. Covariates

Demographic characteristics and insurance coverage were derived from the latest insurance enrollment information preceding the index date. Age was calculated using the time between an individual's date of birth and index date. Sex categories were limited to female and male. Insurance type was based on the coverage during the index month and categorized into the following: Medicaid alone, Medicare alone, Medicaid/Medicare dual enrollment, or private plans.

Clinical characteristics were derived from ICD-9-CM and ICD-10-CM diagnosis codes documented during the 9 months preceding an individual's initial drug use diagnosis date (Figure 4.1). All code lists are included in the supplemental materials. Substance use disorder codes were created for this analysis, in part based on prior studies.[82,84,103] The nonfatal overdose definition was based on previous case definitions.[104] Skin and soft tissue infections and infective endocarditis were based on prior studies and manual review by our study team members.[1,25,52] For the other clinical conditions, we used the Chronic Conditions Warehouse definitions created by the Centers for Medicaid and Medicare Services.[81]

4.4.5. Analysis

We used Aalen-Johansen estimators[105] to calculate the cumulative incidence, a method that accounts for competing events and allows estimation of risk, a measure directly relevant for public health purposes.[106,107] For cause-specific mortality , we treated all other causes of death as a competing event. We estimated the cumulative incidences and their 95% confidence intervals among the total study population and among clinical and demographic subgroups. We visually examined the cumulative incidence curves by age group due to age being so closely associated with mortality. Age groups were chosen to be similar to the CDC estimates of overdose

mortality.[99] If an individual did not have a diagnosis code for a select condition during the specified time period, they were considered as not having that condition.

In a sensitivity analysis, we estimated the cumulative incidence using the second and third infection-associated mortality definitions. We visually compared the cumulative incidence curves and assessed the level of agreement by calculating the percent of individuals with the original definition who also met criteria for the supplemental definition.

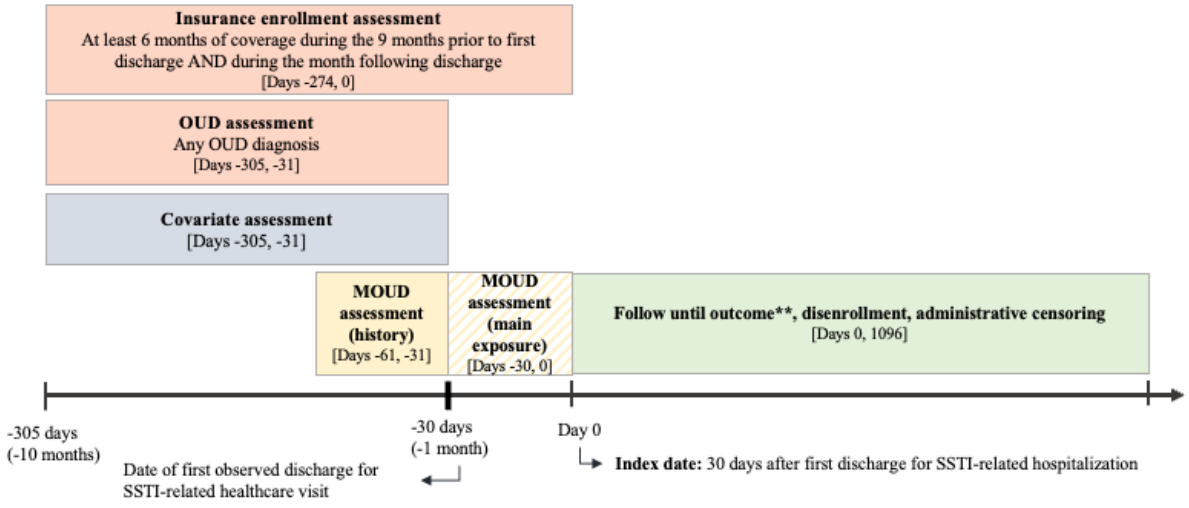
4.5. Aim 2: Estimate the association between MOUD mortality among people with opioid use-associated skin and soft tissue infections.

4.5.1. Study population

This retrospective cohort study included adults who were North Carolina Medicaid enrollees with an opioid use-related skin or soft tissue infection (SSTI) diagnosis during 2007 through 2018. We included people who had a healthcare visit for their infection in either an inpatient or outpatient (e.g., emergency room, primary care office) settings.

We identified each individual's first SSTI diagnosis in which an OUD diagnosis occurred within the preceding 9 months (Figure 4.2). To allow for adequate time to ascertain clinical covariates and OUD inclusion criteria, we included those who had 6 or more months of insurance coverage during the preceding 9 months. Additionally, individuals must have survived and maintained insurance enrollment through the initial 30-days after SSTI discharge to allow for exposure ascertainment. In our primary analysis, we excluded individuals who had a documented MOUD history in the 30 days prior to their initial SSTI discharge. This was done to minimize potential bias from prevalent users of medications.[56]

Figure 4.2. Study design inclusion criteria and variable measurements.



The index date for all people was 30 days after their initial SSTI discharge date. When estimating risk of death, we followed all people from their index date until death, through 3 years of follow-up, or the end of the study period (i.e., December 31, 2018), whichever came first. For subsequent hospitalizations, we followed individuals until one of the following events occurred: the first subsequent hospitalization, death, disenrollment, through 1 year of follow-up, or the end of the study period.

In our main analysis, we excluded people who had a history of MOUD in the 30 days prior to their index SSTI date in order to reduce bias induced by including prevalent users of MOUD.[56] We chose to not extend the MOUD history beyond 30 days due to the transient and intermittent nature of MOUD use patterns. Therefore, we considered those without treatment in this past 30-day window as those who had no observed history of MOUD recently or had a disruption in their treatment. Of the initial 17,643 identified, the following were excluded in the main analysis: 1,233 with enrollment of <6 of the previous 9 months of insurance coverage, 215 who were aged <18 years, 158 whose 30-day MOUD initiation began the last study date (i.e.,

after December 31, 2018), 119 who died within the MOUD initiation window, and 232 who were disenrolled within the first 30 days. The main analysis also excluded 2,829 people who had a history of MOUD use in the 30-days prior to SSTI discharge, ultimately leaving a total of 13,347 people in the main analysis. In a sensitivity analysis, we removed the MOUD history exclusion criteria and assessed MOUD use in the first 30 days of follow-up. Therefore, a total of 15,876 met inclusion criteria for the sensitivity analysis.

4.5.2. Exposure

The exposure was MOUD use in the first 30 days after SSTI discharge. We focused specifically on one or more claims for methadone or buprenorphine. Methadone claims included outpatient procedure codes for methadone administration at an opioid treatment provider (HCPCS codes: H0020, S0109). Buprenorphine claims included prescriptions for FDA-approved formulations of buprenorphine for the treatment of OUD. We compared participants with MOUD use to those without any MOUD use in the initial 30 days following discharge.

4.5.3. Outcome

The primary outcome of interest was all-cause mortality within the first 3 years after discharge. Death was defined as any individual who had date of death from the CMS National Death Index segment.[108] The secondary outcome was the first observed hospitalization within 1 year after index SSTI discharge.

4.5.4. Covariates

We also examined demographic and clinical characteristics of the study population. Demographic characteristics were derived from the Medicaid enrollment file and included age at index SSTI diagnosis, sex (female, male), and race/ethnicity. Race and ethnicity were based on structured categories collected at Medicaid enrollment.[109] Due to small sample sizes, we were unable to analyze the population's race and ethnicity groups as recorded on the enrollment file.

Therefore, we collapsed the groups into the following: non-Hispanic white, non-Hispanic Black, and all other races and ethnicity. We assessed whether or not an individual was enrolled in a managed care organization plan at the time of initial SSTI diagnosis. We also calculated the year of discharge (categorized into 3-year increments beginning in 2007) and the length of stay (categorized as 1 day, 2-7 days, or 8 or more days).

Clinical characteristics were based on an individual's diagnoses in the 9 months prior to their initial SSTI diagnosis date. Other substance use disorders including alcohol, sedative or hypnotics, stimulants, or polysubstance or unspecified substance use disorders. We also assessed anxiety, depression, and chronic pain. For each individual, we calculated a combined comorbidity score.[110]

4.5.5. Analysis

All analyses were conducted using SAS v 9.4 (Cary, NC, USA). In descriptive analyses, we examined the study population's characteristics overall, and by MOUD prevalence. MOUD use was analyzed as a time-fixed variable. We examined the association between MOUD use and mortality and hospitalization using survival estimates generated from Kaplan-Meier estimation. Specifically, for each exposure group, we calculated the outcome risk (i.e., incidence proportion) based on the complement of the estimated survival function generated from the product limit estimator. For the hospitalization outcome models, due to the low percentage of people who died prior to hospitalization (<2%), we did not account for death as a competing event for hospitalization.

To minimize potential bias from confounding factors, we estimated risks using propensity score weighting. Specifically, we estimated the association of MOUD use among MOUD users by using inverse probability weights to reweight non-users to have the same covariate distribution as users. We chose this approach for two reasons. First, these estimates are

recommended in studies of rare exposures, as was the case for this analysis [111]. Second, these estimates are used when it is assumed to be hypothetically infeasible for an entire study population to receive a treatment [112]. This is the case for MOUD, which remains difficult to access for many individuals and may not be the patient's preferred choice of treatment. We used a logistic regression model to estimate the propensity score of treatment (MOUD compared to no MOUD) at baseline for each individual based on a set of confounders that included: age, year, length of stay, and combined comorbidity score. In line with ATT approach, those in the treated group were assigned a weight of 1. Those in the untreated group were assigned a weight of the probability of treatment given their covariates divided by the probability of not being treated given their covariates. To assess performance of the weighted estimates, we compared the distribution of covariates before and after weighting the study populations.

For each exposure-outcome pair, we calculated the risk ratios, risk differences, and their 95% confidence intervals through their follow-up (i.e., 3 years for mortality, 1 year for hospitalization). For the weighted estimates, we calculated the 95% confidence intervals of the risk differences and ratios using bootstrapping with 500 replications at a resampling rate of 1.0. Specifically, the bounds of the interval were the parameter sample means at the 2.5^{th} and 97.5^{th} percentiles. We also visually inspected the weighted risk curves for each exposure-outcome pair.

4.6. Protection of human subjects

This study was review and approved by the UNC IRB. Data use agreements have been completed and approved by the data owners.

CHAPTER 5: MORTALITY ASSOCIATED WITH BACTERIAL AND FUNGAL INFECTIONS AND OVERDOSE AMONG PEOPLE RECEIVING CARE FOR DRUG USE IN NORTH CAROLINA

5.1. Overview

Severe bacterial and fungal infections are increasing among people who use drugs. Mortality from drug overdose is well described, yet mortality related to bacterial and fungal infections among people who use drugs is not known. The objective of this study was to estimate the incidence of bacterial and fungal infection-related mortality and overdose mortality among people with drug use-related healthcare visits. This cohort study used Medicaid, Medicare, and private insurance claims linked with death certificate data to examine mortality among adults with drug use-related healthcare visits during January 1, 2007 through December 31, 2018 in North Carolina. Bacterial and fungal infection-related mortality and overdose mortality were examined using cumulative incidence functions. Individuals were examined from their first drug use-associated healthcare visits until death, insurance disenrollment, or 1-year of follow up. Demographic and clinical characteristics were assessed at baseline and used to examine mortality among subgroups. 131,522 people with drug use-associated healthcare visits were included. The median age was 45 years (interquartile range: 31-57), 58% were women, 65% had an OUD diagnosis, 31% had a stimulant use disorder diagnosis, and 13% had a sedative or hypnotic use disorder diagnosis. The 1-year incidence of bacterial and fungal infection-associated mortality was progressively higher as age increased (35-49 years: 0.09% [95% CI 0.06-0.13%], 50-64 years: 0.23% [95% CI 0.18-0.28%], 65+ years: 0.50% [95% CI 10.40-0.62%]). Conversely, the 1-year incidence of overdose mortality was markedly lower among older adults compared to

those under the age of 65, and the highest 1-year incidence was among those 35-49 years old (18-34 years: 0.34% [95% CI 0.28-0.40%], 35-49 years: 0.47% [95% CI 0.40-0.55%], 50-64 years: 0.41% [95% CI 0.34-0.49%], 65+ years: 0.09% [95% CI 0.05-0.15%]). Bacterial and fungal infections and overdose were notable causes of death among adults who use drugs. Causes of mortality varied by age group, with older adults more likely to experience bacterial and fungal infection-associated mortality among older adults, and younger adults more likely to experience overdose mortality. Future interventions and policies should comprehensively address drug use-associated harms.

5.2. Introduction

Drug overdose has continued to increase in recent years.[99] This increase is largely driven by fluctuations in the drug supply and complex socioeconomic factors that are also associated with drug harms beyond overdose.[57,113,114]. For instance, the number of people impacted by drug use-associated bacterial and fungal infections also has been rising.[1–4,15,16] Compared to drug overdose trends, these drug use-associated infections have received less widespread attention and less is known about their contribution to mortality on a population level.

Bacterial and fungal infections associated with drug use include skin and soft tissue infections, infective endocarditis, and other invasive infections (osteomyelitis, spinal abscesses, sepsis). In the context of drug use, the infections occur from the introduction of bacteria or fungi past the skin via contaminated drugs, via injection and drug use preparation equipment. Skin and soft tissue infections are common, with as many as nearly 70% of people who inject drugs having a lifetime history of these infections.[7,88,115,116] In 2017, national estimates of drug use-associated hospital visits for people with skin and soft tissue infections was nearly 100,000 visits and approximately 10,000 for those with endocarditis.[15] Increases in these infections have been identified in several regions across the United States. Between 2008 and 2018, drug use-

associated serious infections rose 18-fold in Oregon.[4] From 2010 to 2018, hospitalizations for drug use-associated invasive infections increased 12-fold among North Carolina residents.[25] In the general population, the 1-year incidence of sepsis-associated mortality is approximately 50 deaths per 100,000 people[117] However, this number is unknown among people who use drugs.

Marginalized populations, including people who use drugs, face several barriers to quality healthcare, largely due to access, and stigmatizing experiences with healthcare personnel.[118,119] For people who receive care with drug use-associated infections, healthcare providers may be unaware when patients face other urgent health events after they leave the facility.

The objective of this study was to describe the incidence of bacterial and fungal infection-associated mortality and drug overdose mortality among people receiving care for drug use. We also sought to estimate mortality incidence among demographic and clinical subgroups.

5.3. Methods

5.3.1. Data sources and linkage

Our study used administrative data for health insurance claims and death certificates in North Carolina. Healthcare claims included those for Medicaid, Medicare, and private plans were available for all adults in North Carolina with coverage from January 1, 2007 through December 31, 2018.[98] These claims sources account for approximately 70% of the insured population of NC. Claims included date, diagnoses, procedures, and prescriptions for inpatient and non-inpatient encounters and services. Claims data also included information about the enrollees, such as their months of coverage and basic demographic information (date of birth, sex). Death certificate data was available for all North Carolina residents who died during January 1, 2007 through December 31, 2018. Death certificate data included causes and dates of death. We linked death certificate data to the claims cohort data using a combination of

probabilistic and deterministic methods[93] based on individual identifiers including name, date of birth, and gender. Given the possibility of false positive matches (i.e., those who were incorrectly linked with a death certificate), we considered anyone with a death certificate data prior to their index date as a false positive match.

5.3.2. Study design, setting, and participants

We conducted a longitudinal cohort study among publicly and privately insured North Carolina adults (≥18 years old) who had an initial drug use-associated healthcare visit that occurred from January 1, 2007 through December 31, 2018.

The target population was adults with drug use-associated healthcare visits in North Carolina. Our study population included people aged 18-99 years who had ≥1 inpatient visit or ≥2 outpatient visits occurring within a 12-month period with drug use-associated conditions. Specific drug use-associated diagnoses included OUD, stimulant use disorder, sedative/hypnotic use disorder, and hepatitis C virus for those born after 1965 based on prior studies and substance-specific drivers of overdose (Code lists are available in the supplemental material).[82,99,100] To allow times to establish clinical history, we included people who had insurance coverage for at least 6 of the 9 months prior to their index date. We also excluded those who had a death date before index date. To reduce issues with reverse temporality between the index date and death (e.g., the index visit was coded as drug use-associated due to the subsequent cause of death), we excluded those who died within the first 7 days immediately following the drug use diagnosis date.

Of the 132,429 people who met initial criteria, we excluded: 191 for having a date of death prior to index date and 717 for dying within the first 7 days.

We sought to estimate the cumulative incidences of all-cause and cause-specific mortality. The index date was 7 days after an individual's first drug use-associated diagnosis date

(i.e., the first date of either of the following: the date of the first inpatient discharge or the date of the second outpatient visit) (Supplemental Figure A.1). For each individual, we calculated the days from their index date until death, disenrollment, or end of study period at 1 year (whichever occurred first).

5.3.3. Outcomes

In the absence of a standardized definition, bacterial and infection-associated mortality was defined as death records ascertained from death certificate data that were preceded by any hospitalizations for invasive bacterial and fungal infections in the 30 days prior (Supplemental Table A.5).

Prior issues with the sensitivity and specificity of sepsis codes[101] led us to choose the 30-day hospitalization lookback as the primary definition. We also explored two additional infection-associated mortality definitions in sensitivity analyses that were derived from underlying and contributing causes of death on death certificates. On the (the "second definition") was sepsis-associated mortality using the World Health Organizations (WHO) definition.[102] The other ("third definition") included the WHO definition for sepsis-associated mortality, as well as deaths in which other invasive infections associated with injection drug use were indicated (Supplemental Table A.5).[25]

All-cause mortality was defined as any individual who had a linked death certificate during follow up. Cause-specific mortality was defined using the underlying and contributing causes of death ICD-10 codes listed on the death certificates. Overdose mortality included any individuals with an underlying cause of death of drug overdose (Supplemental Table A.5).

5.3.4. Covariates

Demographic characteristics and insurance coverage were derived from the latest insurance enrollment information preceding the index date. Age was calculated using the time

between an individual's date of birth and index date. Sex categories were limited to female and male. Insurance type was based on the coverage during the index month and categorized into the following: Medicaid alone, Medicare alone, Medicaid/Medicare dual enrollment, or private plans.

Clinical characteristics were derived from ICD-9-CM and ICD-10-CM diagnosis codes documented during the 9 months preceding an individual's initial drug use diagnosis date (Supplemental Figure A.1). All code lists are included in the supplemental materials. Substance use disorder codes were created for this analysis, in part based on prior studies.[82,84,103] The nonfatal overdose definition was based on previous case definitions.[104] Skin and soft tissue infections and infective endocarditis were based on prior studies and manual review by our study team members.[1,25,52] For the other clinical conditions, we used the Chronic Conditions Warehouse definitions created by the Centers for Medicaid and Medicare Services.[81]

5.3.5. Statistical analysis

We used Aalen-Johansen estimators[105] to calculate the cumulative incidence, a method that accounts for competing events and allows estimation of risk, a measure directly relevant for public health purposes.[106,107] For cause-specific mortality, we treated all other causes of death as a competing event. We estimated the cumulative incidences among the total study population and among clinical and demographic subgroups. We also estimated the 95% confidence intervals (CI) for incidence estimates based on the variance due to sample sizes. We visually examined the cumulative incidence curves by age group due to age being so closely associated with mortality. Age groups were chosen to be similar to the CDC estimates of overdose mortality.[99] If an individual did not have a diagnosis code for a select condition during the specified time period, they were considered as not having that condition.

In a sensitivity analysis, we estimated the cumulative incidence using the second and third infection-associated mortality definitions. We visually compared the cumulative incidence curves and assessed the level of agreement by calculating the percent of individuals with the original definition who also met criteria for the supplemental definition.

5.3.6. IRB statement

This study was reviewed and approved by the University of North Carolina at Chapel Hill Institutional Review Board (#20-3003).

5.4. Results

A total of 131,522 people with drug use-associated healthcare visits were included in this cohort study. The median age was 45 years-old (interquartile range = 31 – 57 years) (Table 5.1). 76,779 (58.4%) people had recorded identities as women. Medicaid was the most common insurer (47.7%, n=62,731) followed by Medicare (22.5%, n=29,538), Medicaid/Medicare (15.5%, n=20,426), and private insurance (14.3%, n=18,827). 65.0% of people (n=85,521) had a documented diagnosis for OUD, stimulant use disorder was documented among 31.0% (n=40,742) of people, and 25.4% (n=24,757) had an unspecified substance use disorder (substance use diagnoses are not mutually exclusive).

Table 5.1. Demographic characteristics and comorbidity history among a cohort of people with drug use-related healthcare visits from 2007-2018 in North Carolina.

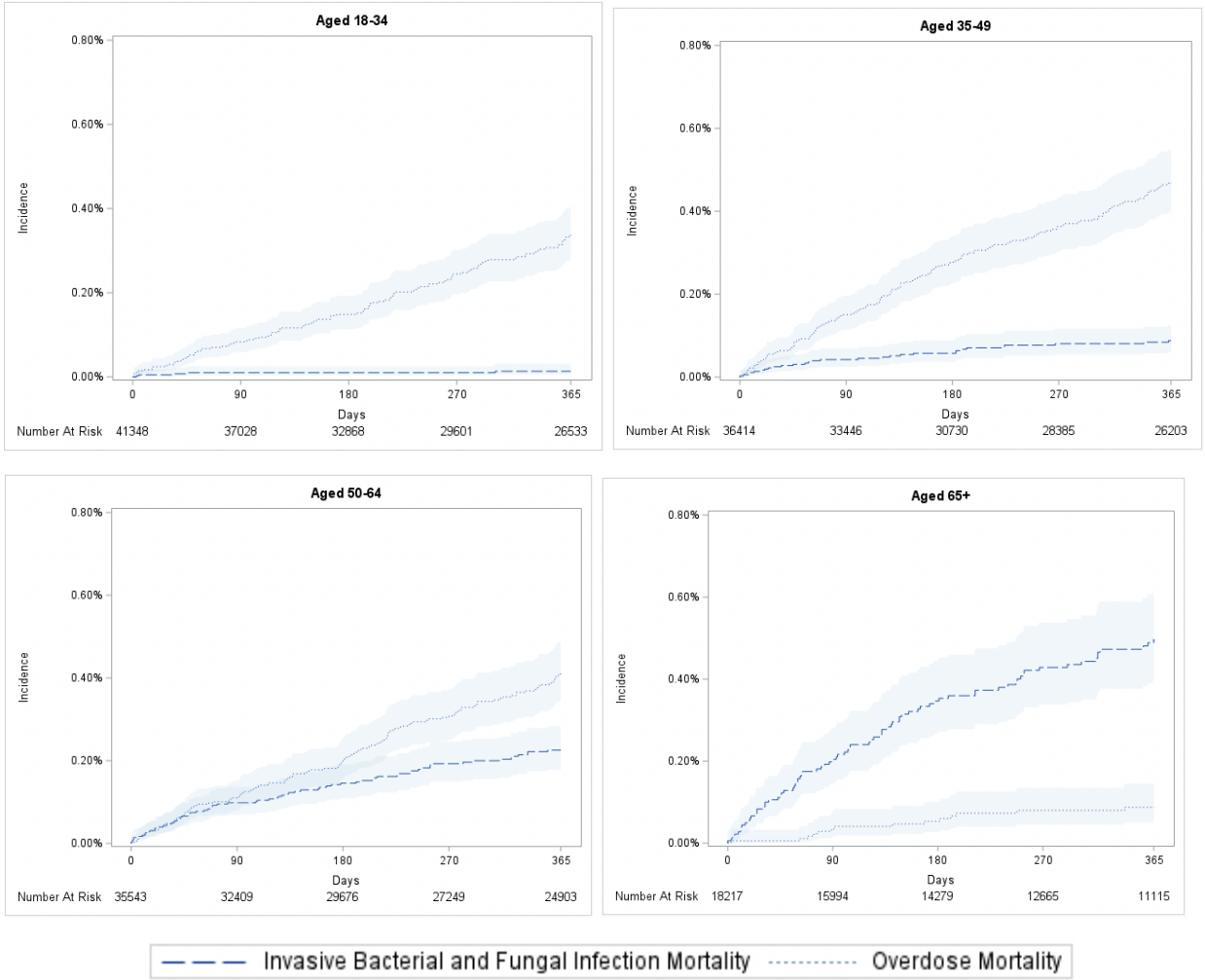
Individual Characteristics	N=131,522
Age, median (IQR)	45.0 (31.0-57.0)
Age group	
18-34	41,348 (31.4%)
35-49	36,414 (27.7%)
50-64	35,543 (27.0%)
65+	18,217 (13.9%)
Sex, women	76,779 (58.4%)
Insurer	
Medicaid	62,731 (47.7%)
Medicare	29,538 (22.5%)
Medicaid/Medicare	20,426 (15.5%)
Private	18,827 (14.3%)
Substance use disorders*	
Alcohol	24,757 (18.8%)
Cannabis	18,547 (14.1%)
Hallucinogen	366 (0.3%)
Opioid	85,521 (65.0%)
Sedative/hypnotic	17,348 (13.2%)
Stimulants	40,742 (31.0%)
Unspecified or polysubstance	33,380 (25.4%)
Nonfatal overdose	24,757 (18.8%)
Mental health conditions	
Anxiety	56,228 (42.8%)
Bipolar	25,864 (19.7%)
Depression	58,494 (44.5%)
Intellectual disabilities	961 (0.7%)
Personality disorders	7,269 (5.5%)
Post-traumatic stress disorder	9,205 (7.0%)
Schizophrenia	15,324 (11.7%)
Infections	
Skin and soft tissue infections	16,419 (12.5%)
Endocarditis	830 (0.6%)
Hepatitis B virus	740 (0.6%)
Hepatitis C virus	10,327 (7.9%)
HIV	2,888 (2.2%)
Other conditions	
Cancer	5,363 (4.1%)
Chronic kidney disease	22,662 (17.2%)
Diabetes	26,548 (20.2%)
Chronic pain/fibromyalgia	65,095 (49.5%)
Heart failure	11,384 (8.7%)
Liver disease	10,972 (8.3%)
Traumatic brain injury	1,215 (0.9%)

*Not mutually exclusive.

Of the 131,522 individuals included in the cohort, 5,055 people died during the first year of follow-up, representing an incidence of 4.5% (95% confidence interval (CI) = 4.34-4.58%). The 1-year cumulative incidence of overdose was slightly higher than bacterial and fungal infection-associated mortality (overdose: 0.36% (95% CI = 0.33-0.40%), N=401 deaths; bacterial and fungal infections: 0.16% (95% CI = 0.14-0.18%%, N=185 deaths); yet, these incidences varied greatly by age group. Of all 185 infection-associated deaths, <11 people also were classified as dying from an overdose.

Overdose mortality was much higher than bacterial and fungal infection-associated mortality among people aged 18-49 years (Figure 5.1). Among people aged 50-64 years, overdose mortality was also higher, but the gap between overdose and bacterial and fungal mortality was less than the difference observed among those 18-49 years old. However, among people aged 65 years and older, the incidence of bacterial and fungal infection-associated mortality was much higher than overdose mortality.

Figure 5.1. Bacterial and fungal-related mortality and overdose mortality among people with drug use-related healthcare visits.



Cause-specific mortality also varied by insurer (Supplemental Figure A.6). The 1-year incidence of bacterial and fungal infection-associated mortality was highest among those covered by Medicare (0.35%, 95% CI = 0.29-0.43%) and lowest among those covered by private insurance (<0.1%, number suppressed due to low cell counts) (Table 5.3). Overdose mortality was highest among those covered by Medicaid/Medicare (0.62%, 95% CI = 0.51-0.73%) and lowest among those covered by private insurance (0.23%, 95% CI = 0.16-0.31%) (Table 5.4).

Among the clinical characteristics explored, the 1-year incidence of bacterial and fungal infection-associated mortality was highest among those with a history of infective endocarditis (4.46%, 95% CI = 3.16-6.07%), followed by those with a history of skin and soft tissue infections (0.64%, 95% CI = 0.53-0.79%) (Table 5.3). The 1-year incidence of overdose was highest among those with a history of nonfatal overdose (1.27%, 95% CI = 1.07-1.49%) (Table 5.4).

Table 5.2. 1-year incidence of all-cause mortality for demographic and clinical characteristics.

Characteristic	At Risk (N)	Events (N)	Incidence (95% Confidence Interval)	1-Year Cumulative Incidence	95% Confidence Interval
Overall	131,522	5,055		4.46%	(4.34%-4.58%)
Age: 18-34	41,348	310		0.93%	(0.83%-1.04%)
Age: 35-49	36,414	845		2.66%	(2.49%-2.84%)
Age: 50-64	35,543	1,906		6.11%	(5.85%-6.38%)
Age: 65+	18,217	1,994		12.49%	(11.98%-13.01%)
Sex: Men	54,743	2,603		5.50%	(5.30%-5.71%)
Sex: Women	76,779	2,452		3.71%	(3.57%-3.86%)
Insurance: Private	18,827	101		0.71%	(0.58%-0.87%)
Insurance: Medicaid/Medicare	20,426	1,083		5.57%	(5.26%-5.90%)
Insurance: Medicaid	62,731	1,579		2.94%	(2.80%-3.09%)
Insurance: Medicare	29,538	2,292		8.90%	(8.55%-9.25%)
Opioid Use Disorder	85,521	3,375		4.58%	(4.43%-4.73%)
Stimulant Use Disorder	40,742	1,262		3.62%	(3.43%-3.83%)
Sedative/Hypnotic Use Disorder	17,348	849		5.71%	(5.34%-6.09%)
Drug Overdose	12,863	734		6.44%	(5.99%-6.90%)
Skin and Soft Tissue Infections	16,419	1,127		7.87%	(7.44%-8.32%)
Infective Endocarditis	830	128		17.19%	(14.56%-20.02%)
Hepatitis C Virus	10,327	646		7.03%	(6.52%-7.57%)
Chronic Pain	65,095	3,591		6.26%	(6.06%-6.46%)

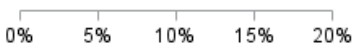


Table 5.3. 1-year incidence of bacterial and fungal Infection-related mortality for demographic and clinical characteristics.

Characteristic	At Risk (N)	Events (N)	Incidence (95% Confidence Interval)	1-Year Cumulative Incidence	95% Confidence Interval
Overall	131,522	185		0.16%	(0.14%-0.18%)
Age: 18-34	41,348				--
Age: 35-49	36,414	29		0.09%	(0.06%-0.13%)
Age: 50-64	35,543	72		0.23%	(0.18%-0.28%)
Age: 65+	18,217	79		0.50%	(0.40%-0.62%)
Sex: Men	54,743	106		0.22%	(0.18%-0.26%)
Sex: Women	76,779	79		0.12%	(0.10%-0.15%)
Insurance: Private	18,827				--
Insurance: Medicaid/Medicare	20,426	55		0.28%	(0.21%-0.36%)
Insurance: Medicaid	62,731	37		0.07%	(0.05%-0.09%)
Insurance: Medicare	29,538	92		0.35%	(0.29%-0.43%)
Opioid Use Disorder	85,521	135		0.18%	(0.15%-0.21%)
Stimulant Use Disorder	40,742	42		0.12%	(0.09%-0.16%)
Sedative/Hypnotic Use Disorder	17,348	18		0.13%	(0.08%-0.21%)
Drug Overdose	12,863	24		0.21%	(0.14%-0.31%)
Skin and Soft Tissue Infections	16,419	95		0.64%	(0.53%-0.79%)
Infective Endocarditis	830	35		4.46%	(3.16%-6.07%)
Hepatitis C Virus	10,327	25		0.27%	(0.18%-0.39%)
Chronic Pain	65,095	148		0.25%	(0.22%-0.30%)

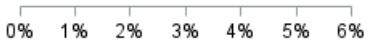


Table 5.4. 1-year incidence of overdose mortality for demographic and clinical characteristics.

Characteristic	At Risk (N)	Events (N)	Incidence (95% Confidence Interval)	1-Year Cumulative Incidence	95% Confidence Interval
Overall	131,522	401		0.36%	(0.33%-0.40%)
Age: 18-34	41,348	111		0.34%	(0.28%-0.40%)
Age: 35-49	36,414	149		0.47%	(0.40%-0.55%)
Age: 50-64	35,543	127		0.41%	(0.34%-0.49%)
Age: 65+	18,217	14		0.09%	(0.05%-0.15%)
Sex: Men	54,743	218		0.47%	(0.41%-0.53%)
Sex: Women	76,779	183		0.28%	(0.24%-0.33%)
Insurance: Private	18,827	34		0.23%	(0.16%-0.31%)
Insurance: Medicaid/Medicare	20,426	119		0.62%	(0.51%-0.73%)
Insurance: Medicaid	62,731	180		0.34%	(0.29%-0.39%)
Insurance: Medicare	29,538	68		0.27%	(0.21%-0.34%)
Opioid Use Disorder	85,521	273		0.38%	(0.33%-0.42%)
Stimulant Use Disorder	40,742	140		0.40%	(0.34%-0.47%)
Sedative/Hypnotic Use Disorder	17,348	105		0.72%	(0.59%-0.87%)
Drug Overdose	12,863	143		1.27%	(1.07%-1.49%)
Skin and Soft Tissue Infections	16,419	78		0.54%	(0.43%-0.68%)
Infective Endocarditis	830				--
Hepatitis C Virus	10,327	61		0.68%	(0.52%-0.87%)
Chronic Pain	65,095	233		0.41%	(0.36%-0.47%)

In sensitivity analyses comparing two additional definitions for infection-associated mortality, the incidence using the original definition (i.e., invasive infection hospitalization in 30 days prior to death) was lower than both definitions derived from the causes of death listed on death certificates (Supplemental Figure A.7). Notably, the sepsis-associated mortality definition appeared to account for the majority of deaths identified via death certificates. Among all people who met the original definition for bacterial and fungal infection related mortality (N=185), 34% (N=63) also met criteria for the sepsis-associated mortality definition (i.e., sepsis as a cause of death) and 43% (N=79) met criteria for the death certificate derived bacterial and fungal infection mortality definition (i.e., invasive infections or sepsis as causes of death).We ultimately

chose to keep the original infection-associated mortality definition derived from hospitalizations due to the inconsistency between definitions, the many etiologic reasons that cause sepsis beyond drug use, and likely inconsistent death certificate coding practices for invasive infections.[101]

5.5. Discussion

Both bacterial and fungal infections are a major, yet underrecognized cause of death among people receiving care for drug use. The contributions of infections and overdose to mortality vary by age. Among our study population, the contribution of these causes to death varied by age group. Specifically, bacterial and fungal infection-associated mortality was more common than overdose among older age groups and overdose mortality was more common than infection mortality among younger age groups. In the general population, the 1-year incidence of sepsis-associated mortality is approximately 50 deaths per 100,000 people[117]; yet, among our study population, the 1-year incidence of bacterial and fungal infection-associated mortality was nearly 160 deaths per 100,000 people-associated. Notably, when examining sepsis-associated mortality in our sensitivity analysis, there were approximately 430 deaths per 100,000 people, speaking to the outsized degree to which severe, life-threatening infections impact people who use drugs.

Among our study population, nearly 5 in every 100 people died during the first year after their first drug use-associated diagnosis. Overdose was a notable contributor to death among our study population, as described in other studies.[120–122] Bacterial and fungal infections were another notable contributor to death among our study population. Few studies have examined bacterial and fungal-infection-associated mortality among people who use drugs. One Baltimore-based study of people who inject drugs recruited from 1988 to 2018 found that 2.5% of all deaths were attributed to sepsis.[31] Our study builds on this prior knowledge by using more recent data,

including a statewide population, and using standardized follow-up periods for more stable estimates.

Existing research has primarily focused on mortality after people are diagnosed with drug use-associated endocarditis, with 1-year mortality incidences ranging from 16-25%[8,9,11], which can include in hospital mortality. However, few studies have examined bacterial and fungal infection-associated mortality among people who use drugs, independent of having a prior infection.

Age group and insurance type were two characteristics that displayed wide variation in cause-specific mortality incidences. All age groups were impacted by overdose mortality, including older adults (an often-overlooked age group in terms of overdose research).[123] Yet, those under 65 years old had higher incidences of overdose mortality, similar to national trends that show higher incidence among younger adults.[99] In our study population, bacterial and fungal infection-associated mortality was higher than overdose among those aged 65 years and older. Although, it is not clear whether older adults are more at risk for drug use-related infectious complications or if, by virtue of their age and presumed comorbidities, are more likely to die as a result of the infection. Cause-specific mortality also differed among insurance populations, representing the importance of appropriate data source selection. Yet, this is often challenging because insurance data systems are often disparate from one another and are not often linked with death certificate data. An exception to this are government agency linked databases, like those in Massachusetts, which have been used for several studies of drug use-associated healthcare outcomes.[53,124]

Federal support for overdose prevention and harm reduction programs has increased in recent years.[125] Given the systematic and individual-level complexity in drug use-associated

harms, additional support is needed to address drug use-associated harms more comprehensively, rather than focusing solely on one health issue at a time or one mechanism of funding. Many successful models for community-based harm reduction programs are present.[126–129] However, in order for these programs to expand services capacity and maintain sustainability, additional and continuous infrastructural support is needed. In healthcare settings, more comprehensive and compassionate care is essential for people who use drugs. Compassionate care is critical, particularly for marginalized populations like people who use drugs. Harm reduction-oriented models based both in clinical and community settings are an approach to improve quality of care.

5.5.1. Limitations

Several limitations should be considered when interpreting study results. First, our primary definition for bacterial and fungal infection-associated mortality required someone to be hospitalized before their death. We assumed that invasive infections would often be severe enough for people to seek care at this hospital. For those who truly died from bacterial and fungal infections within the community (i.e., they did not have a hospitalization in the 30 days prior to their death), we assume that typical death investigation procedures would be unlikely to identify or document infections as a cause of death. Therefore, our estimate of bacterial and fungal infection-associated mortality is likely an underestimate.

To assess this issue further, our sensitivity analyses explored two additional definitions of bacterial and fungal infection-associated mortality using cause of death data, which displayed higher incidence estimates. However, these deaths were largely driven by sepsis codes, which can be non-specific and may or may not be related to factors not directly associated with drug use.[101] Even still, all three definitions showed these infections were notable causes of mortality, even when compared to overdose mortality. To understand these trends on a broader population level, validation studies and standardized case definitions should be created. Second, drug use

measurement in claims data is subject to misclassification and measurement error, creating a variety of study-associated considerations.[130] With this in mind, we created a study population that both represents people at risk of drug use-associated mortality based on population-level trends in substances that had been associated with overdose mortality during this time period[99,100] as well as prior validation studies.[82,84,103] Relatedly, the initial date of drug use diagnosis should be interpreted as the first date the person had care for drug use, not the date of drug use initiation. The gap between these two dates may vary greatly and likely depend on factors not measured in claims data. Third, the diagnosis-derived covariates are also unlikely to truly capture all instances of health conditions. For example, people who experience skin and soft tissue infections and overdose sometimes treat their infections outside of healthcare settings.[7,131] Therefore, we assumed that observed covariates represent those that were severe enough to require medical care, were part of the treatment plan, or were associated with insurance billings practices. Fourth, our population was limited to those who had insurance coverage, received reimbursable care, and had a documented drug use diagnosis. These results may not be generalizable to those who are uninsured (who may be at a higher risk of mortality due to related socioeconomic factors and direct barriers to care), people who use drugs without any drug use-associated complications (who may be at a lower risk of mortality), or those residing outside of North Carolina. For instance, one North Carolina-based study found that 38% of people with drug use-associated invasive infections were uninsured.[25] This population may have a greater risk of death given their lack of access to care and other socioeconomic factors associated with health inequities. Last, given the limited availability of information in claims data, important contextual factors (e.g., drug use behaviors; discrimination due to drug use, racism, and/or socioeconomic position; treatment experiences inside and outside of healthcare settings) are not

available. Future studies that provide additional context, such as qualitative studies and community-based surveys, are needed to understand factors associated with and interventions to prevent bacterial and fungal infection-associated mortality.

5.6. Conclusions

Overdose and bacterial and fungal infection-associated mortality are two preventable causes of death among people with drug use-associated healthcare visits. Older adults had more deaths due to bacterial and fungal infection-associated mortality, while younger adults experienced more overdose mortality. Yet, both causes of deaths were observed across all age groups. In recent years, the United States has faced an unprecedented number of lives lost to overdose. Our study suggests this number is likely an undercount of the total number of lives lost from a toxic drug supply and socioeconomic conditions that drive drug use-associated mortality. Additional efforts are urgently needed to expand support for evidence-based practices that comprehensively address drug use-associated harms, such as community-based harm reduction programs and access to medications for substance use disorders. Systematic factors that drive drug use-associated death, such as policy and social support systems, should also be considered and evaluated to fully understand the pathways towards healthier communities.

CHAPTER 6: ASSOCIATION BETWEEN MEDICATIONS FOR OPIOID USE DISORDER AND THE INCIDENCE OF MORTALITY AND HOSPITALIZATION AMONG PEOPLE WITH OPIOID USE-RELATED SKIN AND SOFT TISSUE INFECTIONS

6.1. Overview

Skin and soft tissue infections (SSTI) have been rising among people who use drugs. Medications for opioid use disorder (MOUD) may improve longer-term outcomes associated with these infections. The objective of this study was to assess the association of MOUD use with mortality and hospitalizations among people discharged with opioid use-related skin and soft tissue infections. We conducted a cohort study of Medicaid enrollees diagnosed with opioid use-related SSTI during 2007-2018 in North Carolina. The intervention included a documented methadone or buprenorphine claim in the first 30 days following initial SSTI discharge. The comparison was no MOUD claim during this time period. Outcomes included 3-year risk of all-cause mortality and 1-year risk of hospitalization. Mortality was measured via linked death records. Hospitalizations were measured by subsequent hospitalization claims. Each individual was followed until they experienced an outcome, the study period ended, or they were disenrolled. The association between MOUD use and outcomes were calculated as the difference in outcome incidence, adjusted for year, age, comorbidities, and length of hospital stay. There were 13,286 people with opioid use-related SSTIs. The median age was 37 years, 68% were women, and 78% were White. Most (89%) had an initial length of healthcare stay of one day or less. In the crude Kaplan-Meier curves for the total study population, 12 of every 100 patients died during the first 3 years and 42 of every 100 patients were hospitalized during the first year.

In weighted models, for every 100 people who used MOUD, there were 4 fewer deaths over three years (95% confidence interval:2 to 6) and 6 (95% confidence interval:1 to 11) fewer people hospitalized over the first year.

6.2 Introduction

Bacterial and fungal infections related to drug use are common and have been increasingly documented in the last 10 years [1–3]. The most common types of these infections include skin and soft tissue infections (SSTI), such as abscesses and cellulitis. As many as 65% of people who inject drugs have a lifetime history of SSTI [5–7]. While these infections often resolve with minimal treatment, more severe forms can result in hospitalization, surgery, or long-term antibiotic use. In their most severe forms, these infections can result in death due to sepsis or other severe infection complications.

One of these infection-related complications associated with drug use is the development of subsequent invasive infections, such as endocarditis. Similar to SSTI, these invasive infections have also increased in recent years [3,132]. In fact, one of the primary reasons why people who inject drugs seek healthcare is for treatment of SSTI, often presenting first to emergency department settings [133,134]. Invasive infections typically require acute care hospitalization, with attendant financial costs. Even though SSTI may be treated in outpatient settings, the number of people with drug use-related SSTI hospitalizations has increased in recent years, with incidence rates increasing 50% from 2012 through 2017 [1,135]. While mortality among people with drug use-related invasive infections has been increasingly noted [8,11], less is known about outcomes among people with SSTI.

Given how common SSTI are, there is an urgent need for comprehensive patient-centered care at the time of the clinical encounter for infection. A natural therapeutic intervention would be initiating medications for opioid use disorder (MOUD). Two types of MOUD, methadone and

buprenorphine, are strongly associated with reductions in mortality and drug-related harms [136]. MOUD use may reduce adverse infection-related outcomes due to decreases in occurrence and frequency of drug use itself, particularly injection drug use. Many people obtaining care for SSTI likely receive care in places where MOUD access has not been integrated, such as in emergency departments or primary care setting. Understanding the association between the use of these medications and mortality and/or later hospitalization would be beneficial to inform the larger scope of potential benefits of MOUD on drug use-related outcomes.

Given the increasing occurrence of drug use-related SSTI, more attention is needed to prevent adverse outcomes among this group of patients, particularly those who meet indication for MOUD treatment. The objective of this study was to examine the role of MOUD on 3-year mortality and 1-year hospitalization among a cohort of people following their diagnosis with opioid use-related SSTI. We also sought to describe the incidence in mortality among people with these infections, as well as the prevalence of MOUD use.

6.3 Methods

6.3.1. Design

This retrospective observational cohort study included people with an opioid use-related skin or soft tissue infection (SSTI) diagnosis. We identified each individual's first SSTI diagnosis where an opioid use disorder diagnosis occurred within the preceding 9 months (Supplemental Figure B.1). To allow for adequate time to ascertain clinical covariates and OUD inclusion criteria, we included those who had any six or more months of insurance coverage during the preceding 9 months. Additionally, individuals must have survived and maintained insurance enrollment through the initial 30-days after the SSTI encounter to allow for MOUD exposure ascertainment. In our primary analysis, we excluded individuals who had a documented

MOUD history in the 30 days prior to their initial SSTI diagnosis date to minimize potential bias from prevalent use of medications [56].

The index date for all people was set 30 days after their initial SSTI diagnosis date. When ascertaining vital status, we followed all people from their index date until death, through 3 years of follow-up, or the end of the study period (December 31, 2018), whichever came first. For subsequent hospitalizations, we followed individuals until one of the following events occurred: the first subsequent hospitalization, death, disenrollment, through 1 year of follow-up, or the end of the study period.

6.3.2. Participants

Study population included adults (>=18 years old) who enrolled in North Carolina Medicaid and had a diagnoses for skin or soft tissue infection (SSTI) diagnosis occurring between 2007 and 2018 where a recent history (past 9 months) of opioid use disorder diagnosis. We included people who had a healthcare visit for their infection in either an inpatient or outpatient (e.g., emergency room, primary care office) setting. Diagnosis codes lists, including those used for inclusion criteria, are provided in Supplemental Table B.1.

6.3.3. Measures

The exposure was MOUD use in the first 30 days after SSTI diagnosis date. We focused specifically on one or more claims for methadone or buprenorphine. Methadone claims included outpatient procedure codes for methadone administration at an opioid treatment provider (Healthcare Common Procedure Coding System (HCPCS) codes H0020 and S0109). Buprenorphine claims included prescriptions for US Food and Drug Administration-approved formulations of buprenorphine for the treatment of opioid use disorder. We compared participants with MOUD use to those without any MOUD use in the initial 30 days following discharge.

The primary outcome of interest was all-cause mortality within the first 3 years after discharge. Death was defined as any individual who had date of death from the CMS National Death Index segment [108]. The secondary outcome was the first observed all-cause hospitalization (i.e. overnight stay) within 1 year after index SSTI discharge.

Covariates included demographic and clinical characteristics. Demographic characteristics were derived from the Medicaid enrollment file and included age at index SSTI diagnosis, sex (female, male), and race/ethnicity. Race and ethnicity were based on structured categories collected at Medicaid enrollment [109]. Due to small sample sizes, we were unable to analyze the population's race and ethnicity groups as recorded. Therefore, we collapsed the groups into the following: non-Hispanic White, non-Hispanic Black, and all other races and ethnicity. We assessed whether an individual was enrolled in a managed care organization plan at the time of initial SSTI diagnosis. We also calculated calendar year of discharge (categorized into 3-year increments beginning in 2007) and the length of stay (categorized as 1 day, 2-7 days, or 8 or more days). Clinical characteristics were based on an individual's International Classification of Disease (ICD) (versions ICD-9-CM and ICD-10-CM) diagnoses codes in the 9 months prior to their initial SSTI diagnosis date (Supplemental Table B.1). Other substance use disorders assessed included alcohol, sedative or hypnotics, stimulants, or polysubstance or unspecified substance use disorders. We assessed diagnoses of anxiety, depression, and chronic pain, and we calculated a combined comorbidity score for each patient [110].

6.3.4. Analyses

All analyses were conducted using SAS v 9.4 (Cary, NC, USA). In descriptive analyses, we examined the study population's characteristics overall, and by MOUD prevalence. MOUD use was analyzed as a time-fixed variable. We examined the association between MOUD use and mortality and hospitalization using survival estimates generated from Kaplan-Meier estimation.

Specifically, for each exposure group, we calculated the outcome risk (i.e., incidence proportion) based on the complement of the estimated survival function generated from the product limit estimator. For the hospitalization outcome models, due to the low percentage of people who died prior to hospitalization (<2%), we did not account for death as a competing event for hospitalization.

To minimize potential bias from confounding factors, we estimated risks using propensity score weighting. Specifically, we estimated the association of MOUD use among MOUD users by using inverse probability weights to reweight non-users to have the same covariate distribution as users. We chose this approach for two reasons. First, these estimates are recommended in studies of rare exposures, as was the case for this analysis [111]. Second, these estimates are used when it is assumed to be hypothetically infeasible for an entire study population to receive a treatment [112]. This is the case for MOUD, which remains difficult to access for many individuals and may not be the patient's preferred choice of treatment. We used a logistic regression model to estimate the propensity score of treatment (MOUD compared to no MOUD) at baseline for each individual based on a set of confounders that included: age, year, length of stay, and combined comorbidity score. In line with ATT approach, those in the treated group were assigned a weight of 1. Those in the untreated group were assigned a weight of the probability of treatment given their covariates divided by the probability of not being treated given their covariates. To assess performance of the weighted estimates, we compared the distribution of covariates before and after weighting the study populations.

For each exposure-outcome pair, we calculated the risk ratios, risk differences, and their 95% confidence intervals through their follow-up (i.e., 3 years for mortality, 1 year for hospitalization). For the weighted estimates, we calculated the 95% confidence intervals of the

risk differences and ratios using bootstrapping with 500 replications at a resampling rate of 1.0. Specifically, the bounds of the interval were the parameter sample means at the 2.5th and 97.5th percentiles. We also visually inspected the weighted risk curves for each exposure-outcome pair.

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

6.4. Results

Of the initial 17,643 patients with OUD-related SSTI identified, the following were excluded in the main analysis: 1,233 with enrollment of <6 of the previous 9 months of insurance coverage, 232 who were disenrolled within the first 30 days, 215 who were aged <18 years, 158 whose 30-day MOUD initiation began after the end of the study period (i.e., after December 31, 2018), and 119 who died within the MOUD initiation window. The main analysis excluded an additional 2,899 people who had a history of MOUD use in the 30-days prior to SSTI discharge, ultimately leaving a total of 13,286 people in the main analysis. In a sensitivity analysis, we removed the MOUD history exclusion criteria and assessed MOUD use in the first 30 days of follow-up. Therefore, a total of 15,876 met inclusion criteria for the sensitivity analysis.

Of the 13,286 people who met inclusion criteria for the main analysis, the median age was 37 years (interquartile range: 29 to 48). The largest age group were those aged 18-34 years old (41.3%) (Table 6.1). Most people were women (68.2%, n=9,059) and white (78.2%, n=10,118). Additionally, the majority of people had a length of stay of 1 day or less (88.9%, n=11,808). Nearly half (43.7%, n=5,810) had a documented substance use disorder diagnosis involving alcohol, sedatives or hypnotics, stimulants, or other unspecified substances, in addition to an OUD diagnosis.

Table 6.1. Characteristics of a cohort of North Carolina Medicaid enrollees with opioid use-associated skin and soft tissue infections during 2007 through 2018, total study population and by medication for opioid use disorder (MOUD) use.

Characteristic	Total		MOUD Use		No MOUD Use	
	N=13,286	%	N=418	%	N=12,868	%
Age Group						
18-34	5,490	41.3%	237	56.7%	5,253	40.8%
35-44	3,172	23.9%	109	26.1%	3,063	23.8%
45-54	2,613	19.7%	42	10.0%	2,571	20.0%
55+	2,011	15.1%	30	7.2%	1,981	15.4%
Sex						
Men	4,227	31.8%	136	32.5%	4,091	31.8%
Women	9,059	68.2%	282	67.5%	8,777	68.2%
Race						
Black	2,022	15.6%	29	7.1%	1,993	15.9%
Other	800	6.2%	17	4.1%	783	6.2%
White	10,118	78.2%	365	88.8%	9,753	77.8%
Missing	346					
Year of discharge						
2007-2009	1,276	9.6%	47	11.2%	1,229	9.6%
2010-2012	2,486	18.7%	89	21.3%	2,397	18.6%
2013-2015	3,647	27.4%	78	18.7%	3,569	27.7%
2016-2018	5,877	44.2%	204	48.8%	5,673	44.1%
Length of stay (days)						
1	11,808	88.9%	382	91.4%	11,426	88.8%
2-7	960	7.2%	30	7.2%	930	7.2%
8+	518	3.9%	*		*	
Managed care organization coverage	12,433	93.6%	397	95.0%	12,036	93.5%
Combined comorbidity score						
-2 to 1	8,064	60.7%	330	78.9%	7,734	60.1%
2 to 4	3,680	27.7%	71	17.0%	3,609	28.0%

5 or more	1,542	11.6%	17	4.1%	1,525	11.9%
Co-occurring substance use disorder	5,810	43.7%	185	44.3%	5,625	43.7%
Alcohol use disorder	1,618	12.2%	45	10.8%	1,573	12.2%
Sedative or hypnotic use disorder	857	6.5%	27	6.5%	830	6.5%
Stimulant use disorder	1,993	15.0%	54	12.9%	1,939	15.1%
Unspecified or polysubstance use disorder	3,983	30.0%	133	31.8%	3,850	29.9%
Anxiety	5,603	42.2%	163	39.0%	5,440	42.3%
Depression	5,498	41.4%	157	37.6%	5,341	41.5%
Chronic pain	6,744	50.8%	133	31.8%	6,611	51.4%

*Data suppressed due to counts <11.

In the crude incidences calculated with Kaplan-Meier estimators, the 3-year incidence of mortality was 12.0%, and the 1-year incidence of hospitalization was 42.0%.

Overall, MOUD use in the first 30-days after an initial SSTI was low (3.1%, n=418) (Table 6.1). MOUD use was highest among those aged 18-34 years old (4.3%, n=237) and lowest among those 55 years and older (1.5%, n=30). Among race and ethnicity groups, MOUD use was lowest among those who were Black (1.4%, n=29) and highest among those who were white (3.6%, n=365). Additionally, those with higher comorbidity scores had a lower percentage receiving MOUD (1.1%, n=17) compared to those with lower comorbidity scores (4.1%, n=330). Of the 418 MOUD users, 68% (n=284) had claims for buprenorphine and 33% (n=136) had claims for methadone.

After applying the weights, the observed differences in year, age, length of stay, and comorbidity score between the MOUD treated and untreated groups became minimal, demonstrating good performance of the weights (Table 6.2). We estimated that, among MOUD users, the risk of mortality was much lower than it would have been without MOUD use (Figure

6.1). In the weighted estimates of the association between MOUD and mortality, the 3-year risk difference was –4.0 (95% CI: -6.4, -1.6) (Table 6.3) per 100 people. This measure can be interpreted as follows: for every 100 MOUD users with opioid use-related SSTIs, MOUD use following SSTI diagnosis was associated with a reduction in approximately 4 deaths (95% CI: 2 to 6 deaths) compared to what it would have been if they had not received MOUD.

Table 6.2. Characteristics of the study population before and after applying inverse probability weights, by medication for opioid use disorder (MOUD) use.

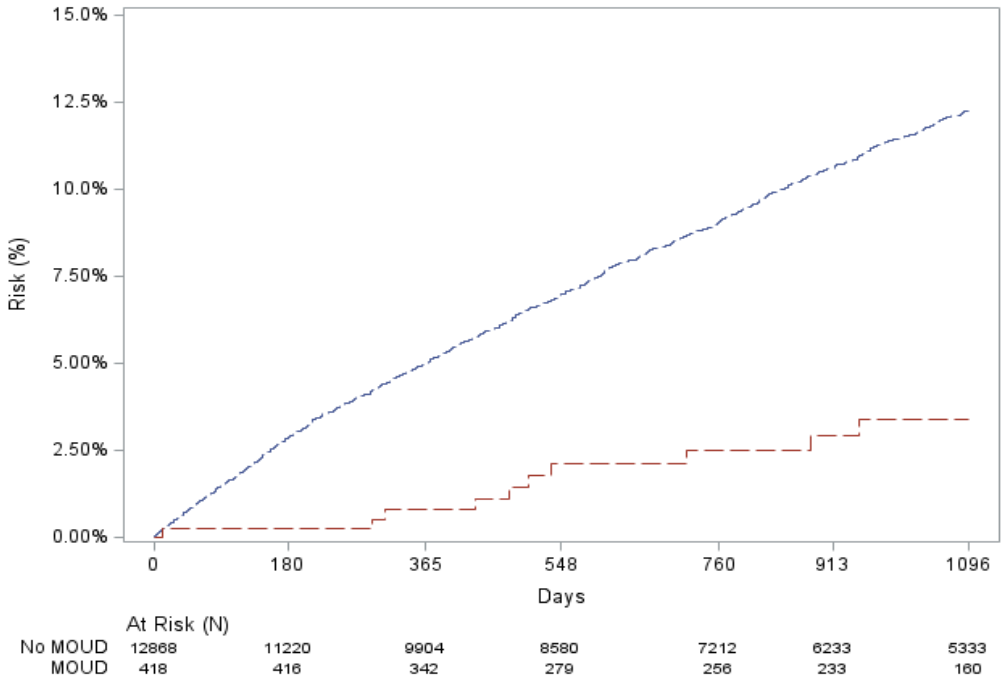
	Unweighted			Weighted*		
	MOUD Use (%)	**No MOUD Use (%)**	**Absolute Difference**	**MOUD (%)**	**No MOUD (%)**	**Absolute Difference**
Year of discharge						
2007-2009	11.2%	9.5%	1.7%	11.2%	11.2%	0.1%
2010-2012	21.3%	18.6%	2.7%	21.3%	21.3%	0.0%
2013-2015	18.7%	27.7%	-9.1%	18.7%	18.7%	0.0%
2016-2018	48.8%	44.1%	4.7%	48.8%	48.9%	-0.1%
Age group (years)						
18-34	56.7%	40.8%	15.9%	56.7%	56.7%	0.0%
35-44	26.1%	23.8%	2.3%	26.1%	26.1%	0.0%
45-54	10.1%	20.0%	-9.9%	10.1%	10.0%	0.0%
55+	7.2%	15.4%	-8.2%	7.2%	7.2%	0.0%
Length of stay (days)						
1	91.4%	88.8%	2.6%	91.4%	91.4%	0.0%
2-7	7.2%	7.2%	-0.1%	7.2%	7.2%	0.0%
8+	1.4%	4.0%	-2.5%	1.4%	1.4%	0.0%
Combined comorbidity score						
-1 to 1	79.0%	60.1%	18.9%	79.0%	79.0%	0.0%
2 to 4	17.0%	28.1%	-11.1%	17.0%	17.0%	0.0%
5+	4.1%	11.9%	-7.8%	4.1%	4.1%	0.0%

*Weights based on all variables listed (year of discharge, age group, length of stay, and combined comorbidity score).

The crude and weighted risks of hospitalization also greatly varied by MOUD group (Figure 6.2). When comparing those who received MOUD use to what their risks would be had they not received MOUD, the difference in the 1-year risk of hospitalization was -6.1 (95% CI: -11.0, -1.2) after weighting for covariates (Table 6.2).

Figure 6.1. Crude (a) and weighted (b) 3-year risk of all-cause mortality by medication for opioid use disorder (MOUD) use. Adjusted curves control for year, age group, length of hospital stay, and combined comorbidity score.

a) Crude Kaplan-Meier curves



b) Weighted Kaplan-Meier curves

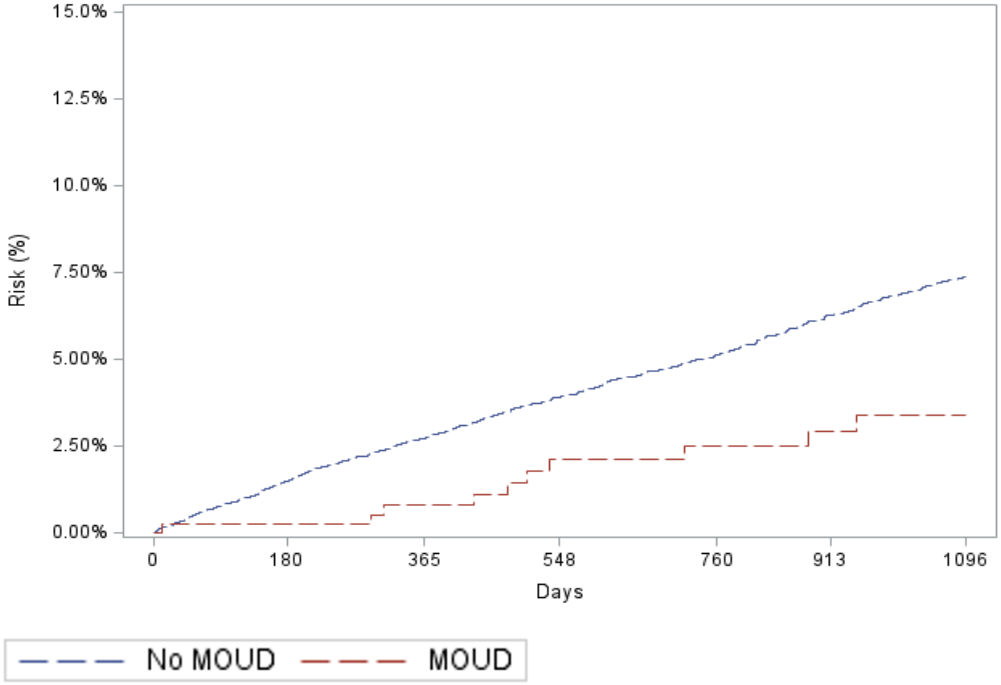
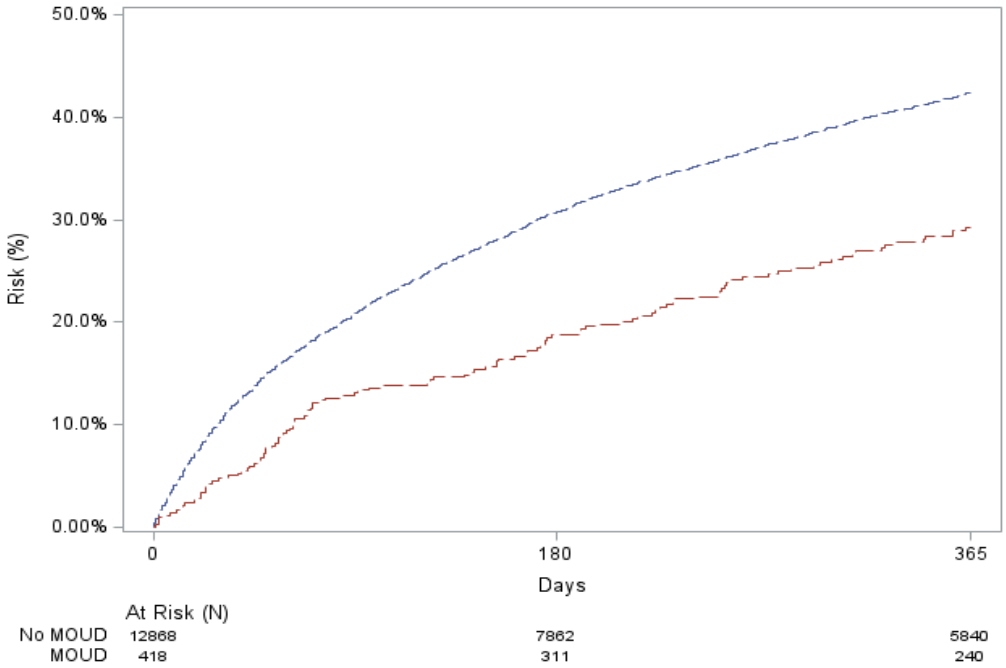
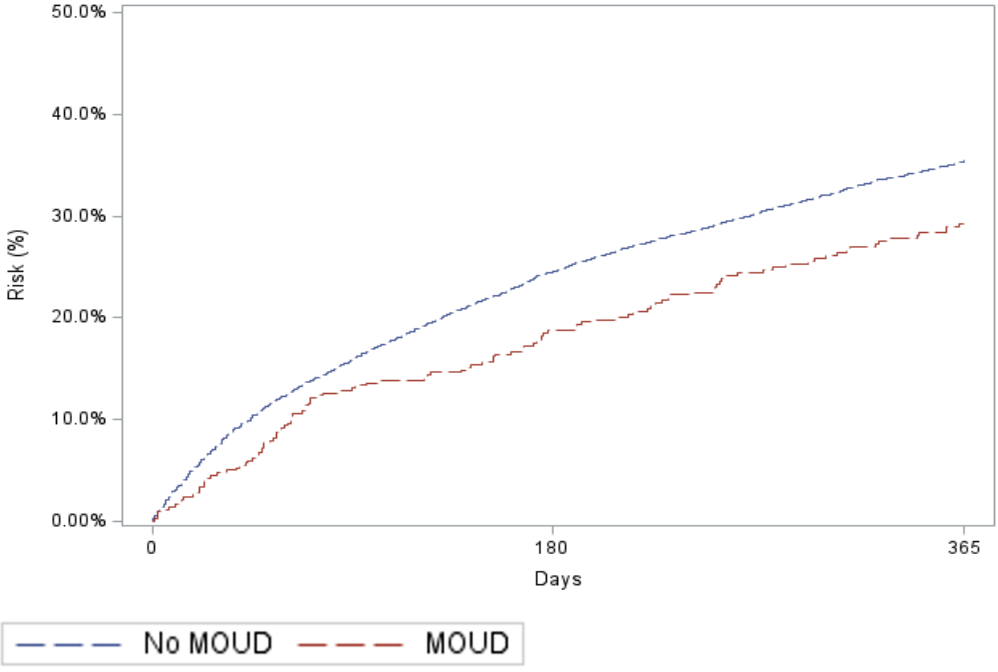


Figure 6.2. Unadjusted (a) and adjusted (b) 12-month risk of any hospitalization by medication for opioid use disorder (MOUD) use, Adjusted curves control for year, age group, length of hospital stay, and combined comorbidity score.

a) Crude Kaplan-Meier curves



a) Weighted Kaplan-Meier curves



In the sensitivity analyses that included both MOUD initiators and and prevalent users of MOUD, the association between MOUD and the outcomes also displayed protective associations (Supplemental Figures B.2 & B.3). For instance, for 3-year risk of mortality, the weighted risk difference in the main analysis was –4.0 (95% CI: -6.4, -1.6) compared to –1.9 (95% CI: -3.1. -0.7) in the sensitivity analysis (Supplemental Table B.4). For the 1-year risk of hospitalization, the weighted risk difference in the in the main analysis was -6.1 (95% CI: -11.0, -1.2) compared to -9.0 (95% CI: -11.1, -6.9) in the sensitivity analysis.

Table 6.3. Risk differences and risk ratios for 3-year all-cause mortality and 1-year any hospitalization by medication for opioid use disorder (MOUD) use.

	Crude Estimates			Weighted Estimates*		
Exposure and Outcome Group	Risk, %	Risk Difference, % (95% CI)	Risk Ratio, (95% CI)	Risk, %	Risk Difference (95% CI)	Risk Ratio (95% CI)
3-Year Mortality						
MOUD use	3.4	-8.9 (-11.1, -6.7)	0.28 (0.15, 0.51)	3.4	-4.0 (-6.4, -1.6)	0.46 (0.24, 0.88)
No MOUD use	12.3	Referent	Referent	7.4	Referent	Referent
1-Year Hospitalization						
MOUD use	29.3	-13.2 (-17.8, -8.5)	0.69 (0.59, 0.81)	29.3	-6.1 (-11.0, -1.2)	0.83 (0.70, 0.97)
No MOUD use	42.4	Referent	Referent	35.4	Referent	Referent

*Weighted for year, age group, length of healthcare visit, and combined comorbidity score.

6.5. Discussion

Among people with opioid use-related SSTI, MOUD use was associated with reductions in both mortality and hospitalization. Nearly 12 out of every 100 people died within 3 years following their initial SSTI discharge. However, for every 100 people on MOUD, there were 4 fewer deaths within 3 years. Among people with SSTI treated with MOUD, the burden of 3-year mortality was one-half that of the comparison group of people not treated by MOUD.

Our study used a large, statewide population of Medicaid enrollees over the course of a 12-year period. The observed protective association between MOUD and mortality was

consistent with another study conducted in Australia, which estimated hazard ratios of the comparison between MOUD and no MOUD on mortality to be 0.63 (95% CI: 0.57-0.70) and rehospitalization to be 0.89 (95% CI: 0.84-0.96) [58]. The protective association between MOUD and hospitalization was also consistent with findings from a study based at a tertiary care center in the United States [50], but inconsistent with another study among private insurance enrollees in which MOUD was associated with an increase in hospitalization [52]. These differences may be explained, in part, due to the differing follow-up times, heterogeneity in study populations, and the specific MOUD measured (e.g., methadone, buprenorphine).

This study expands upon the existing evidence base by also including people who received care for SSTI in both inpatient and outpatient settings, as opposed to inpatient alone [50,52,58]. Given that many people who use drugs seek care for SSTI in the emergency department [7,133,135,137], this study highlights the importance of increasing MOUD access for those who receive care for SSTI in both inpatient and outpatient settings. Several models exist for harm reduction-oriented programs to improve SSTI treatment outcomes among people who injection drug use [128,138]. This can include more individually catered care while people are hospitalized for these infections. These types of models could be expanded to other parts of the country, while reaching people beyond their time during hospitalization. Additionally, given the barriers that people who use drugs face when seeking care, approaches beyond care offered in clinicals settings should be advanced, such as community-based health clinics in harm reduction organizations. Programs that provide wound care, as well as low-threshold MOUD access, have had success.[128,139]

While more people were identified with their initial SSTI diagnosis later in the study period (i.e., from 2016-2018), the prevalence of MOUD use following SSTI discharge did not

notably change over time. In comparison, MOUD trends among all Medicaid enrollees increased from 2014-2018 in some states [140]. Therefore, potential differences in these trends may emphasize the need for more MOUD access among those with SSTI. These results suggest that more programs are needed to increase access to MOUD for people with SSTI, even as the number of authorized MOUD providers has increased [141]. Notably, we also found concerning gaps in MOUD use by racial groups. Fewer Black patients receive MOUD compared to White patients. This is consistent with existing literature about MOUD access [71,72,77], which is often attributed to structural barriers to care due to systemic racism [75], such as neighborhood availability of MOUD providers, other structural barriers to healthcare access, and racism experienced when people seek care in clinical settings.

Our cohort study strengthens the evidence base for evaluations of MOUD by using two study design approaches geared at reducing bias in observational studies of medication use. First, in our main analysis, we excluded those with recent history of MOUD in the past 30 days. We chose to not extend the MOUD history beyond 30 days due to the transient and intermittent nature of MOUD use patterns. Therefore, we considered those without treatment in this past 30-day window as those who had no observed history of MOUD recently or had a disruption in their treatment. Focusing on new users of medications is a standard practice in pharmacoepidemiology study designs in order to reduce survivor bias and more closely model clinical trials [56]. In a sensitivity analysis, we removed the exclusion criteria of "prevalent users" (i.e., those who had a history in the 30 days prior to SSTI diagnosis). These results also displayed a protective association between MOUD and the two outcomes, mortality and hospitalization. In the sensitivity analysis, the estimate of the association between MOUD and mortality was slightly closer to the null. However, the observed differences could also be due, in part, to imprecise

estimates from a smaller sample size. Given the benefits of the new user design, we chose the main analysis as the primary findings. Another study design we used was measuring MOUD use within the first 30 days rather than assessing MOUD use on a continuous basis during follow up. The former approach also more closely resembles a clinical trial, meaning potential attempts for patients to initiate treatment, rather than adhere to treatment over time [142,143].

Several limitations should be noted. This study used claims data, which contain limited information on other factors that may confound the association between MOUD and outcomes. For example, the severity in each individual's OUD-related symptoms is not captured, which could influence their suitability for MOUD treatment, their likelihood of receiving MOUD, as well as risk of death. However, we attempted to reduce potential bias from confounding by using propensity score weighting methods with the available data. Similarly, claims data do not contain relevant information on other drug use behaviors, such as injection drug use, which is likely the main driver of SSTI among people with OUD diagnoses. However, validation studies of people with drug use-associated bacterial and fungal infections display a fair positive predictive value, which supports using these data to identify study cohorts [130]. Additionally, it is possible there is measurement error in MOUD use, specifically with some MOUD not being documented. To reduce potential measurement error due to missing data, we used Medicaid claims data because this was one of the only insurers that covered for methadone in opioid treatment programs during the study period. While using data from this population improves measurement in MOUD, these results are limited to Medicaid enrollees in North Carolina and may not be generalizable to other insured populations or those uninsured. Finally, co-occurrence of claims codes for SSTI and OUD were separated in time, and the SSTI could have been a result of factors independent of substance use. However, given the close proximity of these two diagnoses in time, we decided to

use this approach in order to account for potential undercounting of SSTI events related to opioid use.

In this study, people with opioid use-related SSTI had a high risk of mortality. These infections can be associated with other adverse outcomes, such as invasive infections that further increase risk of mortality, subsequent healthcare costs, and impacts on quality of life. MOUD use is associated with reductions in mortality and hospitalization. However, few people with these infections received MOUD. The lower proportion of people using MOUD use after SSTI diagnosis remained stable over the study period. Given that most people with opioid use-related SSTI seek care in outpatient settings, programs aimed at improving MOUD access in emergency departments and primary care settings are of urgent importance.

CHAPTER 7: DISCUSSION

7.1. Summary of findings

This dissertation systematically evaluated the burden of infection-related mortality and the prevention of adverse infection-related outcomes via MOUD among people who use drugs. The specific aims were to: 1) examine the incidence and risk factors of bacterial and fungal infection-related mortality and drug overdose among people who use drugs, and 2) estimate the association between MOUD mortality among people with opioid use-related SSTI.

In Aim 1, we examined drug use-related mortality outcomes among a cohort of people with drug use diagnoses in the first year following their first observed drug use-related healthcare visits. This population included a large, statewide cohort of privately and publicly insured people in North Carolina with healthcare visits during 2007-2018. We found that both bacterial and fungal infections and overdose were contributors to mortality among people with drug use diagnoses. Specifically, within the first year of follow up, overdose mortality incidence was 36 per 10,000 people (95% confidence interval: 33-40). Bacterial and fungal infection-associated mortality incidence was 16 per 10,000 people (95% confidence interval: 14-18). Bacterial and fungal infection-associated mortality was higher as age increased. In contrast, overdose mortality was higher among younger adults (<50 years). Fatal infection approached overdose among sub-populations, particularly among older age groups (50 and older). Both SSTI and endocarditis were notable predictors of the 1-year incidence of all-cause and infection-associated mortality.

In Aim 2, we examined outcomes among a cohort study of Medicaid enrollees diagnosed with opioid use-related skin and soft tissue infections during 2007-2018 in North Carolina. We

found that people with opioid use-related skin and soft tissue infections have high risk of mortality, with 12% of people dying within the first 3 years after their initial SSI diagnosis. However, MOUD was associated with reductions in both mortality and hospitalization. Specifically, for every 100 people on MOUD, there were 4 fewer deaths (95% confidence interval: 2 to 6) compared to those not on MOUD. People who used MOUD also had a lower incidence of hospitalization in the first year of follow up. However, few people were on MOUD following their SSTI diagnosis. Therefore, expanded access to MOUD is urgently needed among those seeking care for these infections.

Overall, these findings show that bacterial and fungal infections are notable contributors to mortality among people who use drugs. SSTI was a predictor of all-cause, infection-related mortality, and overdose mortality among people who use drugs. However, MOUD was associated with reduced incidences of mortality and hospitalization among those with SSTI. Therefore, while bacterial and fungal infections are contributors to mortality among people who use drugs, MOUD is one potential approach that could likely improve the wellbeing among people who develop these infections.

Future studies that provide additional context, such as qualitative studies and community-based surveys, are needed to understand factors associated with bacterial and fungal infection-associated mortality. Additionally, understanding the generalizability of these results to those outside of the healthcare system would advance the field and guide practices to improve access to care.

7.2. Strengths

These analyses have several important strengths. First, we conducted a novel linkage between statewide public and private insurance claims and death certificate data. Claims data and mortality record data are often two disparate data systems. Oftentimes, analyses using claims

data alone do not have the ability to examine mortality. Our analyses were therefore able to examine cause-specific mortality among people with drug use diagnoses. These two data systems in combination allowed us to examine bacterial and fungal infection-related mortality associated with drug use. To our current knowledge, this is the first study to systematically evaluate this cause of death in a statewide population.

Another notable strength of our study was that we used both private and public insurance claims data. These populations together provide a better picture of this topic among a wider range of populations. Existing research about bacterial and fungal infections associated with drug use have often been limited to one source of data, often times focused on privately insured individuals, people hospitalized in a single hospital system, or inpatient hospitalizations alone. Therefore, our unique dataset not only provides a more comprehensive population of people from different socioeconomic backgrounds, but also include individuals from a variety of healthcare settings. In using claims data, we also can longitudinally follow people across health systems and in both inpatient and outpatient settings.

Our analyses used several advanced epidemiologic methods that strengthen the evidence base. We used survival methods that accounted for competing events in Aim 1. This approach reduces potential overinflation of outcome estimates. In Aim 2, we excluded those with recent history of MOUD in the past 30 days. Focusing on new users of medications and intention to treat analysis reduces survivor bias and more closely models clinical trials.[56]

7.3. Limitations

Given the limited availability of information in claims data, important contextual factors are not available. Such contextual details include: drug use behaviors; factors that lead to health inequities due to drug use stigma and criminalization, racism, and/or socioeconomic position; treatment experiences inside and outside of healthcare settings. In terms of measurement, drug

use diagnoses in claims data are subject to misclassification and measurement error, creating a variety of study design considerations.[130] With this in mind, we created a study population that both represents people at risk of drug use-associated mortality based on population-level trends in substances that had been associated with overdose mortality during this time period[99,100] as well as prior validation studies.[82,84,103] Relatedly, the initial date of drug use diagnosis should be interpreted as the first date the person had care for drug use, not the date of drug use initiation. The gap between these two dates may vary greatly and likely depends on factors not measured in claims data. Additionally, the diagnosis-derived covariates are also unlikely to truly capture all instances of health conditions. For example, people who experience skin and soft tissue infections and overdose sometimes treat their infections outside of healthcare settings.[7,131] Therefore, we assumed that observed covariates represent those that were severe enough to require medical care, were part of the treatment plan, or were associated with insurance billings practices.

Several instances of insufficient sample size for people who used MOUD were present. We had originally intended to examine the association between MOUD and mortality among people with drug use-associated SSTI and endocarditis separately. However, given how few people had documented use of MOUD, we were unable to analyze this exposure among those with the rarer infection of the two - endocarditis. We also originally intended to examine racial and gender disparities in MOUD initiation in detail. Due to similar issues with small sample sizes of those who received MOUD, we were unable to explore this topic further.

Another limitation of these analyses is generalizability of the study population to the general population. Inclusion within these analyses was dependent on several factors directly related to healthcare access and diagnosis. Previous studies have identified a notable proportion

of uninsured patients among people who use drugs diagnosed with serious infections.[3,25] However, comprehensive healthcare utilization data are not available for this population, which makes the study of uninsured individuals infeasible, particularly for MOUD prescription data. In Aim 2, we focused specifically on Medicaid enrollees due to availability of both buprenorphine and methadone data. During this study period, North Carolina was not a Medicaid expansion state, though expansion was signed into law in 2023. Therefore, the study population included those who met very specific criteria for Medicaid coverage, based on a combination of income, family factors, and disability. Last, these results are specific to North Carolina residents and may not be generalizable to other states. Even still, these results both highlight an underrecognized cause of death among a marginalized population, as well as a potential public health strategy to improve their outcomes.

7.4. Contributions to public health

Overdose and bacterial and fungal infection-associated mortality are two preventable causes of death among people with drug use-associated healthcare visits. In recent years, the United States has faced an unprecedented number of lives lost to overdose. Our studies suggest this number is likely an undercount of the total number of lives lost from a toxic drug supply and socioeconomic conditions that drive drug use-associated mortality. Additional efforts are urgently needed to expand support for evidence-based practices that comprehensively address drug use-associated harms, such as community-based harm reduction programs and access to medications for substance use disorders. Systematic factors that drive drug use-associated death, such as policy and social support systems, should also be considered and evaluated to fully understand the pathways towards healthier communities.

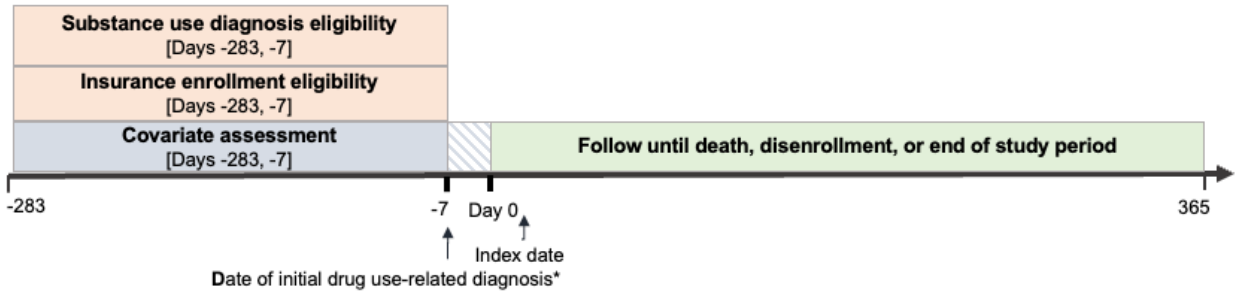
People with opioid use-associated SSTI had a high risk of mortality. These infections can be associated with other adverse outcomes, such invasive infections that further increase risk of mortality, subsequent healthcare costs, and impacts on quality of life. MOUD use is associated with reductions in mortality and other adverse outcomes, such as later hospitalization. However, few people with these infections may be receiving MOUD. Additionally, gaps in MOUD use at SSTI discharge have remained over time. Given that most people with opioid use-associated SSTI seek care in outpatient settings, programs aimed at improving MOUD access should be incorporated into outpatient care, such as emergency departments and primary care. For those with bacterial and fungal infections, MOUD providers should optimize education about treatment options and focus on patient preferences in MOUD treatment decisions.

This study expands upon the existing evidence base by also including people who received care for SSTI in both inpatient and outpatient settings, as opposed to inpatient alone. Given that many people who use drugs seek care for SSTI in the emergency department[7,133,135,137], this study suggests the potential public health impact of increasing MOUD access for those who receive care for SSTI in both inpatient and outpatient settings. Several models exist for harm reduction-oriented programs to improve treatment outcomes among people with SSTI associated with injection drug use.[128,138] These types of models could be extended in other parts of the country, while reaching people beyond their time during hospitalization. Additionally, given the barriers that people who use drugs face when seeking care, approaches beyond care offered in clinicals settings should be advanced. These can include community-based health clinics, such as those based at harm reduction organizations. Programs that provide wound care, as well as low-threshold MOUD access, have had success.[128,139]

Federal support for overdose prevention and harm reduction programs has increased in recent years.[125] Given the systematic and individual-level complexity in drug use-associated harms, additional support is needed to address drug use-associated harms more comprehensively, rather than focusing solely on one health issue at a time or one mechanism of funding. Many successful models for community-based harm reduction programs are present.[126–129] However, in order for these programs to expand services capacity and maintain sustainability, additional and continuous infrastructural support is needed. In healthcare settings, more comprehensive and compassionate care is essential for people who use drugs. Harm reduction-oriented models based both in clinical and community settings are an approach to improve quality of care. In all situations, compassionate approaches are critical.

APPENDIX A: STUDY DESIGN, SUPPLEMENTAL DATA, AND CODE LISTS FOR AIM 1

Supplemental Figure A.1. Study design, eligibility assessment, and covariate assessment.



Supplemental Table A.1. Cohort characteristics by age group.

	18-34 Years N=41,348	35-49 Years N=36,414	50-64 Years N=35,543	65 Years or Older N=18,217
Sex, women	27,084 (65.5%)	20,597 (56.6%)	18,019 (50.7%)	11,079 (60.8%)
Insurer				
Medicaid	7,697 (18.6%)	5,962 (16.4%)	5,023 (14.1%)	145 (0.8%)
Medicare	2,476 (6.0%)	6,978 (19.2%)	7,793 (21.9%)	3,179 (17.5%)
Medicaid/Medicare	30,330 (73.4%)	19,230 (52.8%)	12,350 (34.7%)	821 (4.5%)
Private	845 (2.0%)	4,244 (11.7%)	10,377 (29.2%)	14,072 (77.2%)
Substance use disorders*				
Alcohol	6,698 (16.2%)	8,043 (22.1%)	8,157 (22.9%)	1,859 (10.2%)
Cannabis	9,690 (23.4%)	5,007 (13.8%)	3,358 (9.4%)	492 (2.7%)
Hallucinogen	244 (0.6%)	73 (0.2%)	43 (0.1%)	<11
Opioid	27,380 (66.2%)	21,274 (58.4%)	22,913 (64.5%)	13,954 (76.6%)
Sedative/hypnotic	4,862 (11.8%)	4,166 (11.4%)	4,702 (13.2%)	3,618 (19.9%)
Stimulants	13,786 (33.3%)	13,686 (37.6%)	11,452 (32.2%)	1,818 (10.0%)
Unspecified	11,782 (28.5%)	9,991 (27.4%)	8,473 (23.8%)	3,134 (17.2%)
Nonfatal overdose	3,539 (8.6%)	3,949 (10.8%)	3,882 (10.9%)	1,493 (8.2%)
Mental health conditions*				
Anxiety	14,987 (36.2%)	16,411 (45.1%)	15,973 (44.9%)	8,857 (48.6%)
Bipolar	8,802 (21.3%)	9,273 (25.5%)	6,316 (17.8%)	1,473 (8.1%)
Depression	15,478 (37.4%)	17,550 (48.2%)	16,966 (47.7%)	8,500 (46.7%)
Intellectual disabilities	404 (1.0%)	306 (0.8%)	197 (0.6%)	54 (0.3%)
Personality disorders	2,387 (5.8%)	2,484 (6.8%)	1,786 (5.0%)	612 (3.4%)
Post-traumatic stress disorder	2,941 (7.1%)	3,331 (9.1%)	2,372 (6.7%)	561 (3.1%)
Schizophrenia	3,991 (9.7%)	5,078 (13.9%)	4,532 (12.8%)	1,723 (9.5%)
Infections*				
Skin and soft tissue infections	4,525 (10.9%)	4,762 (13.1%)	4,586 (12.9%)	2,546 (14.0%)
Endocarditis	187 (0.5%)	213 (0.6%)	243 (0.7%)	187 (1.0%)
Hepatitis B virus	104 (0.3%)	251 (0.7%)	341 (1.0%)	44 (0.2%)
Hepatitis C virus	2,362 (5.7%)	3,534 (9.7%)	3,899 (11.0%)	532 (2.9%)
HIV	389 (0.9%)	1,281 (3.5%)	1,114 (3.1%)	104 (0.6%)
Other conditions*				
Cancer	102 (0.2%)	650 (1.8%)	2,116 (6.0%)	2,495 (13.7%)
Chronic kidney disease	1,794 (4.3%)	4,351 (11.9%)	8,956 (25.2%)	7,561 (41.5%)
Diabetes	1,718 (4.2%)	6,429 (17.7%)	11,309 (31.8%)	7,092 (38.9%)
Chronic pain/fibromyalgia	10,210 (24.7%)	18,247 (50.1%)	22,882 (64.4%)	13,756 (75.5%)
Heart failure	432 (1.0%)	1,816 (5.0%)	4,630 (13.0%)	4,506 (24.7%)
Liver disease	1,284 (3.1%)	3,171 (8.7%)	4,574 (12.9%)	1,943 (10.7%)
Traumatic brain injury	320 (0.8%)	395 (1.1%)	345 (1.0%)	155 (0.9%)

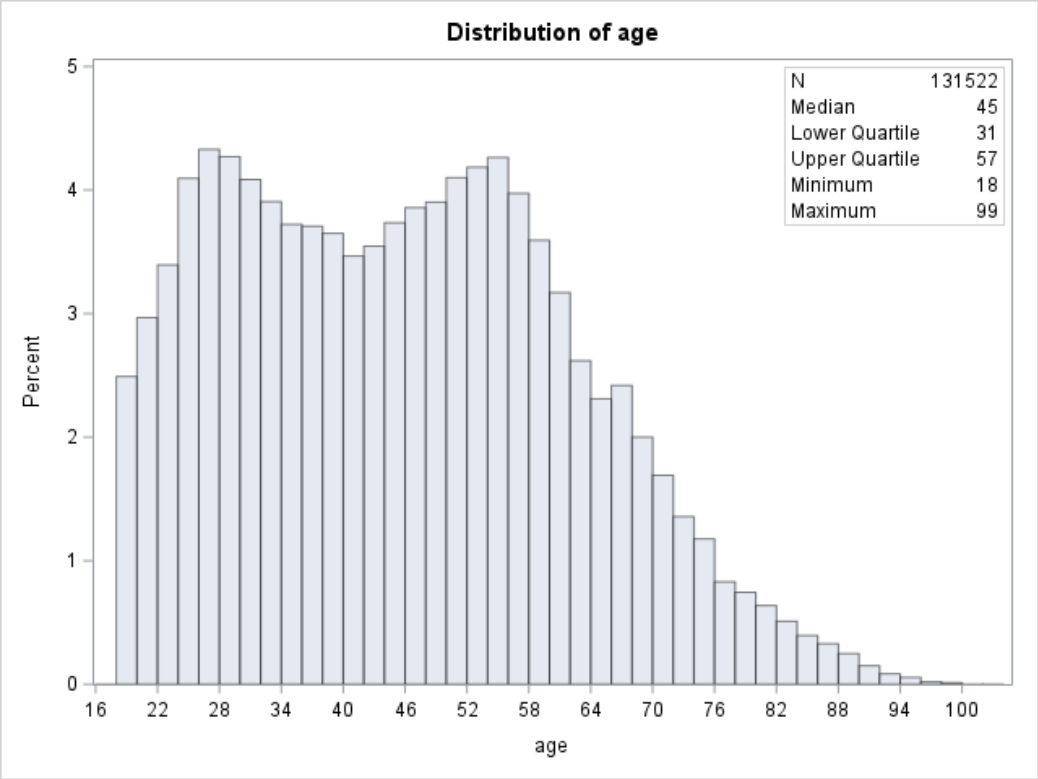
*Not mutually exclusive.

Supplemental Table A.2. Cohort characteristics by insurer.

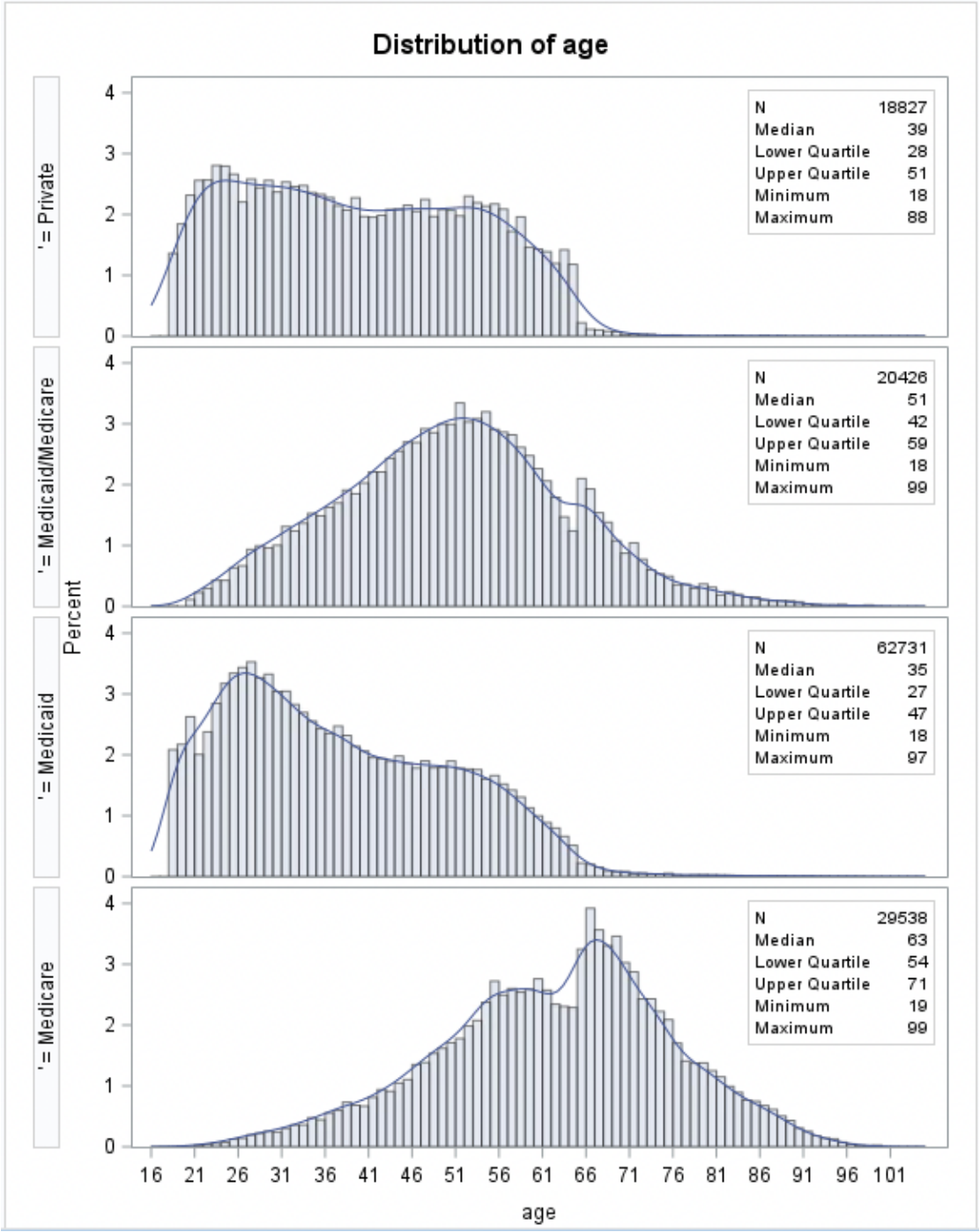
	Medicaid N=62,731	Medicare N=29,538	Medicaid/Medicare N=20,426	Private N=18,827
Sex, women	42,249 (67.3%)	16,034 (54.3%)	11,101 (54.3%)	7,395 (39.3%)
Age Group				
18-34	30,330 (48.3%)	845 (2.9%)	2,476 (12.1%)	7,697 (40.9%)
35-49	19,230 (30.7%)	4,244 (14.4%)	6,978 (34.2%)	5,962 (31.7%)
50-64	12,350 (19.7%)	10,377 (35.1%)	7,793 (38.2%)	5,023 (26.7%)
³65	821 (1.3%)	14,072 (47.6%)	3,179 (15.6%)	145 (0.8%)
Substance use disorders*				
Alcohol	10,925 (17.4%)	4,228 (14.3%)	4,744 (23.2%)	4,860 (25.8%)
Cannabis	9,739 (15.5%)	2,202 (7.5%)	3,233 (15.8%)	3,373 (17.9%)
Hallucinogen	99 (0.2%)	40 (0.1%)	53 (0.3%)	174 (0.9%)
Opioid	36,175 (57.7%)	22,686 (76.8%)	12,648 (61.9%)	14,012 (74.4%)
Sedative/hypnotic	5,273 (8.4%)	5,327 (18.0%)	2,883 (14.1%)	3,865 (20.5%)
Stimulants	23,912 (38.1%)	4,666 (15.8%)	7,314 (35.8%)	4,850 (25.8%)
Unspecified	13,711 (21.9%)	6,981 (23.6%)	6,939 (34.0%)	5,749 (30.5%)
Nonfatal overdose	4,856 (7.7%)	3,106 (10.5%)	3,075 (15.1%)	1,826 (9.7%)
Mental health conditions*				
Anxiety	20,376 (32.5%)	15,505 (52.5%)	11,388 (55.8%)	8,959 (47.6%)
Bipolar	12,304 (19.6%)	4,681 (15.8%)	6,046 (29.6%)	2,833 (15.0%)
Depression	22,898 (36.5%)	15,432 (52.2%)	11,853 (58.0%)	8,311 (44.1%)
Intellectual disabilities	442 (0.7%)	130 (0.4%)	374 (1.8%)	15 (0.1%)
Personality disorders	2,663 (4.2%)	1,669 (5.7%)	1,876 (9.2%)	1,061 (5.6%)
Post-traumatic stress disorder	4,006 (6.4%)	2,006 (6.8%)	2,096 (10.3%)	1,097 (5.8%)
Schizophrenia	6,237 (9.9%)	3,630 (12.3%)	4,313 (21.1%)	1,144 (6.1%)
Infections*				
Skin and soft tissue infections	7,267 (11.6%)	4,263 (14.4%)	3,322 (16.3%)	1,567 (8.3%)
Endocarditis	306 (0.5%)	264 (0.9%)	198 (1.0%)	62 (0.3%)
Hepatitis B virus	341 (0.5%)	147 (0.5%)	219 (1.1%)	33 (0.2%)
Hepatitis C virus	5,783 (9.2%)	1,305 (4.4%)	2,547 (12.5%)	692 (3.7%)
HIV	1,605 (2.6%)	379 (1.3%)	823 (4.0%)	81 (0.4%)
Other conditions*				
Cancer	1,193 (1.9%)	2,769 (9.4%)	1,067 (5.2%)	334 (1.8%)
Chronic kidney disease	5,708 (9.1%)	10,083 (34.1%)	5,261 (25.8%)	1,610 (8.6%)
Diabetes	7,788 (12.4%)	10,322 (34.9%)	6,621 (32.4%)	1,817 (9.7%)
Chronic pain/fibromyalgia	21,283 (33.9%)	22,445 (76.0%)	13,887 (68.0%)	7,480 (39.7%)
Heart failure	2,670 (4.3%)	5,317 (18.0%)	2,944 (14.4%)	453 (2.4%)
Liver disease	3,758 (6.0%)	3,406 (11.5%)	2,595 (12.7%)	1,213 (6.4%)
Traumatic brain injury	439 (0.7%)	331 (1.1%)	317 (1.6%)	128 (0.7%)

*Not mutually exclusive.

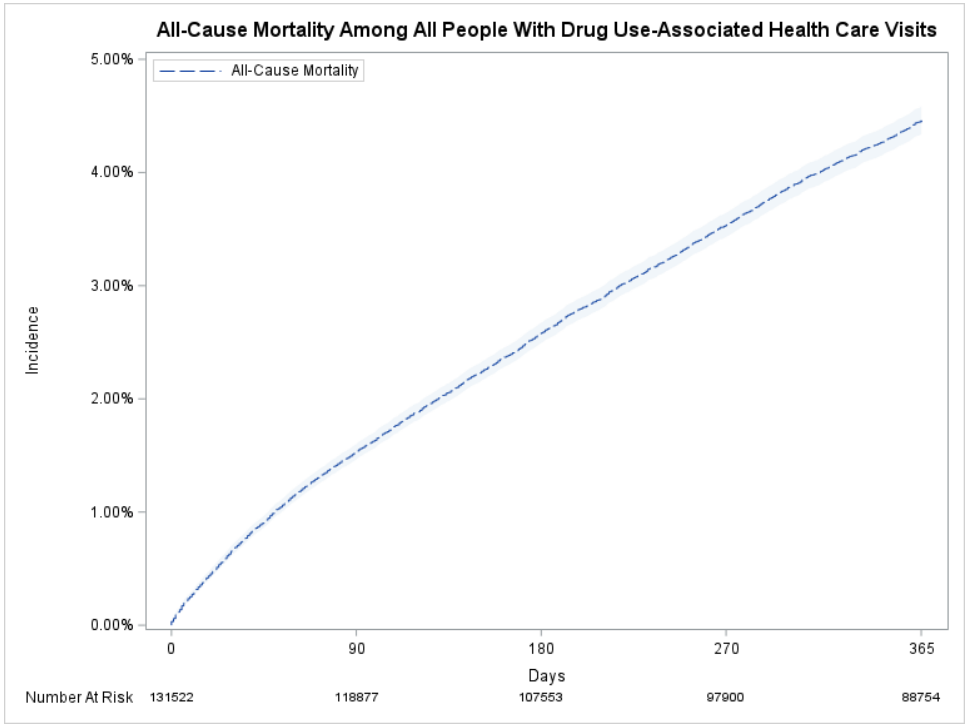
Supplemental Figure A.2. Age distribution of analytic cohort.

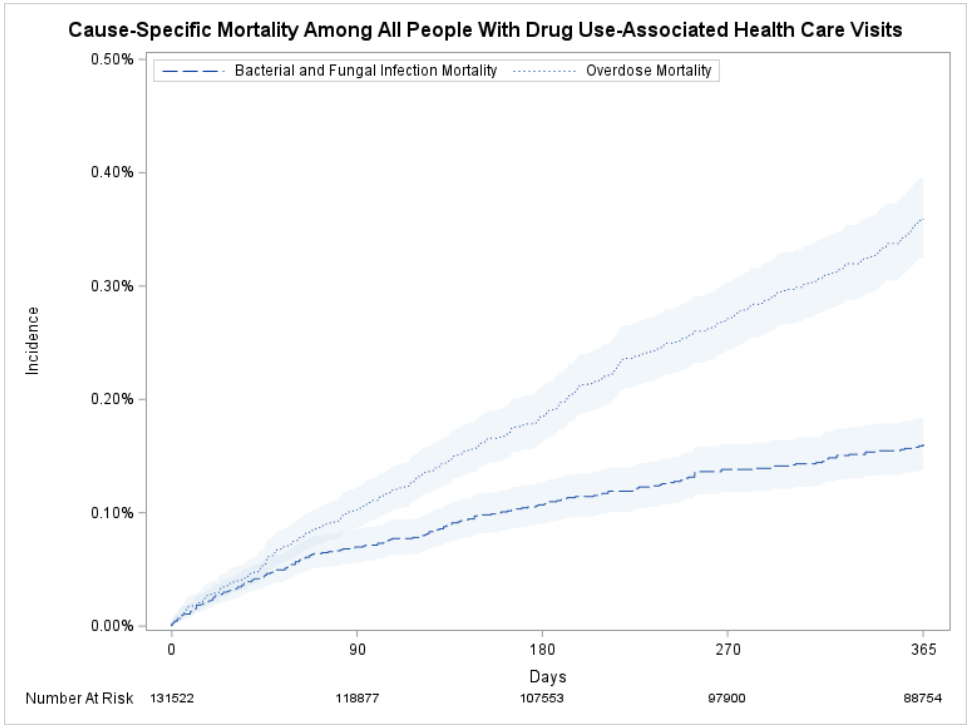


Supplemental Figure A.3. Age distribution of analytic cohort by insurer.

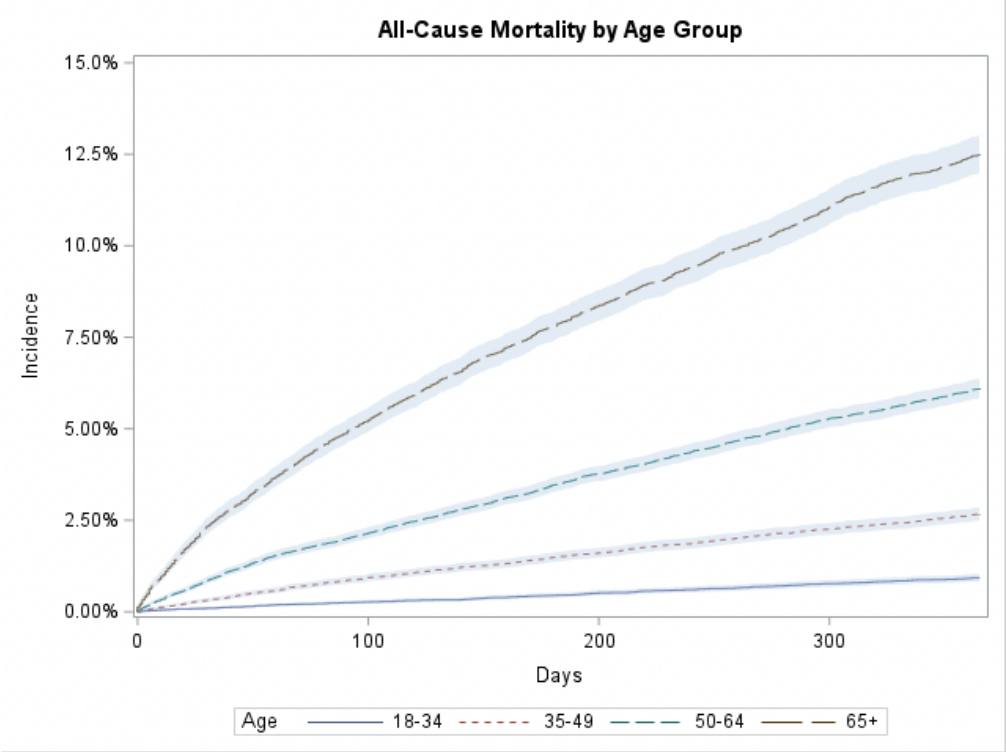


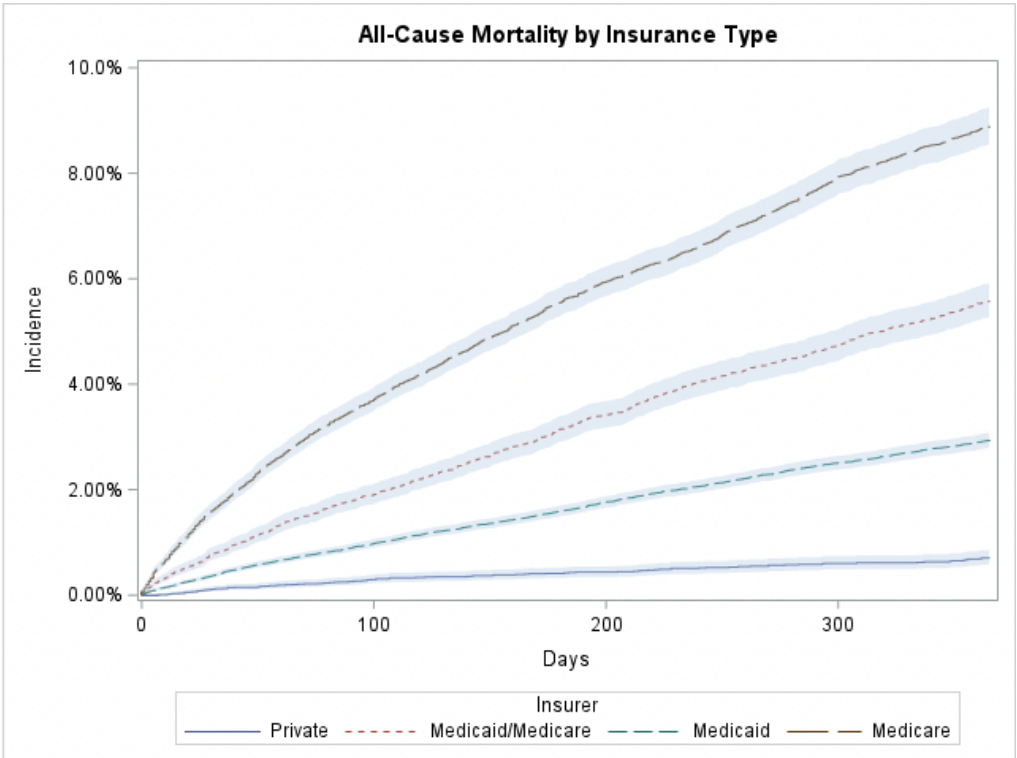
Supplemental Figure A.4. All-cause and cause specific mortality among analytic cohort.



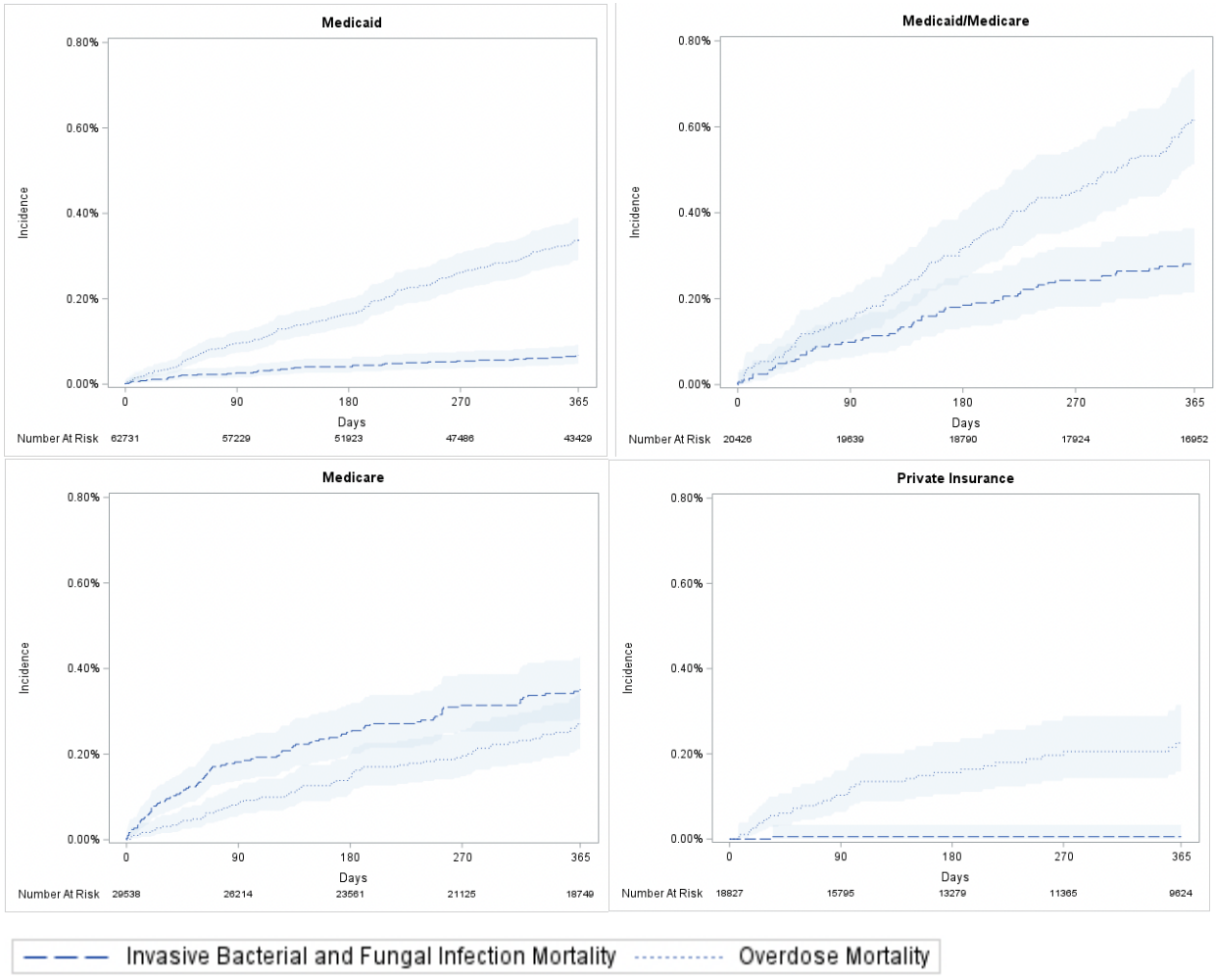


Supplemental Figure A.5. All-cause mortality by age group and insurer.

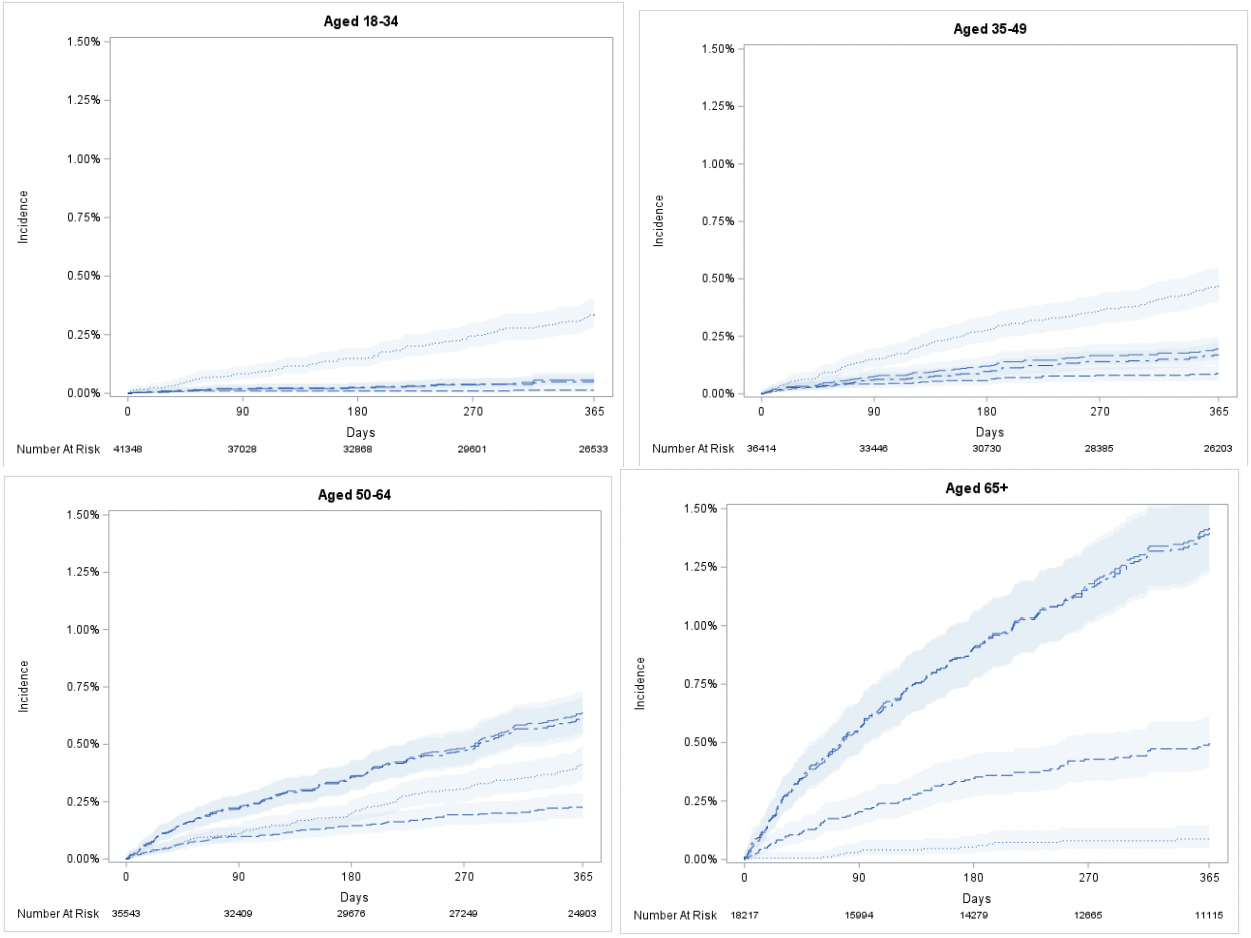




Supplemental Figure A.6. Cause-specific mortality by insurer.

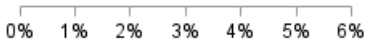


Supplemental Figure A.7. Comparison of three different infection-related mortality definitions alongside overdose mortality by age group.



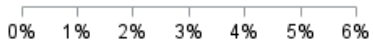
Supplemental Table A.3. Risk factors for 1-year incidence of sepsis-related mortality defined via death certificates.

Characteristic	At Risk (N)	Events (N)	Incidence (95% Confidence Interval)	1-Year Cumulative Incidence	95% Confidence Interval
Overall	131,522	487		0.43%	(0.39%-0.47%)
Age: 18-34	41,348	17		0.05%	(0.03%-0.08%)
Age: 35-49	36,414	54		0.17%	(0.13%-0.22%)
Age: 50-64	35,543	193		0.61%	(0.53%-0.70%)
Age: 65+	18,217	223		1.40%	(1.22%-1.59%)
Sex: Men	54,743	226		0.47%	(0.41%-0.53%)
Sex: Women	76,779	261		0.39%	(0.35%-0.44%)
Insurance: Private	18,827				--
Insurance: Medicaid/Medicare	20,426	107		0.55%	(0.45%-0.66%)
Insurance: Medicaid	62,731	130		0.24%	(0.20%-0.28%)
Insurance: Medicare	29,538	248		0.96%	(0.84%-1.08%)
Opioid Use Disorder	85,521	350		0.47%	(0.42%-0.52%)
Stimulant Use Disorder	40,742	103		0.29%	(0.24%-0.36%)
Sedative/Hypnotic Use Disorder	17,348	65		0.44%	(0.34%-0.56%)
Drug Overdose	12,863	67		0.58%	(0.46%-0.74%)
Skin and Soft Tissue Infections	16,419	148		1.03%	(0.87%-1.20%)
Infective Endocarditis	830	24		3.14%	(2.07%-4.56%)
Hepatitis C Virus	10,327	56		0.61%	(0.46%-0.78%)
Chronic Pain	65,095	381		0.66%	(0.59%-0.73%)



Supplemental Table A.4. Risk factors for 1-year incidence of bacterial and fungal infection-related mortality defined via death certificates.

Characteristic	At Risk (N)	Events (N)	Incidence (95% Confidence Interval)	1-Year Cumulative Incidence	95% Confidence Interval
Overall	131,522	508		0.45%	(0.41%-0.49%)
Age: 18-34	41,348	19		0.06%	(0.04%-0.09%)
Age: 35-49	36,414	63		0.20%	(0.15%-0.25%)
Age: 50-64	35,543	200		0.64%	(0.55%-0.73%)
Age: 65+	18,217	226		1.42%	(1.24%-1.61%)
Sex: Men	54,743	236		0.49%	(0.43%-0.56%)
Sex: Women	76,779	272		0.41%	(0.37%-0.46%)
Insurance: Private	18,827				--
Insurance: Medicaid/Medicare	20,426	110		0.57%	(0.47%-0.68%)
Insurance: Medicaid	62,731	139		0.26%	(0.22%-0.30%)
Insurance: Medicare	29,538	257		0.99%	(0.88%-1.12%)
Opioid Use Disorder	85,521	361		0.49%	(0.44%-0.54%)
Stimulant Use Disorder	40,742	110		0.32%	(0.26%-0.38%)
Sedative/Hypnotic Use Disorder	17,348	64		0.43%	(0.34%-0.55%)
Drug Overdose	12,863	63		0.55%	(0.43%-0.70%)
Skin and Soft Tissue Infections	16,419	161		1.12%	(0.96%-1.30%)
Infective Endocarditis	830	36		4.77%	(3.40%-6.47%)
Hepatitis C Virus	10,327	58		0.63%	(0.48%-0.81%)
Chronic Pain	65,095	396		0.69%	(0.62%-0.76%)



Supplemental Table A.5. Definitions for cause-specific mortality definitions.

Variable	Code Type	Codes
Drug overdose	ICD-10	X40, X41, X42, X43, X44, X60, X61, X62, X63, X64, X85, Y10, Y11, Y12, Y13, Y14
Bacterial and fungal-related mortality (derived from death certificates)	ICD-10	Used WHO definition for sepsis-related mortality or the presence of any of the following codes listed as a cause of death: Endocarditis: B376, I33, I38, I39, T826 Intracranial and intraspinal abscess: G06, G07 Osteomyelitis: M86 Infective arthritis: M00, M01 SSTI: L02, L03, A480, I80, I96, M540, M726, M793 Spinal Infection: G06, G07, M462, M463, M464, M465 Sepsis: A40, A41, A327, A021, A427, B377, R652
Bacterial and fungal-related mortality (derived from hospitalizations in 30 days prior to death)	ICD-9-CM	Infective endocarditis: 11281, 421, 4249 Intracranial and intraspinal abscess: 324, 3241, 3249 Non-Spinal Osteomyelitis: 7300, 7301, 7302, 7303, 7308, 7309 Osteomyelitis: 730, 73001, 73002, 73003, 73004, 73005, 73006, 73007, 73008, 73009, 7302, 73021, 73022, 73023, 73024, 73025, 73026, 73027, 73028, 73029 Septic Arthritis: 7110, 7114, 7116, 7118, 7119 Spinal Infections: 3240, 3241, 3249
Bacterial and fungal-related mortality (derived from hospitalizations in 30 days prior to death)	ICD-10-CM	Infective endocarditis: A3282, B376, I330, I339, I38, I39, T826 Intracranial and intraspinal abscess: G060, G061, G062, G07 Non-Spinal Osteomyelitis: M860, M861, M862, M863, M864, M865, M868, M869 Osteomyelitis: M8600, M8610, M8620, M86011, M86012, M86019, M86111, M86112, M86119, M86211, M86212, M86219, M86021, M86022, M86029, M86121, M86122, M86129, M86221, M86222, M86229, M86031, M86032, M86039, M86131, M86132, M86139, M86231, M86232, M86239, M86041, M86042, M86049, M86141, M86142, M86149, M86241, M86242, M86249, M86051, M86052, M86059, M86151, M86152, M86159, M86251, M86252, M86259, M86061, M86062, M86069, M86161, M86162, M86169, M86261, M86262, M86269, M86071, M86072, M86079, M86171, M86172, M86179, M86271, M86272, M86279, M8608, M8618, M8628, M8609, M8619, M8629, M869, M869, M869, M869, M869, M869, M869, M869, M4620, M4621, M4622, M4623, M4624, M4625, M4626, M4627, M4628, M869, M869 Septic Arthritis: M0000, M0001, M0001, M0001, M0002, M0002, M0002, M0003, M0003, M0003, M0004, M0004, M0004, M0005, M0005, M0005, M0006, M0006, M0006, M0007, M0007, M0007, M0009, M0010, M0011, M0011, M0011, M0012, M0012, M0012, M0013, M0013, M0013, M0014, M0014, M0014, M0015, M0015, M0015, M0016, M0016, M0016, M0017, M0017, M0017, M0019, M0020, M0021, M0021, M0021, M0022, M0022, M0022, M0023, M0023, M0023, M0024, M0024, M0024, M0025, M0025, M0025, M0026, M0026, M0026, M0027, M0027, M0027, M0029, M0080, M0081, M0081, M0081, M0082, M0082, M0082, M0083, M0083, M0083, M0084, M0084, M0084, M0085, M0085, M0085, M0086, M0086, M0086, M0087, M0087, M0087, M0089, M009, M01X0, M01X1, M01X1, M01X1, M01X2, M01X2, M01X2, M01X3, M01X3, M01X3, M01X4, M01X4, M01X4, M01X5, M01X5, M01X5, M01X6, M01X6, M01X6, M01X7, M01X7, M01X7, M01X9 Spinal Infections: G060, G061, G062, G07, M0008, M0018, M0028, M0088, M01X8, M4620, M4630, M464, M465

Supplemental Table A.6. Definitions for variables derived from diagnosis and procedure codes documented during healthcare encounters.

Variable	Code Type	Codes
Substance Use Conditions		
Opioid use disorder	ICD-9-CM Dx	304.0, 304.7, 305.5
Opioid use disorder	ICD-10-CM Dx	F11
Stimulant use disorder	ICD-9-CM Dx	304.2, 304.4, 305.6, 305.7
Stimulant use disorder	ICD-10-CM Dx	F14, F15
Sedative and hypnotic use disorder	ICD-9-CM Dx	304.1, 305.4
Sedative and hypnotic use disorder	ICD-10-CM Dx	F13
Other and unspecified substance use disorders	ICD-9-CM Dx	292, 304.6, 304.7, 304.8, 304.9, 305.9
Other and unspecified substance use disorders	ICD-10-CM Dx	F19
Alcohol use disorder	ICD-9-CM Dx	291, 303, 305.0
Alcohol use disorder	ICD-10-CM Dx	F10
Cannabis use disorder	ICD-9-CM Dx	304.3, 305.2
Cannabis use disorder	ICD-10-CM Dx	F12
Hallucinogen use disorder	ICD-9-CM Dx	304.5, 305.3
Hallucinogen use disorder	ICD-10-CM Dx	F16
Overdose	ICD-9-CM Dx	960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, E850, E851, E852, E853, E854, E855, E856, E857, E858, E9800, E9801, E9802, E9803, E9804, E9805
Overdose	ICD-10-CM Dx	T360X1A, T360X2A, T360X3A, T360X4A, T361X1A, T361X2A, T361X3A, T361X4A, T362X1A, T362X2A, T362X3A, T362X4A, T363X1A, T363X2A, T363X3A, T363X4A, T364X1A, T364X2A, T364X3A, T364X4A, T365X1A, T365X2A, T365X3A, T365X4A, T366X1A, T366X2A, T366X3A, T366X4A, T367X1A, T367X2A, T367X3A, T367X4A, T368X1A, T368X2A, T368X3A, T368X4A, T3691XA, T3692XA, T3693XA, T3694XA, T370X1A, T370X2A, T370X3A, T370X4A, T371X1A, T371X2A, T371X3A, T371X4A, T372X1A, T372X2A, T372X3A, T372X4A, T373X1A, T373X2A, T373X3A, T373X4A, T374X1A, T374X2A, T374X3A, T374X4A, T375X1A, T375X2A, T375X3A, T375X4A, T378X1A, T378X2A, T378X3A, T378X4A, T3791XA, T3792XA, T3793XA, T3794XA,

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Mental Health Conditions		
Anxiety disorder	ICD-9-CM Dx	293.84, 300.00, 300.01, 300.02, 300.09, 300.10, 300.20, 300.21, 300.22, 300.23, 300.29, 300.3, 300.5, 300.89, 300.9, 308.0, 308.1, 308.2, 308.3, 308.4, 308.9, 309.81, 313.0, 313.1, 313.21, 313.22, 313.3, 313.82, 313.83
Anxiety disorder	ICD-10-CM Dx	F06.4, F40.00, F40.01, F40.02, F40.10, F40.11, F40.210, F40.218, F40.220, F40.228, F40.230, F40.231, F40.232, F40.233, F40.240, F40.241, F40.242, F40.243, F40.248, F40.290, F40.291, F40.298, F40.8, F40.9, F41.0, F41.1, F41.3, F41.8, F41.9, F42, F42.2, F42.3, F42.4,

		F42.8, F42.9, F43.0, F43.10, F43.11, F43.12, F44.9, F45.8, F48.8, F48.9, F93.8, F99, R45.2, R45.5, R45.6, R45.7
Bipolar disorder	ICD-9-CM Dx	296.00, 296.01, 296.02, 296.03, 296.04, 296.05, 296.06, 296.10, 296.11, 296.12, 296.13, 296.14, 296.15, 296.16, 296.40, 296.41, 296.42, 296.43, 296.44, 296.45, 296.46, 296.50, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.7, 296.80, 296.81, 296.82, 296.89, 296.90, 296.99
Bipolar disorder	ICD-10-CM Dx	F30.10, F30.11, F30.12, F30.13, F30.2, F30.3, F30.4, F30.8, F30.9, F31.0, F31.10, F31.11, F31.12, F31.13, F31.2, F31.30, F31.31, F31.32, F31.4, F31.5, F31.60, F31.61, F31.62, F31.63, F31.64, F31.70, F31.71, F31.72, F31.73, F31.74, F31.75, F31.76, F31.77, F31.78, F31.81, F31.89, F31.9, F33.8, F34.81, F34.89, F34.9, F39
Depressive disorders	ICD-9-CM Dx	296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.89, 298.0, 300.4, 309.1, 311
Depressive disorders	ICD-10-CM Dx	F31.30, F31.31, F31.32, F31.4, F31.5, F31.60, F31.61, F31.62, F31.63, F31.64, F31.75, F31.76, F31.77, F31.78, F31.81, F32.0, F32.1, F32.2, F32.3, F32.4, F32.5, F32.9, F33.0, F33.1, F33.2, F33.3, F33.40, F33.41, F33.42, F33.8, F33.9, F34.1, F43.21, F43.23
Intellectual disabilities and related condition	ICD-9-CM Dx	317, 318, 318.0, 318.1, 318.2, 319, 758, 758.0, 758.1, 758.2, 758.3, 758.31, 758.32, 758.33, 758.39, 758.5, 759.7, 759.81, 759.83, 759.89, 760.71
Intellectual disabilities and related condition	ICD-10-CM Dx	E78.71, E78.72, F70, F71, F72, F73, F78, F78.A1, F78.A9, F79, P04.3, Q86.0, Q87.1, Q87.11, Q87.19, Q87.2, Q87.3, Q87.5, Q87.81, Q87.89, Q89.7, Q89.8, Q90.0, Q90.1, Q90.2, Q90.9, Q91.0, Q91.1, Q91.2, Q91.3, Q91.4, Q91.5, Q91.6, Q91.7, Q92.0, Q92.1, Q92.2, Q92.5, Q92.61, Q92.62, Q92.7, Q92.8, Q92.9, Q93.0, Q93.1, Q93.2, Q93.3, Q93.4, Q93.5, Q93.51, Q93.59, Q93.7, Q93.81, Q93.88, Q93.89, Q93.9, Q95.2, Q95.3, Q99.2
Personality disorders	ICD-9-CM Dx	301.0, 301.10, 301.11, 301.12, 301.13, 301.20, 301.21, 301.22, 301.3, 301.4, 301.50, 301.51, 301.59, 301.6, 301.7, 301.81, 301.82, 301.83, 301.84, 301.89, 301.9
Personality disorders	ICD-10-CM Dx	F21, F34.0, F34.1, F60.0, F60.1, F60.2, F60.3, F60.4, F60.5, F60.6, F60.7, F60.81, F60.89, F60.9, F68.10, F68.11, F68.12, F68.13, F69
Post-traumatic stress disorder	ICD-9-CM Dx	309.81
Post-traumatic stress disorder	ICD-10-CM Dx	F43.10, F43.11, F43.12
Schizophrenia and other psychotic disorders	ICD-9-CM Dx	293.81, 293.82, 295.00, 295.01, 295.02, 295.03, 295.04, 295.05, 295.10, 295.11, 295.12, 295.13, 295.14, 295.15, 295.20, 295.21, 295.22, 295.23, 295.24, 295.25, 295.30, 295.31, 295.32, 295.33, 295.34, 295.35, 295.40, 295.41, 295.42, 295.43, 295.44, 295.45, 295.50, 295.51, 295.52, 295.53, 295.54, 295.55, 295.60, 295.61, 295.62, 295.63, 295.64, 295.65, 295.70, 295.71, 295.72, 295.73, 295.74, 295.75, 295.80, 295.81, 295.82, 295.83, 295.84, 295.85, 295.90, 295.91, 295.92, 295.93, 295.94, 295.95, 297.0, 297.1, 297.2, 297.3, 297.8, 297.9, 298.0, 298.1, 298.2, 298.3, 298.4, 298.8, 298.9
Schizophrenia and other psychotic disorders	ICD-10-CM Dx	F06.0, F06.2, F20.0, F20.1, F20.2, F20.3, F20.5, F20.81, F20.89, F20.9, F21, F22, F23, F24, F25.0, F25.1, F25.8, F25.9, F28, F29, F32.3, F33.3, F44.89
Infectious Diseases		
Infective endocarditis	ICD-9-CM Dx	11281, 421, 4249

Infective endocarditis	ICD-10-CM Dx	A3282, B376, I330, I339, I38, I39, T826
Hepatitis C virus	ICD-9-CM Dx	070.41, 070.51, 070.44, 070.54, V02.62, 070.7, 070.70, 070.71
Hepatitis C virus	ICD-10-CM Dx	B17.10, B17.11, B18.2, Z22.52, B19.20, B19.21
Hepatitis B virus	ICD-9-CM Dx	070.2, 070.20, 070.21, 070.3, 070.30, 070.31, 070.22, 070.23, 070.32, 070.33, V02.61
Hepatitis B virus	ICD-10-CM Dx	B16.0, B16.1, B16.2, B16.9, B19.10, B19.11, B18.0, B18.1, Z22.51
HIV	ICD-9-CM Dx	042, 042.0, 042.1, 042.2, 042.9, 043, 043.1, 043.2, 043.3, 043.9, 044, 044.0, 044.9, 079.53, V08
HIV	ICD-10-CM Dx	B20, B97.35, Z21
Skin and soft tissue infections	ICD-9-CM Dx	451, 45111, 45119, 4512, 45181, 45182, 45183, 45184, 45189, 4519, 5283, 56731, 681, 68101, 6811, 68111, 6819, 682, 6821, 6822, 6823, 6824, 6825, 6826, 6827, 6828, 6829, 7236, 72886, 7293, 72939, 7854
Skin and soft tissue infections	ICD-10-CM Dx	A480, I8000, I8001, I8002, I8003, I8010, I8011, I8012, I8013, I80201, I80202, I80203, I80209, I80211, I80212, I80213, I80219, I80221, I80222, I80223, I80229, I80231, I80232, I80233, I80239, I80291, I80292, I80293, I80299, I803, I808, I809, I96, L02, L0201, L0202, L0203, L0211, L0212, L0213, L02211, L02212, L02213, L02214, L02215, L02216, L02219, L02221, L02222, L02223, L02224, L02225, L02226, L02229, L02231, L02232, L02233, L02234, L02235, L02236, L02239, L0231, L0232, L0233, L02411, L02412, L02413, L02414, L02415, L02416, L02419, L02421, L02422, L02423, L02424, L02425, L02426, L02429, L02431, L02432, L02433, L02434, L02435, L02436, L02439, L02511, L02512, L02519, L02521, L02522, L02529, L02531, L02532, L02539, L02611, L02612, L02619, L02621, L02622, L02629, L02631, L02632, L02639, L02811, L02818, L02821, L02828, L02831, L02838, L0291, L0292, L0293, L03, L03011, L03012, L03019, L03021, L03022, L03029, L03031, L03032, L03039, L03041, L03042, L03049, L03111, L03112, L03113, L03114, L03115, L03116, L03119, L03121, L03122, L03123, L03124, L03125, L03126, L03129, L03211, L03212, L03213, L03221, L03222, L03311, L03312, L03313, L03314, L03315, L03316, L03317, L03319, L03321, L03322, L03323, L03324, L03325, L03326, L03327, L03329, L03811, L03818, L03891, L03898, L0390, L0391, M5402, M726, M793
Other Conditions		
Cancers (breast, colorectal, endometrial, lung, prostate, urologic)	ICD-9-CM Dx	174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175.0, 175.9, 233.0, V10.3, 153.0, 153.1, 153.2, 153.3, 153.4, 153.5, 153.6, 153.7, 153.8, 153.9, 154.0, 154.1, 230.3, 230.4, V10.05, V10.06, 182.0, 233.2, V10.42, 162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 231.2, V10.11, 185, 233.4, V10.46
Cancers (breast, colorectal, endometrial, lung, prostate, urologic)	ICD-10-CM Dx	C50.011, C50.012, C50.019, C50.021, C50.022, C50.029, C50.111, C50.112, C50.119, C50.121, C50.122, C50.129, C50.211, C50.212, C50.219, C50.221, C50.222, C50.229, C50.311, C50.312, C50.319, C50.321, C50.322, C50.329, C50.411, C50.412, C50.419, C50.421, C50.422, C50.429, C50.511, C50.512, C50.519, C50.521, C50.522, C50.529, C50.611, C50.612, C50.619, C50.621, C50.622, C50.629, C50.811, C50.812, C50.819, C50.821, C50.822, C50.829, C50.911, C50.912, C50.919, C50.921, C50.922, C50.929, D05.00, D05.01, D05.02, D05.10, D05.11, D05.12, D05.80, D05.81, D05.82, D05.90, D05.91, D05.92, Z85.3, C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19, C20, D01.0, D01.1, D01.2, Z85.038, Z85.040,

		Z85.048, C54.1, C54.2, C54.3, C54.8, C54.9, D07.0, Z85.42, C34.00, C34.01, C34.02, C34.10, C34.11, C34.12, C34.2, C34.30, C34.31, C34.32, C34.80, C34.81, C34.82, C34.90, C34.91, C34.92, D02.20, D02.21, D02.22, Z85.110, Z85.118, C61, D07.5, Z85.46
Chronic kidney disease	ICD-9-CM Dx	016.00, 016.01, 016.02, 016.03, 016.04, 016.05, 016.06, 095.4, 189.0, 189.9, 223.0, 236.91, 249.40, 249.41, 250.40, 250.41, 250.42, 250.43, 271.4, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 440.1, 442.1, 572.4, 580.0, 580.4, 580.81, 580.89, 580.9, 581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586, 587, 588.0, 588.1, 588.81, 588.89, 588.9, 591, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.20, 753.21, 753.22, 753.23, 753.29, 794.4
Chronic kidney disease	ICD-10-CM Dx	A18.11, A52.75, B52.0, C64.1, C64.2, C64.9, C68.9, D30.00, D30.01, D30.02, D41.00, D41.01, D41.02, D41.10, D41.11, D41.12, D41.20, D41.21, D41.22, D59.3, E08.21, E08.22, E08.29, E08.65, E09.21, E09.22, E09.29, E10.21, E10.22, E10.29, E10.65, E11.21, E11.22, E11.29, E11.65, E13.21, E13.22, E13.29, E74.8, I12.0, I12.9, I13.0, I13.10, I13.11, I13.2, I70.1, I72.2, K76.7, M10.30, M10.311, M10.312, M10.319, M10.321, M10.322, M10.329, M10.331, M10.332, M10.339, M10.341, M10.342, M10.349, M10.351, M10.352, M10.359, M10.361, M10.362, M10.369, M10.371, M10.372, M10.379, M10.38, M10.39, M32.14, M32.15, M35.04, N00.0, N00.1, N00.2, N00.3, N00.4, N00.5, N00.6, N00.7, N00.8, N00.9, N00.A, N01.0, N01.1, N01.2, N01.3, N01.4, N01.5, N01.6, N01.7, N01.8, N01.9, N01.A, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N02.A, N03.0, N03.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N03.8, N03.9, N03.A, N04.0, N04.1, N04.2, N04.3, N04.4, N04.5, N04.6, N04.7, N04.8, N04.9, N04.A, N05.0, N05.1, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N05.8, N05.9, N05.A, N06.0, N06.1, N06.2, N06.3, N06.4, N06.5, N06.6, N06.7, N06.8, N06.9, N06.A, N07.0, N07.1, N07.2, N07.3, N07.4, N07.5, N07.6, N07.7, N07.8, N07.9, N07.A, N08, N13.1, N13.2, N13.30, N13.39, N14.0, N14.1, N14.2, N14.3, N14.4, N15.0, N15.8, N15.9, N16, N17.0, N17.1, N17.2, N17.8, N17.9, N18.1, N18.2, N18.3, N18.30, N18.31, N18.32, N18.4, N18.5, N18.6, N18.9, N19, N25.0, N25.1, N25.81, N25.89, N25.9, N26.1, N26.9, Q61.02, Q61.11, Q61.19, Q61.2, Q61.3, Q61.4, Q61.5, Q61.8, Q62.0, Q62.2, Q62.10, Q62.11, Q62.12, Q62.31, Q62.32, Q62.39, R94.4
Diabetes	ICD-9-CM Dx	249.00, 249.01, 249.10, 249.11, 249.20, 249.21, 249.30, 249.31, 249.40, 249.41, 249.50, 249.51, 249.60, 249.61, 249.70, 249.71, 249.80, 249.81, 249.90, 249.91, 250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 357.2, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 366.41
Diabetes	ICD-10-CM Dx	E08.00, E08.01, E08.10, E08.11, E08.21, E08.22, E08.29, E08.311, E08.319, E08.321, E08.3211, E08.3212, E08.3213, E08.3219, E08.329, E08.3291, E08.3292, E08.3293, E08.3299, E08.331, E08.3311, E08.3312, E08.3313, E08.3319, E08.339, E08.3391, E08.3392, E08.3393, E08.3399, E08.341, E08.3411, E08.3412, E08.3413, E08.3419, E08.349, E08.3491, E08.3492, E08.3493, E08.3499, E08.351, E08.3511, E08.3512, E08.3513, E08.3519, E08.3521, E08.3522, E08.3523, E08.3529, E08.3531, E08.3532, E08.3533, E08.3539, E08.3541, E08.3542, E08.3543, E08.3549, E08.3551, E08.3552, E08.3553, E08.3559, E08.359, E08.3591, E08.3592, E08.3593, E08.3599, E08.36, E08.37X1, E08.37X2,

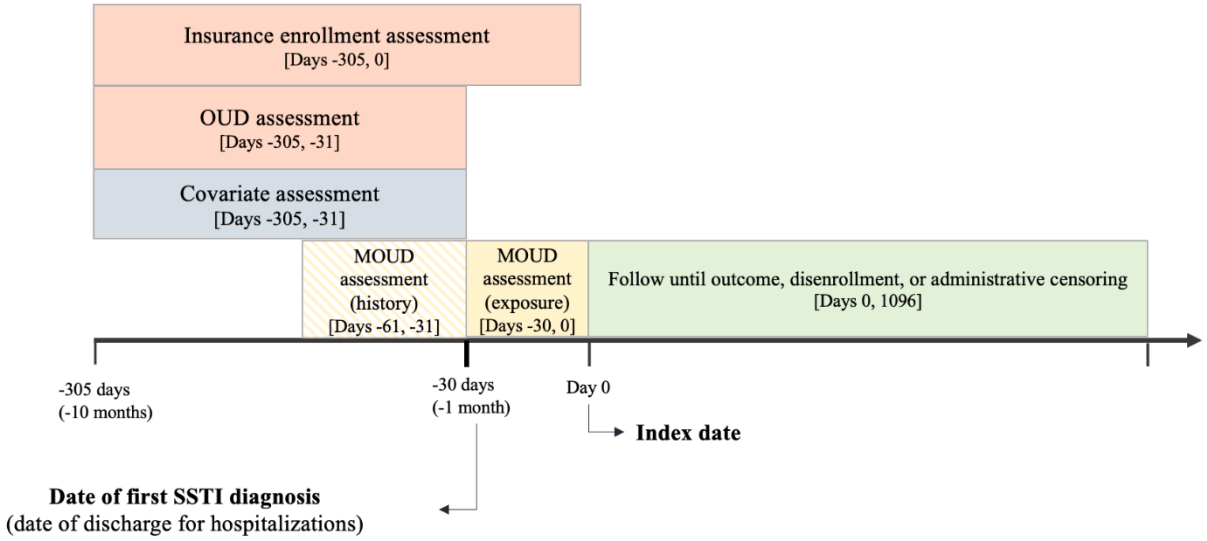
		E08.37X3, E08.37X9, E08.39, E08.40, E08.41, E08.42, E08.43, E08.44, E08.49, E08.51, E08.52, E08.59, E08.610, E08.618, E08.620, E08.621, E08.622, E08.628, E08.630, E08.638, E08.641, E08.649, E08.65, E08.69, E08.8, E08.9, E09.00, E09.01, E09.10, E09.11, E09.21, E09.22, E09.29, E09.311, E09.319, E09.321, E09.3211, E09.3212, E09.3213, E09.3219, E09.329, E09.3291, E09.3292, E09.3293, E09.3299, E09.331, E09.3311, E09.3312, E09.3313, E09.3319, E09.339, E09.3391, E09.3392, E09.3393, E09.3399, E09.341, E09.3411, E09.3412, E09.3413, E09.3419, E09.349, E09.3491, E09.3492, E09.3493, E09.3499, E09.351, E09.3511, E09.3512, E09.3513, E09.3519, E09.3521, E09.3522, E09.3523, E09.3529, E09.3531, E09.3532, E09.3533, E09.3539, E09.3541, E09.3542, E09.3543, E09.3549, E09.3551, E09.3552, E09.3553, E09.3559, E09.359, E09.3591, E09.3592, E09.3593, E09.3599, E09.36, E09.37X1, E09.37X2, E09.37X3, E09.37X9, E09.39, E09.40, E09.41, E09.42, E09.43, E09.44, E09.49, E09.51, E09.52, E09.59, E09.610, E09.618, E09.620, E09.621, E09.622, E09.628, E09.630, E09.638, E09.641, E09.649, E09.65, E09.69, E09.8, E09.9, E10.10, E10.11, E10.21, E10.22, E10.29, E10.311, E10.319, E10.321, E10.3211, E10.3212, E10.3213, E10.3219, E10.329, E10.3291, E10.3292, E10.3293, E10.3299, E10.331, E10.3311, E10.3312, E10.3313, E10.3319, E10.339, E10.3391, E10.3392, E10.3393, E10.3399, E10.341, E10.3411, E10.3412, E10.3413, E10.3419, E10.349, E10.3491, E10.3492, E10.3493, E10.3499, E10.351, E10.3511, E10.3512, E10.3513, E10.3519, E10.3521, E10.3522, E10.3523, E10.3529, E10.3531, E10.3532, E10.3533, E10.3539, E10.3541, E10.3542, E10.3543, E10.3549, E10.3551, E10.3552, E10.3553, E10.3559, E10.359, E10.3591, E10.3592, E10.3593, E10.3599, E10.36, E10.37X1, E10.37X2, E10.37X3, E10.37X9, E10.39, E10.40, E10.41, E10.42, E10.43, E10.44, E10.49, E10.51, E10.52, E10.59, E10.610, E10.618, E10.620, E10.621, E10.622, E10.628, E10.630, E10.638, E10.641, E10.649, E10.65, E10.69, E10.8, E10.9, E11.00, E11.01, E11.10, E11.11, E11.21, E11.22, E11.29, E11.311, E11.319, E11.321, E11.3211, E11.3212, E11.3213, E11.3219, E11.329, E11.3291, E11.3292, E11.3293, E11.3299, E11.331, E11.3311, E11.3312, E11.3313, E11.3319, E11.339, E11.3391, E11.3392, E11.3393, E11.3399, E11.341, E11.3411, E11.3412, E11.3413, E11.3419, E11.349, E11.3491, E11.3492, E11.3493, E11.3499, E11.351, E11.3511, E11.3512, E11.3513, E11.3519, E11.3521, E11.3522, E11.3523, E11.3529, E11.3531, E11.3532, E11.3533, E11.3539, E11.3541, E11.3542, E11.3543, E11.3549, E11.3551, E11.3552, E11.3553, E11.3559, E11.359, E11.3591, E11.3592, E11.3593, E11.3599, E11.36, E11.37X1, E11.37X2, E11.37X3, E11.37X9, E11.39, E11.40, E11.41, E11.42, E11.43, E11.44, E11.49, E11.51, E11.52, E11.59, E11.610, E11.618, E11.620, E11.621, E11.622, E11.628, E11.630, E11.638, E11.641, E11.649, E11.65, E11.69, E11.8, E11.9, E13.00, E13.01, E13.10, E13.11, E13.21, E13.22, E13.29, E13.311, E13.319, E13.321, E13.3211, E13.3212, E13.3213, E13.3219, E13.329, E13.3291, E13.3292, E13.3293, E13.3299, E13.331, E13.3311, E13.3312, E13.3313, E13.3319, E13.339, E13.3391, E13.3392, E13.3393, E13.3399, E13.341, E13.3411, E13.3412, E13.3413, E13.3419, E13.349, E13.3491, E13.3492, E13.3493, E13.3499, E13.351, E13.3511, E13.3512, E13.3513, E13.3519, E13.3521, E13.3522, E13.3523, E13.3529, E13.3531, E13.3532, E13.3533, E13.3539, E13.3541, E13.3542, E13.3543, E13.3549, E13.3551, E13.3552, E13.3553, E13.3559, E13.359, E13.3591, E13.3592, E13.3593, E13.3599, E13.36, E13.39, E13.40, E13.41, E13.42, E13.43, E13.44, E13.49, E13.51, E13.52, E13.59, E13.610, E13.618, E13.620, E13.621, E13.622, E13.628, E13.630, E13.638, E13.641, E13.649, E13.65, E13.69, E13.8, E13.9

Fibromyalgia, chronic pain and fatigue	ICD-9-CM Dx	338.2, 338.21, 338.22, 338.28, 338.29, 338.3, 338.4, 780.7, 780.71, 729.1, 729.2
Fibromyalgia, chronic pain and fatigue	ICD-10-CM Dx	G89.21, G89.22, G89.28, G89.29, G89.3, G89.4, M54.10, M54.11, M54.12, M54.13, M54.14, M54.15, M54.16, M54.17, M54.18, M60.80, M60.811, M60.812, M60.819, M60.821, M60.822, M60.829, M60.831, M60.832, M60.839, M60.841, M60.842, M60.849, M60.851, M60.852, M60.859, M60.861, M60.862, M60.869, M60.871, M60.872, M60.879, M60.88, M60.89, M60.9, M79.1, M79.10, M79.11, M79.12, M79.18, M79.2, M79.7, R53.82
Heart failure	ICD-9-CM Dx	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9
Heart failure	ICD-10-CM Dx	I09.81, I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.810, I50.811, I50.812, I50.813, I50.814, I50.82, I50.83, I50.84, I50.89, I50.9
Liver disease, cirrhosis, and other liver conditions	ICD-9-CM Dx	570, 571, 571.0, 571.1, 571.2, 571.3, 571.5, 571.6, 571.8, 571.9, 572, 572.0, 572.1, 572.2, 572.3, 572.4, 572.8, 573, 573.0, 573.4, 573.5, 573.8, 573.9, 576.1, 789.1, V42.7
Liver disease, cirrhosis, and other liver conditions	ICD-10-CM Dx	K70.0, K70.10, K70.11, K70.2, K70.30, K70.31, K70.40, K70.41, K70.9, K71.0, K71.11, K71.7, K71.8, K71.9, K72.00, K72.01, K72.10, K72.11, K72.90, K72.91, K74.0, K74.00, K74.01, K74.02, K74.1, K74.2, K74.3, K74.4, K74.5, K74.60, K74.69, K75.0, K75.1, K75.81, K75.89, K75.9, K76.0, K76.1, K76.2, K76.3, K76.5, K76.6, K76.7, K76.81, K76.89, K76.9, K77, K80.30, K80.31, K80.32, K80.33, K80.34, K80.35, K80.36, K80.37, K83.0, R16.0, R16.2, Z48.23, Z94.4
Liver disease, cirrhosis, and other liver conditions	ICD-9 Px	42.91, 44.91, 54.91, 96.06
Liver disease, cirrhosis, and other liver conditions	ICD-10 Px	06L20ZZ, 06L23ZZ, 06L24ZZ, 06L30ZZ, 06L33ZZ, 06L34ZZ, 0DL57DZ, 0DL58DZ, 0D9S30Z, 0D9S3ZZ, 0D9S40Z, 0D9S4ZZ, 0D9T30Z, 0D9T3ZZ, 0D9T40Z, 0D9T4ZZ, 0D9V30Z, 0D9V3ZZ, 0D9V40Z, 0D9V4ZZ, 0D9W30Z, 0D9W3ZZ, 0D9W40Z, 0D9W4ZZ, 0W9F30Z, 0W9F3ZZ, 0W9F40Z, 0W9F4ZZ, 0W9G30Z, 0W9G3ZZ, 0W9G40Z, 0W9G4ZZ, 0W9J30Z, 0W9J3ZZ
Traumatic brain injury and nonpsychotic mental health disorders due to brain damage	ICD-9-CM Dx	310, 310.0, 310.1, 310.2, 310.8, 310.81, 310.89, 907, 907.0, 907.1
Traumatic brain injury and nonpsychotic mental health disorders due to brain damage	ICD-10-CM Dx	F07.0, F07.81, F07.89, F48.2, S04.011S, S04.012S, S04.019S, S04.02XS, S04.031S, S04.032S, S04.039S, S04.041S, S04.042S, S04.049S, S04.10XS, S04.11XS, S04.12XS, S04.20XS, S04.21XS, S04.22XS, S04.30XS, S04.31XS, S04.32XS, S04.40XS, S04.41XS, S04.42XS, S04.50XS, S04.51XS, S04.52XS, S04.60XS, S04.61XS, S04.62XS, S04.70XS, S04.71XS, S04.72XS, S04.811S, S04.812S, S04.819S, S04.891S, S04.892S, S04.899S, S04.9XXS, S06.0X0S, S06.0X1S, S06.0X2S, S06.0X3S, S06.0X4S, S06.0X5S, S06.0X6S, S06.0X7S, S06.0X8S, S06.0X9S, S06.1X0S, S06.1X1S, S06.1X2S, S06.1X3S, S06.1X4S, S06.1X5S, S06.1X6S, S06.1X7S, S06.1X8S, S06.1X9S, S06.2X0S, S06.2X1S, S06.2X2S, S06.2X3S, S06.2X4S, S06.2X5S, S06.2X6S, S06.2X7S, S06.2X8S, S06.2X9S, S06.300S, S06.301S, S06.302S, S06.303S, S06.304S, S06.305S, S06.306S, S06.307S,

		S06.308S, S06.309S, S06.310S, S06.311S, S06.312S, S06.313S, S06.314S, S06.315S, S06.316S, S06.317S, S06.318S, S06.319S, S06.320S, S06.321S, S06.322S, S06.323S, S06.324S, S06.325S, S06.326S, S06.327S, S06.328S, S06.329S, S06.330S, S06.331S, S06.332S, S06.333S, S06.334S, S06.335S, S06.336S, S06.337S, S06.338S, S06.339S, S06.340S, S06.341S, S06.342S, S06.343S, S06.344S, S06.345S, S06.346S, S06.347S, S06.348S, S06.349S, S06.350S, S06.351S, S06.352S, S06.353S, S06.354S, S06.355S, S06.356S, S06.357S, S06.358S, S06.359S, S06.360S, S06.361S, S06.362S, S06.363S, S06.364S, S06.365S, S06.366S, S06.367S, S06.368S, S06.369S, S06.370S, S06.371S, S06.372S, S06.373S, S06.374S, S06.375S, S06.376S, S06.377S, S06.378S, S06.379S, S06.380S, S06.381S, S06.382S, S06.383S, S06.384S, S06.385S, S06.386S, S06.387S, S06.388S, S06.389S, S06.4X0S, S06.4X1S, S06.4X2S, S06.4X3S, S06.4X4S, S06.4X5S, S06.4X6S, S06.4X7S, S06.4X8S, S06.4X9S, S06.5X0S, S06.5X1S, S06.5X2S, S06.5X3S, S06.5X4S, S06.5X5S, S06.5X6S, S06.5X7S, S06.5X8S, S06.5X9S, S06.6X0S, S06.6X1S, S06.6X2S, S06.6X3S, S06.6X4S, S06.6X5S, S06.6X6S, S06.6X7S, S06.6X8S, S06.6X9S, S06.810S, S06.811S, S06.812S, S06.813S, S06.814S, S06.815S, S06.816S, S06.817S, S06.818S, S06.819S, S06.820S, S06.821S, S06.822S, S06.823S, S06.824S, S06.825S, S06.826S, S06.827S, S06.828S, S06.829S, S06.890S, S06.891S, S06.892S, S06.893S, S06.894S, S06.895S, S06.896S, S06.897S, S06.898S, S06.899S, S06.9X0S, S06.9X1S, S06.9X2S, S06.9X3S, S06.9X4S, S06.9X5S, S06.9X6S, S06.9X7S, S06.9X8S, S06.9X9S, S06.A0XS, S06.A1XS

APPENDIX B: STUDY DESIGN FIGURE, SUPPLEMENTAL ANALYSES, AND CODE LISTS FOR AIM 2

Supplemental Figure B.1. Study design inclusion criteria and variable measurements.



Supplemental Table B.1. Study population characteristics by year.

Characteristic	2007-2009		2010-2012		2013-2015		2016-2018	
	N=1,276	%	N=2,486	%	N=3,647	%	N=5,877	%
Age Group								
18-34	506	39.7%	1,116	44.9%	1,621	44.4%	2,247	38.2%
35-44	355	27.8%	580	23.3%	850	23.3%	1,387	23.6%
45-54	290	22.7%	512	20.6%	684	18.8%	1,127	19.2%
55+	125	9.8%	278	11.2%	492	13.5%	1,116	19.0%
Sex								
Men	508	39.8%	884	35.6%	1,137	31.2%	1,698	28.9%
Women	768	60.2%	1602	64.4%	2,510	68.8%	4,179	71.1%
Race								
Black	174	14.0%	354	14.5%	487	13.7%	1,007	17.7%
Other	54	4.3%	143	5.8%	258	7.3%	345	6.1%
White	1,017	81.7%	1,952	79.7%	2,806	79.0%	4,343	76.3%
Missing	31		37		96		182	
Combined comorbidity score								
-2 to 1	1,144	89.7%	2,257	90.8%	3,213	88.1%	5,194	88.4%
2 to 4	93	7.3%	156	6.3%	310	8.5%	401	6.8%
5 or more	39	3.1%	73	2.9%	124	3.4%	282	4.8%
Co-occurring substance use disorder	814	63.8%	1,390	55.9%	1,449	39.7%	2,157	36.7%
Alcohol use disorder	277	21.7%	393	15.8%	340	9.3%	608	10.3%
Sedative or hypnotic use disorder	160	12.5%	228	9.2%	167	4.6%	302	5.1%
Stimulant use disorder	289	22.6%	420	16.9%	336	9.2%	948	16.1%

Unspecified or polysubstance use disorder	611	47.9%	1,084	43.6%	1,097	30.1%	1,191	20.3%
Anxiety	277	21.7%	393	15.8%	340	9.3%	608	10.3%
Depression	160	12.5%	228	9.2%	167	4.6%	302	5.1%
Chronic pain	289	22.6%	420	16.9%	336	9.2%	948	16.1%

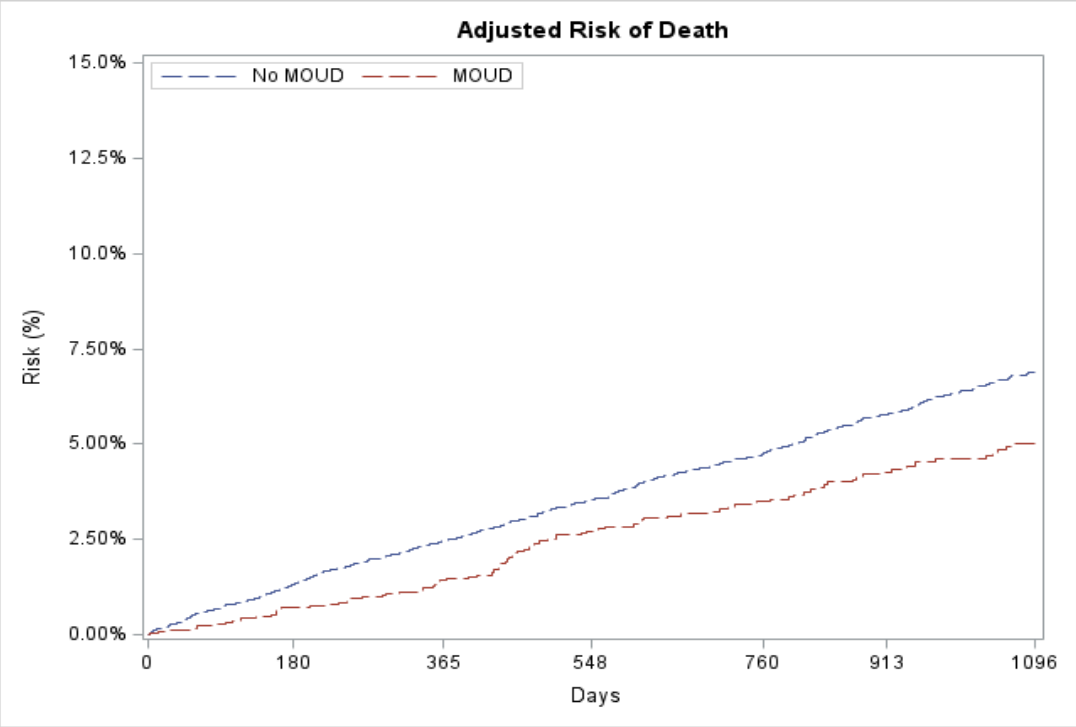
Supplemental Table B.2. Study population characteristics by medication for opioid use disorder (MOUD) use for all people, total population and by MOUD use, regardless of MOUD history in the 30 days prior.

Characteristic	Total		MOUD Use		No MOUD Use	
	N=15,876	%	N=2,522	%	N=13,354	%
Age Group						
18-34	6,949	43.8%	1,417	56.2%	5,532	41.4%
35-44	3,770	23.7%	594	23.6%	3,176	23.8%
45-54	2,944	18.5%	313	12.4%	2,631	19.7%
55+	2,213	13.9%	198	7.9%	2,015	15.1%
Sex						
Men	5,163	32.5%	888	35.2%	4,275	32.0%
Women	10,713	67.5%	1634	64.8%	9,079	68.0%
Race						
Black	2,190	13.8%	175	6.9%	2,015	15.1%
Other	892	5.6%	86	3.4%	806	6.0%
White	12,394	78.1%	2,207	87.5%	10,187	76.3%
Missing	400		54		346	
Year of discharge						
2007-2009	1,673	10.5%	398	15.8%	1,275	9.5%
2010-2012	3,265	20.6%	746	29.6%	2,519	18.9%
2013-2015	4,086	25.7%	396	15.7%	3,690	27.6%
2016-2018	6,852	43.2%	982	38.9%	5,870	44.0%
Length of stay (days)						
1	14,337	90.3%	*		*	
2-7	1,008	6.3%	*		*	
8+	518	3.9%	*		*	
Managed care organization coverage	14,898	93.8%	2,390	94.8%	12,508	93.7%

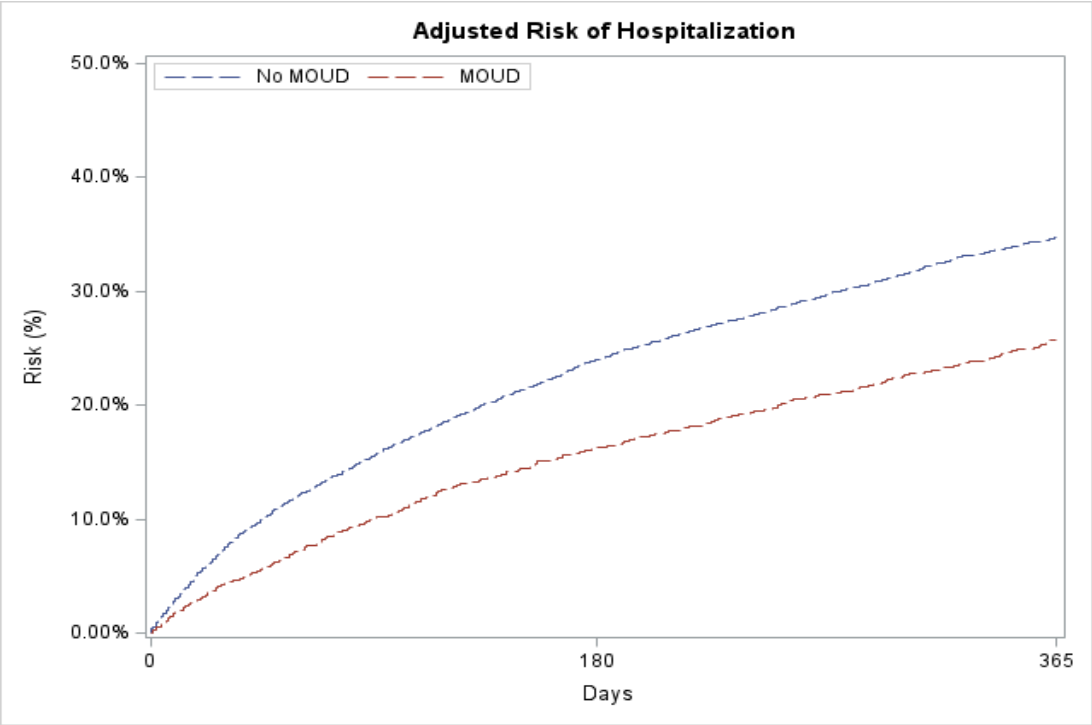
Combined comorbidity score						
-2 to 1	10,204	64.3%	2,094	83.0%	8,110	60.7%
2 to 4	4,048	25.5%	351	13.9%	3,697	27.7%
5 or more	1,624	10.2%	77	3.1%	1,547	11.6%
Co-occurring substance use disorder	6,711	42.3%	874	34.7%	5,837	43.7%
Alcohol use disorder	1,803	11.4%	178	7.1%	1,625	12.2%
Sedative or hypnotic use disorder	975	6.1%	110	4.4%	865	6.5%
Stimulant use disorder	2,261	14.2%	258	10.2%	2,003	15.0%
Unspecified or polysubstance use disorder	4,633	29.2%	633	25.1%	4,000	30.0%
Anxiety	6,407	40.4%	791	31.4%	5,616	42.1%
Depression	6,295	39.7%	786	31.2%	5,509	41.3%
Chronic pain	7,458	47.0%	692	27.4%	6,766	50.7%

*Suppressed due to counts within group of <11.

Supplemental Figure B.2. 3-year risk of mortality by medication for opioid use disorder (MOUD) use for all people, regardless of their MOUD history before SSTI discharge. Curves adjusted for year, age group, length of stay, and combined comorbidity score.



Supplemental Figure B.3. 1-year risk of hospitalization by medication for opioid use disorder (MOUD) use for all people, regardless of their MOUD history before SSTI discharge. Curves adjusted for year, age group, length of stay, and combined comorbidity score.



Supplemental Table B.3. Risk differences and risk ratios for 3-year mortality and 1-year hospitalization by medication for opioid use disorder (MOUD) use or all people, regardless of their MOUD history before SSTI discharge.

	Unadjusted Estimates			Adjusted Estimates*		
Exposure and Outcome Group	Risk, %	Risk Difference, % (95% CI)	Risk Ratio, % (95% CI)	Risk, %	Risk Difference (95% CI)	Risk Ratio (95% CI)
3-Year Mortality						
MOUD use	5.0	-7.0 (-8.2, -5.8)	0.42 (0.34, 0.52)	5.0	-1.9 (-3.1, -0.7)	0.73 (0.58, 0.91)
No MOUD use	12.0	--	--	7.5	--	--
1-Year Hospitalization						
MOUD use	25.8	-16.1 (-18.1, -14.1)	0.62 (0.57, 0.66)	25.8	-9.0 (-11.1, -6.9)	0.74 (0.69, 0.80)
No MOUD use	41.9	--	--	34.9	--	--

*Adjusted for year, age group, length of stay, and combined comorbidity score.

Supplemental Table B.4. Diagnosis-derived variable definitions.

Variable	Code Type	Codes
Skin and soft tissue infections	ICD-9-CM Dx	451, 45111, 45119, 4512, 45181, 45182, 45183, 45184, 45189, 4519, 5283, 56731, 681, 68101, 6811, 68111, 6819, 682, 6821, 6822, 6823, 6824, 6825, 6826, 6827, 6828, 6829, 7236, 72886, 7293, 72939, 7854
Skin and soft tissue infections	ICD-10-CM Dx	A480, I8000, I8001, I8002, I8003, I8010, I8011, I8012, I8013, I80201, I80202, I80203, I80209, I80211, I80212, I80213, I80219, I80221, I80222, I80223, I80229, I80231, I80232, I80233, I80239, I80291, I80292, I80293, I80299, I803, I808, I809, I96, L02, L0201, L0202, L0203, L0211, L0212, L0213, L02211, L02212, L02213, L02214, L02215, L02216, L02219, L02221, L02222, L02223, L02224, L02225, L02226, L02229, L02231, L02232, L02233, L02234, L02235, L02236, L02239, L0231, L0232, L0233, L02411, L02412, L02413, L02414, L02415, L02416, L02419, L02421, L02422, L02423, L02424, L02425, L02426, L02429, L02431, L02432, L02433, L02434, L02435, L02436, L02439, L02511, L02512, L02519, L02521, L02522, L02529, L02531, L02532, L02539, L02611, L02612, L02619, L02621, L02622, L02629, L02631, L02632, L02639, L02811, L02818, L02821, L02828, L02831, L02838, L0291, L0292, L0293, L03, L03011, L03012, L03019, L03021, L03022, L03029, L03031, L03032, L03039, L03041, L03042, L03049, L03111, L03112, L03113, L03114, L03115, L03116, L03119, L03121, L03122, L03123, L03124, L03125, L03126, L03129, L03211, L03212, L03213, L03221, L03222, L03311, L03312, L03313, L03314, L03315, L03316, L03317, L03319, L03321, L03322, L03323, L03324, L03325, L03326, L03327, L03329, L03811, L03818, L03891, L03898, L0390, L0391, M5402, M726, M793
Stimulant use disorder	ICD-9-CM Dx	304.2, 304.4, 305.6, 305.7
Stimulant use disorder	ICD-10-CM Dx	F14, F15
Sedative and hypnotic use disorder	ICD-9-CM Dx	304.1, 305.4
Sedative and hypnotic use disorder	ICD-10-CM Dx	F13
Other and unspecified substance use disorders	ICD-9-CM Dx	292, 304.6, 304.7, 304.8, 304.9, 305.9
Other and unspecified substance use disorders	ICD-10-CM Dx	F19
Alcohol use disorder	ICD-9-CM Dx	291, 303, 305.0
Alcohol use disorder	ICD-10-CM Dx	F10
Anxiety disorder	ICD-9-CM Dx	293.84, 300.00, 300.01, 300.02, 300.09, 300.10, 300.20, 300.21, 300.22, 300.23, 300.29, 300.3, 300.5, 300.89, 300.9, 308.0, 308.1, 308.2, 308.3, 308.4, 308.9, 309.81, 313.0, 313.1, 313.21, 313.22, 313.3, 313.82, 313.83
Anxiety disorder	ICD-10-CM Dx	F06.4, F40.00, F40.01, F40.02, F40.10, F40.11, F40.210, F40.218, F40.220, F40.228, F40.230, F40.231, F40.232, F40.233, F40.240, F40.241, F40.242, F40.243, F40.248, F40.290, F40.291, F40.298, F40.8,

		F40.9, F41.0, F41.1, F41.3, F41.8, F41.9, F42, F42.2, F42.3, F42.4, F42.8, F42.9, F43.0, F43.10, F43.11, F43.12, F44.9, F45.8, F48.8, F48.9, F93.8, F99, R45.2, R45.5, R45.6, R45.7
Depressive disorders	ICD-9-CM Dx	296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.89, 298.0, 300.4, 309.1, 311
Depressive disorders	ICD-10-CM Dx	F31.30, F31.31, F31.32, F31.4, F31.5, F31.60, F31.61, F31.62, F31.63, F31.64, F31.75, F31.76, F31.77, F31.78, F31.81, F32.0, F32.1, F32.2, F32.3, F32.4, F32.5, F32.9, F33.0, F33.1, F33.2, F33.3, F33.40, F33.41, F33.42, F33.8, F33.9, F34.1, F43.21, F43.23
Chronic pain	ICD-9-CM Dx	338.2, 338.21, 338.22, 338.28, 338.29, 338.3, 338.4, 780.7, 780.71, 729.1, 729.2
Chronic pain	ICD-10-CM Dx	G89.21, G89.22, G89.28, G89.29, G89.3, G89.4, M54.10, M54.11, M54.12, M54.13, M54.14, M54.15, M54.16, M54.17, M54.18, M60.80, M60.811, M60.812, M60.819, M60.821, M60.822, M60.829, M60.831, M60.832, M60.839, M60.841, M60.842, M60.849, M60.851, M60.852, M60.859, M60.861, M60.862, M60.869, M60.871, M60.872, M60.879, M60.88, M60.89, M60.9, M79.1, M79.10, M79.11, M79.12, M79.18, M79.2, M79.7, R53.82

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