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INVESTIGATING THE RELATIONSHIPS BETWEEN SOCIOECONOMIC STATUS, KRATOM LEGISLATION, AND THE COVID-19 PANDEMIC ON OPIOID OVERDOSE MORTALITY IN THE UNITED STATES

By

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A Dissertation Approved on

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DEDICATION

This dissertation is lovingly dedicated to my children, Jalon and Lylian. They have sacrificed more than anyone through this journey, and I am grateful to call them mine.
ACKNOWLEDGMENTS

First and foremost, I praise and thank my Lord and savior, Jesus Christ. Without Him I am nothing and this work is meaningless.

I am most grateful to the members of my committee, Dr. Nicholas Peiper, Dr. Kira Taylor, Dr. Bert Little, and Dr. Richard Baumgartner for their time, encouragement and expertise throughout this dissertation journey. A very special thanks to my chair and mentor, Dr. Natalie DuPre. An academic mentor can be defined as a positive role model of a student who supports their mentee by giving academic advice, sharing resources, and caring about their student’s success. Dr. DuPre is that and so much more. Having the opportunity to learn from her has made a substantial, lasting impact on my career and in my life. Our relationship is based on trust, confidentiality, and mutual respect, and without her support I would not be where I am today.

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ABSTRACT

INVESTIGATING THE RELATIONSHIPS BETWEEN SOCIOECONOMIC STATUS, KRATOM LEGALIZATION, AND THE COVID-19 PANDEMIC ON OPIOID OVERDOSE MORTALITY IN THE UNITED STATES

Lyndsey Blair

April 15, 2022

Background

585,000 people have died from an opioid overdose in the US between 1999 and 2020. The current opioid epidemic has been described as a quadruple wave of overdoses, due in part to the changes in prescription and illicit opioid supply as well as the underlying social and structural factors that led to a subsequent increase in demand. In order to mitigate the opioid epidemic through prevention and protection strategies, we must first understand the social and structural factors that are driving the increase in opioid misuse and abuse. To better understand the socioeconomic factors, we described socioeconomic profiles of US counties and examined their associations with rates of opioid overdose mortality in Aim 1. Since the beginning of the epidemic, rates of opioid-related overdose death have differed in rural and urban counties. We examined the association between urban residence and subsequent opioid overdose mortality in Kentucky, a state highly impacted by the opioid epidemic, and whether this association was modified by the COVID-19 pandemic (Aim 2). With the rise in opioid overdose deaths, people have sought out alternative substances that are advertised to have less side effects and lower abuse potential,
such as kratom. Kratom is an herbal extract from evergreen tree leaves indigenous to Southeast Asia that has opiate-like properties. Six states have banned kratom over concerns about its potential for addiction; however, there is no scientific evidence regarding the impact of these laws on the opioid epidemic. Therefore, we examined this association between state-level kratom legislation and opioid overdose mortality across US states (Aim 3).

Methods

In all analyses, opioid overdose mortality was classified using the International Statistical Classification of Diseases, 10th revision (ICD-10). Among deaths with drug overdose as the underlying cause, we captured those specifically involving an opioid analgesic including opium, heroin, prescription opioids (i.e., natural and semisynthetic opioids and methadone), synthetic opioids other than methadone, and other and unspecified narcotics. In a nationwide analysis (Aim 1), we identified patterns of demographic, socioeconomic and housing characteristics in US counties using principal components (PC) analysis and used Poisson regression to estimate adjusted relative risks (RRs) and 95% confidence intervals (CIs) of opioid overdose mortality for a one standard deviation increase in PC scores. We used data from all Kentucky inpatient and outpatient hospitalizations from 2016-2020 to estimate odds ratios (ORs) and 95% CIs of opioid overdose mortality for urban versus rural patients with multivariable logistic regression (Aim 2). Analyses were conducted separately for hospitalizations occurring before the pandemic and during the pandemic (April 2020 or later). Lastly, in Aim 3, we used an interrupted time series (ITS) analysis to estimate the association between state-level legislation banning kratom and opioid overdose mortality in the US.

Results
We found that counties with an extremely disadvantaged socioeconomic profile had the highest rates of prescription opioid mortality (RR=1.17; 95% CI=1.13,1.21), but had inverse associations with illicit opioid mortality (RR=0.93 and 95% CI=0.88, 0.95). Counties with a high percentage of single individuals, high poverty rates and high education had the highest mortality rates from illicit opioids (RR=1.46; 95% CI=1.40, 1.53). Before the pandemic, Kentucky patients living in urban counties had 63% higher odds of opioid overdose death (OR=1.63; 95% CI=1.34, 1.97); however, during the COVID-19 pandemic, patients in urban and rural counties became more similar in regard to opioid overdose mortality (OR=0.72; 95% CI=0.45, 1.16; p-value for interaction =0.02). In regard to state-level legislation banning kratom and opioid overdose mortality, we found that a law banning kratom increased opioid overdose mortality in Indiana (RR=1.09; 95% CI=1.06, 1.12), Vermont (RR=1.11; 95% CI=1.05, 1.17), Wisconsin (RR=1.03; 95% CI=1.00, 1.05), Arkansas (RR=1.10; 95% CI=1.04, 1.15), and Alabama (RR=1.05; 95% CI=1.01, 1.09), but not in Rhode Island (RR=1.05; 95% CI=0.97, 1.13).

Conclusions

In summary, we found that socioeconomic profiles were significantly associated with opioid overdose mortality rates in the US, and these profiles differed depending on the opioids involved. Though prescription and illicit opioid overdoses are closely intertwined, it is important to differentiate the deaths and examine them as distinct epidemics in order to craft more appropriate prevention and response efforts. In regard to urbanicity, we found that before the pandemic, living in urban counties was associated with higher opioid overdose mortality in Kentucky. However, urban and rural differences in opioid overdose mortality washed away during the pandemic, suggesting that the protective mechanisms that were preventing rural overdose deaths prior to the pandemic were no longer preventing rural deaths when the pandemic hit in
2020. Lastly, we observed that public health policy banning kratom that was put into place in an effort to thwart the addictive and dangerous properties of kratom, did not have a significant impact on the opioid epidemic.
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INTRODUCTION

Drug overdose is the leading cause of accidental death in the United States, with the majority resulting from opioids (1). Opioids, including prescription analgesics (e.g., morphine oxycodone), and illicit opioids (e.g., heroin, illicitly manufactured fentanyl) are derivatives of opium and synthetic surrogates that bind to μ-opioid receptors of cells involved in feelings of pain and pleasure (2,3). When opioids attach to the μ-opioid receptor, they block the pain signals sent from the brain to the body and release large amounts of dopamine – a compound responsible for feelings of pleasure (3,4). When these reward processes are activated in the absence of significant pain, they can lead one to misuse and addiction (4). The consumption of an excessive amount of opioids can also lead to respiratory depression and even death (1). More than 585,000 people have died from an opioid overdose in the United States since 1999 (5). In October 2017, the Health and Human Services declared the opioid crisis a public health emergency (6).

History of the Opioid Epidemic

The current opioid epidemic has been described as a quadruple wave of overdoses (7), with the beginning dating back to the 1990s (8). The first wave of the epidemic is attributed to an increase in opioid prescribing by physicians that led to a steady rise in prescription opioid consumption and addiction (9,10). In the 1990s physicians began prescribing opioids for chronic pain and pharmaceutical companies jumped on the opportunity to create more innovative and
potent prescriptions while simultaneously assuring that patients would not become addicted (11). In 1991, there were around 76 million opioid prescriptions written in the United States and by its peak in 2011, there were 219 million prescriptions written, a nearly 200% increase (12). Oxycodone is an opioid analgesic that is used to manage pain, and in 1995, the FDA approved the reformulation of an extended release version of oxycodone, OxyContin®, manufactured by Purdue Pharma (13). The pharmaceutical company successfully marketed and promoted OxyContin®, with an increase in sales from $48 million in 1996 to almost $1.1 billion in 2000 (14). Purdue Pharma misled health care providers, consumers and government officials by claiming that the extended release formulation was “less addictive, less subject to abuse and diversion, and less likely to cause tolerance and withdrawal than other pain medications” (15). Citing studies by Porter and Jick (16), and by Perry and Heidrich (17), Purdue Pharma alleged that the risk of addiction was less than one percent (14). Despite this claim, by 2004, Oxycontin® was the most abused prescription opioid in the United States (18). In order to combat the slow release of OxyContin®, patients would crush and inject or snort the pill, resulting in a rapid release and increased absorption, which greatly increased the risk of fatal overdose (19). This prompted the development, in 2010, of a new formulation that was harder to crush in an effort to prevent abuse (13). Unfortunately, patients found innovative ways to abuse the new formulation or transitioned to other addictive drugs, such as heroin (13).

In an effort to decrease prescription opioid death rates in the United States, the Centers for Disease Control and Prevention (CDC) issued comprehensive guidelines to providers for the prescribing of opioids for chronic pain other than cancer treatment, palliative care, and end-of-life care (20). An increase in the illicit opioid supply to meet the demand that was left in the wake of decreased access to prescription opioids led to the second wave of the epidemic beginning in 2010 (21). After remaining relatively stable for years, heroin overdose deaths
began to rise, increasing by more than 400% from 2010 to 2016 (5). Heroin was readily available and relatively inexpensive, making it a viable alternative to the more expensive and harder to obtain prescription opioid (22).

An increasingly efficient global supply chain and an increase in imported illicitly manufactured synthetic opioids gave way to the third wave of the epidemic, characterized by an increase in deaths involving synthetic opioids; specifically illicitly manufactured fentanyl and fentanyl analogs (10,23). Illicitly manufactured fentanyl entered the US market in 2013 and is currently the opioid responsible for the majority of opioid overdose deaths in the United States (24–26). Fentanyl, traditionally a prescribed opioid analgesic, is much more potent and leads to faster brain uptake than other opioids, which increases its rewarding effects (27). It has been estimated that fentanyl is fifty times more potent than heroin and 100 times stronger than morphine (28). In addition to its potency, fentanyl is also easy to manufacture with low production costs, making it extremely profitable for drug dealers (29). The majority of opioid-related overdose deaths in the US are the result of drugs, including heroin, cocaine, and methamphetamine, that had been adulterated with illicitly manufactured fentanyl, that many users were not aware of (27). According to the CDC, more than 150 people died every day due to a synthetic opioid overdose in 2020 (26).

Though synthetic opioids are still the leading cause of death, the US is grappling with a fourth wave of the epidemic, characterized by an increase in polysubstance use – combining opioids with other drugs such as benzodiazepines, amphetamines, and cocaine (8). The CDC analyzed trends in age-adjusted overdose death rates involving synthetic opioids, psychostimulants, cocaine, heroin, and prescription opioids, and found that the synthetic opioid-involved death rate increased 1,040% from 2013-2019. The psychostimulant-involved death rate increased by 317% during that same time period. In the presence of synthetic opioid
co-involvement, death rates for prescription opioids, heroin, psychostimulants, and cocaine increased. In the absence of synthetic opioid co-involvement, death rates increased only for psychostimulants and cocaine (25).

In addition to the increase in supply, there are social and structural factors behind the demand, that have also contributed to the current opioid crisis that need to be better understood in order to mitigate the epidemic (10). The motivation for this dissertation work is to better understand these social and structural factors through innovative methodology, as well as seeking to understand how the current COVID-19 pandemic has affected the opioid epidemic. In addition, we will evaluate a current public health policy that was aimed at slowing the epidemic to determine its impact.

**Socioeconomic Status**

Socioeconomic status (SES) is an independent risk factor for opioid overdose mortality in the United States (30), and the macrosocial factors of opioid overdose deaths have long been established (9,31,32). SES risk factors for overdose death include middle-aged men and women (31), poverty, insecure housing (32), high rates of unemployment (33), no high school diploma and people who are divorced or separated (34). Low-income communities that have multiple macroeconomic stressors (i.e., high unemployment, poverty, and low education) are disproportionately affected by substance use disorder (SUD) (35). When comparing those with multiple markers of high SES versus low SES (e.g. poverty, education), the risk of opioid overdose mortality was greater among people with markers of lower SES (32). A recent study in Orange County, California (36) found that zip codes with at least 16.86% of the population below the poverty level had a 2.9 fold increased odds of opioid overdose death compared to zip codes with less than 6.35% of the population below the poverty level (mortality ratio 2.90, 95%
CI 1.02, 4.68). The researchers also found that a higher percentage of the population with a Bachelor’s degree or higher, as well as a higher median income had lower odds of opioid overdose mortality (mortality ratio 0.45, 95% CI 0.28, 0.72 and mortality ratio 0.50, 95% CI 0.33, 0.74, respectively) (36).

Studies have shown that communities with greater economic stressors have higher rates of opioid overdose (35). The reasoning behind this trend can be traced, at least to some degree, to macroeconomic factors, including limited access to healthcare, social disadvantages, and economic hardships. These community-level stressors can create an environment of despair that enables and encourages drug use among residents (37). Once drug use is initiated, individuals living in poorer neighborhoods may have a harder time quitting perhaps due to a social network of users, as well as less access to treatment or positive influencers in their lives.

There are different dimensions of disadvantage that operate synergistically with the opioid epidemic. We will use a factor analysis approach to evaluate county-level variation in US socioeconomic patterns that will allow us to observe patterns of socioeconomic variables that are at play in the opioid epidemic as opposed to single markers (e.g., poverty alone).

**Urbanicity**

At the beginning of the opioid epidemic, opioid overdose death rates were higher in urban than in rural areas (38). By 2004, opioid overdose rates in rural counties were similar to rates in urban counties (35,38,39). This trend continued until 2007, when rural counties surpassed urban counties for opioid overdose deaths (39). However, the rise of illicitly manufactured opioids reversed this trend, and by 2016, opioid overdose rates were once again highest among urban counties (39,40).
The opioid epidemic has taken different forms in urban and rural America (41). The urban opioid epidemic has been a crisis of predominately heroin and illicitly manufactured opioids, whereas the rural epidemic is characterized by deaths largely involving natural and semisynthetic opioids (i.e., prescription opioids) (39,42). There are many factors that influence the differences in opioid overdose mortality rates between urban and rural counties, including socioeconomic differences, health-related behaviors, and access to health care services (40). Residents of rural areas in the US tend to be more economically challenged and in poorer health than their urban counterparts, with rural residents in the South, including Kentucky, experiencing some of the worst health outcomes (43). In rural counties, opioid mortality rates are strongly influenced by economic distress, whereas opioid supply factors are more strongly associated with opioid mortality rates in urban counties (44).

COVID-19 Pandemic

The current COVID-19 pandemic has placed a greater risk of death on an already vulnerable population struggling with opioid use disorder (45). Social isolation (46), loneliness (47), economic distress, mental stress, and decreased access to healthcare and treatment services increase the risk of opioid use and overdose mortality (40,48–50), all of which have been heightened during the COVID-19 pandemic (51). Escalating substance use may be a common social response to traumatic events especially when experienced by people with lower socioeconomic status (52). A study on alcohol use and binge drinking after Hurricanes Katrina and Rita found that people of lower income were particularly vulnerable to the stressors that result from disaster (49). People who used heroin in a deindustrialized steel production area of Pennsylvania cited economic hardship, social isolation, and hopelessness as reasons for drug use, explicitly calling for jobs and community reinvestment to reduce overdoses (50). A study measuring the impact of the COVID-19 lockdown on workers’ economic hardship and mental
health found that individuals that experienced an instant loss of income during the lockdown was associated with a 33.2% higher risk of feeling depressed compared to those that maintained their income (53).

These stressors from the COVID-19 pandemic could push someone who is in recovery into relapse or trigger individuals in a high-risk group to initiate substance use, as well as increase the incidence of substance use among the general population (51). In addition, social distancing to prevent the spread of the coronavirus may lead to more individuals using drugs alone, raising the risk of overdose death because no one is present to intervene, either with Narcan or social support, or bystanders may be reluctant to intervene for fear of contracting coronavirus (54,55). Social isolation, economic distress, mental stress, and decreased access to healthcare and treatment services during the pandemic has caused unparalleled stress among many individuals, and the pandemic is in many ways a perfect storm for those struggling with addiction. This dissertation work will evaluate whether the COVID-19 pandemic has modified the relationship between urbanicity and opioid overdose mortality.

**Kratom**

With the rise in opioid overdose deaths, patients previously using prescription and illicit opioids have sought out alternative substances that are advertised to have less side effects and lower abuse potential (56). One such alternative substance is kratom. Kratom (*Mitragyna speciosa*), an evergreen tree indigenous to Southeast Asia, was first described in 1839 by the botanist Pieter Willem Korthal. Kratom leaves were traditionally brewed into a tea or chewed by laborers in parts of Asia to increase productivity (57). At low doses of 1-5 grams, kratom provides mild stimulant effects, but as the dose increases analgesic and opioid-like effects can
occur (58,59). Reports of users feeling “high” after consumption led to increasing popularity and in 1946, the substance was legally banned in Thailand and other parts of Asia (60).

Kratom was introduced in the United States in the early 2000’s (57) and is regulated as an herbal supplement under US Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA) policies (58). According to SAMSHA’s 2020 Annual National Report, 2.1 million people used kratom in the past year (61). The percentage was lower among adolescents aged 12 to 17 (0.2 percent or 48,000 people) than among young adults aged 18 to 25 (0.9 percent or 286,000 people) or adults aged 26 or older (0.8 percent or 1.8 million people) (61). Emerging reports of kratom use in the US and Europe suggest a considerable abuse potential with adverse health effects (62). Kratom was evaluated using the FDA’s Public Health Assessment via Structural Evaluation (PHASE) methodology – a 3-D computer technology tool that simulates how the chemical constituents of a substance are structured at a molecular level and how they will affect the body and brain. The model found that 22 of the 25 compounds in kratom bind to μ-opioid receptors and 2 of the top 5 most prevalent compounds (mitragynine and 7-hydroxy-mitragynine) are known opioid agonists (56,63). However, there are noted differences between kratom and opioids. Kratom does not generally produce the same euphoric effects and is relatively less likely to cause fatal overdose, even at high doses, compared to opioids (64).

Kratom leaves can be chewed, smoked, or ground to powder and prepared as a tea or taken orally (65). It is marketed as an herbal supplement (66) and sold at gas stations, convenience stores, head shops and over the internet (65). Kratom is increasingly used to self-treat opioid dependence and is not detected by commercial drug screens (66,67). A study of treatment-seeking individuals with a history of substance use disorder found that 68.9% of these individuals used kratom to wean off of or as a substitute for heroin and other opioids and
more than 40% also used it to bypass a drug test (65). Kratom is also easier to obtain than illicit opioids and is more cost-effective (65). In August 2016, the DEA announced its plan to add kratom to the list of Schedule I Substances (58); other drugs on this list are heroin, marijuana, lysergic acid diethylamide (LSD), and ecstasy (57). Amidst a public outcry of supporters who claimed that kratom had helped them manage opioid addiction withdrawals and chronic pain, the DEA placed a temporary hold on the ban pending further scientific research. The DEA has listed kratom on its Drugs and Chemicals of Concern list while awaiting more convincing data on the addictive properties and/or health hazards to become available (68). Despite its current legal status, a handful of states including Alabama, Arkansas, Wisconsin, Indiana, Rhode Island and Vermont, have banned the sale and possession of kratom (58); however, the impact of these bans on the opioid epidemic have not been evaluated.

To summarize, given the steep rise in opioid overdose deaths due to aggressive and misleading promotion by pharmaceutical companies, combined with an influx of cheaper illicit opioids such as heroin and fentanyl, this dissertation seeks to further understand the role that social and structural factors may play on the opioid epidemic. This work will focus on investigating the relationships between socioeconomic status (Aim 1), urbanicity and the COVID-19 pandemic within Kentucky hospitalizations (Aim 2), and kratom legislation (Aim 3) on opioid overdose mortality within the United States.
AIM 1: SOCIOECONOMIC STATUS PATTERNS IN RELATION TO OPIOID OVERDOSE MORTALITY RATES IN UNITED STATES COUNTIES, 2010-2019

Objectives: To describe socioeconomic profiles in US counties and examine their associations with rates of opioid overdose mortality.

Methods: We identified patterns of demographic, socioeconomic and housing characteristics in US counties using principal components (PC) analysis. County opioid overdose mortality rates involving prescription opioids and illicit opioids during 2010-2019 were obtained. We used Poisson regression to estimate adjusted relative risks (RRs) and 95% confidence intervals (CIs) of opioid overdose mortality for a one standard deviation increase in PC scores.

Results: Counties with an extremely disadvantaged profile had the highest rates of prescription opioid mortality (RR=1.17; 95% CI=1.13,1.21), but had inverse associations with illicit opioid mortality (RR=0.93 and 95% CI=0.88, 0.95). Counties with a high percentage of single individuals, high poverty rates and high education had the highest mortality rates from illicit...
opioids (RR=1.46; 95% CI=1.40, 1.53) and were not associated with prescription overdose deaths (RR= 1.01 95% CI 0.96, 1.05).

Conclusion: Socioeconomic profiles differed for counties with higher prescription opioid deaths compared to illicit opioid deaths. Distinct prevention strategies are needed to prevent deaths from prescription opioids versus illicit opioids.
Introduction

Opioid-involved overdose deaths have increased over 600% since 1999 (5). In 2019 alone, nearly 50,000 people died from an opioid overdose (25). The current opioid epidemic has been described as a quadruple wave of overdoses (7). The first wave is attributed to an increase in opioid prescribing by physicians that led to a steady rise in prescription opioid consumption and addiction (9,10). In an effort to decrease prescription opioid death rates in the United States, the Centers for Disease Control and Prevention (CDC) issued comprehensive guidelines to providers for the prescribing of opioids for chronic pain other than cancer treatment, palliative care, and end-of-life care (20). An increase in the illicit opioid supply to meet the demand was left in the wake of decreased access to prescription opioids and led to the second wave of the epidemic, characterized by escalating heroin deaths (21). An increasingly efficient global supply chain and an increase in imported illicitly-manufactured synthetic opioids (e.g., illicitly manufactured fentanyl) gave way to the third phase of the epidemic (10). Though synthetic opioids are still the leading cause of death, the US is grappling with a fourth wave of the epidemic, characterized by an increase in polysubstance use – combining opioids with other drugs such as benzodiazepines, amphetamines, and cocaine (8).

Socioeconomic status (SES) is an independent risk factor for opioid overdose mortality in the United States (30), and the macrosocial factors of opioid overdose deaths have long been established (9,31,32). SES risk factors for overdose death include middle-aged men and women (31), poverty, insecure housing (32), high rates of unemployment (33), no high school diploma and people who are divorced or separated (34). Low-income communities that have multiple macroeconomic stressors (i.e., high unemployment, poverty, and low education) are disproportionately affected by substance use disorder (SUD) (35).
Deaths involving prescription and illicit opioids involve complex interrelated socioeconomic components. The purpose of the present study is to evaluate county-level variation in US socioeconomic patterns and to analyze differential opioid overdose mortality rates for different classes of opioids across US counties.

Methods

Data Sources

Outcome: County Opioid Overdose Mortality Rates

This ecological study of the United States examined the association of county-level SES patterns with county-level opioid overdose mortality rates between 2010-2019. The annual opioid overdose mortality rates in each county from 2010 to 2019 were abstracted using the CDC Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database on multiple cause-of-death of US residents (34). Opioid overdose mortality was classified with the International Statistical Classification of Diseases, 10th revision (ICD-10; Geneva, Switzerland: World Health Organization; 1992) underlying cause of death codes X40-X44 (unintentional), X60-X64 (suicide), X85 (homicide) and Y10-Y14 (undetermined intent). Among deaths with drug overdose as the underlying cause, we captured those specifically involving an opioid analgesic using the following ICD-10 cause-of-death codes: T40.0 (opium), T40.1 (heroin), T40.2 (natural and semisynthetic opioids), T40.3 (methadone), T40.4 (synthetic opioids other than methadone), and T40.6 (other and unspecified narcotics). The primary outcome of interest was overdose deaths of any intent involving prescription opioids, using the Centers for Disease Control and Prevention’s (CDC) recommendation for quantifying prescription opioid overdoses as deaths involving natural and semisynthetic opioids (i.e., T40.2) and methadone (i.e., T40.3) (21,69), (i.e., prescription overdose deaths [POD]). The secondary outcome of interest was
overdose deaths of any intent involving illicit and synthetic opioids other than methadone: *ICD-10* codes T40.0, T40.1 and T40.4 (i.e., illicit overdose deaths). Lastly, we examined overdose deaths of any intent involving all opioids: *ICD-10* codes T40.0-T40.4, and T40.6.

In this analysis, we excluded 1 county with missing information on opioid overdose mortality. We also excluded 6 counties that had either been joined with another county (n=4) or renamed and assigned a new FIPS code (n=2) during the study period.

*Exposure and Covariates from the American Community Survey*

The American Community Survey (ACS) is an annual survey on demographic, social, economic, and housing factors conducted by the US Census Bureau from a large sample of US addresses (70). We linked the county-level 5-year estimates for 2015-2019 ACS characteristics to the county-level opioid overdose mortality rates. County-level demographic and social factors considered were age, race, ethnicity, marital status, educational attainment, grandparent responsibility for grandchildren, family structure, and physical disability. Economic factors evaluated included income inequality and poverty, health insurance coverage, and employment. Housing information included residential stability and vacant housing.

*Statistical Analyses*

Counties with death counts <20 were included in the suppressed/unreliable category; counties with death counts ≥20 were divided into tertiles based on their mortality rates per 100,000. The crude relationship between prescription opioid mortality rate categories (i.e., suppressed or unreliable, Tertile 1, Tertile 2 and Tertile 3) and 37 socioeconomic variables are presented in Supplemental Table 1.1. Bivariate intercorrelation patterns of 37 socioeconomic variables were computed using Pearson correlation coefficients, with many significantly correlated with one other (Supplemental Table 1.2). Strong variable intercorrelations prompted
the use of the principal component analysis (PCA) to identify a reduced set of socioeconomic patterns across 3,140 US counties. Poisson regression was used to estimate the associations between the socioeconomic principal component (PC) scores with opioid overdose mortality rates.

**Principal Component Analysis (PCA)**

PCA is a data reduction technique frequently used in neighborhood-level research (71). We chose PCA for this study because we sought to reduce the dimensionality of the 37 county-level socioeconomic variables and provide an empirical summary of the total variance explained by these variables. We conducted the PCA in SAS version 9.4 (SAS Institute Inc, Cary, NC) using PROC FACTOR to generate statistically uncorrelated PC scores that reflect patterns of social and economic variables. We used a scree plot and a threshold of 75% of cumulative variation explained to select the number of PCs to include in subsequent outcome analyses. For easier interpretation of the PCs, we selected a reduced set of 11 SES variables to include in the PCA based on data observations from Table 1.1 and a review of the literature to include SES variables most relevant to opioid overdose (9,31,32,72–74). The variables included in the PCA were the percentage of the county’s population: living below the poverty line, who were disabled, who have a bachelor’s degree or higher, who had a different residence from last year, who are receiving public health insurance, the percentage who are employed, the percentage of grandparents responsible for their grandchildren that are less than 18 years of age, the percentage of vacant housing units, the percentage of males and females aged 15 and older that have never been married, as well as the GINI index of income inequality (Table 1.2). We examined the factor loadings and labeled each PC according to the variables with the largest absolute value of the coefficients.
We mapped quintiles of the PC scores in ArcGIS to visualize the geospatial distribution of the socioeconomic PC scores across the United States, which health officials may find useful to find their counties’ score for the identified PC patterns (Figure 1.1).

**Outcome Analysis**

We used Poisson regression for count data to estimate relative risks (RRs) and 95% confidence intervals (CIs) for a 1-standard-deviation increase in each county-level PC z-score with a scaled deviance to account for overdispersion. The county’s opioid overdose mortality count was the dependent variable, and we included the natural log of county population size as the offset term. All Poisson regression models were adjusted to account for confounding by population size; to account for residual confounding, we included a quadratic term for population size. Adjustment variables included county median age, percentage of the county that was White, percentage of females in the county, and percentage of the county that were non-Hispanic. There were 1,535 counties with suppressed death counts because the annual number of opioid overdose deaths were <10 for the years 2010-2019. These counties were assigned a value of 1 for inclusion in the Poisson regression analysis. In the main analyses, counties with small counts <20 opioid deaths were included in the statistical analyses. As a sensitivity analysis, analyses were restricted to counties with more than 20 opioid overdose mortality cases (n=1,406). All statistical analyses were done in SAS version 9.4.

**Results**

In the United States, the median prescription opioid overdose mortality rate was 3.6 per 100,000 people (IQR=1.19, 7.67). Compared with low prescription opioid overdose counties, counties with the highest prescription opioid overdose rates were slightly older with a larger White population, higher proportion of grandparents responsible for grandchildren, more
disabled individuals, higher frequency of never married individuals who tended to live below the poverty level and were less likely to have a bachelor’s degree or higher (Table 1.1).

**Principal Component Results**

Four principal components explained 76.8% of the variation in eleven county-level socioeconomic factors (Table 1.2) and were the location of the elbow in the scree plot (Supplemental Figure 1.1). High PC1 scores were correlated with lower education (bachelor’s degree or higher, \( \rho = -0.715 \)), high disability (\( \rho = 0.847 \)), lower employment (\( \rho = -0.886 \)), higher public health insurance (\( \rho = 0.877 \)), higher poverty (\( \rho = 0.738 \)), higher vacant housing (\( \rho = 0.477 \)), higher grandparents responsible for grandchildren (\( \rho = 0.436 \)), and higher income-inequality (\( \rho = 0.412 \)). Counties with high PC1 scores have socioeconomic factors related to extreme disadvantage. Counties in the highest quintile of PC1 scores were distributed in the Appalachian region, the South and parts of the Northeast (Figure 1.1a).

High PC2 scores occurred in counties with a high proportion of never-married males (\( \rho = 0.893 \)) and females (\( \rho = 0.902 \)), high income inequality (\( \rho = 0.586 \)), high poverty (\( \rho = 0.529 \)), high residential instability (\( \rho = 0.469 \)), higher education (bachelor’s degree or higher, \( \rho = 0.292 \)). High PC2 scores indicate a profile of single individuals that have never been married, living below the poverty line with high income inequality, but have higher education than other poor counties. Counties in the highest quintile of PC2 were distributed along the southern half of the US, with clusters on the east and west coast (Figure 1.1b).

High PC3 scores were in counties with a higher proportion of grandparents responsible for grandchildren (\( \rho = 0.675 \)), residential instability (\( \rho = 0.416 \)) and lower percentage of vacant housing (\( \rho = -0.488 \)). High PC3 scores indicate a profile of grandparents responsible for
grandchildren with residential instability. Counties in the highest quintile of PC3 were distributed heterogeneously throughout the US (Figure 1.1c).

High PC4 scores were correlated with counties with high residential instability ($p=0.706$), high vacant housing ($p=0.388$), yet at least a bachelor’s degree ($p=0.284$). High PC4 scores show the pattern of educated individuals with a different address from last year. Counties in the highest quintile were mainly in the western and northeastern US (Figure 1.1d).

**Outcome Poisson Regression Results**

**Prescription Opioid Overdose Mortality**

Results are presented in Figure 1.2 and Supplemental Table 1.4. Extreme disadvantage (PC1) was significantly associated with higher prescription opioid overdose mortality rates in the unadjusted (RR=1.15 per SD increase; 95% CI=1.12, 1.18; Supplemental Table 1.4) and adjusted models (RR=1.17; 95% CI=1.13,1.21). A high percentage of single males and females, in poverty with high income inequality, yet educated (PC2) was not associated with prescription opioid overdose death rates after adjusting for confounders (RR=1.01; 95% CI=0.96, 1.05). A high percentage of grandparents raising grandchildren with high residential stability (PC3) showed a 5% increased rate of prescription overdose mortality (RR=1.05; 95% CI=1.02, 1.09), even after adjusting for confounders (RR=1.05; 95% CI=1.00, 1.10). Counties characterized by a high percentage of individuals with a bachelor’s degree or higher with a different address from last year (PC4), also showed a higher prescription opioid overdose mortality rate (RR=1.10; 95% CI=1.07, 1.13), though results were slightly attenuated after adjustments (RR=1.07; 95% CI=1.04, 1.11) (Figure 1.2). Results for PC1 remained positively associated with prescription opioid overdose death rates (RR=1.33; 95% CI 1.27, 1.39) when restricting to counties with at least 20 reported prescription opioid overdose deaths, and showed non-statistically significant
associations for PC2, PC3 and PC4 scores and prescription opioid overdose mortality rates (Supplemental Table 1.3).

Regarding demographics, the greatest rates of prescription opioid overdose deaths were seen in county populations with a higher percentage of females (RR=1.17 per SD increase; 95% CI=1.11, 1.23; Table 1.3), as well as a higher percentage of non-Hispanics (RR=1.11; 95% CI=1.08, 1.14; Table 1.3), and a higher proportion of whites (RR=1.11; 95% CI=1.08, 1.15; Table 1.3). Counties with older median age of the county population was not associated with increased prescription opioid overdose mortality rates (RR=0.99 per SD increase; 95% CI=0.94, 1.05) (Supplemental Table 1.4).

**Illicit Opioid Overdose Mortality**

In the analyses of illicit opioid deaths, the association of PC scores and deaths were different than what was observed for prescription opioid overdose deaths (Figure 1.2). Extreme disadvantage (PC1) was associated with lower illicit opioid overdose death rates (RR=0.93 per SD increase; 95% CI=0.90, 0.96). However, a high percentage of single adults, in poverty with high income inequality, yet educated (PC2) was significantly associated with higher illicit overdose deaths in both the unadjusted (RR=1.13; 95% CI=1.10, 1.17; Supplemental Table 1.4) and adjusted models (RR=1.46; 95% CI=1.40, 1.53; Figure 1.2). A high percentage of grandparents raising grandchildren with high residential stability (PC3) was also associated with higher rates of illicit opioid overdoses (RR=1.13; 95% CI=1.08, 1.19); whereas a high percentage of individuals with a bachelor’s degree or higher with a different address from last year (PC4) had lower illicit opioid overdose mortality rates (RR=0.82; 95% CI=0.79, 0.84).

**All Opioid Overdose Mortality**

The analysis of all opioid overdose deaths included prescription (T40.2-T40.3) and illicit opioids (T40.0, T40.1 & T40.4), as well as those coded as other and unspecified opioids (T40.6).
Extreme disadvantage (PC1) was significantly associated with higher overdose rates, though the results were attenuated compared to deaths from prescription opioids (RR=1.03 per SD increase; 95% CI=1.00, 1.07; Figure 1.2). However, a high percentage of single adults, in poverty with high income inequality, yet educated (PC2) had higher deaths when illicit opioids were included, compared to prescription opioids (RR=1.28; 95% CI=1.23, 1.33). A high percentage of grandparents raising grandchildren with high residential stability (PC3) showed an 8% increased risk of mortality (RR=1.08; 95% CI=1.03, 1.12), and counties characterized by a high percentage of individuals with a bachelor’s degree or higher with a different address from last year (PC4) had lower mortality rates (RR=0.89; 95% CI=0.86, 0.92) (Supplemental Table 1.4).

**Discussion**

In summary, the four most prominent socioeconomic profiles derived from the PCA were generally geographically dispersed throughout the United States, with extremely disadvantaged counties being observed in nearly every region of the United States. Counties scoring high on the extremely disadvantaged county-level socioeconomic profile were significantly associated with higher prescription overdose rates. County-level risk factors for prescription overdose mortality included low education, high disability, low employment, high public health insurance, high poverty, high vacant housing, high grandparents responsible for grandchildren, and high income-inequality. Counties scoring high on the single adult, high poverty, high income inequality, yet educated were associated with illicit opioid overdose mortality. County-level risk factors for deaths involving illicit opioids were a high proportion of never married males and females, high income inequality, high poverty, high residential instability, high education (bachelor’s degree or higher), and a lack of an association between grandparents raising grandchildren. There are different dimensions of disadvantage that operate synergistically with the opioid epidemic. Using a factor analysis approach allowed us to
observe patterns of socioeconomic variables that are at play in the opioid epidemic as opposed to single markers (e.g., poverty alone). Interventions should be considered within local contexts that address the variables outlined in each profile.

PC1 had a high proportion of disabled citizens that the other PC scores did not have. Prescription opioids are a necessary and effective treatment for chronic and acute pain, and though most people use these medications appropriately, more than 20% misuse their medication (75–77). Adults with disabilities have 1.5 times higher risk of misusing opioids for pain and a 40% decreased risk of receiving treatment for prescription opioid use than adults without a disability (78). This could be leading to the higher rates of prescription opioid deaths in counties with a high proportion of disabled citizens.

One of the main differences between PC1 and PC2 is the importance of the high proportion of single males and females in PC2 that is not observed with other PC scores. There are documented benefits of having a spouse, including behavioral, physical, and economic benefits (79), that may be contributing to the higher rates of illicit opioid overdose deaths in counties with a high proportion of single males and females (Figures 1.2b and 1.2c). Being in a relationship limits the amount of time spent alone (47) or socially isolated that increase the risk of lethal opioid overdoses, especially due to illicit opioids (80).

In response to the growing number of deaths due to opioids, policymakers focused their attention on strengthening the laws governing opioid prescribing practices and reducing prescriptions written for opioids (31). As a result, the number of opioid prescriptions decreased by 13% nationally from 2012-2015, yet the opioid overdose death rate continued to rise (31). The observed risk and protective factors in this study could help explain the differences in prescription opioid overdose mortality rates observed across the country that have not been
impacted by laws governing prescribing practices. Opioid overdose death rates under both
definitions (prescription versus illicit) remain alarmingly high, and understanding the
socioeconomic factors associated with opioid overdose mortality is necessary for describing
effective public health strategies to prevent deaths involving prescription and illicit opioids (21).

The findings of this report are subject to several limitations. First, this was an ecologic
study of county-level data subject to ecologic fallacies because the socioeconomic profiles of the
individual overdose death cases are not known. Second, death certificates were used to identify
causes of death from opioid overdoses that may not fully capture classes of opioids involved. In
approximately 20% of all overdose deaths, the drug is not specified and therefore these deaths
are coded as other and unspecified narcotics (T40.6), which can lead to an underestimation of
the type of opioid-involved deaths (21). Also, in almost half of all overdose deaths, multiple
drugs are involved (81). Therefore, opioids may not have been the only drug involved, or
multiple opioids may have been involved in some deaths. We also do not know if the individuals
that died as a result of prescription opioids were prescribed these medications and using them
as prescribed, or using them inappropriately, or if they were purchased illegally. Third, we
included deaths involving synthetic opioids other than methadone (i.e., T40.4) in the illicit
opioids definition even though deaths involving other synthetic opioids, like tramadol, are also
included. However, the overwhelming majority of overdose deaths in this category are
attributed to illicitly manufactured fentanyl (21,24,82). We also conducted an analysis that
included T40.4 in the prescription opioid definition and the results more closely resembled the
associations of illicit opioids than prescription opioids. Illicitly manufactured fentanyl and
analogs do not have their own ICD code; however, a new code has been introduced (i.e.,
T40.411) that can be used in future studies. Lastly, there were 1,535 counties with suppressed
prescription opioid overdose death counts and 457 counties with prescription opioid overdose
death counts between 10 and 19, inclusive, that were included in the analyses. We assigned a
value of 1 to each county with suppressed counts, which may be an under or over
representation of death in those counties leading to outcome measurement error. However, a
sensitivity analysis that included only counties with death counts of 20 or more were similar to
the primary analysis findings.

A major strength of this study is that we considered various classes of opioid overdose
deaths for nearly all US counties. Deaths from fentanyl, whether pharmaceutical or illicitly
manufactured, are coded under T40.4 (21,69), and have been traditionally included in the
prescription opioid definition. However, in this analysis, these T40.4 deaths were not included in
the prescription opioid overdose definition as there is increasing evidence (21,24,82), including
from this study, that the high proportion of fentanyl overdose deaths in recent years is
predominantly due to illicitly manufactured fentanyl as opposed to prescription fentanyl; and,
the fentanyl epidemic is operating distinctly from the prescription opioid epidemic (23). Using
this more recent conservative approach that separates T40.4 codes from other prescription
opioids (T40.2-T40.3) likely provided a more accurate representation of deaths involving
prescription opioids.

Public Health Implications

Although prescription and illicit opioid overdoses are closely intertwined (81,83), it is
important to differentiate the deaths and examine them as distinct epidemics in order to craft
more appropriate prevention and response efforts. Socioeconomic county profiles were
significantly associated with opioid overdose mortality rates in the US, and these profiles
differed depending on the opioids involved. These risk factor profiles may help federal and state
agencies as well as local health departments tailor prevention strategies to curb the opioid
epidemic depending on the different socioeconomic profiles of their county. Our study contributes to the ongoing efforts to strengthen the opioid response and enhance public health interventions targeted at specific high-risk groups.
The overall objective of this dissertation is to describe the underlying structural and social factors that are driving the increase in opioid overdose mortality. In the preceding chapter we described the socioeconomic factors at the population level that are acting synergistically with each other to fuel the opioid crisis. Since the beginning of the epidemic, rates of opioid-related overdose death have differed in rural and urban counties, due in part to the socioeconomic patterns that were explained in the previous chapter. Where one lives has the ability to reinforce or exacerbate these social determinants of health. The following chapter focuses on the study of the opioid epidemic in relation to urbanicity within Kentucky counties.

Residents of rural areas in the US tend to be more heavily burdened by the socioeconomic risk factors of opioid overdose mortality and exhibit poorer health than their urban counterparts, with rural residents in the South, including Kentucky, experiencing some of the worst health outcomes (43). In rural counties, opioid mortality rates are strongly influenced by distinct individual and structural factors, including economic distress, whereas opioid supply factors are more strongly associated with opioid mortality rates in urban counties (44).

The COVID-19 pandemic has heightened many of the individual stressors already known to increase opioid use and overdose. In addition to estimating the association between urbanicity and opioid overdose mortality, we will investigate whether this relationship was modified by the COVID-19 pandemic.
AIM 2: RESIDENCE IN URBAN OR RURAL COUNTIES IN RELATION TO OPIOID OVERDOSE MORTALITY IN KENTUCKY BEFORE AND DURING THE COVID-19 PANDEMIC

Objectives: At the beginning of the opioid epidemic, death rates were higher in urban than in rural areas. We examined the association between residence in an urban or rural county and subsequent opioid overdose mortality in Kentucky, a state highly impacted by the opioid epidemic, and whether this was modified by the COVID-19 pandemic.

Methods: We captured hospitalizations in KY from 2016 to 2020, involving an opioid using ICD-10-CM codes T40.0-T40.4 and T40.6. Patient’s county was classified as urban or rural based on the NCHS Urban-Rural Classification Scheme. Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of opioid overdose mortality, adjusted for demographics, hospitalization severity, and zip code SES. We assessed effect modification by the COVID-19 pandemic.
Results: Overall, patients living in urban counties had 46% higher odds of opioid overdose death than patients residing in rural counties (OR=1.46; 95% CI=1.22, 1.74). Before the pandemic, patients in urban counties had 63% increased odds of opioid overdose death (OR=1.63; 95% CI=1.34, 1.97); however, during the COVID-19 pandemic, patients in urban and rural counties became more similar in regard to opioid overdose mortality (OR=0.72; 95% CI=0.45, 1.16; p-value for interaction =0.02).

Discussion: Before the pandemic, living in urban counties was associated with higher opioid overdose mortality among KY hospitalizations; however, the COVID-19 pandemic evened the playing field, despite a continued rise in overdose deaths. COVID-19 posed social, economic, and healthcare challenges that may be contributing to worsening mortality trends affecting both urban and rural patients.
Introduction

In 2020, there were more than 70,000 opioid-related overdose deaths in the US, a 37% increase from 2019 (26). The opioid epidemic includes deaths from prescription opioids as well as deaths from illegal opioids such as heroin and illicitly manufactured fentanyl (84). At the beginning of the opioid epidemic, opioid overdose death rates were higher in urban than in rural areas (38). By 2004, opioid overdose rates in rural counties were similar to rates in urban counties (35,38,39). This trend continued until 2007, when rural counties surpassed urban counties for opioid overdose deaths (39). However, the rise of illicitly manufactured opioids reversed this trend, and by 2016, opioid overdose rates were once again highest among urban counties (39,40).

The opioid epidemic has taken different forms in urban and rural America (41). The urban opioid epidemic has been a crisis of predominately heroin and illicitly manufactured opioids, whereas the rural epidemic is characterized by deaths largely involving natural and semisynthetic opioids (i.e., prescription opioids) (39,42). Rural counties had higher age-adjusted rates of prescription opioids from 2004 through 2017, however, urban and rural rates became similar in 2018. Urban counties have had higher rates of heroin overdose deaths since 1999. From 2001 to 2014, age-adjusted rates of deaths involving synthetic opioids other than methadone (e.g., fentanyl) were higher in rural than in urban counties. However, this trend reversed and by 2015, rates were higher in urban than in rural counties (85). There are many factors that influence the differences in opioid overdose mortality rates between urban and rural counties, including socioeconomic differences, health-related behaviors, and access to health care services (40). Residents of rural areas in the US tend to be more economically challenged and in poorer health than their urban counterparts, with rural residents in the South,
including Kentucky, experiencing some of the worst health outcomes (43). Reasons and motivation for substance use differ by geography. In rural counties, opioid mortality rates are strongly influenced by distinct individual and structural factors, including economic distress, whereas opioid supply factors are more strongly associated with opioid mortality rates in urban counties (44).

Kentucky, a predominantly rural state, has been hit hard by the opioid epidemic. In 2020, Kentucky had the fourth highest age-adjusted opioid overdose mortality rate in the US (41.5 per 100,000) (5) with over 1,700 opioid overdose deaths, which was 67% more deaths than in 2019 (26). An estimated $13 million is spent annually on fatal opioid overdoses in Kentucky (86). Historically, overprescribing of opioids coupled with cultural, environmental, and economic stressors stemming from high rates of unemployment and disease and injury have amplified the opioid epidemic in Kentucky (78,87–92). Furthermore, social isolation, loneliness, mental stress and decreased access to healthcare also increase the risk of opioid use and overdose mortality (40,46–50).

The current COVID-19 pandemic has placed a greater risk of death on an already vulnerable population impacted by substance use (45), and has heightened many of the individual stressors already known to increase opioid use and overdose. However, it remains unknown whether the current pandemic has affected the association between urbanicity and opioid overdose mortality. The purpose of this study was to determine the individual-level association between residence in an urban or rural county and subsequent opioid overdose mortality in Kentucky during 2016-2020 and whether the association was modified by the COVID-19 pandemic in 2020.

Methods
Study Population

Health Facility and Services (HFS) data from Kentucky’s Cabinet for Health and Family Services (CHFS) is a collection of records describing single inpatient stays or outpatient encounters in Kentucky hospitals and ambulatory facilities. Each record includes the patient’s demographic data (gender, age group, race [American Indian or Alaska Native, Asian, Black, missing, Native Hawaiian or Pacific Islander, and White], and ethnicity), zip code of residence, county of residence, diagnoses codes, vital status at discharge, discharge codes, length of stay, and admission type (i.e., emergency: the patient required immediate medical intervention; urgent: the patient required immediate attention for the treatment of a physical or mental disorder; elective: the patient’s condition permitted adequate time to schedule a suitable accommodation; trauma: the patient visited a trauma center; missing).

We used HFS data from 2016-2020 to capture inpatient and outpatient hospitalizations with any diagnosis code related to poisonings by opioids identified by International Statistical Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM; Geneva, Switzerland: World Health Organization; 1992) codes. We included hospitalizations with diagnosis codes related to opioid overdose, specifically those involving an opioid analgesic using the ICD-10-CM discharge codes: T40.0 (opium), T40.1 (heroin), T40.2 (natural and semisynthetic opioids), T40.3 (methadone), T40.4 (synthetic opioids other than methadone), and T40.6 (other and unspecified narcotics) (54). Deaths were identified by the discharge status that included: expired/did not recover, expired at home, expired in a medical facility, or expired-place unknown. Our primary outcome of interest in this study was opioid overdose mortality from all opioids (ICD-10-CM T40.0-T40.4 and T40.6) and the secondary outcome was opioid overdose mortality from
prescription opioids (*ICD-10-CM* T40.2-T40.3). We also examined the relationship between binary urbanicity and deaths from illicit opioids (*ICD-10-CM* T40.0, T40.1 & T40.4).

For this analysis, we excluded patients with missing discharge status (n=729), unknown sex (n=1), unknown ethnicity (n=4), and anyone younger than 18 years of age (n=937). A total of 63,106 opioid-related hospitalizations remained in the analysis. Where appropriate, billable *ICD-10-CM* codes have a more specific 7th character that identifies whether this is the initial encounter or subsequent encounter for a particular code. Less than 2% of opioid-related overdoses were determined to be a subsequent encounter. This study was reviewed by the Institutional Review Board at the University of Louisville and was considered exempt.

**Exposure**

The exposure of interest was whether the patient resided in an urban or rural county, defined dichotomously (i.e., rural or urban) and into six categories (i.e., large central metro, large fringe metro, medium metro, small metro, micropolitan and non-core). Urbanicity was defined using the National Center for Health Statistics (NCHS) Urban-Rural Classification Scheme for Counties (93). The NCHS is based on the Office of Management and Budget’s (OMB) February 2013 delineation of metropolitan statistical areas (MSA) and micropolitan statistical areas and vintage 2012 postcensal estimates of the resident U.S. population. The NCHS urban-rural classification scheme was developed for use in studying and monitoring health disparities across the urban-rural continuum. Counties were classified into urban (i.e., large central metro, large fringe metro, medium metro, small metro) and rural (i.e., micropolitan and non-core) based on metropolitan-micropolitan status, population size of the metropolitan statistical areas (MSA), and the location of principal city populations within the largest MSAs (≥1 million population) (93). Large counties include counties in MSAs of at least 1 million population as well.
as the fringes of large counties (e.g., suburbs); medium counties include counties in MSAs with a population between 250,000 and 999,999; and small counties include counties in MSAs with a population less than 250,000. Micropolitan statistical areas and noncore areas include areas with populations of 2,500–49,999 that are not part of larger labor market areas (MSA) as well as open countryside and rural towns with a population less than 2,500 (93).

We mapped county-level urban and rural categories with ArcGIS, version 10.6 (Environmental Systems Research Institute Inc, Redlands, CA) within Kentucky (Figure 2.1).

**Covariates**

Neighborhood socioeconomic factors at the zip-code level were obtained from the American Community Survey, an annual survey on demographic, social, economic, and housing factors conducted by the US Census Bureau from a sample of US addresses (70). We linked the zip code-level 2015-2019 5-year estimates to the zip code of residence for each hospitalization to obtain the percentage of the ≥25-year-old population in the zip code who graduated high school and the percentage of population living below the poverty level.

**Statistical analyses**

We used multivariable logistic regression to estimate the association between urbanicity with overdose mortality from any opioid (ICD-10-CM codes T40.0-T40.4 & T40.6) and with overdose mortality from specifically prescription opioids (ICD-10-CM T40.2-T40.3), and illicit opioids (ICD-10-CM T40.0, T40.1 & T40.4). Multivariable models were adjusted for age-group (18-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, 70 or older years and missing), categories of race (Black, missing, Other, and White), ethnicity, gender, admission type (emergency, urgent, elective, trauma and missing), inpatient/outpatient status, length of stay, and zip-code level socioeconomic variables. Participants with missing socioeconomic variables
(i.e., zip-code level % high school graduates [n=516] and % below the poverty level [n=522]) were assigned the median value, and a missing indicator variable was included in the regression models.

To investigate whether the association was modified by the COVID-19 pandemic, analyses were conducted separately for hospitalizations that occurred pre-pandemic from those occurring during the pandemic. Hospitalizations that occurred prior to April 2020 were coded as pre-pandemic, and any hospitalization occurring in the second, third or fourth quarter 2020 (i.e., April-December 2020) were coded as occurring during the COVID-19 pandemic. We used the likelihood ratio test (LRT) to identify statistical interactions between the six categories of urbanicity and the COVID-19 pandemic. We used the Wald Chi-square test for interaction terms between dichotomous urbanicity and the COVID-19 pandemic. Analyses were conducted using SAS (version 9.4).

**Results**

Of the 120 counties in Kentucky, 71% (n=85) are categorized as rural and 29% (n=35) are categorized as urban based on the binary NCHS Urban-Rural Classification Scheme (Figure 2.1a). When categorized into six levels of urbanicity, 0.8% (n=1) of Kentucky counties are large metro, 10.8% (n=13) are large fringe metro, 9.2% (n=11) are medium metro, 8.3% (n=10) are small metro, 21.7%(n=26) are micropolitan, and 49.2% (n=59) are non-core (Figure 2.1b).

In rural counties, there were 22,393 opioid overdose-related hospitalizations and 266 (1.2%) opioid overdose deaths. In urban counties, there were 40,713 opioid overdose-related hospitalizations and 543 (1.3%) opioid overdose deaths. The overall opioid overdose mortality rate among opioid-related hospitalizations in Kentucky from 2016-2020 was 12.8 per 1,000
hospitalizations. Patients residing in urban counties had a death rate of 13.3 deaths per 1,000 hospitalizations and rural patients had a death rate of 11.9 deaths per 1,000 hospitalizations.

Characteristics of Opioid-involved Hospitalizations

Characteristics of opioid-involved hospitalizations varied by patients’ county urbanicity (Table 2.1). In terms of the opioid involved, the majority of rural hospitalizations were attributed to natural and semisynthetic opioids (56.3%), followed by other and unspecified narcotics (18.6%) and heroin (17.4%). The most common opioid for urban hospitalizations was heroin (46.3%), followed by natural and semisynthetic opioids (33.3%) and other and unspecified narcotics (15.6%). Compared to rural patients, patients living in urban counties were more likely to be seen in an emergency room (77.9% versus 55.5%), in outpatient settings (73.2% versus 62.4%), and were more likely to be male (53.7% versus 46.7%), non-Hispanic (99.1% versus 98.8%), and a race other than white (9.5% versus 2.4%). Rural patients were older than their urban counterparts (36.0% of rural patients were ≥60 years compared to 22.4% of urban patients) and were more likely to have an admission type of elective than urban patients (32.7% versus 16.8%). Urban patients were also more likely to be living in a zip-code with a higher percentage of high-school graduates (87.9% versus 81.4%) and less likely to be living below the poverty level (17.2% versus 22.1%). 98.4% of urban patients were admitted to an urban hospital, and 42.3% of rural patients were admitted to an urban hospital (Table 2.1). 82.7% of rural patients admitted to an urban hospital were discharged to home/self-care whereas 67.7% of rural patients admitted to rural hospitals were discharged to home/self-care (Table 2.2). Urban patients were more commonly discharged to home or self-care (77.0% versus 74.0%), or to leave against medical advice (8.5% versus 5.6%) than rural patients (Table 2.2).
A sensitivity analysis comparing the study sample to the patients excluded due to missing patient discharge status revealed that patients missing discharge status were more commonly hospitalized due to heroin and were younger than the study sample but were otherwise comparable (Supplemental Table 2.2). However, only 1% of hospitalizations were missing patient discharge status.

**Multivariable Logistic Regression Results**

After adjusting for age-group, race, ethnicity, gender, length of stay, admission type, inpatient/outpatient status, and zip-code level socioeconomic status, patients living in urban counties who made it to a hospital had 46% higher odds of dying from an opioid overdose than patients living in rural counties who made it to a hospital (OR=1.46; 95% CI=1.22, 1.74). Similarly, when limiting to illicit opioid-related hospitalizations (T40.0, T40.1 & T40.4; n=26,328), patients from urban counties had 51% higher odds of dying from an illicit opioid overdose than hospitalized patients from rural counties (adjusted OR=1.51; 95% CI=1.12, 2.03) (Table 2.3). However, when restricting specifically to prescription opioid hospitalizations (T40.2-T40.3; n=26,888), there was not a statistically significant difference between patients residing in urban and rural counties in relation to prescription opioid overdose mortality within the hospital setting (adjusted OR=1.23; 95% CI=0.91, 1.67) (Table 2.3).

Compared to patients residing in noncore rural counties, large central metro counties had the highest odds of opioid overdose mortality (adjusted OR=1.92; 95% CI=1.49, 2.47), followed by medium metro counties (adjusted OR=1.62; 95% CI=1.24, 2.13) and small metro counties (adjusted OR=1.42; 95% CI=1.01, 2.00). Interestingly, patients residing in large fringe metro counties (i.e., suburbs) were not statistically different from those living in noncore rural counties (adjusted OR=1.15; 95% CI=0.87, 1.52). Patients living in micropolitan rural counties
also did not differ statistically from patients living in noncore rural counties in relation to opioid overdose mortality among opioid hospitalizations (adjusted OR=1.11; 95% CI=0.86, 1.43) (Table 2.3).

There was a statistically significant interaction between the COVID-19 pandemic and the binary urbanicity (p=0.02) and finer categories of urbanicity (p=0.01) (Table 2.4). Before the pandemic, patients living in urban counties had 63% higher odds of dying from an opioid overdose (adjusted OR=1.63; 95% CI=1.34, 1.97). During the COVID-19 pandemic, hospitalized patients living in urban and rural counties became more similar in regard to their risk of opioid overdose death (adjusted OR=0.72; 95% CI=0.45, 1.16). When restricting to prescription opioid hospitalizations, we did not observe a statistically significant interaction between urbanicity and the COVID-19 pandemic for prescription opioid overdose mortality (p-value for interaction =0.91). There was, however, an interaction between the COVID-19 pandemic and urbanicity (p=0.04) when limiting to illicit opioid overdose hospitalizations. Compared to patients living in rural counties, patients living in urban counties had 74% higher odds of illicit opioid overdose mortality before the COVID-19 pandemic (adjusted OR=1744; 95% CI=1.26, 2.40; Table 2.4); during the COVID-19 pandemic, the association between patient’s residence was no longer associated with death from illicit opioid overdose (adjusted OR=0.56; 95% CI=0.26, 1.20), (Table 2.4).

Discussion

Prior to the pandemic, hospitalized people from urban counties were more likely to die from an opioid overdose than people living in rural counties. During the pandemic, urban and rural counties became more similar in regard to their association with opioid overdose mortality. The same held true when limiting the analysis to hospitalizations involving an illicit
opioid, but not for prescription opioid-related hospitalizations. In regard to the finer categories of urbanicity, hospitalized people from large metro counties, medium metro counties and small metro counties had higher odds of dying from an opioid overdose than people living in noncore rural counties prior to the pandemic, but these counties became more similar in regard to their association with opioid overdose mortality during the pandemic. To our knowledge this is the first study to address how the COVID-19 pandemic has affected the association between urbanicity and opioid overdose mortality within Kentucky hospitalizations.

Consistent with our pre-pandemic findings, Mack et. al. (40) found that opioid overdose death rates in rural counties across the US increased from 2010 to 2015, but in 2016, rates stabilized in rural counties and the largest increases were seen in urban counties. The majority of rural hospitalizations in this study were attributed to natural and semisynthetic opioids (56.3%), whereas heroin was the main driver of opioid-related hospitalizations in urban counties (46.3%), though prescription opioids also largely contributed (33%). Similarly, an analysis of urban-rural differences in drug overdose deaths by the type of drug conducted by the CDC for all United States counties (39) found that the rate of heroin overdose deaths was higher in urban (5.2 per 100,000) than in rural (2.9 per 100,000) counties and the rate of overdose deaths from natural and semisynthetic opioids (e.g., oxycodone, hydrocodone, and morphine) were moderately higher in rural (4.9 per 100,000) than in urban (4.3 per 100,000) counties (39).

While our analysis does not provide insight into the underlying cause of higher opioid overdose deaths in urban counties, we found higher rates of illicit opioid overdose mortality in urban counties compared to rural counties. One likely explanation is the higher availability and accessibility of more lethal drugs such as heroin and illicitly manufactured opioids in urban areas (10) that may be driving the geographical variation observed in this study prior to the COVID-19 pandemic.
pandemic. The low amount of overdose hospitalizations due to synthetic opioids other than methadone (e.g., fentanyl) in this study also support the likelihood of a narrowed therapeutic window for fentanyl overdose response (92,94), i.e., people are dying from fentanyl prior to healthcare intervention. Fentanyl-related respiratory depression can occur within five minutes of administration and can require up to four hours to recover, increasing the risk for sudden death and reducing the response window (95).

Escalating substance use may be a common social response to traumatic events especially when experienced by people with lower socioeconomic status (52). A study on alcohol use and binge drinking after Hurricanes Katrina and Rita found that people of lower income were particularly vulnerable to the stressors that result from disaster (49). People who used heroin in a deindustrialized steel production area of Pennsylvania cited economic hardship, social isolation, and hopelessness as reasons for drug use, explicitly calling for jobs and community reinvestment to reduce overdoses (50). To fight the spread of COVID-19, Kentucky enacted several lockdown measures, including remote learning for schools, closing restaurants, bars and shops to indoor services, restricting travel and implementing social distancing measures or cancelling events altogether (96). Many individuals that were directly affected by these measures experienced economic hardship, as evidenced by a rise in unemployment rates from 5.2% in March 2020 to 16.6% in April 2020 (97). A study measuring the impact of the COVID-19 lockdown on workers’ economic hardship and mental health found that individuals that experienced an instant loss of income during the lockdown was associated with a 33.2% higher risk of feeling depressed compared to those that maintained their income (53). These stressors from the COVID-19 pandemic could push someone who is in recovery into relapse or
trigger individuals in a high-risk group to initiate substance use, as well as increase the incidence of substance use among the general population (51).

Decreased access to healthcare and treatment services during the pandemic has also driven individuals with opioid use disorder to procure illegal opioids (51), which have a greater risk of opioid overdose mortality (23), in order to prevent withdrawal due to a sudden lack of MAT availability. Furthermore, social distancing to prevent the spread of the coronavirus may lead to more individuals using drugs alone, raising the risk of overdose death because no one is present to intervene, either with Narcan or social support, or bystanders may be reluctant to intervene for fear of contracting coronavirus (54,55). Social isolation, economic distress, mental stress, and decreased access to healthcare and treatment services during the pandemic has caused unparalleled stress among many individuals, and the pandemic is in many ways a perfect storm for those struggling with addiction. In addition to the social and economic impacts that are notable from a population health perspective, there are more proximal factors that led to an alarming increase in opioid overdose deaths during the pandemic, especially among those at highest risk of opioid use disorder. These factors include disruptions to MAT, opioid use disorder recovery services and syringe service programs as well as naloxone shortages (98).

The sheer number of opioid-related hospitalization encounters in Kentucky each year present countless opportunities to intervene in the opioid epidemic by linking patients to resources for treatment or harm reduction programs (99). However, the majority of patients, whether from rural or urban counties were discharged to home/self-care (76%) rather than to a treatment facility. The high number of rural residents admitted to urban hospitals with opioid overdoses and discharged to home/self-care underscores the need for urban hospitals to develop relationships with substance use treatment and chronic pain services in rural areas and
to facilitate linkage to treatment at discharge (99). Failure to connect patients with a treatment plan can have severe consequences (100). One study reported 27% of people relapse on the day of discharge, 65% within a month of discharge, and 90% within a year of discharge (101). In addition, emergency departments can play a key role in the epidemic by initiating treatment with buprenorphine as well as distribution of naloxone (102,103). Strengthening services and support for non-healthcare related needs, including referrals for housing, transportation, food, and mental health services, are other ways that emergency departments can impact the opioid epidemic—by addressing the underlying determinants of opioid use.

This study is not without limitations. First, there was not a unique patient identifier within the HFS dataset, and as such there was not a way to determine whether each hospital encounter was for a unique person; hence, it is possible that the outcomes may be dependent and violate statistical assumptions, which could lead to falsely significant observations. However, when examining the ICD-10-CM codes, only a small proportion (<2%) were for subsequent encounters of opioid overdose. Second, we used hospitalization encounters in this study to examine the association between urbanicity and opioid overdose deaths. Between 2016 and 2020, 13% (5) of opioid-related deaths in those aged 18 and older occurred in the hospital setting; which limits the generalizability of our findings to individuals that make it to a hospital when only a small percentage of opioid-related deaths occur in the hospital setting. However, the CDC analyzed data from the National Vital Statistics System and reported similar relationships between urbanicity and opioid overdose mortality as those that we found in this study on hospitalized opioid-related deaths by urbanicity (104). In addition, there is a growing interest in utilizing syndromic surveillance systems, such as hospitalization discharge records, to monitor the opioid epidemic and help inform prompt intervention and prevention responses.
(105). We also adjusted for severity of the case, including inpatient/outpatient status, length of stay and facility admission type. Third, differences in patient reporting, physician documentation, drug screening availability, and facility reporting policies could result in differences in medical coding accuracy. However, discharge data from hospitals, standardized using ICD-10-CM are generally considered complete, comparable and reliable (106). Fourth, hospital discharge data are collected for billing purposes and tend to reflect care for which the payer is billed, but not necessarily accurately reflect the primary reasons for a visit. A medical chart review would have been necessary to validate the ICD-10-CM discharge codes to determine the sensitivity and specificity of the codes for identifying opioid overdoses. Lastly, hospital discharge records for residents that were treated out of state were not included in this study and therefore the opioid overdose hospitalization rates presented here may underestimate the true extent of the opioid overdose epidemic among Kentucky residents.

Since the beginning of the opioid epidemic, urbanicity has been associated with opioid-related overdose death, flip-flopping between rural and urban counties over time. Here, we observed that the COVID-19 pandemic evened the playing field in terms of opioid overdose mortality for rural and urban residents who made it to a hospital or healthcare facility. Future studies that seek to understand where people who use opioids live and the underlying environment or drugs that increase risk of opioid death are needed to enhance specific overdose prevention interventions and response efforts.

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TRANSITION CHAPTER

In the absence of available prescription opioids and in lieu of the deadliness of heroin and illicitly manufactured fentanyl, patients previously using prescription and/or illicit opioids have sought out alternatives that are advertised to have less side effects and lower abuse potential (56). One such opioid alternative is kratom. Kratom was introduced in the United States in the early 2000’s (57) and is regulated as an herbal supplement under US Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA) policies (58). Kratom is marketed as a legal recreational drug that can replace prescription and illicit opioids, while maintaining the same “high”, despite a lack of scientific evidence to support these claims (64).

Multiple states, including Indiana, Vermont, Wisconsin, Arkansas, Alabama and Rhode Island, have banned the use and possession of kratom (58). Because kratom is used as a substitute for heroin and other opioids, laws that limit access to kratom may impact opioid overdose mortality in states that have enacted them. In the following chapter, we seek to estimate the ecological association between state-level kratom laws in relation to opioid overdose mortality rates at the state-level using an interrupted time series analysis.
AIM 3: EVALUATING STATE-LEVEL KRATOM LEGISLATION AND OPIOID OVERDOSE MORTALITY IN THE UNITED STATES: AN INTERRUPTED TIME SERIES ANALYSIS

Background and Aim: Opioid overdose mortality continues to rise in the United States, leaving individuals to seek out alternative substances advertised to have fewer side effects and lower abuse potential, such as kratom. Because kratom is used as a substitute for heroin and other opioids, laws that limit access to kratom may impact opioid overdose mortality in states that have enacted them. We evaluated state-level kratom legislation and subsequent change in opioid overdose mortality.

Methods: We conducted an interrupted time series analysis to assess whether the introduction of a law banning kratom resulted in a change in the trend of opioid overdose mortality rates compared with the preintervention period in Indiana, Vermont, Wisconsin, Arkansas, Alabama and Rhode Island. Opioid overdose mortality rates were abstracted using the CDC Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database on multiple cause-of-death of US residents. Poisson regression was used to estimate rate ratios (RRs) and 95% confidence intervals (CIs) of opioid overdose mortality rates.
Results: There was a significant slope change from pre- to post-intervention in Indiana (RR=1.09; 95% CI=1.06, 1.12), Vermont (RR=1.11; 95% CI=1.05, 1.17), Wisconsin (RR=1.03; 95% CI=1.00, 1.05), Arkansas (RR=1.10; 95% CI=1.04, 1.15), and Alabama (RR=1.05; 95% CI=1.01, 1.09), but no change in Rhode Island (RR=1.05; 95% CI=0.97, 1.13).

Conclusion: Kratom was banned in an effort to thwart the addictive and dangerous properties of kratom, yet this study showed that opioid overdose rates continued to increase despite implementation of policies designed to eliminate access to kratom. Policymakers should focus their attention on regulating kratom, and future studies should assess the potential benefits of kratom use.
Introduction

Opioid overdose deaths increased by more than 700% from 1999 to 2020, resulting in more than 585,000 deaths (5). With the rise in opioid overdose deaths, patients previously using prescription and illicit opioids have sought out alternative substances that are advertised to have fewer side effects and lower abuse potential (56). One such alternative substance is kratom. Kratom (*Mitragyna speciosa*) is an evergreen tree indigenous to Southeast Asia (57) whose leaves were traditionally brewed into a tea or chewed by laborers in parts of Asia to increase productivity (57). At low doses of 1-5 grams, kratom provides mild stimulant effects, but as the dose increases analgesic and opioid-like effects can occur (58,59). Reports of users feeling “high” after consumption led to increasing popularity and in 1946, the substance was legally banned in Thailand and other parts of Asia (60).

Kratom was introduced in the United States in the early 2000s (57) and according to SAMSHA’s 2020 Annual National Report, an estimated 2.1 million people used kratom in the past year (61). Kratom leaves can be chewed, smoked, or ground to powder and prepared as a tea or taken orally (65). It is marketed as an herbal supplement (66) and sold at gas stations, convenience stores, head shops and over the internet (65). It is increasingly being used to self-treat opioid dependence and as a substitute for other opioids (66,67). A study of treatment-seeking individuals with a history of substance use disorder found that 68.9% of these individuals used kratom to wean off of or as a substitute for heroin and other opioids (65). Kratom is also easier to obtain than illicit opioids and is more cost-effective (65). Emerging reports of kratom use in the US and Europe suggest a considerable abuse potential with adverse health effects (62). Kratom is composed of 25 compounds, 22 of which bind to μ-opioid receptors and two of the top five most prevalent compounds (mitragynine and 7-hydroxy-mitragynine) are known opioid agonists (56,63). However, kratom does not generally produce
the same euphoric effects as opioids and even at very high doses, kratom is much less likely to
induce respiratory depression (that can lead to death) compared to other opioids (e.g.,
prescription opioids, heroin, fentanyl) (107). A CDC analysis of over 27,000 overdose deaths
that occurred from July 2016-December 2017, found that <1% of deaths involved kratom,
including only seven decedents for whom kratom was the only substance found on postmortem
toxicology reports (108).

In August 2016, the DEA announced its plan to add kratom to the list of Schedule I
Substances out of concern that kratom may have properties that expose users to addiction,
abuse, and dependence (58). Amidst a public outcry of supporters who claimed that kratom had
helped them manage opioid addiction withdrawals and chronic pain, the DEA placed a
temporary hold on the ban pending further scientific research. Despite its current legal status, a
handful of states including Alabama, Arkansas, Wisconsin, Indiana, Rhode Island and Vermont,
have banned the sale and possession of kratom (58); however, the impact of these bans on the
opioid epidemic have not been evaluated. The purpose of this study was to evaluate state-level
legislation banning kratom and subsequent opioid overdose mortality in the United States.

Methods

Data Sources

*Outcome: State Opioid Overdose Mortality Rates*

The annual opioid overdose mortality rates in each state from 2005 to 2020 were
abstracted using the Centers for Disease Control and Prevention Wide-ranging Online Data for
Epidemiologic Research (CDC WONDER) database on multiple cause-of-death of US residents
(5). Opioid overdose mortality was classified with the *International Statistical Classification of
Diseases, 10th revision (ICD-10; Geneva, Switzerland: World Health Organization; 1992)

underlying cause of death codes X40-X44 (unintentional), X60-X64 (suicide), X85 (homicide) and Y10-Y14 (undetermined intent). Among deaths with drug overdose as the underlying cause, we captured those specifically involving an opioid analgesic using the following ICD-10 cause-of-death codes: T40.0 (opium), T40.1 (heroin), T40.2 (natural and semisynthetic opioids), T40.3 (methadone), T40.4 (synthetic opioids other than methadone), and T40.6 (other and unspecified narcotics). The primary outcome of interest was fatal overdose deaths of any intent involving all opioids, including prescription overdose deaths and deaths from illicit opioids (e.g., heroin and illicitly manufactured fentanyl): ICD-10 codes T40.0-T40.4, and T40.6. The secondary outcome of interest was overdose deaths of any intent involving prescription opioids, using the Centers for Disease Control and Prevention’s (CDC) recommendation for quantifying prescription opioid overdoses as deaths involving natural and semisynthetic opioids (i.e., T40.2) and methadone (i.e., T40.3) (21,69), (i.e., prescription overdose deaths [POD]). Lastly, we examined overdose deaths of any intent involving illicit and synthetic opioids other than methadone: ICD-10 codes T40.0, T40.1 and T40.4 (i.e., illicit overdose deaths).

Exposure: State law against kratom

Six states implemented legislation banning the possession, sale or use of kratom (or its compounds) between the years 2012 and 2017: Indiana in 2012, Vermont in 2013, Wisconsin in 2014, Arkansas in 2016, Alabama in 2016, and Rhode Island in 2017 (64). For each year from 2005 to 2020, we plotted the mean crude opioid overdose mortality rate in states that had legislation banning kratom (Figure 3.1).

Statistical Analysis

We conducted an interrupted time series (ITS) analysis to examine the impact of state-level legislation banning kratom on annual rates of opioid overdose mortality in the United
States. The impact was modeled using Poisson regression with an autocorrelation structure at lag order 1. The state’s annual opioid overdose mortality count was the dependent variable, and we included the natural log of the state’s population size as the offset term. In an ITS analysis, a time series of an outcome is used to model an underlying trend (i.e., pre-intervention trend), which is “interrupted” by an intervention at a particular point in time. The expected trend in the absence of the intervention serves as the “counterfactual,” to which the impact of the intervention is compared (109). In this study, the pre-intervention period was defined as the years prior to the legislation implementation, and the post-intervention period was defined as the years after the legislation was implemented in each state. The Durbin-Watson test was used to test for the presence of residual autocorrelation. We performed a single interrupted time series separately for each state with a legislation banning kratom. More specifically, we assessed whether the introduction of the kratom ban resulted in a change in the level and trend of opioid overdose mortality rates compared with the pre-intervention period.

**Single Interrupted Time Series**

The single-ITS model follows the regression where $Y_t$ is the outcome variable (opioid overdose mortality rate), $T_t$ is a continuous variable which indicates the time (years) since the start of the study, and $X_t$ is a dummy variable indicating whether the observation was collected before ($X = 0$) or after the intervention ($X = 1$) (legislation banning kratom). For the single-ITS, the $\beta_0$ is the intercept, $\beta_1$ is the slope prior to the intervention, $\beta_2$ is the change in level in the period following the intervention compared with the counterfactual (i.e., an immediate treatment effect) and $\beta_3$ is the difference between the pre-intervention and post-intervention slopes (i.e., a treatment effect over time). The post-interruption slope is determined by summing $\beta_1 + \beta_3$ (110).

$$Log(E(Y_t)) = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 T_t X_t + \epsilon_t$$
All statistical analyses were done in SAS version 9.4, and statistical modeling was carried out with the SAS GLIMMIX procedure, allowing adjustment for autocorrelation.

Results

From 2005 to 2020, a total of 31,632 opioid-related overdose deaths occurred in the six states under observation. In 2005, there were 819 opioid-related overdose deaths and in 2020, there were 4,624 deaths, an increase of nearly 465%. Deaths rose by 1,096% in Indiana, 257% in Vermont, 355% in Wisconsin, 128% in Arkansas, 653% in Alabama, and 172% in Rhode Island (Table 3.1). Results from the single-ITS for each state are displayed in Table 2.1 and discussed below.

All Opioid Overdose Mortality

Before the kratom ban, there was a significant opioid overdose mortality trend in Indiana (RR=1.12; 1.10, 1.15), Wisconsin (RR=1.08; 95% CI=1.06, 1.09), Arkansas (RR=1.02; 95% CI=1.00, 1.03), Alabama (RR=1.07; 95% CI=1.06, 1.09), and Rhode Island (RR=1.09; 95% CI=1.08, 1.11), but not in Vermont (RR=1.01; 95% CI=0.96, 1.05). After controlling for the pre-intervention trend, there was a significant level change from pre- to post-intervention, with rates decreasing in Indiana (RR= 0.71; 95% CI=0.64, 0.79), and Arkansas (RR=0.76; 95% CI=0.63, 0.92). However, the level did not change significantly in Vermont (RR=1.14; 95% CI=0.88, 1.49), Wisconsin (RR=1.02; 95% CI=0.93, 1.11), Alabama (RR=1.14; 95% CI=0.99, 1.31), or Rhode Island (RR=0.98; 95% CI=0.82, 1.18). In addition, there were significant slope changes from pre- to post-intervention in Indiana (RR=1.09; 95% CI=1.06, 1.12), Vermont (RR=1.11; 95% CI=1.05, 1.17), Wisconsin (RR=1.03; 95% CI=1.00, 1.05), Arkansas (RR=1.10; 95% CI=1.04, 1.15), and Alabama (RR=1.05; 95% CI=1.01, 1.09), but no change in Rhode Island (RR=1.05; 95% CI=0.97, 1.13).
**Prescription Opioid Overdose Mortality**

When we limited the deaths to those involving a prescription opioid (ICD-10 codes T40.2 and T40.3), there was a significant pre-intervention trend in Indiana (RR=1.14; 95% CI=1.10, 1.18), Wisconsin (1.03; 95% CI=1.01, 1.05), and Rhode Island (RR=1.08; 95% CI=1.06, 1.10), but not in Vermont (RR=0.99; 95% CI=0.94, 1.04), Arkansas (RR=1.01; 95% CI=0.99, 1.03), or Alabama (RR=1.00; 95% CI=0.98, 1.02). After controlling for the pre-intervention trend, there was a significant level change in Indiana, with opioid overdose mortality rates decreasing by 46% (RR=0.54; 95% CI=0.47, 0.63), but no change in any of the other states (Vermont: RR=1.03; 95% CI=0.73, 1.47); Wisconsin: RR=1.10; 95% CI=0.97, 1.25); Arkansas: RR=0.90; 95% CI=0.72, 1.13); Alabama: RR=1.08; 95% CI=0.87, 1.34; Rhode Island: RR=0.82; 95% CI=0.60, 1.11). Contrary to the observed effects when all opioids were involved, there was a significant decrease in the slope between pre- and post-intervention in Wisconsin (RR=0.96; 95% CI=0.93, 0.99), Arkansas (RR=0.92; 95% CI=0.86, 0.98), and Rhode Island (RR=0.87; 95% CI=0.78, 0.97), but not in Indiana (RR=1.01; 95% CI=0.98, 1.05), Vermont (RR=0.99; 95% CI=0.91, 1.07) or Alabama (RR=1.02; 95% CI=0.96, 1.08).

**Illicit Opioid Overdose Mortality**

When we considered only deaths involving an illicit opioid (ICD-10 codes T40.0, T40.1 and T40.4), we found significant pre-intervention trends in Indiana (RR=1.14; 95% CI=1.09, 1.20), Wisconsin (RR=1.18; 95% CI=1.15, 1.21), Alabama (RR=1.29; 95% CI=1.25, 1.33) and Rhode Island (RR=1.41; 95% CI=1.37, 1.46), but not in Vermont (RR=1.06; 95% CI=0.96, 1.16) or Arkansas (RR=1.02; 95% CI=0.98, 1.05). After controlling for the pre-intervention trend, we observed a significant level change in Vermont (RR=2.21; 95% CI=1.45, 3.38), but not in any of the other states (Indiana: RR=0.88; 95% CI=0.75, 1.04; Wisconsin: RR=1.05; 95% CI=0.93, 1.19; Arkansas: RR=0.85; 95% CI=0.61, 1.17; Alabama: RR=1.14; 95% CI=0.94, 1.37; Rhode Island: 51
RR=0.81; 95% CI=0.66, 1.01). There was a significant increase in slope in Indiana (RR=0.17; 95% CI=1.11, 1.22), Vermont (RR=1.12; 95% CI=1.01, 1.24), and Arkansas (RR=1.37; 95% CI=1.27, 1.47), a significant decrease in slope in Alabama (RR=0.92; 95% CI=0.88, 0.97) and Rhode Island (RR=0.78; 95% CI=0.73, 0.84), and no observed treatment effect in Wisconsin (RR=1.01; 95% CI=0.98, 1.04).

**Sensitivity Analysis**

With the increasing rates of opioid overdose mortality as a result of the COVID-19 pandemic (111), we conducted a sensitivity analysis limiting the data to 2019, in an effort to eliminate the potential confounding effects of COVID-19-related overdoses. In this analysis, we found an immediate decrease in opioid overdose deaths in Indiana (RR=0.75; 95% CI=0.68, 0.84), a significant increase in opioid overdose deaths in Alabama (RR=1.34; 95% CI=1.14, 1.57), and no immediate effect in Vermont (RR=1.19; 95% CI=0.90, 1.58), Wisconsin (RR=1.19; 95% CI=0.90, 1.58), Arkansas (RR=0.85; 95% CI=0.69, 1.06) or Rhode Island (RR=1.19; 95% CI=0.96, 1.48). Over time, there was a significant increase in opioid overdose deaths in Indiana (RR=1.08; 95% CI=1.05, 1.11) and Vermont (RR=1.09; 95% CI=1.03, 1.17), and a significant decrease in Rhode Island (RR=0.85; 95% CI=0.77, 0.94). There was no sustained treatment effect in Wisconsin (RR=1.00; 95% CI=0.98, 1.03), Arkansas (RR=1.04; 95% CI=0.97, 1.12) or Alabama (RR=0.97; 95% CI=0.92, 1.02) (Supplemental Table 3.1).

**Discussion**

In an analysis of opioid overdose death rates from 2005 to 2020, we found that after controlling for the pre-intervention trend, Indiana, Vermont, Wisconsin, Arkansas and Alabama had higher opioid overdose deaths rates following the kratom ban implementation. Rhode Island did not show a significant trend following the kratom ban; however, there were few points following the ban implementation and this result may not hold with additional years of
opioid overdose mortality data. When we limited the analysis to prescription opioid overdose deaths, we observed a decrease in mortality in Wisconsin, Arkansas and Rhode Island, but no effect in Indiana, Vermont or Alabama. In regard to illicit opioids, there was a significant increase in deaths in Indiana, Vermont, and Arkansas, a significant decrease in deaths in Alabama and Rhode Island, and no observed treatment effect in Wisconsin. Results of a sensitivity analysis limiting the deaths to those that occurred prior to the COVID-19 pandemic showed an increase in opioid overdose deaths in Indiana and Vermont, a decrease in opioid overdose deaths in Rhode Island, and no treatment effect in Wisconsin, Arkansas, or Alabama. These results taken together suggest that decreased access to prescription opioids (21), and a subsequent increase in imported illicitly manufactured synthetic opioids (10,23) as well as the COVID-19 pandemic had a greater effect on the opioid epidemic than did banning kratom. To our knowledge, this is the first study to estimate the association between state-level kratom legislation and opioid overdose mortality.

There are opposing views when it comes to kratom (56). One common view is that kratom is thought to be a safer alternative for prescription and illicit opioids, providing effective pain management and a novel way for people with opioid use disorder to wean off of more dangerous opioids (112). The alternative view is that kratom itself is a dangerous and addictive opioid and may lead users to more opioid use and ultimately higher rates of opioid overdose mortality (113). Similar views were previously shared in regard to increased naloxone access and overdose-related Good Samaritan laws (114,115). However, a study examining the influence of naloxone laws and overdose-related Good Samaritan laws on opioid overdose mortality found that states with naloxone access laws had a 14% (p=0.033) lower incidence of opioid-overdose mortality and states with Good Samaritan laws had a 15% (p=0.050) lower incidence of opioid-overdose mortality compared to states without such laws (116).
authors also examined whether these laws were associated with increased non-medical opioid use, but they did not find a significant relationship between these measures and opioid use. Likewise, syringe service programs have reduced negative outcomes of opioid use without increasing community levels of drug use (117).

Kratom users have reported using kratom for managing chronic pain, supplementing prescription opioid treatments, or as a means of alleviating opioid dependence because they believe kratom carries less risk of overdose than opioids (62,118), though there have not been any clinical trials that have evaluated kratom as a safe and effective treatment of opioid use disorder or pain relief (56). In a cross-sectional study of kratom users, 91.3% of participants endorsed using kratom for pain relief, and 40.9% used kratom in place of other opioids, including prescription opioids and heroin (119). In a study of kratom users with a history of substance use disorder that were enrolled in a treatment program, 68.9% used kratom to cut back on or get off of heroin, opiates, or prescription pain killers, 60.2% used kratom as a way to reduce or stop using opiates or heroin, and 64.1% used kratom as a substitute for opiates or heroin (65). A majority of chronic kratom users remain in good health and do not engage in other drug-seeking behaviors (120). A study examining whether prolonged kratom use impairs the social functioning of regular kratom users found that 90% of participants reported no medical problems in the past 30 days, 87% retained employment, and no chronic kratom users that were interviewed reported any use of illicit drugs in the past 30 days, which was confirmed by urine toxicology tests (120). People that used kratom in place of prescription or illicit opioids were no longer afforded this luxury in the presence of a law banning kratom, or it became more difficult to find. Without the kratom alternative, one may turn to or return to more dangerous opioids, which could have resulted in the increase we saw in opioid overdose deaths (56).
There are currently no quality control procedures or standardization in regard to kratom production and distribution (62). In 2018, there were over 200 people infected with *Salmonella* across 41 states, 74% of whom consumed kratom that was purchased locally or through online retailers (121). The FDA has also issued warnings about high levels of heavy metals in kratom products, that can potentially lead to heavy metal poisoning and increased risk of certain cancers (122). Contamination with illicit substances and infectious agents demonstrates the need to establish manufacturing standards and governmental oversight to ensure standardization and safe kratom production. There have not been any reports of kratom deaths in Southeast Asia when used in the traditional setting as unadulterated, pure kratom leaf (56). Currently in the US, consumers cannot guarantee that what they are consuming is pure kratom, which increases the risk of adverse events due to poor manufacturing practices.

A key strength of this study was the use of time-series analysis, which accounts for secular trends by design and is therefore the strongest method for assessing the effects of a broad-based intervention, such as a state-level policy. Specifically, the ITS design is a strong quasi-experimental study design for evaluating the long term effects of policies applied to an entire population (123). Additionally, we utilized a Poisson regression which allowed for the correction of residual autocorrelation in order to produce more robust standard errors and confidence intervals.

There are several limitations of this study. First, this is a population-based study and we do not know whether the rise in opioid overdose deaths after the kratom ban arose from patients turning or returning to more dangerous opioids, or whether they were already using opioids. Second, we had only three data points after the intervention in Rhode Island, and the results in this state should be interpreted with caution. Lastly, we did not adjust for any confounders; however, ITS studies are generally unaffected by typical confounders that remain
fairly constant over time (e.g., age, race, ethnicity, poverty, education), as their measurements would be very similar both before and after the intervention (109). Potential confounding is limited to factors that are related to the outcome and change after the time of the intervention.

**Conclusion**

State-level kratom bans in Indiana, Vermont, Wisconsin, Arkansas and Alabama were associated with sustained increases in opioid overdose mortality rates. Despite controlling for the pre-intervention trend, we cannot definitively state that state-level kratom bans caused the significant increase in opioid overdose deaths that were seen in this study. We understand that there are many factors, including social and structural factors, that influence the opioid epidemic and only a small proportion of the population uses kratom (61). However, it is important to note that bans were put into place in an effort to thwart the addictive and dangerous properties of kratom, yet this study has shown that opioid overdose rates continued to increase at alarming levels even with these bans in place. It is essential that policymakers base decisions regarding kratom on data concerning the benefits (e.g., safer alternative to opioids) or potential negative impacts of kratom legality (e.g., delaying research efforts by scientists), and the use of kratom in its pure, unadulterated form.
DISCUSSION

Through this dissertation we have aimed to understand the social and structural factors that are driving the increase in opioid demand in an effort to mitigate the opioid epidemic and describe data-driven prevention and protection strategies. Specifically, we focused on investigating the relationships between socioeconomic status (Aim 1), urbanicity and the COVID-19 pandemic within Kentucky hospitalizations (Aim 2), and kratom legislation (Aim 3) on opioid overdose mortality within the United States. The major findings are summarized below.

Aim 1: Socioeconomic Status Patterns in Relation to Opioid Overdose Mortality Rates in United States Counties, 2010-2019

To better understand the socioeconomic factors, we first described socioeconomic profiles of US counties and examined their associations with rates of opioid overdose mortality. County-level risk factors for prescription overdose mortality included low education, high disability, low employment, high public health insurance, high poverty, high vacant housing, high grandparents responsible for grandchildren, and high income-inequality. Counties scoring high on the single adult, high poverty, high income inequality, yet educated were associated with illicit opioid overdose mortality. County-level risk factors for deaths involving illicit opioids were a high proportion of never married males and females, high income inequality, high poverty, high residential instability, high education (bachelor’s degree or higher), and a lack of an association between grandparents raising grandchildren.
Aim 2: Residence in Urban or Rural Counties in relation to Opioid Overdose Mortality in Kentucky before and during the COVID-19 Pandemic

Since the beginning of the epidemic, rates of opioid-related overdose death have differed in rural and urban counties. We examined the association between urban residence and subsequent opioid overdose mortality in Kentucky and whether this association was modified by the COVID-19 pandemic. Prior to the pandemic, hospitalized people from urban counties were more likely to die from an opioid overdose than people living in rural counties. During the pandemic, urban and rural counties became more similar in regard to their association with opioid overdose mortality. The same held true when limiting the analysis to hospitalizations involving an illicit opioid, but not for prescription opioid-related hospitalizations.

Aim 3: Evaluating State-Level Kratom Legislation and Opioid Overdose Mortality in the United States: an interrupted time series analysis

With the rise in opioid overdose deaths, people have sought out alternative substances that are advertised to have less side effects and lower abuse potential, such as kratom. We examined the association between state-level kratom legislation and opioid overdose mortality across US states and found that after controlling for the pre-intervention trend, Indiana, Vermont, Wisconsin, Arkansas and Alabama had higher opioid overdose deaths rates following the kratom ban implementation. Rhode Island did not show a significant trend following the kratom ban; however, there were few points following the ban implementation and this result may not hold with additional years of opioid overdose mortality data. When we limited the analysis to prescription opioid overdose deaths, we observed a decrease in mortality in Wisconsin, Arkansas and Rhode Island, but no effect in Indiana, Vermont or Alabama. In regard to illicit opioids, there was a significant increase in deaths in Indiana, Vermont, and Arkansas, a
significant decrease in deaths in Alabama and Rhode Island, and no observed treatment effect in Wisconsin. These results suggest that there are other interventions, such as an increase in illicitly manufactured fentanyl, reduced supply of prescription opioids, and the COVID-19 pandemic, all of which have had a greater effect on the opioid epidemic than did legislation banning kratom.

Strengths and Limitations

This dissertation has several strengths worth mentioning. One strength is that we considered various classes of opioid overdose deaths. Though prescription and illicit opioid overdoses are closely intertwined, it is important to differentiate the deaths and examine them as distinct epidemics in order to craft more appropriate prevention and response efforts. Therefore, within each aim we looked at the exposure separately for prescription opioids and illicit opioids as well as all opioids combined.

We also chose to follow the Center for Disease Control and Prevention’s (CDC) recommendations for quantifying prescription opioid overdoses as deaths involving natural and semisynthetic opioids (i.e., T40.2) and methadone (i.e., T40.3) (21,69). Deaths from fentanyl, whether pharmaceutical or illicitly manufactured, are coded under T40.4 (21,69), and have been traditionally included in the prescription opioid definition. However, there is increasing evidence (21,24,82), including from this dissertation, that the high proportion of fentanyl overdose deaths in recent years is predominantly due to illicitly manufactured fentanyl as opposed to prescription fentanyl; and, the fentanyl epidemic is operating distinctly from the prescription opioid epidemic (23). Using the current conservative approach that separates T40.4 codes from other prescription opioids (T40.2-T40.3) likely provided a more accurate representation of deaths involving prescription opioids.
There are different dimensions of disadvantage that operate synergistically with the opioid epidemic. Using a factor analysis approach in aim 1 allowed us to observe patterns of socioeconomic variables that are at play in the opioid epidemic as opposed to single markers (e.g., poverty alone). Another key strength of this dissertation was the use of time-series analysis, which accounts for secular trends by design and is therefore the strongest method for assessing the effects of a broad-based intervention, such as a state-level policy. Specifically, the ITS design is a strong quasi-experimental study design for evaluating the long term effects of policies applied to an entire population (123).

The findings of this dissertation are subject to several limitations. While two of the aims were ecological in nature, and therefore prohibit causal inference about individuals, the underlying social and structural factors that are discussed as fueling the opioid epidemic are population-level characteristics that require population-level public health interventions. Focusing on the individual will help that one person but focusing on the population characteristics that are exacerbating the opioid crisis will have an effect on generations to come.

In each aim we considered synthetic opioids other than methadone (ICD-10 code T40.4) within the illicit opioid definition. However, there are deaths from prescription opioids (e.g., Tramadol), that are also included within this aim. Including these deaths in the illicit opioid definition may have biased our results, especially in the years prior to 2013 when deaths from illicitly manufactured fentanyl began to emerge. At the time of this analysis, illicitly manufactured fentanyl and analogs did not have their own ICD code; however, a new code has been introduced (i.e., T40.411) that can be used in future studies.

An additional limitation is that we used opioid overdose deaths from death certificates as our outcome. As with any analysis based on death certificate data, there is undoubtedly
some misclassification of cause of death as a result of the physician failing to list a correctly
diagnosed disease on the death certificate. In addition, diseases on death certificates are
sometimes miscoded. Specifically relating to opioid overdose-related deaths, many times the
exact opioid is unknown and whether a prescription or illicit opioid was involved, the death is
coded under other and unknown narcotics (ICD-10 code T40.6). These deaths were included in
the overall analyses, but they were left out of the specific cause of death analyses as it is
unknown which category each death would fall under. Therefore, we have not included all of
the deaths within the individual analyses, and results may be biased. Also, in some cases more
than one class of opioid was involved and these individuals would have been included in both
the prescription and illicit opioid analyses.

Broader Conclusions

The opioid epidemic may have been fueled by aggressive and misleading promotion by
pharmaceutical companies, combined with an influx of cheaper illicit opioids such as heroin and
fentanyl, but there are underlying root causes that have played an important role in increasing
the demand and continuing the epidemic. Focusing solely on the increase in supply and ignoring
the underlying structural and social determinants that are at play will hinder the efforts to
reverse the opioid crisis that is ever evolving as different opioids come into play. This was
proven when opioid overdose rates continued to climb despite a decline in the number of
prescriptions that were written due to legislative action on physician prescribing practices.

More than poverty or a lack of education lead to the opioid epidemic. There are multiple
socioeconomic factors that are working synergistically to further the burden of disease. We
found that the fundamental drivers differed for areas with a greater amount of prescription
opioid overdose deaths compared to illicit opioid overdose deaths. The two can be thought of
as distinct epidemics and it is important to examine them separately in order to craft appropriate prevention and response efforts, which is why we separated the deaths by the opioids involved in each analysis.

Another risk factor for opioid overdose that was not examined in the first aim but was in the second aim is the urban-rural status of where one lives. At the beginning of the opioid epidemic, opioid overdose death rates were higher in urban than in rural areas (38). By 2007, rural counties surpassed urban counties for opioid overdose deaths (39), however, by 2016, opioid overdose rates were once again highest among urban counties (39,40). Reasons and motivation for substance use differ by geography. In rural counties, opioid mortality rates are strongly influenced by distinct individual and structural factors, including economic distress, whereas opioid supply factors are more strongly associated with opioid mortality rates in urban counties (44). The current COVID-19 pandemic has placed a greater risk of death on an already vulnerable population impacted by substance use (45), and has heightened many of the individual stressors already known to increase opioid use and overdose. Urban and rural differences in opioid overdose mortality washed away during the pandemic, suggesting that the protective mechanisms that were preventing rural overdose deaths prior to the pandemic were no longer preventing rural deaths when the pandemic hit in 2020.

Opioid overdose mortality continues to rise in the United States, leaving individuals to seek out alternative substances advertised to have fewer side effects and lower abuse potential, such as kratom. States enacted legislation banning kratom in an attempt to thwart the addictive and dangerous properties of kratom, yet this study has shown that opioid overdose rates continued to increase at alarming levels even with these bans in place.

**Public Health Significance**
In our first aim we found that socioeconomic county profiles were significantly associated with opioid overdose mortality rates in the US, and these profiles differed depending on the opioids involved. These risk factor profiles may help federal and state agencies as well as local health departments tailor prevention strategies to curb the opioid epidemic depending on the different socioeconomic profiles of their county. Our study contributes to the ongoing efforts to strengthen the opioid response and enhance public health interventions targeted at specific high-risk groups.

The second aim provided evidence of the significance of the underlying structural and social determinants of the opioid epidemic. The pandemic heightened many of the individual stressors already known to increase opioid use and overdose and placed a greater risk of death on an already vulnerable population. The rates of opioid overdose mortality during the pandemic are higher than we have ever experienced in the United States, exacerbating the need to address the underlying risk factors in addition to the opioid supply chain. Future studies that seek to understand where people who use opioids live and the underlying environment or drugs that increase risk of opioid death are needed to enhance specific overdose prevention interventions and response efforts.

The results of our last aim identified increasing rates of opioid overdose mortality in states that had enacted legislation banning kratom. People are currently using kratom in an effort to wean off of or as a substitute for prescription and illicit opioids, however, there are no regulations in place to ensure the quality and safety of the product. A recent study has shown that risk of death from opioids is more than 1000 times greater than the risk of death from kratom (124). Lawmakers should focus their attention on regulating kratom production and future studies should seek to confirm the proposed benefits that may come from using this substance in its organic, unadulterated form.
Ending the opioid epidemic is not going to be as simple as removing the supply of opioids. We argue that public health leaders should focus on prevention efforts that target the underlying social determinants that are outlined in this dissertation and in the meantime, attention should be given to regulating and standardizing safer alternatives, such as kratom. For example, efforts to alleviate neighborhood-level poverty and the promotion of access to education, employment, and housing would likely strengthen overdose prevention efforts, though it may be many generations before we see a measurable change in the outcome. In order to target the upstream factors most effectively, there needs to be a focus on health equity. According to the CDC, “health equity is the state in which everyone has a fair and just opportunity to attain their highest level of health” (125). In order to achieve health equity, efforts should focus on historical and contemporary injustices (e.g., overcoming economic, social, and other barriers to health and healthcare) and eliminate preventable health disparities. The conditions and areas in which people live contribute to health inequities and focusing more attention on these factors of drug overdose would likely have a positive effect on the downstream factors as well (126). The results of this dissertation have outlined many of the factors that need to be addressed in order to reach health equity in regard to the opioid epidemic.

Public health 3.0 is a model in which public health leaders leverage data and resources to address social, economic, and environmental conditions that affect health (127). One of the recommendations to achieve Public Health 3.0 is to provide timely, reliable, and actionable data to communities throughout the country to develop, guide and assess the impact of policy and prevention programs that target the social determinants of health and increase health equity. The results of this dissertation can be used to develop programs directed at addressing the underlying structural and social risk factors that were identified as increasing the risk of opioid
overdose mortality. Without treating everyone as equals, regardless of their socioeconomic status or where they live, and providing equal access to resources and opportunities, we will continue to see preventable opioid overdose deaths in the United States.
### Table 1.1. County-Level Socioeconomic Characteristics of US Counties by Prescription Opioid Overdose Mortality Rates per 100,000 people, 2010-2019

<table>
<thead>
<tr>
<th></th>
<th>Suppressed(^a)/Unreliable(^b)</th>
<th>Tertile 1(^c)</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Counties</td>
<td>n=1,992</td>
<td>n=382</td>
<td>n=383</td>
<td>n=383</td>
</tr>
<tr>
<td>Median death rate per 100,000 (IQR)</td>
<td>1.6 (0.8, 4.2)</td>
<td>4.2 (3.1, 4.9)</td>
<td>7.6 (6.7, 8.5)</td>
<td>13.6 (11.3, 17.8)</td>
</tr>
<tr>
<td>% civilian noninstitutionalized population with a disability</td>
<td>16.5 (4.4)</td>
<td>12.6 (3.1)</td>
<td>14.6 (3.2)</td>
<td>18.0 (4.7)</td>
</tr>
<tr>
<td>% Bachelor’s degree or higher</td>
<td>19.3 (7.5)</td>
<td>32.4 (11.9)</td>
<td>26.5 (9.4)</td>
<td>20.8 (7.9)</td>
</tr>
<tr>
<td>% of grandparents responsible for grandchildren</td>
<td>48.5 (20.4)</td>
<td>36.5 (10.9)</td>
<td>41.2 (11.2)</td>
<td>48.4 (12.4)</td>
</tr>
<tr>
<td>% vacant housing units</td>
<td>21.8 (11.7)</td>
<td>11.0 (6.4)</td>
<td>13.9 (8.7)</td>
<td>17.1 (9.1)</td>
</tr>
<tr>
<td>% with income below poverty level</td>
<td>15.6 (6.7)</td>
<td>13.0 (5.3)</td>
<td>13.5 (4.5)</td>
<td>16.3 (5.6)</td>
</tr>
<tr>
<td>% with public health insurance</td>
<td>40.3 (8.8)</td>
<td>33.7 (8.1)</td>
<td>37.8 (7.6)</td>
<td>42.5 (9.5)</td>
</tr>
<tr>
<td>% civilian noninstitutionalized population employed</td>
<td>54.3 (8.6)</td>
<td>59.8 (6.5)</td>
<td>57.4 (5.9)</td>
<td>52.7 (7.7)</td>
</tr>
<tr>
<td>Gini Index of Income Inequality</td>
<td>0.443 (0.039)</td>
<td>0.452 (0.034)</td>
<td>0.446 (0.030)</td>
<td>0.450 (0.032)</td>
</tr>
<tr>
<td>% with different residence 1 year ago</td>
<td>12.0 (4.2)</td>
<td>14.5 (4.1)</td>
<td>13.5 (3.7)</td>
<td>12.8 (3.4)</td>
</tr>
<tr>
<td>% males ≥15 year never married</td>
<td>30.7 (7.6)</td>
<td>35.8 (6.4)</td>
<td>33.2 (5.5)</td>
<td>30.6 (5.3)</td>
</tr>
<tr>
<td>% females ≥15 year never married</td>
<td>22.9 (7.2)</td>
<td>29.7 (6.7)</td>
<td>26.5 (5.7)</td>
<td>23.5 (5.2)</td>
</tr>
<tr>
<td>County median age</td>
<td>42.2 (5.6)</td>
<td>38.2 (4.7)</td>
<td>40.4 (4.6)</td>
<td>41.7 (4.6)</td>
</tr>
<tr>
<td>% who are White</td>
<td>83.7 (17.9)</td>
<td>76.2 (16.8)</td>
<td>82.3 (13.1)</td>
<td>86.4 (11.5)</td>
</tr>
<tr>
<td>% who are female</td>
<td>49.5 (2.7)</td>
<td>50.7 (1.3)</td>
<td>50.5 (1.3)</td>
<td>50.5 (1.5)</td>
</tr>
<tr>
<td>% who are non-Hispanic</td>
<td>90.8 (14.9)</td>
<td>87.1 (13.6)</td>
<td>90.2 (11.0)</td>
<td>93.0 (10.0)</td>
</tr>
</tbody>
</table>

**Note.** Values are means (SD) unless otherwise noted. The following multiple cause-of-death codes were used to define prescription opioid overdose deaths: T40.2 (natural and semisynthetic opioids) and T40.3 (methadone).

\(^a\)Suppressed counties with <10 deaths were assigned a value of 1 (n=1535)

\(^b\)Counties with 10-19 deaths were considered unreliable by the CDC (n=457)

\(^c\)Tertiles of opioid death rates.
Table 1.2. Principal Component (PC) Loadings Showing the Correlations Between the PC Scores and the 11 County-Level Social and Economic Variables and Percentage of the Variance Explained and Eigenvalues for Each PC

<table>
<thead>
<tr>
<th>Percentage of Variability Explained</th>
<th>PC1</th>
<th>PC2</th>
<th>PC3</th>
<th>PC4</th>
</tr>
</thead>
<tbody>
<tr>
<td>% males ≥15 years who never married</td>
<td>-0.01</td>
<td>0.89</td>
<td>0.00</td>
<td>-0.09</td>
</tr>
<tr>
<td>% females ≥15 years who never married</td>
<td>-0.13</td>
<td>0.90</td>
<td>-0.05</td>
<td>-0.18</td>
</tr>
<tr>
<td>% of grandparents responsible for grandchildren</td>
<td><strong>0.44</strong></td>
<td>-0.08</td>
<td><strong>0.67</strong></td>
<td>-0.09</td>
</tr>
<tr>
<td>% Bachelor's degree or higher</td>
<td>-0.71</td>
<td>0.29</td>
<td>-0.20</td>
<td>0.28</td>
</tr>
<tr>
<td>% civilian noninstitutionalized population with a disability</td>
<td>0.85</td>
<td>-0.16</td>
<td>0.09</td>
<td>0.19</td>
</tr>
<tr>
<td>% with different residence 1 year ago</td>
<td>-0.21</td>
<td>0.47</td>
<td><strong>0.42</strong></td>
<td><strong>0.71</strong></td>
</tr>
<tr>
<td>% vacant housing units</td>
<td><strong>0.48</strong></td>
<td>-0.21</td>
<td><strong>-0.49</strong></td>
<td>0.39</td>
</tr>
<tr>
<td>% civilian noninstitutionalized population employed</td>
<td><strong>-0.89</strong></td>
<td>-0.11</td>
<td>0.06</td>
<td>-0.11</td>
</tr>
<tr>
<td>% with public health insurance</td>
<td>0.88</td>
<td>-0.03</td>
<td>-0.10</td>
<td>0.04</td>
</tr>
<tr>
<td>% with income below poverty level</td>
<td><strong>0.74</strong></td>
<td><strong>0.53</strong></td>
<td>0.05</td>
<td>-0.14</td>
</tr>
<tr>
<td>Gini Index of Income Inequality</td>
<td><strong>0.41</strong></td>
<td>0.59</td>
<td>-0.24</td>
<td>-0.01</td>
</tr>
</tbody>
</table>

*Note*-Counties with high PC1 scores reflect socioeconomic factors related to extreme disadvantage; counties with high PC2 scores reflect a pattern of single and in poverty yet educated; counties with high PC3 scores reflect a pattern of grandparents raising grandchildren with residential instability; and counties with high PC4 scores reflect a pattern of education with residential instability. Values in bold indicate component loadings >0.40.
### Supplemental Table 1.1. County-Level Socioeconomic Characteristics of US Counties by Groups of County Prescription Opioid Overdose Mortality Rates per 100,000 people, 2010-2019

<table>
<thead>
<tr>
<th></th>
<th>Suppressed(^a/) Unreliable(^b)</th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Counties</strong></td>
<td>1,992</td>
<td>382</td>
<td>383</td>
<td>383</td>
</tr>
<tr>
<td><strong>Median death rate per 100,000 (IQR)</strong></td>
<td>1.6 (0.8, 4.2)</td>
<td>4.2 (3.1, 4.9)</td>
<td>7.6 (6.7, 8.5)</td>
<td>13.6 (11.3, 17.8)</td>
</tr>
<tr>
<td>% of married household families</td>
<td>50.9 (6.9)</td>
<td>49.7 (7.4)</td>
<td>50.0 (6.0)</td>
<td>50.2 (6.1)</td>
</tr>
<tr>
<td>% of families that are male head of household</td>
<td>18.4 (3.3)</td>
<td>17.3 (2.9)</td>
<td>17.3 (2.4)</td>
<td>17.4 (2.5)</td>
</tr>
<tr>
<td>% of families that are female head of household</td>
<td>25.2 (5.8)</td>
<td>26.8 (4.9)</td>
<td>26.2 (4.2)</td>
<td>26.3 (3.8)</td>
</tr>
<tr>
<td>% males ≥15 y never married</td>
<td>30.7 (7.6)</td>
<td>35.8 (6.4)</td>
<td>33.2 (5.5)</td>
<td>30.6 (5.3)</td>
</tr>
<tr>
<td>% married males, except separated</td>
<td>52.7 (8.1)</td>
<td>50.5 (6.3)</td>
<td>51.4 (5.2)</td>
<td>51.9 (5.4)</td>
</tr>
<tr>
<td>% separated males</td>
<td>1.7 (1.2)</td>
<td>1.5 (0.7)</td>
<td>1.6 (0.6)</td>
<td>1.9 (0.8)</td>
</tr>
<tr>
<td>% widowed males</td>
<td>3.5 (1.4)</td>
<td>2.6 (0.7)</td>
<td>3.0 (0.8)</td>
<td>3.5 (1.0)</td>
</tr>
<tr>
<td>% separated males</td>
<td>11.5 (3.0)</td>
<td>9.5 (2.0)</td>
<td>10.9 (2.1)</td>
<td>12.1 (2.2)</td>
</tr>
<tr>
<td>% females ≥15 y never married</td>
<td>22.9 (7.2)</td>
<td>29.7 (6.7)</td>
<td>26.5 (5.7)</td>
<td>23.5 (5.2)</td>
</tr>
<tr>
<td>% married females, except separated</td>
<td>51.8 (8.0)</td>
<td>47.7 (6.6)</td>
<td>48.9 (5.3)</td>
<td>49.6 (5.2)</td>
</tr>
<tr>
<td>% separated females</td>
<td>2.0 (1.4)</td>
<td>2.0 (0.9)</td>
<td>2.0 (0.8)</td>
<td>2.3 (0.9)</td>
</tr>
<tr>
<td>% widowed females</td>
<td>11.5 (2.9)</td>
<td>8.7 (2.0)</td>
<td>9.6 (1.8)</td>
<td>10.9 (2.3)</td>
</tr>
<tr>
<td>% divorced females</td>
<td>11.8 (3.0)</td>
<td>12.0 (1.8)</td>
<td>13.0 (1.9)</td>
<td>13.7 (2.1)</td>
</tr>
<tr>
<td>% of grandparents responsible for grandchildren</td>
<td>49.2 (19.7)</td>
<td>36.5 (10.9)</td>
<td>41.2 (11.2)</td>
<td>48.4 (12.4)</td>
</tr>
<tr>
<td>% less than high school</td>
<td>5.1 (4.0)</td>
<td>4.2 (2.8)</td>
<td>3.9 (2.5)</td>
<td>4.9 (2.7)</td>
</tr>
<tr>
<td>% high school graduates</td>
<td>86.3 (6.8)</td>
<td>89.5 (4.8)</td>
<td>88.9 (4.5)</td>
<td>86.1 (5.2)</td>
</tr>
<tr>
<td>% Bachelor’s degree or higher</td>
<td>19.3 (7.5)</td>
<td>32.4 (11.9)</td>
<td>26.5 (9.4)</td>
<td>20.8 (7.9)</td>
</tr>
<tr>
<td>% civilian noninstitutionalized population with a disability</td>
<td>16.5 (4.4)</td>
<td>12.6 (3.1)</td>
<td>14.6 (3.2)</td>
<td>18.0 (4.7)</td>
</tr>
<tr>
<td>% with different residence 1 y ago</td>
<td>12.0 (4.2)</td>
<td>14.5 (4.1)</td>
<td>13.5 (3.7)</td>
<td>12.8 (3.4)</td>
</tr>
<tr>
<td>% born in the United States</td>
<td>95.6 (5.1)</td>
<td>89.0 (9.0)</td>
<td>92.3 (6.4)</td>
<td>95.5 (3.8)</td>
</tr>
<tr>
<td>SMOCAPI ≥ 35%</td>
<td>8.8 (3.3)</td>
<td>9.9 (3.4)</td>
<td>9.8 (3.3)</td>
<td>8.6 (2.7)</td>
</tr>
<tr>
<td>GRAPI ≥ 35%</td>
<td>33.0 (9.9)</td>
<td>39.1 (5.5)</td>
<td>37.8 (5.9)</td>
<td>37.1 (6.0)</td>
</tr>
<tr>
<td>% occupied housing units</td>
<td>78.2 (11.7)</td>
<td>89.0 (6.4)</td>
<td>86.1 (8.7)</td>
<td>82.9 (9.1)</td>
</tr>
<tr>
<td>% vacant housing units</td>
<td>21.8 (11.7)</td>
<td>11.0 (6.4)</td>
<td>13.9 (8.7)</td>
<td>17.1 (9.1)</td>
</tr>
<tr>
<td>% owner occupied housing</td>
<td>73.0 (7.9)</td>
<td>66.4 (9.7)</td>
<td>69.5 (8.3)</td>
<td>71.5 (6.4)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>% renter occupied housing</td>
<td>27.0 (7.9)</td>
<td>33.6 (9.7)</td>
<td>30.5 (8.3)</td>
<td>28.5 (6.4)</td>
</tr>
<tr>
<td>Home value</td>
<td>129477.6</td>
<td>234737.2</td>
<td>196983.8</td>
<td>156343.3</td>
</tr>
<tr>
<td></td>
<td>(70360.8)</td>
<td>(144946.6)</td>
<td>(105972.4)</td>
<td>(72456.9)</td>
</tr>
<tr>
<td>% of civilian noninstitutionalized population in the labor force</td>
<td>57.3 (8.2)</td>
<td>63.6 (6.1)</td>
<td>61.0 (5.7)</td>
<td>56.1 (7.6)</td>
</tr>
<tr>
<td>% civilian noninstitutionalized population employed</td>
<td>54.3 (8.6)</td>
<td>59.8 (6.5)</td>
<td>57.4 (5.9)</td>
<td>52.7 (7.7)</td>
</tr>
<tr>
<td>Median Household income</td>
<td>50286.6 (11550.8)</td>
<td>65838.6 (18354.0)</td>
<td>59962.3 (14065.8)</td>
<td>51346.9 (13132.6)</td>
</tr>
<tr>
<td>% of all people receiving food stamps</td>
<td>12.8 (6.8)</td>
<td>10.9 (4.9)</td>
<td>12.3 (4.8)</td>
<td>15.0 (5.8)</td>
</tr>
<tr>
<td>Per capita income</td>
<td>26635.8 (5712.0)</td>
<td>33672.8 (8880.6)</td>
<td>31088.4 (6719.9)</td>
<td>27029.8 (5534.6)</td>
</tr>
<tr>
<td>% with private health insurance</td>
<td>64.4 (11.0)</td>
<td>70.8 (9.0)</td>
<td>68.4 (8.0)</td>
<td>63.0 (8.9)</td>
</tr>
<tr>
<td>% with public health insurance</td>
<td>40.3 (8.8)</td>
<td>33.7 (8.1)</td>
<td>37.8 (7.6)</td>
<td>42.5 (9.5)</td>
</tr>
<tr>
<td>% with no health insurance</td>
<td>10.3 (5.6)</td>
<td>8.2 (4.1)</td>
<td>8.0 (3.6)</td>
<td>9.1 (3.6)</td>
</tr>
<tr>
<td>% with income below poverty level</td>
<td>15.6 (6.7)</td>
<td>13.0 (5.3)</td>
<td>13.5 (4.5)</td>
<td>16.3 (5.6)</td>
</tr>
<tr>
<td>Gini Index of income inequality</td>
<td>0.4 (0.0)</td>
<td>0.5 (0.0)</td>
<td>0.4 (0.0)</td>
<td>0.4 (0.0)</td>
</tr>
</tbody>
</table>

Note: Values are means (SD) unless otherwise noted. The following multiple cause-of-death codes were used to define prescription opioid overdose deaths: T40.2 (natural and semisynthetic opioids) and T40.3 (methadone).

*suppressed counties with <10 deaths were assigned a value of 1 (n=1535)

*counties with 10-19 deaths were considered unreliable by the CDC (n=457)
### Supplemental Table 1.2. Pearson Correlation Coefficients for County-Level American Community Survey Social and Economic Variables, 2015-2019

<table>
<thead>
<tr>
<th>Variable Description</th>
<th>Pearson Correlation Coefficient</th>
<th>Significance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population in Below Poverty Level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>House occupancy owner</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Houses that are occupied</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross rent as a percentage of HH income ≥35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disabled non-institutionalized civilians</td>
<td></td>
<td></td>
</tr>
<tr>
<td>College graduate or higher</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults females who are divorced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults females who are widowed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult males who are divorced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males ≥15 who are single, never married</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The table contains detailed correlation coefficients and significance levels for various social and economic variables at the county level, spanning the years 2015 to 2019.
Supplemental Table 1.3. Mutually Adjusted Relative Risk (RR) Estimates (95% Confidence Intervals [CIs]) of Prescription Opioid Overdose Mortality for counties with at least 20 deaths in the US 2010-2019 for 4 Principal Components (PCs) and County-Level Adjustment Factors (n=1406)

<table>
<thead>
<tr>
<th></th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;, RR (95% CI)</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt;, RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC1</td>
<td>1.28 (1.23, 1.32)</td>
<td>1.33 (1.27, 1.39)</td>
</tr>
<tr>
<td>PC2</td>
<td>0.93 (0.89, 0.96)</td>
<td>0.94 (0.89, 1.00)</td>
</tr>
<tr>
<td>PC3</td>
<td>1.07 (1.02, 1.12)</td>
<td>1.00 (0.94, 1.07)</td>
</tr>
<tr>
<td>PC4</td>
<td>1.07 (1.02, 1.11)</td>
<td>1.04 (0.99, 1.09)</td>
</tr>
<tr>
<td>County median age</td>
<td></td>
<td>0.93 (0.87, 0.99)</td>
</tr>
<tr>
<td>% in county who are White</td>
<td></td>
<td>1.09 (1.05, 1.13)</td>
</tr>
<tr>
<td>% in county who are non-Hispanic</td>
<td></td>
<td>1.13 (1.09, 1.17)</td>
</tr>
<tr>
<td>% in county who are female</td>
<td></td>
<td>1.02 (0.97, 1.06)</td>
</tr>
</tbody>
</table>

Note. The following multiple cause-of-death codes were used to define prescription opioid overdose deaths: T40.2 (natural and semisynthetic opioids) and T40.3 (methadone).
All estimates are for a 1-standard-deviation (SD) increase. SD for age is 4.84 years, SD for race is 14.56%, SD for non-Hispanic is 11.86%, and SD for female is 1.38%.

<sup>a</sup>Model 1 included the PCs, population size and a square term for population size.

<sup>b</sup>Model 2 included Model 1 covariates and county median age, percentage of the population that was White, percentage of the population that was non-Hispanic and percentage of the population that was female.
### Supplemental Table 1.4. Mutually Adjusted Relative Risk (RR) Estimates (95% Confidence Intervals [CIs]) for Different Outcome Definitions of Opioid Overdose Mortality in the US 2010-2019 for 4 Principal Components (PCs) and County-Level Adjustment Factors (n=3,140)

<table>
<thead>
<tr>
<th></th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Model 3&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Model 4&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prescription Opioids (T40.2-T40.3)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC1</td>
<td>1.15 (1.12, 1.18)</td>
<td>1.10 (1.06, 1.13)</td>
<td>1.15 (1.12, 1.19)</td>
<td>1.17 (1.13, 1.21)</td>
</tr>
<tr>
<td>PC2</td>
<td>0.96 (0.94, 0.99)</td>
<td>1.05 (1.01, 1.09)</td>
<td>1.05 (1.01, 1.09)</td>
<td>1.01 (0.96, 1.05)</td>
</tr>
<tr>
<td>PC3</td>
<td>1.05 (1.02, 1.09)</td>
<td>1.15 (1.10, 1.20)</td>
<td>1.06 (1.02, 1.11)</td>
<td>1.05 (1.00, 1.10)</td>
</tr>
<tr>
<td>PC4</td>
<td>1.10 (1.07, 1.13)</td>
<td>1.06 (1.02, 1.09)</td>
<td>1.04 (1.01, 1.07)</td>
<td>1.07 (1.04, 1.11)</td>
</tr>
<tr>
<td>County median age</td>
<td>--</td>
<td>1.16 (1.10, 1.21)</td>
<td>1.04 (0.99, 1.10)</td>
<td>0.99 (0.94, 1.05)</td>
</tr>
<tr>
<td>% in county who are White</td>
<td>--</td>
<td>--</td>
<td>1.10 (1.06, 1.13)</td>
<td>1.11 (1.08, 1.15)</td>
</tr>
<tr>
<td>% in county who are non-Hispanic</td>
<td>--</td>
<td>--</td>
<td>1.13 (1.10, 1.16)</td>
<td>1.11 (1.08, 1.14)</td>
</tr>
<tr>
<td>% in county who are female</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1.17 (1.11, 1.23)</td>
</tr>
<tr>
<td><strong>Illicit Opioids (T40.0, T40.1 &amp; T40.4)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC1</td>
<td>1.01 (0.98, 1.04)</td>
<td>0.84 (0.81, 0.87)</td>
<td>0.91 (0.88, 0.95)</td>
<td>0.93 (0.90, 0.96)</td>
</tr>
<tr>
<td>PC2</td>
<td>1.13 (1.10, 1.17)</td>
<td>1.55 (1.49, 1.62)</td>
<td>1.56 (1.50, 1.63)</td>
<td>1.46 (1.40, 1.53)</td>
</tr>
<tr>
<td>PC3</td>
<td>0.96 (0.92, 0.99)</td>
<td>1.32 (1.26, 1.38)</td>
<td>1.15 (1.10, 1.21)</td>
<td>1.13 (1.08, 1.19)</td>
</tr>
<tr>
<td>PC4</td>
<td>0.95 (0.92, 0.98)</td>
<td>0.81 (0.78, 0.84)</td>
<td>0.78 (0.76, 0.81)</td>
<td>0.82 (0.79, 0.84)</td>
</tr>
<tr>
<td>County median age</td>
<td>--</td>
<td>1.73 (1.65, 1.83)</td>
<td>1.45 (1.37, 1.54)</td>
<td>1.35 (1.27, 1.43)</td>
</tr>
<tr>
<td>% in county who are White</td>
<td>--</td>
<td>--</td>
<td>1.18 (1.14, 1.22)</td>
<td>1.22 (1.18, 1.26)</td>
</tr>
<tr>
<td>% in county who are non-Hispanic</td>
<td>--</td>
<td>--</td>
<td>1.21 (1.17, 1.24)</td>
<td>1.18 (1.15, 1.22)</td>
</tr>
<tr>
<td>% in county who are female</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1.30 (1.23, 1.38)</td>
</tr>
<tr>
<td><strong>All Opioids (T40.0-T40.4 &amp; T40.6)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC1</td>
<td>1.08 (1.05, 1.11)</td>
<td>0.94 (0.91, 0.97)</td>
<td>1.02 (0.99, 1.05)</td>
<td>1.03 (1.00, 1.07)</td>
</tr>
<tr>
<td>PC2</td>
<td>1.06 (1.03, 1.08)</td>
<td>1.34 (1.29, 1.39)</td>
<td>1.35 (1.30, 1.40)</td>
<td>1.28 (1.23, 1.33)</td>
</tr>
<tr>
<td>PC3</td>
<td>0.98 (0.95, 1.01)</td>
<td>1.25 (1.20, 1.30)</td>
<td>1.09 (1.05, 1.14)</td>
<td>1.08 (1.03, 1.12)</td>
</tr>
<tr>
<td>PC4</td>
<td>1.00 (0.97, 1.02)</td>
<td>0.89 (0.86, 0.91)</td>
<td>0.86 (0.83, 0.89)</td>
<td>0.89 (0.86, 0.92)</td>
</tr>
<tr>
<td>County median age</td>
<td>--</td>
<td>1.51 (1.44, 1.58)</td>
<td>1.27 (1.20, 1.33)</td>
<td>1.19 (1.14, 1.26)</td>
</tr>
<tr>
<td>% in county who are White</td>
<td>--</td>
<td>--</td>
<td>1.18 (1.15, 1.22)</td>
<td>1.21 (1.17, 1.25)</td>
</tr>
<tr>
<td>% in county who are non-Hispanic</td>
<td>--</td>
<td>--</td>
<td>1.22 (1.19, 1.25)</td>
<td>1.20 (1.17, 1.23)</td>
</tr>
<tr>
<td>% in county who are female</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1.22 (1.16, 1.28)</td>
</tr>
</tbody>
</table>

*Note.* The following multiple cause-of-death codes were used to identify specific opioids involved in overdose mortality: T40.0 (opium), T40.1 (heroin), T40.2 (natural and semisynthetic opioids), T40.3 (methadone), T40.4 (synthetic opioids other than methadone), and T40.6 (other and unspecified narcotics).

All estimates are for a 1-standard-deviation (SD) increase. SD for age is 5.4 years, SD for race is 16.78%, SD for non-Hispanic is 13.87%, and SD for female is 2.35%.

<sup>a</sup>Model 1 included the PCs, population size and a square term for population size.

<sup>b</sup>Model 2 included model 1 and county median age.

<sup>c</sup>Model 3 included model 2 and percentage of the population that was White and percentage of the population that was non-Hispanic.

<sup>d</sup>Model 4 included model 3 covariates and additionally included the percentage of the population that was female.
Table 2.1. Opioid-Related Hospitalizations (ICD-10 Codes: T40.0-T40.4, & T40.6) in Kentucky between 2016-2020 by patient residence in a rural or urban county

<table>
<thead>
<tr>
<th>Diagnoses codes related to overdose</th>
<th>Rural, % (n)</th>
<th>Urban, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Opium (T40.0)</td>
<td>0.7 (148)</td>
<td>0.6 (254)</td>
</tr>
<tr>
<td>- Heroin (T40.1)</td>
<td>17.4 (3906)</td>
<td>46.3 (18850)</td>
</tr>
<tr>
<td>- Prescription: Natural and semisynthetic opioids (T40.2)</td>
<td>56.3 (12604)</td>
<td>33.3 (13554)</td>
</tr>
<tr>
<td>- Prescription: Methadone (T40.3)</td>
<td>1.6 (346)</td>
<td>1.1 (431)</td>
</tr>
<tr>
<td>- Synthetic opioids other than methadone (T40.4)</td>
<td>7.0 (1572)</td>
<td>4.3 (1742)</td>
</tr>
<tr>
<td>- Other and unspecified narcotics (T40.6)</td>
<td>18.6 (4155)</td>
<td>15.6 (6332)</td>
</tr>
<tr>
<td>Patient died from overdose, % (n)</td>
<td>1.2 (266)</td>
<td>1.3 (543)</td>
</tr>
<tr>
<td>Female</td>
<td>53.3 (11944)</td>
<td>46.3 (18856)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- White</td>
<td>97.6 (21855)</td>
<td>90.5 (36838)</td>
</tr>
<tr>
<td>- Black</td>
<td>1.9 (429)</td>
<td>8.4 (3421)</td>
</tr>
<tr>
<td>- Asian</td>
<td>0.0 (11)</td>
<td>0.2 (93)</td>
</tr>
<tr>
<td>- Native Hawaiian or Pacific Islander</td>
<td>0.0 (8)</td>
<td>0.1 (21)</td>
</tr>
<tr>
<td>- American Indian or Alaska Native</td>
<td>0.0 (10)</td>
<td>0.1 (34)</td>
</tr>
<tr>
<td>- Missing</td>
<td>0.4 (80)</td>
<td>0.8 (306)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.2 (265)</td>
<td>0.9 (373)</td>
</tr>
<tr>
<td>Age Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 18-29 years</td>
<td>12.4 (2773)</td>
<td>21.8 (8856)</td>
</tr>
<tr>
<td>- 30-39 years</td>
<td>15.7 (3516)</td>
<td>24.9 (10139)</td>
</tr>
<tr>
<td>- 40-49 years</td>
<td>15.3 (3420)</td>
<td>15.4 (6251)</td>
</tr>
<tr>
<td>- 50-59 years</td>
<td>20.2 (4523)</td>
<td>15.1 (6134)</td>
</tr>
<tr>
<td>- 60-69 years</td>
<td>19.1 (4287)</td>
<td>11.1 (4529)</td>
</tr>
<tr>
<td>- 70+ years</td>
<td>16.9 (3775)</td>
<td>11.3 (4602)</td>
</tr>
<tr>
<td>- Missing</td>
<td>0.4 (99)</td>
<td>0.5 (202)</td>
</tr>
<tr>
<td>Admission Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Emergency</td>
<td>55.5 (12438)</td>
<td>77.9 (31725)</td>
</tr>
<tr>
<td>- Urgent</td>
<td>11.2 (2497)</td>
<td>5.0 (2040)</td>
</tr>
<tr>
<td>- Elective</td>
<td>32.7 (7331)</td>
<td>16.8 (6848)</td>
</tr>
<tr>
<td>- Trauma</td>
<td>0.5 (123)</td>
<td>0.2 (95)</td>
</tr>
<tr>
<td>- Missing</td>
<td>0.0 (4)</td>
<td>0.0 (5)</td>
</tr>
<tr>
<td>Inpatient</td>
<td>37.6 (8421)</td>
<td>26.8 (10900)</td>
</tr>
<tr>
<td>Length of Stay for Inpatient Hospitalizations, Days, mean (SD)</td>
<td>5.7 (6.3)</td>
<td>5.7 (6.2)</td>
</tr>
<tr>
<td>COVID-19 pandemic</td>
<td>14.9 (3345)</td>
<td>15.6 (6354)</td>
</tr>
<tr>
<td>% of zip code with at least a High School degree, mean (SD)³</td>
<td>81.4 (7.5)</td>
<td>87.9 (5.0)</td>
</tr>
<tr>
<td>% of zip code living below the poverty level, mean (SD)³</td>
<td>22.1 (8.4)</td>
<td>17.2 (10.1)</td>
</tr>
<tr>
<td>Admitted to urban hospital</td>
<td>42.3 (9473)</td>
<td>98.4 (40066)</td>
</tr>
</tbody>
</table>

³Missing values coded to the median value (0.82% missing % of the zip code with at least a high school degree; 0.83% missing % of the zip code living below the poverty level)
Table 2.2. Patient Discharge Status by Urbanicity in Kentucky opioid hospitalizations\(^a\), 2016-2020

<table>
<thead>
<tr>
<th>Patient Discharge Status</th>
<th>Rural Patients Overall, %(n) (n=22,393)</th>
<th>Rural Patients seen in Rural Hospital, %%(n) (n=12,920)</th>
<th>Rural Patients seen in Urban Hospital, %%(n) (n=9,473)</th>
<th>Urban Patients(^b) Overall, %%(n) (n=40,713)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine discharge (home/self-care)</td>
<td>74.01 (16574)</td>
<td>67.67 (8743)</td>
<td>82.67 (7831)</td>
<td>76.97 (31338)</td>
</tr>
<tr>
<td>Long-term care and other facilities</td>
<td>9.89 (2215)</td>
<td>11.90 (1537)</td>
<td>7.15 (678)</td>
<td>8.42 (3428)</td>
</tr>
<tr>
<td>Home health care</td>
<td>6.64 (1488)</td>
<td>7.40 (956)</td>
<td>5.61 (532)</td>
<td>3.64 (1483)</td>
</tr>
<tr>
<td>Against medical advice</td>
<td>5.63 (1261)</td>
<td>7.62 (985)</td>
<td>2.91 (276)</td>
<td>8.51 (3464)</td>
</tr>
<tr>
<td>Another short-term hospital</td>
<td>2.54 (568)</td>
<td>3.97 (513)</td>
<td>0.58 (55)</td>
<td>1.11 (451)</td>
</tr>
<tr>
<td>In-hospital deaths</td>
<td>1.19 (266)</td>
<td>1.26 (163)</td>
<td>1.09 (103)</td>
<td>1.33 (543)</td>
</tr>
<tr>
<td>Inpatient</td>
<td>0.11 (24)</td>
<td>0.18 (23)</td>
<td>0.01 (1)</td>
<td>0.01 (6)</td>
</tr>
</tbody>
</table>

Note- Percentages are column percentages.

\(^a\)The following billable codes were used to identify specific opioids involved: T40.0 (opium), T40.1 (heroin), T40.2 (natural and semisynthetic opioids), T40.3 (methadone), T40.4 (synthetic opioids other than methadone), and T40.6 (other and unspecified narcotics).

\(^b\)98.4% of urban patients seen in urban hospitals
Table 2.3. Adjusted Odds Ratio (OR) Estimates (95% Confidence Intervals [CIs]) of Overdose Mortality from any Opioids (n=63,106) and from prescription opioids (n=26,888) in Kentucky opioid hospitalizations, 2016-2020

<table>
<thead>
<tr>
<th></th>
<th># of deaths</th>
<th># of opioid hospitalizations</th>
<th>Model 1(^a) aOR (95% CI)</th>
<th>Model 2(^b) aOR (95% CI)</th>
<th>Model 3(^c) aOR (95% CI)</th>
<th>Model 4(^d) aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Opioid Hospitalizations (T40.0-T40.4 &amp; T40.6)</strong>(^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban-Rural binary Classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>543</td>
<td>40,713</td>
<td>1.16 (0.99, 1.35)</td>
<td>1.32 (1.13, 1.53)</td>
<td>1.32 (1.13, 1.54)</td>
<td>1.46 (1.22, 1.74)</td>
</tr>
<tr>
<td>Rural</td>
<td>266</td>
<td>22,393</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td><strong>Categories of Urbanicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large central metro</td>
<td>221</td>
<td>13,244</td>
<td>1.39 (1.12, 1.72)</td>
<td>1.61 (1.30, 2.00)</td>
<td>1.65 (1.32, 2.05)</td>
<td>1.92 (1.49, 2.47)</td>
</tr>
<tr>
<td>Large fringe metro</td>
<td>122</td>
<td>12,686</td>
<td>0.79 (0.62, 1.01)</td>
<td>0.99 (0.77, 1.27)</td>
<td>0.99 (0.77, 1.26)</td>
<td>1.15 (0.87, 1.52)</td>
</tr>
<tr>
<td>Medium metro</td>
<td>146</td>
<td>12,081</td>
<td>0.95 (0.75, 1.19)</td>
<td>1.37 (1.09, 1.74)</td>
<td>1.40 (1.11, 1.77)</td>
<td>1.62 (1.24, 2.13)</td>
</tr>
<tr>
<td>Small metro</td>
<td>54</td>
<td>2,702</td>
<td>1.57 (1.15, 2.15)</td>
<td>1.21 (0.88, 1.67)</td>
<td>1.24 (0.90, 1.71)</td>
<td>1.42 (1.01, 2.00)</td>
</tr>
<tr>
<td>Micropolitan</td>
<td>120</td>
<td>11,007</td>
<td>0.86 (0.67, 1.09)</td>
<td>1.00 (0.79, 1.28)</td>
<td>1.01 (0.79, 1.30)</td>
<td>1.11 (0.86, 1.43)</td>
</tr>
<tr>
<td>Noncore</td>
<td>146</td>
<td>11,386</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td><strong>Prescription Opioid Hospitalizations (T40.2-T40.3)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban-Rural binary Classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>143</td>
<td>13,966</td>
<td>1.18 (0.92, 1.52)</td>
<td>1.10 (0.85, 1.42)</td>
<td>1.08 (0.84, 1.40)</td>
<td>1.23 (0.91, 1.67)</td>
</tr>
<tr>
<td>Rural</td>
<td>111</td>
<td>12,922</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td><strong>Illicit Opioid Hospitalizations (T40.0, T40.1 &amp; T40.4)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban-Rural binary Classification</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>293</td>
<td>20,742</td>
<td>1.02 (0.79, 1.31)</td>
<td>1.50 (1.16, 1.95)</td>
<td>1.53 (1.18, 1.98)</td>
<td>1.51 (1.12, 2.03)</td>
</tr>
<tr>
<td>Rural</td>
<td>79</td>
<td>5,586</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
</tbody>
</table>

\(^{a}\)Model 1 adjusted for age group

\(^{b}\)Model 2 - model 1 + length of stay, facility admission type, and inpatient/outpatient status

\(^{c}\)Model 3 - model 2+ race, ethnicity, and gender

\(^{d}\)Model 4 - model 3 + zip-code level % high school graduates and zip-code level % below poverty

\(^{e}\)The following billable codes were used to identify specific opioids involved: T40.0 (opium), T40.1 (heroin), T40.2 (natural and semisynthetic opioids), T40.3 (methadone), T40.4 (synthetic opioids other than methadone), and T40.6 (other and unspecified narcotics).
Table 2.4. Adjusted\(^a\) Odds Ratio (OR) Estimates (95% Confidence Intervals [CIs]) of Opioid Overdose Mortality before (n=53,407) and during the COVID-19 pandemic (n=9,699) in Kentucky opioid hospitalizations, 2016-2020

<table>
<thead>
<tr>
<th></th>
<th># of deaths</th>
<th># of opioid hospitalizations</th>
<th>Before COVID-19 aOR (95% CI)</th>
<th># of deaths</th>
<th>n</th>
<th>During COVID-19 aOR (95% CI)</th>
<th>p-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Opioid Hospitalizations (T40.0-T40.4 &amp; T40.6)(^b)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban-Rural binary Classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>482</td>
<td>34,359</td>
<td>1.63 (1.34, 1.97)</td>
<td>61</td>
<td>6,354</td>
<td>0.72 (0.45, 1.16)</td>
<td>0.02</td>
</tr>
<tr>
<td>Rural</td>
<td>223</td>
<td>19,048</td>
<td>REF</td>
<td>43</td>
<td>3,345</td>
<td>REF</td>
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</tr>
<tr>
<td><strong>Categories of Urbanicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>482</td>
<td>34,359</td>
<td></td>
<td>61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>223</td>
<td>19,048</td>
<td>REF</td>
<td>43</td>
<td></td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>Large central metro</td>
<td>193</td>
<td>10,902</td>
<td>2.10 (1.59, 2.76)</td>
<td>28</td>
<td>2,342</td>
<td>1.07 (0.53, 2.17)</td>
<td></td>
</tr>
<tr>
<td>Large fringe metro</td>
<td>111</td>
<td>10,891</td>
<td>1.27 (0.95, 1.72)</td>
<td>11</td>
<td>1,795</td>
<td>0.55 (0.24, 1.26)</td>
<td></td>
</tr>
<tr>
<td>Medium metro</td>
<td>128</td>
<td>10,304</td>
<td>1.77 (1.33, 2.36)</td>
<td>18</td>
<td>1,777</td>
<td>0.95 (0.45, 2.00)</td>
<td></td>
</tr>
<tr>
<td>Small metro</td>
<td>50</td>
<td>2,262</td>
<td>1.60 (1.12, 2.29)</td>
<td>4</td>
<td>440</td>
<td>0.56 (0.18, 1.76)</td>
<td></td>
</tr>
<tr>
<td>Micropolitan</td>
<td>98</td>
<td>9,347</td>
<td>1.08 (0.81, 1.43)</td>
<td>22</td>
<td>1,660</td>
<td>1.23 (0.65, 2.35)</td>
<td></td>
</tr>
<tr>
<td>Noncore</td>
<td>125</td>
<td>9,701</td>
<td>REF</td>
<td>21</td>
<td>1,685</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td><strong>Prescription Opioid Hospitalizations (T40.2-T40.3)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Urban-Rural binary Classification</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>120</td>
<td>11,755</td>
<td>1.34 (0.96, 1.86)</td>
<td>23</td>
<td>2,211</td>
<td>0.83 (0.38, 1.82)</td>
<td>0.91</td>
</tr>
<tr>
<td>Rural</td>
<td>95</td>
<td>11,098</td>
<td>REF</td>
<td>16</td>
<td>1,824</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td><strong>Illicit Opioid Hospitalizations (T40.0, T40.1 &amp; T40.4)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td>Urban-Rural binary Classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>267</td>
<td>17,670</td>
<td>1.74 (1.26, 2.40)</td>
<td>26</td>
<td>3,072</td>
<td>0.56 (0.26, 1.20)</td>
<td>0.04</td>
</tr>
<tr>
<td>Rural</td>
<td>64</td>
<td>4,582</td>
<td>REF</td>
<td>15</td>
<td>1,004</td>
<td>REF</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Estimates are adjusted for age-groups, race, ethnicity, gender, facility admission type, length of stay, inpatient or outpatient status, zip-code level % high school graduates and zip-code level % below poverty

\(^b\)The following billable codes were used to identify specific opioids involved: T40.0 (opium), T40.1 (heroin), T40.2 (natural and semisynthetic opioids), T40.3 (methadone), T40.4 (synthetic opioids other than methadone), and T40.6 (other and unspecified narcotics).
Supplemental Table 2.1. Adjusted Odds Ratio (OR) Estimates (95% Confidence Intervals [CIs]) of Overdose Mortality from any Opioids (n=63,106) in Kentucky opioid hospitalizations, 2016-2020

<table>
<thead>
<tr>
<th></th>
<th>Model 1 aOR (95% CI)</th>
<th>Model 2 aOR (95% CI)</th>
<th>Model 3 aOR (95% CI)</th>
<th>Model 4 aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urban-Rural binary Classification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Urban</td>
<td>1.16 (0.999, 1.35)</td>
<td>1.32 (1.13, 1.53)</td>
<td>1.32 (1.13, 1.54)</td>
<td>1.46 (1.22, 1.74)</td>
</tr>
<tr>
<td>- Rural</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td><strong>Age Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 18-29 years</td>
<td>0.95 (0.76, 1.20)</td>
<td>1.04 (0.82, 1.32)</td>
<td>1.03 (0.82, 1.31)</td>
<td>1.04 (0.82, 1.32)</td>
</tr>
<tr>
<td>- 30-39 years</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>- 40-49 years</td>
<td>1.26 (1.00, 1.58)</td>
<td>0.95 (0.75, 1.20)</td>
<td>0.98 (0.76, 1.24)</td>
<td>0.98 (0.77, 1.23)</td>
</tr>
<tr>
<td>- 50-59 years</td>
<td>1.12 (0.89, 1.41)</td>
<td>0.67 (0.53, 0.85)</td>
<td>0.70 (0.55, 0.89)</td>
<td>0.70 (0.55, 0.89)</td>
</tr>
<tr>
<td>- 60-69 years</td>
<td>1.00 (0.78, 1.29)</td>
<td>0.52 (0.40, 0.68)</td>
<td>0.55 (0.42, 0.71)</td>
<td>0.56 (0.43, 0.72)</td>
</tr>
<tr>
<td>- 70+ years</td>
<td>1.43 (1.14, 1.81)</td>
<td>0.61 (0.48, 0.77)</td>
<td>0.66 (0.52, 0.84)</td>
<td>0.67 (0.53, 0.86)</td>
</tr>
<tr>
<td>- Missing</td>
<td>0.28 (0.04, 2.02)</td>
<td>0.18 (0.03, 1.31)</td>
<td>0.19 (0.03, 1.35)</td>
<td>0.19 (0.03, 1.37)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- White</td>
<td>--</td>
<td>--</td>
<td>0.89 (0.67, 1.18)</td>
<td>0.85 (0.64, 1.14)</td>
</tr>
<tr>
<td>- Black</td>
<td>--</td>
<td>--</td>
<td>1.40 (0.51, 3.83)</td>
<td>1.42 (0.52, 3.90)</td>
</tr>
<tr>
<td>- Other</td>
<td>--</td>
<td>--</td>
<td>1.30 (0.63, 2.70)</td>
<td>1.31 (0.63, 2.73)</td>
</tr>
<tr>
<td>- Missing</td>
<td>--</td>
<td>--</td>
<td>1.51 (0.83, 2.74)</td>
<td>1.53 (0.84, 2.79)</td>
</tr>
<tr>
<td>- Hispanic</td>
<td>--</td>
<td>--</td>
<td>0.78 (0.61, 0.81)</td>
<td>0.78 (0.61, 0.81)</td>
</tr>
<tr>
<td>- Female</td>
<td>--</td>
<td>--</td>
<td>0.94 (0.85, 1.03)</td>
<td>0.94 (0.85, 1.03)</td>
</tr>
<tr>
<td><strong>% of zip code with at least a High School degree</strong></td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1.32 (0.52, 3.30)</td>
</tr>
<tr>
<td><strong>% of zip code living below the poverty level</strong></td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1.32 (0.52, 3.30)</td>
</tr>
<tr>
<td><strong>Admission Type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Emergency</td>
<td>--</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>- Urgent</td>
<td>--</td>
<td>1.04 (0.86, 1.26)</td>
<td>1.04 (0.86, 1.27)</td>
<td>1.04 (0.86, 1.26)</td>
</tr>
<tr>
<td>- Elective</td>
<td>--</td>
<td>0.36 (0.27, 0.48)</td>
<td>0.37 (0.27, 0.49)</td>
<td>0.37 (0.28, 0.50)</td>
</tr>
<tr>
<td>- Trauma</td>
<td>--</td>
<td>2.62 (1.55, 4.43)</td>
<td>2.63 (1.56, 4.45)</td>
<td>2.61 (1.55, 4.42)</td>
</tr>
<tr>
<td><strong>Length of Stay for Inpatient Hospitalizations</strong></td>
<td>--</td>
<td>1.02 (0.97, 1.07)</td>
<td>1.02 (0.97, 1.07)</td>
<td>1.02 (0.97, 1.07)</td>
</tr>
<tr>
<td><strong>Length of Stay for Inpatient Hospitalizations</strong></td>
<td>--</td>
<td>11.71 (9.57, 14.33)</td>
<td>12.05 (9.84, 14.74)</td>
<td>12.09 (9.87, 14.79)</td>
</tr>
</tbody>
</table>

*Estimates are for a 1-standard deviation (SD) increase. SD for % of zip code with at least a high school degree is 6.78%, SD for % of zip code living below the poverty level is 9.84%, and SD for length of stay for inpatient hospitalizations is 4.34 days.
Supplemental Table 2.2. Sensitivity Analysis comparing patients missing discharge status to patients kept in the analysis

<table>
<thead>
<tr>
<th>Diagnoses codes related to overdose, %(n)</th>
<th>All Opioid-Related Hospitalizations, %(n)</th>
<th>Missing Patient Status, %(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Opium (T40.0)</td>
<td>0.6 (402)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>- Heroin (T40.1)</td>
<td>36.1 (22,756)</td>
<td>43.5 (317)</td>
</tr>
<tr>
<td>- Prescription: Natural and semisynthetic opioids (T40.2)</td>
<td>41.5 (26,158)</td>
<td>28.7 (282)</td>
</tr>
<tr>
<td>- Prescription: Methadone (T40.3)</td>
<td>1.2 (777)</td>
<td>0.6 (4)</td>
</tr>
<tr>
<td>- Synthetic opioids other than methadone (T40.4)</td>
<td>5.3 (3,314)</td>
<td>2.6 (19)</td>
</tr>
<tr>
<td>- Other and unspecified narcotics (T40.6)</td>
<td>16.6 (10,487)</td>
<td>15.2 (111)</td>
</tr>
<tr>
<td>Patient vital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Deceased</td>
<td>1.3 (809)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>- N/A</td>
<td>0.0 (0.0)</td>
<td>100.0 (729)</td>
</tr>
<tr>
<td>COVID-19 pandemic, %(n)</td>
<td>15.4 (9699)</td>
<td>17.1 (125)</td>
</tr>
<tr>
<td>Admission Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ER, %(n)</td>
<td>70.0 (44163)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>- Urgent, %(n)</td>
<td>7.2 (4537)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>- Elective, %(n)</td>
<td>22.5 (14179)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>- Trauma, %(n)</td>
<td>0.3 (218)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>- N/A, %(n)</td>
<td>0.0 (9)</td>
<td>100.0 (729)</td>
</tr>
<tr>
<td>Inpatient, %(n)</td>
<td>30.6 (19321)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>Length of Stay for Inpatients</td>
<td>5.7 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Female, %(n)</td>
<td>48.8 (30800)</td>
<td>47.9 (349)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- White, %(n)</td>
<td>93.0 (58693)</td>
<td>97.0 (707)</td>
</tr>
<tr>
<td>- Black, %(n)</td>
<td>6.1 (3850)</td>
<td>2.9 (21)</td>
</tr>
<tr>
<td>- Asian, %(n)</td>
<td>0.2 (104)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>- Native Hawaiian or Pacific Islander, %(n)</td>
<td>0.0 (29)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>- American Indian or Alaska Native, %(n)</td>
<td>0.1 (44)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>- Missing, %(n)</td>
<td>0.6 (386)</td>
<td>0.1 (1)</td>
</tr>
<tr>
<td>Hispanic, %(n)</td>
<td>1.0 (638)</td>
<td>1.0 (7)</td>
</tr>
<tr>
<td>Age Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 18-29 years, %(n)</td>
<td>18.4 (11629)</td>
<td>20.4 (149)</td>
</tr>
<tr>
<td>- 30-39 years, %(n)</td>
<td>21.6 (13655)</td>
<td>27.0 (197)</td>
</tr>
<tr>
<td>- 40-49 years, %(n)</td>
<td>15.3 (9671)</td>
<td>11.9 (87)</td>
</tr>
<tr>
<td>- 50-59 years, %(n)</td>
<td>16.9 (10657)</td>
<td>15.9 (116)</td>
</tr>
<tr>
<td>- 60-69 years, %(n)</td>
<td>14.0 (8816)</td>
<td>15.5 (113)</td>
</tr>
<tr>
<td>- 70+ years, %(n)</td>
<td>13.3 (8377)</td>
<td>9.2 (67)</td>
</tr>
<tr>
<td>- Missing, %(n)</td>
<td>0.5 (301)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>% High School Grad or Higher</td>
<td>85.6 (6.8)</td>
<td>83.6 (8.3)</td>
</tr>
<tr>
<td>% Below Poverty or Higher</td>
<td>18.9 (9.8)</td>
<td>20.2 (7.7)</td>
</tr>
<tr>
<td>County-Level Urbanicity, %(n)</td>
<td>64.5 (40713)</td>
<td>58.0 (423)</td>
</tr>
</tbody>
</table>
Table 3.1. Number of opioid overdose deaths and crude rates per 100,000** by year for each state with a legislation banning kratom

<table>
<thead>
<tr>
<th>Year</th>
<th>Indiana</th>
<th>Vermont</th>
<th>Wisconsin</th>
<th>Arkansas</th>
<th>Alabama</th>
<th>Rhode Island</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>rate</td>
<td>n</td>
<td>rate</td>
<td>n</td>
<td>rate</td>
</tr>
<tr>
<td>2005</td>
<td>163</td>
<td>3.5</td>
<td>46</td>
<td>9.5</td>
<td>278</td>
<td>6.6</td>
</tr>
<tr>
<td>2006</td>
<td>183</td>
<td>3.9</td>
<td>57</td>
<td>11.7</td>
<td>347</td>
<td>8.2</td>
</tr>
<tr>
<td>2007</td>
<td>246</td>
<td>5.2</td>
<td>53</td>
<td>10.8</td>
<td>370</td>
<td>8.7</td>
</tr>
<tr>
<td>2008</td>
<td>316</td>
<td>6.6</td>
<td>58</td>
<td>11.8</td>
<td>366</td>
<td>8.5</td>
</tr>
<tr>
<td>2009</td>
<td>336</td>
<td>6.9</td>
<td>46</td>
<td>9.3</td>
<td>398</td>
<td>9.2</td>
</tr>
<tr>
<td>2010</td>
<td>297</td>
<td>6.1</td>
<td>45</td>
<td>9.1</td>
<td>417</td>
<td>9.6</td>
</tr>
<tr>
<td>2011</td>
<td>371</td>
<td>7.5</td>
<td>60</td>
<td>12.0</td>
<td>477</td>
<td>10.9</td>
</tr>
<tr>
<td>2012</td>
<td>389</td>
<td>7.9</td>
<td>57</td>
<td>11.4</td>
<td>493</td>
<td>11.2</td>
</tr>
<tr>
<td>2013</td>
<td>380</td>
<td>7.6</td>
<td>75</td>
<td>14.9</td>
<td>597</td>
<td>13.5</td>
</tr>
<tr>
<td>2014</td>
<td>485</td>
<td>9.7</td>
<td>72</td>
<td>14.3</td>
<td>636</td>
<td>14.3</td>
</tr>
<tr>
<td>2015</td>
<td>559</td>
<td>11.1</td>
<td>83</td>
<td>16.4</td>
<td>629</td>
<td>14.1</td>
</tr>
<tr>
<td>2016</td>
<td>823</td>
<td>16.3</td>
<td>103</td>
<td>20.4</td>
<td>867</td>
<td>19.3</td>
</tr>
<tr>
<td>2017</td>
<td>1203</td>
<td>23.6</td>
<td>119</td>
<td>23.5</td>
<td>939</td>
<td>20.8</td>
</tr>
<tr>
<td>2018</td>
<td>1135</td>
<td>22.2</td>
<td>128</td>
<td>25.1</td>
<td>857</td>
<td>18.9</td>
</tr>
<tr>
<td>2019</td>
<td>1288</td>
<td>24.9</td>
<td>117</td>
<td>22.9</td>
<td>934</td>
<td>20.5</td>
</tr>
<tr>
<td>2020</td>
<td>1949</td>
<td>37.6</td>
<td>164</td>
<td>32.1</td>
<td>1264</td>
<td>27.6</td>
</tr>
</tbody>
</table>

% Increase from 2005-2020:

<table>
<thead>
<tr>
<th>Year</th>
<th>Indiana</th>
<th>Vermont</th>
<th>Wisconsin</th>
<th>Arkansas</th>
<th>Alabama</th>
<th>Rhode Island</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,096%</td>
<td>974%</td>
<td>257%</td>
<td>238%</td>
<td>355%</td>
<td>318%</td>
</tr>
</tbody>
</table>

*bold indicates year of legislation implementation

**in adults aged 18 years or older
### Table 3.2. Rate Ratio (RR) Estimates (95% Confidence Intervals [CIs]) of Opioid Overdose Mortality in States with a Legislation Banning Kratom

<table>
<thead>
<tr>
<th>Intervention Year</th>
<th>Indiana RR (95% CI)</th>
<th>Vermont RR (95% CI)</th>
<th>Wisconsin RR (95% CI)</th>
<th>Arkansas RR (95% CI)</th>
<th>Alabama RR (95% CI)</th>
<th>Rhode Island* RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Opioids (T40.0-T40.4 &amp; T40.6)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-intervention trend</td>
<td>1.12 (1.10, 1.15)</td>
<td>1.01 (0.96, 1.05)</td>
<td>1.08 (1.06, 1.09)</td>
<td>1.02 (1.00, 1.03)</td>
<td>1.07 (1.06, 1.09)</td>
<td>1.09 (1.08, 1.11)</td>
</tr>
<tr>
<td>Level change from pre-to post-intervention</td>
<td>0.71 (0.64, 0.79)</td>
<td>1.14 (0.88, 1.49)</td>
<td>1.02 (0.93, 1.11)</td>
<td>0.76 (0.63, 0.92)</td>
<td>1.14 (0.99, 1.31)</td>
<td>0.98 (0.82, 1.18)</td>
</tr>
<tr>
<td>Slope change from pre-to post-intervention</td>
<td>1.09 (1.06, 1.12)</td>
<td>1.11 (1.05, 1.17)</td>
<td>1.03 (1.00, 1.05)</td>
<td>1.10 (1.04, 1.15)</td>
<td>1.05 (1.01, 1.09)</td>
<td>0.96 (0.90, 1.02)</td>
</tr>
<tr>
<td><strong>Prescription Opioids (T40.2-T40.3)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-intervention trend</td>
<td>1.14 (1.10, 1.18)</td>
<td>0.99 (0.94, 1.04)</td>
<td>1.03 (1.01, 1.05)</td>
<td>1.01 (0.99, 1.03)</td>
<td>1.00 (0.98, 1.02)</td>
<td>1.08 (1.06, 1.10)</td>
</tr>
<tr>
<td>Level change from pre-to post-intervention</td>
<td>0.54 (0.47, 0.63)</td>
<td>1.03 (0.73, 1.47)</td>
<td>1.10 (0.97, 1.25)</td>
<td>0.90 (0.72, 1.13)</td>
<td>1.08 (0.87, 1.34)</td>
<td>0.82 (0.60, 1.11)</td>
</tr>
<tr>
<td>Slope change from pre-to post-intervention</td>
<td>1.01 (0.98, 1.05)</td>
<td>0.99 (0.91, 1.07)</td>
<td>0.96 (0.93, 0.99)</td>
<td>0.92 (0.86, 0.98)</td>
<td>1.02 (0.96, 1.08)</td>
<td>0.87 (0.78, 0.97)</td>
</tr>
<tr>
<td><strong>Illicit Opioids (T40.0, T40.1 &amp; T40.4)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-intervention trend</td>
<td>1.14 (1.09, 1.20)</td>
<td>1.06 (0.96, 1.16)</td>
<td>1.18 (1.15, 1.21)</td>
<td>1.02 (0.98, 1.05)</td>
<td>1.29 (1.25, 1.33)</td>
<td>1.41 (1.37, 1.46)</td>
</tr>
<tr>
<td>Level change from pre-to post-intervention</td>
<td>0.88 (0.75, 1.04)</td>
<td>2.21 (1.45, 3.38)</td>
<td>1.05 (0.93, 1.19)</td>
<td>0.85 (0.61, 1.17)</td>
<td>1.14 (0.94, 1.37)</td>
<td>0.81 (0.66, 1.01)</td>
</tr>
<tr>
<td>Slope change from pre-to post-intervention</td>
<td>1.17 (1.11, 1.22)</td>
<td>1.12 (1.01, 1.24)</td>
<td>1.01 (0.98, 1.04)</td>
<td>1.37 (1.27, 1.47)</td>
<td>0.92 (0.88, 0.97)</td>
<td>0.78 (0.73, 0.84)</td>
</tr>
</tbody>
</table>

*only 3 datapoints after intervention
Supplemental Table 3.1. Rate Ratio (RR) Estimates (95% Confidence Intervals [CIs]) of Opioid Overdose Mortality in States with a Legislation Banning Kratom in the years 2005-2019

<table>
<thead>
<tr>
<th>Intervention Year</th>
<th>Indiana RR (95% CI)</th>
<th>Vermont RR (95% CI)</th>
<th>Wisconsin RR (95% CI)</th>
<th>Arkansas RR (95% CI)</th>
<th>Alabama RR (95% CI)</th>
<th>Rhode Island* RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-intervention trend</td>
<td>1.12 (1.10, 1.15)</td>
<td>1.01 (0.96, 1.05)</td>
<td>1.08 (1.06, 1.09)</td>
<td>1.02 (1.00, 1.03)</td>
<td>1.07 (1.06, 1.09)</td>
<td>1.09 (1.08, 1.11)</td>
</tr>
<tr>
<td>Level change from pre-to post-intervention</td>
<td>0.75 (0.68, 0.84)</td>
<td>1.19 (0.90, 1.58)</td>
<td>1.09 (0.98, 1.20)</td>
<td>0.85 (0.69, 1.06)</td>
<td>1.34 (1.14, 1.57)</td>
<td>1.19 (0.96, 1.48)</td>
</tr>
<tr>
<td>Slope change from pre-to post-intervention</td>
<td>1.08 (1.05, 1.11)</td>
<td>1.09 (1.03, 1.17)</td>
<td>1.00 (0.98, 1.03)</td>
<td>1.04 (0.97, 1.12)</td>
<td>0.97 (0.92, 1.02)</td>
<td>0.85 (0.77, 0.94)</td>
</tr>
</tbody>
</table>

*only 3 datapoints after intervention
FIGURES

Figure 1.1a-1.1d United States map showing the Spatial Distribution of Quintiles of Principal Component Scores (a) “Extremely Disadvantaged” (PC1); (b) “Single and in Poverty, yet Educated” (PC2); (c) “Grandparents raising grandchildren” (PC3); and (d) “Educated and residentially unstable” (PC4)

(a) Extremely Disadvantaged (PC1)  
(b) Single and in poverty, yet educated (PC2)  
(c) Grandparents raising grandchildren (PC3)  
(d) Educated and residentially unstable (PC4)
Figure 1.2. Mutually Adjusted\textsuperscript{a} Relative Risk (RR) Estimates (95\% Confidence Intervals [CIs]) for Different Outcome Definitions\textsuperscript{b} of Opioid Overdose Mortality in the US 2010-2019 for a one-standard deviation increase in each principle component (PC) score

\begin{center}
\begin{tabular}{|c|c|c|c|}
\hline
PC1 & PC2 & PC3 & PC4 \\
\hline
1.17 (1.13, 1.21) & 1.01 (0.96, 1.05) & 1.05 (1.00, 1.10) & 1.07 (1.04, 1.11) \\
\hline
1.46 (1.40, 1.53) & 1.13 (1.08, 1.19) & 1.03 (1.00, 1.07) & 1.08 (1.03, 1.12) \\
\hline
1.28 (1.23, 1.33) & 0.93 (0.90, 0.96) & 0.82 (0.79, 0.84) & 0.89 (0.86, 0.92) \\
\hline
\end{tabular}
\end{center}

- (a) Prescription Opioids\textsuperscript{c}
- (b) Illicit & Synthetic Opioids other than Methadone (e.g., fentanyl)\textsuperscript{d}
- (c) All Opioids\textsuperscript{e}

\begin{itemize}
\item \textit{Note:} Counties with high PC1 scores reflect socioeconomic factors related to extreme disadvantage; counties with high PC2 scores reflect a pattern of single and in poverty yet educated; counties with high PC3 scores reflect a pattern of grandparents raising grandchildren with residential instability; and counties with high PC4 scores reflect a pattern of education with residential instability.
\item \textsuperscript{a}Adjusted for population size, a square term for population size, county median age, percentage of the population that was White, percentage of the population that was female, and percentage of the population that was non-Hispanic.
\item \textsuperscript{b}The following multiple cause-of-death codes were used to identify specific opioids involved in overdose mortality: T40.0 (opium), T40.1 (heroin), T40.2 (natural and semisynthetic opioids), T40.3 (methadone), T40.4 (synthetic opioids other than methadone), and T40.6 (other and unspecified narcotics).
\item \textsuperscript{c}Prescription opioids include ICD-10 codes T40.2-T40.3
\item \textsuperscript{d}Illicit and Synthetic Opioids other than Methadone include ICD-10 codes T40.0, T40.1 & T40.4
\item \textsuperscript{e}All opioids include ICD-10 codes T40.0-T40.4 & T40.6
\end{itemize}
Figure 2.1 County-level urbanicity in Kentucky by (a) binary urban-rural status and (b) six categories of Urbanicity

a)

**Urbanicity**
- Urban
- Rural

b)

**Categories of Urbanicity**
- Large metro
- Large fringe metro
- Medium metro
- Small metro
- Micropolitan
- Non-core
Figure 3.1 Annual Mean Crude Opioid Overdose Mortality Rates per 100,000 from any opioid, 2005-2020, for states with legislation banning kratom; center line indicates year of kratom law

(a) Vermont (2013)  
(b) Wisconsin (2014)  
(c) Indiana (2012)  
(d) Arkansas (2016)  
(e) Alabama (2016)  
(f) Rhode Island (2017)
REFERENCES


CURRICULUM VITA

Lyndsey Blair

EDUCATION
University of Louisville  
Graduation May 2022
Doctor of Philosophy in Public Health Science: Specialization in Epidemiology (PhD)
Dissertation: “Investigating the relationships between socioeconomic status, kratom legalization, urbanicity and the COVID-19 pandemic on opioid overdose mortality in the United States”

University of Louisville
Master of Public Health  
2009

University of Louisville
Bachelor of Science (BS)  
2007
Major: Biology

AWARDS AND GRANTS
Graduate Dean’s Citation  
May 2022
Doctoral Dissertation Completion Award  
Spring 2022
Student Ambassador for the 2019 KY Harm Reduction Summit  
Apr 2019
Travel Award, CDART Workshop on Statistical Methods in Drug Abuse and Health-Related Research  
Oct 2008
Golden Key International Honour Society  
Sept 2008

TEACHING EXPERIENCE
University of Louisville  
Apr 2022
Guest Lecturer – “A Day in the Life of a Community Epidemiologist”
Invited to lecture to the PHEP 441-Epidemiological Concepts and Methods for Public Health- class about the responsibilities of an Epidemiologist at a Local Health Department.

University of Louisville  
Mar 2021
Guest Lecturer – “A Day in the Life of a Community Epidemiologist”
Invited to lecture to the PHEP 441-Epidemiological Concepts and Methods for Public Health- class about the
responsibilities of an Epidemiologist at a Local Health Department.

University of Louisville

**Guest Lecturer – “A Day in the Life of a Community Epidemiologist”**

Nov 2020

Invited to lecture to the PHEP 441-Epidemiological Concepts and Methods for Public Health- class about the responsibilities of an Epidemiologist at a Local Health Department.

**Teaching Assistant (TA) Epi Methods II (PHEP 618)**

Spring 2020

University of Louisville School of Public Health and Information Sciences

As a TA, I answered student questions via email, developed and led office hours in which content was reviewed, and graded homework assignments.

University of Louisville

**Guest Lecturer – “A Day in the Life of a Community Epidemiologist”**

Nov 2019

Invited to lecture to the PHEP 441-Epidemiological Concepts and Methods for Public Health- class about the responsibilities of an Epidemiologist at a Local Health Department.

University of Louisville

**Guest Lecturer – “A Day in the Life of a Community Epidemiologist”**

Mar 2019

Lectured to the PHEP 441- Epidemiological Concepts and Methods for Public Health- class about the responsibilities of an Epidemiologist at a Local Health Department.

**OTHER PROFESSIONAL POSITIONS**

University of Louisville

**Graduate Student Lead Researcher**

June 2019 - Mar 2022

*Department of Epidemiology, University of Louisville School of Public Health and Information Sciences*

- Under the direction of Dr. Natalie DuPre, performed multivariable linear regression and Cox proportional hazards regressions analyses
- Collaborated and coordinated with faculty and fellow graduate students across multiple universities
- First author on manuscript in submission describing the examination of the association between greenness, as measured by the Normalized Difference Vegetation Index (NDVI), and mammographic density to determine whether greenness directly influences breast tissue composition independent of lifestyle factors.

Lincoln Trail District Health Department
Community Epidemiologist  
Feb 2018-May 2019
Senior Community Epidemiologist  
Aug 2019-Present

- Conducts studies designed to identify segments of the population at greater risk of occurrences of disease
- Performs statistical analyses of data
- Designs descriptive and analytical epidemiologic investigations, including hypothesis generation
- Manages large datasets and performs complex data analyses – particularly related to COVID-19
- Assists in the formulation of recommendations for interventions to reduce the occurrence and/or severity of disease or injuries of public health significance
- Interprets and prepares technical reports on epidemiological studies and investigations
- Experience communicating data to both internal and external stakeholders
- Prepares and submits grant proposals for public health projects based on identified needs
- Plans and organizes new methods for obtaining additional health data and for improving the reliability and validity of health data being collected by the local health department and KY Department for Public Health

PUBLICATIONS AND PAPERS


MANUSCRIPTS IN SUBMISSION


MANUSCRIPTS IN PREPARATION


**ABSTRACTS, POSTER PRESENTATIONS AND EXHIBITS AT PROFESSIONAL MEETINGS**

1. **LK Blair**, J Howard, NC Peiper, BB Little, KC Taylor, R Baumgartner, L Creel, NC DuPre. Residence in Urban or Rural Counties in relation to Opioid Overdose Mortality in Kentucky before and during the COVID-19 Pandemic. SER June 2022

2. **LK Blair**, J Howard, NC Peiper, BB Little, KC Taylor, R Baumgartner, L Creel, NC DuPre. Residence in Urban or Rural Counties in relation to Opioid Overdose Mortality in Kentucky before and during the COVID-19 Pandemic. KPHA April 2022


5. **L. K. Blair**, J. D. Newton, N. C. DuPre. Socioeconomic Patterns and Environmental Greenness in Relation to County-Level All-cause Mortality Rates in Kentucky. Kentucky Public Health Association (KPHA) Annual Conference. April 2020; Covington, KY.


**MEMBERSHIPS**

- International Society for Environmental Epidemiology (ISEE) 2020-Present
- Society for Epidemiologic Research (SER) 2021