Spring 2020

Associations Between County-Level Socioeconomic Status and Opioid Overdose Rates in Northern New England

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Associations Between County-Level Socioeconomic Status and Opioid Overdose Rates in Northern New England

by

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Bachelor of Science
University of Maine at Farmington, 2018

Submitted in Partial Fulfillment of the Requirements

For the Degree of Master of Science in Public Health in

Epidemiology

Arnold School of Public Health

University of South Carolina

2020

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ABSTRACT

Background – The opioid epidemic persists as a significant concern to public health as the proliferation of fentanyl presents additional risks for illicit opioid users. States such as Maine and New Hampshire experience far greater opioid overdose rates compared to the overall US opioid overdose rate. Many studies on the opioid epidemic use socioeconomic and macroeconomic factors individually but few use a composite index of multiple of these measures. Limited attention has been paid to the need for a composite index of socioeconomic status at the small area (county) level designed to quantify the impact of socioeconomic status on the opioid epidemic.

Methods – Negative binomial regression was used to compare the opioid overdose rate between quartiles of county-level socioeconomic status (SES) amongst the 40 counties of the three northern New England states of Maine, New Hampshire, and Vermont between the years of 2015 and 2017. Data sources include CDC Wonder, NIH SEER*Stat, US Census, and SAMHSA.

Results – Counties in the lowest two quartiles of county-level SES had 1.35 (95% CI=1.02, 1.79) and 1.31 (95% CI=1.01, 1.71) times the opioid overdose death rate compared to counties in the third quartile respectively after controlling for county-level urbanicity and county-level population density of practitioners waived to prescribe buprenorphine. Metropolitan counties had 1.24 (95% CI=1.01, 1.55) times the opioid overdose death

rate compared to rural counties after controlling for county-level SES and county-level population density of level practitioners waived to prescribe buprenorphine.

Conclusions – County-level SES and county urbanicity may play a role in the opioid epidemic within the Northern New England Region of the United States. Studies designed to consider the longitudinal implications of increased access to buprenorphine treatment are required to properly assess the effect of the availability of this treatment on the opioid crisis. Fentanyl also poses a substantial threat to public health and safety, especially amongst illicit drug users who may be unaware to the presence of fentanyl in their drug supply.

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LIST OF ABBREVIATIONS

ACS	American Community Survey
BDMD	Brain Disease Model of Addiction
CDC	Centers for Disease Control and Prevention
DEA	United States Drug Enforcement Agency
MME	Morphine Milligram Equivalents
MMWR	Morbidity and Mortality Weekly Report
M-PMP	Maine Prescription Monitoring Program
NCHS	National Center for Health Statistics
NIH	National Institutes of Health
SAMHSA	Substance Abuse and Mental Health Services Administration
SEER	Surveillance, Epidemiology, and End Results Program
SES	Socioeconomic Status

CHAPTER 1

INTRODUCTION AND BACKGROUND

1.1 Opioids Defined

Opioids are defined as “broad-spectrum analgesics utilized for the treatment of nociceptive and neuropathic pain” (Smith, 2008). There is evidence to suggest that mankind has cultivated the opium poppy going as far back in history as 3,000 BC (Pathan & Williams, 2012). Modern opioids come in many forms consisting of three broad categories of natural (e.g. Morphine and codeine), semi-synthetic (e.g. hydrocodone and oxycodone), and synthetic opioids (e.g. fentanyl and methadone). Natural and semi-synthetic opioids partially derive from the opium poppy, whereas synthetic opioids are manmade to resemble the effects of opioids (Bolshakova et al., 2019; Pathan & Williams, 2012). These opioids treat pain through “activating the body’s endogenous opioid receptors in the pain-modulating systems, which may dampen nociceptive input. Almost all clinically useful opioid analgesics are μ opioid receptor (MOR) agonists” (Smith, 2008). That is, opioids effectively dampen pain signals to the brain resulting in a diminished perception of pain by the individual. Opioid use is accompanied by side effects including dizziness, euphoria, delirium, fatigue, nausea, vomiting, constipation, muscular rigidity, sedation, respiratory depression, physical dependence and tolerance (Bolshakova et al., 2019; Pathan & Williams, 2012; Schuckit, 2016; Smith, 2008).

1.2 Opioid Addiction

Koob describes a “3-stage heuristic framework” for opioid addiction that consists of binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. These three stages are represented by "incentive salience and/or habits, negative emotional states, and executive function" respective to the three stages (Koob, 2019; Uhl, Koob, & Cable, 2019). The pathway for addiction starts with initial usage of an opioid such as heroin, which is commonly reported to be accompanied by a euphoric experience and intense intoxication (Evans & Cahill, 2016; Fitzgerald, Louie, Rosenthal, & Crofts, 1999; Schuckit, 2016), tolerance development, and usage of a higher dose of the drug to compensate for increased tolerance (Koob, 2019). Prolonged time since prior use can result in withdrawal symptoms of which include hypohedonia, hyperalgesia, and hyperkatifeia (Koob, 2019). Hypohedonia can be defined as “abnormally reduced ability to experience pleasure or enjoyment in ordinarily pleasurable activities, falling short of anhedonia or depression” (Colman, 2009). Hyperalgesia is defined as "abnormally heightened sensitivity to pain” (Colman, 2009). Hyperkatifeia is defined as "an increase in intensity of the constellation of negative emotional or motivational signs and symptoms of withdrawal from drugs of abuse" (Koob, 2019; Shurman, Koob, & Gutstein, 2010). Experiencing these symptoms can facilitate negative reinforcement which drives motivation for further use of the drug. Using the drug can then initiate the same process all over again. A vicious cycle that grows in severity as tolerance and dependence increase and withdrawal symptoms become more pronounced. Evans and Cahill propose that this cycle can produce learned associations such that opioids are associated with alleviation from the negative emotional and physical states felt before usage of the opioid (Evans & Cahill, 2016). If an individual can break the cycle of opioid addiction there is still potential that life stressors can cause a recall of these learned associations and reinstate drug cravings (Evans & Cahill, 2016; Gardner, 2011; Koob et al., 2014). This recall of learned associations presents the potential to relapse back in the cycle of opioid addiction (Evans & Cahill, 2016; Koob et al., 2014). Those individuals who are living in conditions that predispose them to frequent life stressors would be subject to additional risk for relapse under this proposed framework for opioid addiction.

There is opposition to this framework, which is commonly referred to as the 'Brain Disease Model of Addiction' or BDMD. One area of contention is that the model removes 'free-will' and choice from the addiction equation as well as ignoring individual ability to abstain from use outside of drug treatment (Hall, Carter, & Forlini, 2015; Racine, Sattler, & Escande, 2017; Satel & Lilienfeld, 2014). Hall et al. suggest that neurobiological mechanisms are focal point for treatment and intervention which undermines large scale public health intervention and policy development (Hall et al., 2015). Satel and Lilienfield cite what is commonly called 'Operation Golden Flow' from the Vietnam War where soldiers were not allowed to board their flight home until passing a urine test due to widespread heroin abuse. They state that most soldiers passed the test on their second try provided that they were permitted to receive armysponsored detoxification after a failure (Satel & Lilienfeld, 2014). Based on the relative ease by which soldiers were able to abstain from using heroin and pass the test, Satel and Lilienfeld suggest that individuals are not incapable of overriding the addictive mechanisms. Therefore, people aren't overridden by the substance they are abusing, drawing into question the legitimacy of the BDMD (Satel & Lilienfeld, 2014). Furthermore, critics also claim that the model is not supported by animal models or neuroimaging studies (Hall et al., 2015).

1.3 The Opioid Epidemic in the United States

The opioid epidemic in the United States continues to grow and evolve as highly potent forms of opioids proliferate throughout the illicit opioid market following changes to strict and monitored opioid prescribing practices/policy. In 2017, the CDC estimated the United States opioid overdose rate to be approximately 14.9 per 100,000 individuals which is an approximate 12% increase from 2016 (Scholl, Seth, Wilson, Baldwin, & Kariisa, 2018). This estimate is the most recent published data for the entirety of the United States at the time of this review.

The continued persistence of the opioid epidemic places a measurable strain on the healthcare system. The total economic burden of the opioid epidemic on the United States is estimated to be approximately $78.5 billion, roughly one-third of these costs are utilized for health care and substance abuse treatment, the remaining cost is attributed to lost productivity (both fatal and nonfatal), and criminal justice (Florence, Zhou, Luo, & Xu, 2016). The substantial fiscal burden can also represent the respective time and resource demand that is responsible for this substantial cost.

In the United States, opioids are also responsible for the most considerable proportion of overall drug overdose deaths. From 1999 to 2017, there were an estimated 702,568 drug overdose deaths; among those, an estimated 399,230 (56.8%) were attributed to opioids (Scholl et al., 2018). This proportion of drug overdose deaths is large for just one substance, given the variety of substances that are commonly abused in the United States.

1.4 Regional Specific Differences in the Opioid Epidemic

From 2013 to 2017, many US states observed increases in overdoses attributed to opioid use (Gladden, Martinez, & Seth, 2016; O'Donnell, Gladden, & Seth, 2017; Scholl et al., 2018). From 2016 to 2017, fifteen US states observed significant increases in opioid overdose rates, the largest increases were observed in North Carolina (28.6%), Ohio (19.1%), and Maine (18.7%) (Scholl et al., 2018). Although, some states such as Maine, Tennessee, Maryland, Oklahoma, and Washington have been observing decreases in prescription opioid overdose rates (Scholl et al., 2018). Notably, Maine belonged to both the group of states that saw a significant increase in the opioid overdose rate, as well as the group of states that saw a decrease in prescription opioid specific overdose rates. Because the overall opioid overdose rate increased while the prescription opioid overdose rate decreased, this would suggest that the role of illicit opioids may be becoming more prominent within the opioid epidemic in Maine.

1.5 Opioid Prescribing

Greater rates of opioid prescribing have been found to be associated with opioid mortality rates (Grigoras et al., 2017). Opioid prescribing in morphine milligram equivalents (MME) began increasing in the United States during the 1990s until reaching 782 MME per capita in 2010, followed by a decline to approximately 640 MME per capita in 2015 (Guy Jr et al., 2015). Opioid prescription rates also saw increases from 2006 to 2010, where prescribing rates increased from 72.4 per prescriptions per 100 to 81.2 prescriptions per 100 persons (Guy Jr et al., 2015). This prescription rate stagnated from 2010 to 2012 until decreasing to 70.6 per 100 persons between 2012 and 2015 (Guy Jr et al., 2015). During this period, the rate of prescriptions with an excess of 30 days' supply also increased (Guy Jr et al., 2015). There were also county-level differences in opioid prescribing such that counties with greater proportions of white non-Hispanic individuals, greater prevalence of arthritis and/or diabetes, greater rates of unemployment, and those classified as micropolitan had higher rates of opioid prescribing (Guy Jr et al., 2015).

In 2016 the CDC published its recommendations for opioid prescribing practices which focused on providing more robust guidelines on opioid treatment for non-cancer related pain, improve communication with patients regarding opioid treatment, and reducing the risks of long term opioid treatment (Dowell, Haegerich, & Chou, 2016). Following the release of these new guidelines, Bohnert, Guy Jr., and Losby analyzed opioid prescribing rates prior to and following the release of the 2016 CDC guidelines. What they determined was that opioid prescribing was declining leading up to the release of the guidelines, but the release of the guidelines was still associated with a significant decline in opioid prescribing (Bohnert, Guy Jr., & Losby, 2018).

1.6 Fentanyl

The synthetic opioid "fentanyl" has rapidly progressed from an emerging threat to an immediate crisis in the United States. During 2015, both the CDC and the Drug Enforcement Administration (DEA) issued statements identifying 'illicitly manufactured fentanyl' as a threat to public health and safety (DEA Strategic Intelligence Section, 2016; Gladden et al., 2016). Fentanyl is a Schedule II synthetic opioid under the Controlled Substances Act that is approximately 50 to 100 times as potent as morphine (US Drug Enforcement Administration, 2016). Fentanyl's primary usage is intended to be in the surgical setting and for patients with severe pain that is unable to be managed by less potent opioids (Suzuki & El-Haddad, 2017). While some individuals may intend to purchase illicit fentanyl, fentanyl is also being mixed with heroin or even pressed and sold as counterfeit name-brand opioid pills (Ciccarone, Ondocsin, Mars, Francisco, & Francisco, 2018; DEA Strategic Intelligence Section, 2016; US Drug Enforcement Administration, 2016). Because heroin and fentanyl are believed to be the dominant factors in the continued rise in opioid overdose rates in the United States during the past five years, this development of fentanyl in the illicit opioid market poses an extreme risk to those who are unaware of its presence (McGowan, Harris, Platt, Hope, & Rhodes, 2018).

The rapid rise of fentanyl and heroin in the illicit opioid market is driven by massive profit margins from the sale of fentanyl as counterfeit name-brand prescription opioid medication and/or mixing fentanyl with heroin (DEA Strategic Intelligence Section, 2016). The DEA suggests that the customer is not often aware that the heroin or opioid pill they are purchasing contains fentanyl (DEA Strategic Intelligence Section, 2016). The DEA reports that on the black market, a pill press capable of producing pills at 5,000 per hour can be purchased for as little as $995 along with molds for popular name brand opioid medications for between $115 to $130. A kilogram of pure fentanyl can also be purchased for "a few thousand dollars" from suppliers in China which can be turned into roughly 666,666 counterfeit pills. The DEA suggests that based on retail prices of between $10 and $20 per pill in the illicit drug market, the estimated revenue from one kilogram of fentanyl is between $5 and $20 million from the sale of the counterfeit pills (DEA Strategic Intelligence Section, 2016).

While it is evident that fentanyl is dangerous and of significant concern to public health and safety, its presence is not uniformly distributed within regions of the United States. According to the DEA, in 2015 there were approximately 13,002 submissions to laboratories that were confirmed to contain fentanyl; that is a 65% increase from 2014 where there was an estimated 7,864 laboratory submissions (DEA Strategic Intelligence Section, 2016). The increase in submissions has not been uniform across all states. In 2017, Ohio, Pennsylvania, and Massachusetts comprised approximately 48% of all fentanyl submissions (Springer, Gladden, O'Donnell, & Seth, 2019). Also, a 2016 CDC report identified 8 "high burden" states based on laboratory submissions which include, Maine, Massachusetts, New Hampshire, Florida, Maryland, North Carolina, Ohio, and Kentucky (Gladden et al., 2016).

1.7 The Opioid Epidemic in Maine, New Hampshire, and Vermont

The opioid epidemic has not manifested uniformly across the United States; regions such as New England have experienced greater rates of opioid overdose than other regions of the country (Ghertner & Groves, 2018). Despite decreases in opioid prescribing, opioid overdose rates remain high in Maine, New Hampshire, and Vermont where the observed opioid overdose rates in 2017 were 29.9, 34.0, and 20.0 per 100,000 respectively compared to the United States opioid overdose rate of 14.9 per 100,000 (National Institute on Drug Abuse, 2018a, 2018b, 2019; Scholl et al., 2018). Maine and New Hampshire rank near the top of all US states regarding rates of opioid overdose deaths, such that Maine is in the top 10 US states and New Hampshire is in the top 5 (National Institute on Drug Abuse, 2018a, 2019). The National Institute on Drug Abuse reports that Maine and New Hampshire have also observed increases in opioid overdoses attributable to synthetic opioids other than methadone (National Institute on Drug Abuse, 2018a, 2019). Between the years of 2012 and 2017, the observed number of cases of synthetic opioid overdose climbed from 15 to 278 in Maine (National Institute on Drug Abuse, 2019). Between 2013 and 2017, the observed number of cases of synthetic opioid overdose climb from 30 to 374 in New Hampshire (National Institute on Drug Abuse, 2018a). Maine's population rose from 1,327,691 in 2012 to 1,335,063 in 2017 and New Hampshire's Population rose from 1,326,408 in 2013 to 1,349,767 in 2017 (U.S. Census Bureau, 2019b).

1.8 Rural vs. Urban Differences in the Opioid Epidemic

There are discernible differences in the opioid epidemic between rural and urban areas in the United States (García et al., 2019; Ghertner & Groves, 2018; Pear et al., 2019; Stewart, Cao, Hsu, Artigiani, & Wish, 2017; Wagner et al., 2019). Many rural counties in the United States exhibit disproportionate rates of opioid prescribing (García et al., 2019). In 2017 rural counties comprised 14 of the 15 counties with the highest rates of opioid prescribing (García et al., 2019). The high rates of opioid prescribing in rural counties is a concern because there is a shortage of physicians trained to treat opioid use disorder in rural regions of the United States (Rosenblatt, Catlin, & Larson, 2015). If opioids are frequently prescribed, patients could be at risk of becoming addicted and require treatment. If there is a shortage of physicians available to treat opioid use disorder, then these individuals may experience significant barriers to getting the care they need.

Nonetheless, opioid overdose rates have also been shown to be inconsistent across urban and rural neighborhoods, with even more sub-level variation by neighborhood socioeconomic composition (Wagner et al., 2019). While there are differences within the urbanicity of neighborhoods, there is potential for differences by socioeconomic composition within neighborhoods. This variation may extend to counties within states; however, the decreased specificity accompanied by analyzing larger geographic regions causes considerable uncertainty. A 2017 study by Stewart et al. suggests that based on “spatial Empirical Baye’s estimated age-adjusted rates” for the years 2000 to 2014, small metropolitan or non-metropolitan counties had greater heroin mortality rates than large-metropolitan counties (Stewart et al., 2017). The substantial differences in the manifestation of the opioid epidemic by the urbanicity of a region suggest that research into regional differences in opioid overdose and/or abuse rates should take this factor into account.

1.9 Macro-Economics and the Opioid Epidemic

Macroeconomic conditions are routinely assessed to evaluate workforce performance, engagement, prosperity within regions of the US. Some physical health characteristics such as smoking, heavy drinking, and obesity in the population have been shown to increase as macroeconomic conditions improve (Ruhm, 2003). However, some mental health can be shown to be the opposite such that non-psychotic mental health disorders become more common in the population as macroeconomic conditions decline (Ruhm, 2003). While some attention has been paid to macroeconomic conditions and health outcomes, more limited attention has been paid to the opioid epidemic in the same regard (Ghertner & Groves, 2018; Hollingsworth, Ruhm, & Simon, 2017; Pear et al., 2019). There is evidence suggesting that while there is an association between opioid mortality rates and counties that are experiencing economic decline, that the association is weak and possibly explained by confounding factors described as county characteristics like “sex, race/ethnicity differences, shares of female-headed households and foreign-born persons” (Ruhm, 2018). A hypothetical explanation for this observation is that adverse changes in economic conditions may not be the characteristic that would result in increases in opioid mortality rates. Instead, if an area was initially economically deprived and continued to be economically deprived, this could still produce an environment conducive to adverse mental health conditions and/or despair. Especially if many areas and/or large proportions of the population in that region continue to experience the same degree of deprivation or marginal improvements over time. The potential for this kind of scenario can be observed in the work of Emmanuel Saez. His work states that the majority of the economic gains since 1993 have been captured by a small minority of the wealthiest individuals in the United States (Saez, 2016).

There is evidence for associations between macroeconomic characteristics and opioid overdose death rates. Unemployment rates are a significant predictor of opioid overdose and/or abuse rates (Hollingsworth et al., 2017; Pear et al., 2019; Wright et al., 2014). Hollingsworth et al. suggest that a one percent increase in the county-level unemployment rate is associated with a 3.6% increase in opioid fatality rates (Hollingsworth et al., 2017). Pear et al., suggests that increases in unemployment rates are not associated with increases in prescription opioid overdose rates, but are associated with increases in heroin overdose rates (Pear et al., 2019).

However, unemployment rates are only one marker of macroeconomic conditions. According to Pear et al., increases in the poverty rate and percentage of adults 25 years of age or older with a high school education or less are shown to be associated with increases in prescription opioid and heroin overdose rates (Pear et al., 2019). Furthermore, greater median household income was found to be protective against both prescription opioid and heroin overdose rates (Pear et al., 2019). Pear et al. also state that differences in these associations were observed by differing classifications of urbanicity (Pear et al., 2019). While these measures all collectively comprise the macroeconomic conditions in a region, they individually measure different factors. If macroeconomic factors all collectively contribute to the environment within a region, viewing only one of these factors fails to describe the overall macroeconomic conditions and its collective influence on the population.

1.11 Current Theory on the Opioid Epidemic

There are two major theories on the genesis and persistence of the opioid epidemic, the theory of “excess opioid supply” and “deaths of despair” (Bohnert & Ilgen, 2019; Case & Deaton, 2015, 2017; Ruhm, 2018). The first theory is that the opioid epidemic is due to excess supply and access (Ruhm, 2018). This theory is based on the close adherence of overdose rates to rates of prescribing and/or supply and access to illicit opioids. An example of this theory can be observed in the Australian heroin epidemic during the 1990s and early 2000s. A 2006 study by Degenhardt, Day, Gilmour, and Hall found that the heroin mortality rate declined immediately following a heroin shortage (Degenhardt, Day, Gilmour, & Hall, 2006). Further corroboration for this theory can be found in evidence suggesting that when the price of heroin declines, heroin overdose rates begin to climb (Unick, Rosenblum, Mars, & Ciccarone, 2014). The decline in the price of heroin could suggest greater access as the financial barrier to engagement in the usage of the drug is weakened. If the barriers to engaging in the behavior are weakened or removed, then drug usage in the population could increase, and in turn, the overdose rate could also increase. The effect of reduced cost for access to an opioid was observed in a study conducted in Philadelphia and San Francisco in

2014 which found that heroin users commonly became addicted using prescription opioids before transitioning to heroin due to “cost and/or ease of access” (Mars, Bourgois, Karandinos, Montero, & Ciccarone, 2014). Even users of a prescription opioid that has defined production procedures to ensure accuracy in each dosage of the medication can transition to a far more dangerous and risky opioid such as heroin if the cost is more favorable and is easier to acquire.

The second theory is that the epidemic is due to “deaths of despair”, such that increases in suicide and overdose are due to a lack of opportunity and upward socio-economic mobility for working-class and impoverished individuals (Case & Deaton, 2015, 2017). Substance abuse is then a coping mechanism to deal with the negative emotional states of depression, anxiety, and despair (Case & Deaton, 2017). This theory very closely aligns with observations stated earlier amongst economic measures such as unemployment, poverty, education, and income in relation to opioid overdose rates. As these measures shift towards being more ‘deprived’, the opioid mortality rate begins to increase (Hollingsworth et al., 2017; Pear et al., 2019; Wright et al., 2014).

It is not improbable that both theories can both be catalysts in the opioid crisis or even work in unison to drive further grown and expansion of the opioid crisis. The drivers of despair proposed by Case and Deaton could create additional vulnerability to the draw of opioids that have become more easily accessible and affordable. Rather than existing in competition with one another both theories propose factors that should be considered when conducting research on the opioid crisis.

1.12 Area Level Socioeconomic Indexes

Statistical indexes are commonly used in countries such as the United Kingdom and New Zealand to measure deprivation, socioeconomic variation, assess community needs, inform research, adjust clinical funding, allocate community resources, and determine policy impact throughout communities and regions (Phillips et al., 2016). Phillips states that following the 2008 World Health Organization report, *Closing the Gap in a Generation: Health Equity through Action on the Social Determinants of Health*, greater interest has been paid in the United States to social determinants of health. However, efforts to quantify and capture the social gradient have not been sufficient (Phillips et al., 2016).

Individual level socioeconomic status is a combination of occupation, education, income, and at least two of these variables should be studied together when studying SES (Liberatos, Link, & Kelsey, 1988). A composite index allows for multiple measurements to be aggregated to quantify the environment (Lian, Struthers, & Liu, 2016). A composite index used to quantify area-level SES is capable of incorporating a suite of influential variables. A study by Kathleen Yost published in 2001 created a composite index to measure area-level SES. She applied the index to breast cancer incidence and found that breast cancer incidence is positively associated with area-level SES (Yost, Perkins, Cohen, Morris, & Wright, 2001). This work was later used to develop a composite indexes of county-level SES from the US Census and the American Community Survey (ACS) to be used in the absence of individual SES information or to preserve the confidentiality of patient information (National Cancer Institute, 2019). The index uses factor loadings based on census tract US Census and ACS values for occupation, unemployment, poverty, income, education, and housing values (National Cancer Institute, 2019). A study by Yu et al. found that Yost's index had high agreement with another comparable index called the "Kreiger Index". Furthermore, the Yost index was able to explain roughly 90% of the common variance (Yu, Tatalovich, Gibson, & Cronin, 2014). Yu et al. also found that census-tract SES based on Yost's index was positively associated with breast cancer incidence, negatively associated with lung cancer incidence, and positively associated with cancer survival rates (Yu et al., 2014). This index later became available through the National Institutes of Health (NIH) Surveillance, Epidemiology, and End Results Program (SEER) SEER*Stat cancer registry and software at the county level (National Cancer Institute, 2019). This index has not seen usage outside of the context of cancer research.

1.13 Treatment for Opioid Dependence with Buprenorphine

Buprenorphine became the first medication used to treat opioid dependency that can be prescribed by practitioners in 2002 after being approved by the FDA (Substance Abuse and Mental Health Services Administration, 2019a). Buprenorphine is a "partial opioid agonist of the μ receptor", which mediates reinforcement following activation of the receptor (Ling, Mooney, & Torrington, 2012). It is stated to be safer than methadone due to buprenorphine's low potential for overdose and low toxicity at high dosages (Ling et al., 2012). Unlike methadone, buprenorphine is not restricted to usage at "federally authorized opioid-treatment clinics" and can be prescribed in an office-based setting (Parida et al., 2019; Schuckit, 2016). Due to this ability to prescribe buprenorphine in more settings than methadone, as well as the low potential for overdose and low toxicity, buprenorphine and other drug combinations with buprenorphine possess very positive capabilities to treat those with opioid dependence and/or addiction. The state of Maine has pronounced capabilities to monitor opioid prescribing through the Maine Prescription Monitoring Program (M-PMP) which includes buprenorphine. In 2014, Buprenorphine accounted for just under half of all opioid prescriptions issued to young adults in the state or more precisely 46.3% for women and 49.3% for men (Piper et al., 2016). These percentages suggest that buprenorphine is seeing frequent usage in the state.

1.14 Summary

The opioid epidemic continues to be a significant concern to public health. The epidemic is not experienced uniformly across the United States where regions such as New England are experiencing very high rates of opioid overdose deaths. Illicitly manufactured Fentanyl presents a substantial concern as it is proliferating throughout the illicit opioid market alongside substantial increases in overdose deaths attributable to fentanyl in states like Maine and New Hampshire. County-level economic characteristics such as the poverty rate, median housing value, percentage of adults 25 years of age or older with a high school education or less, and unemployment have been observed to be significantly associated with opioid overdose death rates. However, limited efforts have been made to consider the utilization of a composite index of multiple census measures designed to quantify county-level SES in relation to the opioid epidemic.

CHAPTER 2

METHODS

The aim of this study was to examine the associations between ***county-level*** SES, urbanicity, access to treatment for opioid dependency, and county-level opioid overdose death rates in the northern New England states of Maine, New Hampshire, and Vermont. Based on the literature, it was hypothesized that more deprived SES counties would experience greater rates of opioid overdose deaths compared to more affluent SES counties after controlling for urbanicity and county-level population density of practitioners who can prescribe buprenorphine.

This study is of an ecological design as the data utilized are aggregated counts and census measures and overdose death counts at the county level. Data collected was restricted to counties within the US states of Maine, New Hampshire, and Vermont during the years of 2015-2017. Maine, New Hampshire, Vermont are comprised of 16,10, and 14 counties respectively, providing for a sample of 40 counties overall. The outcome measured was the opioid overdose death rate for the years 2015-2017. These data were requested from the CDC Wonder database (Centers for Disease Control and Prevention, 2019) as counts of opioid overdose deaths for each county within the described time period; the corresponding population counts as the sum of the population in each year of the time period were provided in the data request.

Therefore, the opioid overdose rate calculation using these two variables is the average opioid overdose death rate for 2015-2017. CDC Wonder multiple cause of death (MCD) codes X40-44, X60-64, X85, Y10-14, and T40.0-40.4 were selected for inclusion in the counts of opioid overdose deaths. This selection of codes is representative of those suggested by the CDC, those used in CDC MMWR reports, and elsewhere in the literature (Centers for Disease Control and Prevention, 2013; Mack, Jones, & Ballesteros, 2017; Scholl et al., 2018; Stewart et al., 2017). The years 2015-2017 were selected due to data suppression in small counties where counts of opioid overdose deaths within a single year were less than ten and therefore suppressed. This data suppression would potentially introduce bias as only counties with large enough counts of overdose deaths would have been included. MCD codes were used to reduce the chances of undercounting opioid overdose deaths due to misclassification which has been described to be of potential concern in drug-related suicide cases (Rockett, Kapusta, & Coben, 2014). After aggregation of the selected years of 2015, 2016, and 2017 no counties were suppressed.

The measure for county-level SES was taken from The National Cancer Institute's census tract-level socioeconomic status index which is derived from seven U.S. Census measures selected based on a 2001 study by Yost et al. (Yost, Perkins, Cohen, Morris, & Wright, 2001). The variables included in the calculation of the index are median household income, median house value, median rent, percent below 150% of poverty line, percent working-class, percent unemployed, as well as an education index based on a study by Liu et al. (Liu, Deapen, & Bernstein, 1998; National Cancer Institute, 2019).

This measure is available in the National Cancer Institute's SEER*Stat database at the county-level. County-level SES was categorized into quartiles, similar to what was conducted in previous studies using this index (Yost et al., 2001; Yu et al., 2014). Thus, the highest quartile will represent the highest SES counties and the lowest quartile will represent the lowest SES counties. The index was chosen because it was available as a precalculated variable in the SEER*Stat database. It was also chosen due to having previous examples in the literature of its utilization.

A measure of county-level urbanicity was included in the CDC Wonder data request. This measure is derived from the 2013 National Center for Health Statistics (NCHS) Urban-Rural Classification Scheme for Counties (Ingram & Franco, 2014). A two-level simplification of the six-level classification scheme was used based on the metropolitan and non-metropolitan categories described on pages 2 and 3 of the NCHS scheme documentation (Ingram & Franco, 2014). The two-level simplification was chosen due to the small overall sample size as well as small overall counts for the various subcategories of metropolitan counties. The subcategories of large central metro, large fringe metro, medium metro, and small metro were combined into the metropolitan designation. The non-metropolitan category is analogous to the term "rural" and thus the subcategories of micropolitan and noncore were combined to form the rural designation.

County-level access to treatment for opioid dependence was measured by the count of practitioners listed in the SAMHSA website for state-specific practitioners who have received a waiver to prescribe buprenorphine per 100,000 individuals in the population (Substance Abuse and Mental Health Services Administration, 2019b). Counts of these practitioners in each county were collected by geocoding the location of each practitioner's practice location using the state, zip code, and address included in the data file using ArcGIS version 10.2.2 (Environmental Systems Research Institute, 2019) and summing the practitioners within a county's border. Due to the population variable included in the CDC Wonder data request being the sum of the population during the years 2015-2017, a separate estimate for county population size was requested from the US Census 5-year ACS estimates for each county in Maine, New Hampshire, and Vermont (U.S. Census Bureau, 2019a). Five-year estimates were used to ensure that a population estimate was obtained for each of the 40 counties as the five-year estimates are performed for all population areas.

Negative binomial regression was performed using SAS software version 9.4 (SAS Institute Inc., 2019) and the GENMOD procedure to model opioid overdose death rates using the count of opioid overdose deaths as the outcome and the log of the population as the offset parameter to calculate rates. This was done to account for the variability in population size. By examining rates, a fair comparison can be made between counties of different population sizes. The main effects model included the count of opioid overdose deaths as the dependent variable, county-level SES as the independent variable, and the variable for the state as the fixed effect to account for unobservable state-level differences that may impact opioid mortality. Measures for county-level urbanicity, the population density of practitioners who have received a waiver to prescribe buprenorphine were added to the model as potential confounders. Each variable was added individually to assess confounding and model fit if the variable was determined to be a confounder in the association between county-level SES and opioid overdose rates based on a 10% magnitude change in the rate ratios of the pairwise comparisons of county-level SES quartiles, the variable was kept in the model. The final model included counts of opioid overdose deaths as the dependent variable, county-level SES, county-level urbanicity, population density of practitioners who have received a waiver to prescribe buprenorphine, and a variable for the state as a fixed effect.

The data for this study was restricted to the county-level, except for the data on practitioners waived to prescribe buprenorphine which is publicly available through SAMHSA (and was subsequently aggregated to the county level). That data only pertains to the location of practice for each practitioner and thus does not pose any potential breach in privacy as each location is readily available information to the general public. As this study does not include human subjects or any identifiable private information, institutional IRB approval was not requested for this study.

CHAPTER 3

RESULTS

The characteristics of the sample of 40 counties are presented in Table 3.1. Amongst the 40 counties that comprise Maine, New Hampshire, and Vermont, the mean county-level opioid overdose death rate per 100,000 individuals was 24.65 (95% CI=21.77, 27.52). Amongst the counties in each of the three states of Maine, New Hampshire, and Vermont the mean county-level opioid overdose rate per 100,000 individuals for each state individually was 24.53 (95% CI=19.75, 29.31), 31.78 (95% CI=25.29, 38.27), and 19.68 (95% CI=16.68, 22.68) respectively. When comparing the mean county-level opioid overdose death rate per 100,000 individuals by urbanicity, counties classified as metropolitan had a mean of 28.54 (95% CI=22.09, 35.00) compared to counties classified as rural which had a mean of 23.17 (95% CI=19.95, 26.38). Within the quartiles of county-level SES, county-level opioid overdose death rate per 100,000 individuals was 25.07 (95% CI=17.41, 32.74), 23.17 (95% CI=19.76, 26.57), 20.59 (95% CI=15.42, 25.77), 29.75 (95% CI=22.23, 37.28) for the first, second, third, and fourth quartiles respectively. A graphical representation of the crude county-level opioid overdose rates for Maine, New Hampshire, and Vermont is presented in Figure 3.1.

The mean county-level practitioners waived to prescribe buprenorphine per 100,000 amongst all 40 counties was 25.32 (95% CI=21.27, 29.37). State-specific averages for county-level practitioners waived to prescribe buprenorphine per 100,000 in Maine, New Hampshire, and Vermont were 26.62 (95% CI=19.04, 34.20), 23.76 (95% CI=15.52, 31.99), and 24.95 (95% CI=17.84, 32.06) respectively. Within county-level urbanicity classification, those which are classified as metropolitan had an average rate of practitioners waived to prescribe buprenorphine per 100,000 of 20.38 (95% CI=11.92, 28.84) compared to those which classified as rural which was 27.20 (95% CI=22.48, 31.91). Within the quartiles of county-level SES, the average number of practitioners waived to prescribe buprenorphine per 100,000 was 24.78 (95% CI=13.31, 36.25), 29.94 (95% CI=23.31, 35.98), 26.64 (95% CI=16.23, 37.05), 20.22 (95% CI=13.22, 27.22) for the first, second, third, and fourth quartiles respectively. A graphical representation of the geographical distribution of practitioners waived to prescribe buprenorphine is presented in Figure 3.2. A second graphical representation of the population density of practitioners waived to prescribe buprenorphine per 100,000 individuals is presented in Figure 3.3.

Based on all 40 counties comprising the three state of Maine, New Hampshire, and Vermont, counties in Maine most often fell into the first quartile of county-level SES (43.75% of Maine's 16 counties). Counties in New Hampshire were most frequently placed in the fourth quartile of county-level SES (50% of New Hampshire's 10 counties). The counties in Vermont were most frequently placed in the third quartile of county-level SES (35.71% of Vermont's 14 counties). Metropolitan counties were most frequently ranked in the fourth quartile of county-level socioeconomic status with 63.64% of the 11 counties compared to rural counties which received only 10.34% of the 39 counties receiving the same rank. Rural counties were more frequently ranked in the first and second counties with both quartiles receiving 31.03% of the 29 rural counties.

The results of the negative binomial regression with a population offset to estimate average county-level rates of opioid overdose including variables for county-level SES, county urbanicity, the county-level population density of level practitioners waived to prescribe buprenorphine, and a state fixed effect are presented in Table 3.2. After controlling for county-level urbanicity and county-level population density of level practitioners waived to prescribe buprenorphine, counties in the first and second quartiles of county-level socioeconomic status had 1.35 (95% CI=1.02, 1.79) and 1.31 (95% CI=1.01, 1.71) times the opioid overdose death rate compared to counties in the third quartile respectively. Furthermore, after controlling for county-level socioeconomic status and county-level population density of level practitioners waived to prescribe buprenorphine, metropolitan counties had 1.24 (95% CI=1.01, 1.55) times the opioid overdose death rate compared to rural counties.

A statistically significant association was also observed between county-level population density of practitioners who have received a waiver to prescribe buprenorphine and county-level opioid overdose death rates. For every 10 unit increase in the county-level population density of practitioners waived to prescribe buprenorphine per 100,000 individuals, the county-level opioid overdose death rate per 100,000 individuals increased by 10.08 (95% CI=10.01, 10.15) after controlling for county-level socioeconomic status and county urbanicity. While this association seems to imply that increases in practitioners who can prescribe buprenorphine in a county will potentially drive an increase in the opioid overdose death rate, there is a notable lack of a temporal sequence for this association. Thus, it is also possible that practitioners who are practicing in counties that are experiencing high rates of opioid abuse and overdose would choose to seek out the waiver to prescribe buprenorphine to provide such treatment to patients. Therefore, the observed association could potentially be that greater density of practitioners who have received the waiver to prescribe buprenorphine are practicing in regions that are struggling with the opioid epidemic.

Table 3.1 Summary of County-Level Characteristics for Opioid Overdose, Socioeconomic Status, and Practitioners Waived to Prescribe Buprenorphine in Maine, New Hampshire, and Vermont

Characteristic	County-Level Opioid Overdose Deaths Per 100,000 Mean (95% CI)	County-Level Practitioners Licensed to Prescribe Buprenorphine Per 100,000 Mean (95% CI)	1st Quartile of County-Level SES N (%)	2nd Quartile of County-Level SES N (%)	3rd Quartile of County-Level SES N (%)	4th Quartile of County-Level SES N (%)
All Counties (N = 40)	24.65 (21.77 – 27.52)	25.32 (21.27 – 29.37)	10 (25.00%)	10 (25.00%)	10 (25.00%)	10 (25.00%)
State						
Maine (N = 16)	24.53 (19.75 – 29.31)	26.62 (19.04 – 34.20)	7 (42.75%)	6 (37.50%)	1 (6.25%)	2 (12.50%)
New Hampshire (N= 10)	31.78 (25.29 – 38.27)	23.76 (15.52 – 31.99)	1 (10.00%)	0 (0.00%)	4 (40.0%)	5 (50.00%)
Vermont (N = 14)	19.68 (16.68 – 22.68)	24.95 (17.84 – 32.06)	2 (14.29%)	4 (28.57%)	5 (35.71%)	3 (21.43%)
County-Level Urbanicity						
Metropolitan (N = 11)	28.54 (22.09 – 35.00)	20.38 (11.92 – 28.84)	1 (9.09%)	1 (9.09%)	2 (18.18%)	7 (63.64%)
Rural (N = 29)	23.17 (19.95 – 26.38)	27.20 (22.48 – 31.91)	9 (31.03%)	9 (31.03%)	8 (27.59%)	3 (10.34%)
County-Level Quartile of Socioeconomic Status						
1st	25.07 (17.41 – 32.74)	24.78 (13.31 – 36.25)	---	---	---	---
2nd	23.17 (19.76 – 26.57)	29.64 (23.31 – 35.98)	---	---	---	---
3rd	20.59 (15.42 – 25.77)	26.64 (16.23 – 37.05)	---	---	---	---
4th	29.75 (22.23 – 37.28)	20.22 (13.22 – 27.22)	---	---	---	---

Table 3.2 Negative Binomial Regression Model Results for Opioid Overdose Rates in Maine, New Hampshire, and Vermont Counties 2015-2017

Comparison	Rate Ratio (95% CI)	P-Value
Quartiles of County-Level Socioeconomic Status		
1st to 2nd	1.03 (0.81 – 1.31)	0.8071
1st to 3rd	**1.35 (1.02 – 1.79)**	**0.0358**
1st to 4th	1.08 (0.80 – 1.46)	0.6047
2nd to 3rd	**1.31 (1.01 – 1.71)**	**0.0463**
2nd to 4th	1.05 (0.78 – 1.42)	0.7461
3rd to 4th	0.80 (0.62 – 1.04)	0.0909
County-Level Urbanicity		
Metropolitan to Rural	**1.24 (1.01 – 1.55)**	**0.0499**

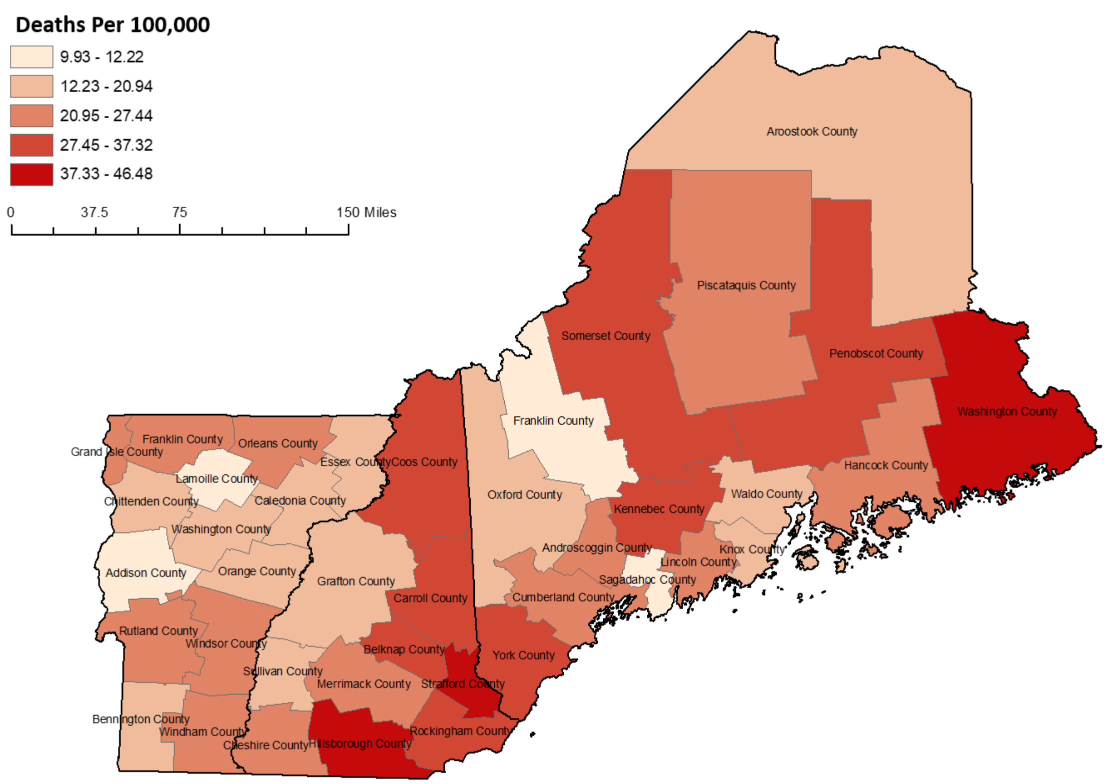

Figure 3.1: 2015 – 2017 Opioid Overdose Death Rate Per 100,000

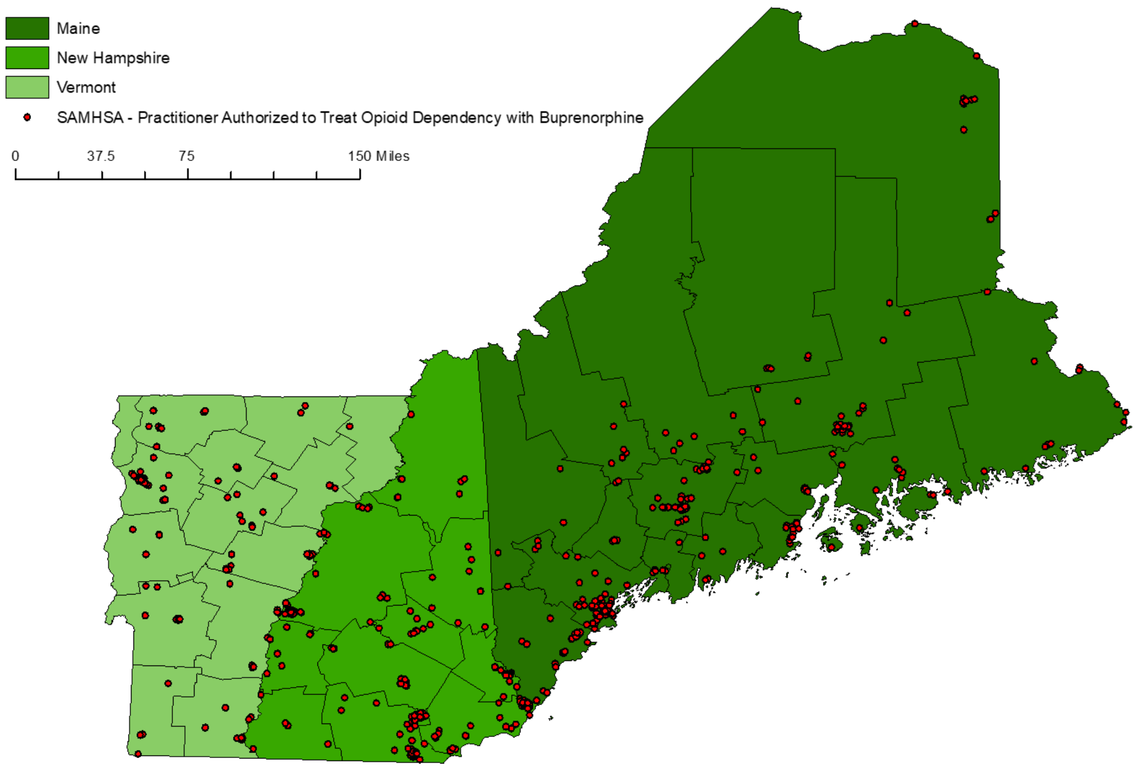

Figure 3.2: Distribution of Practitioners Waived to Prescribe Buprenorphine

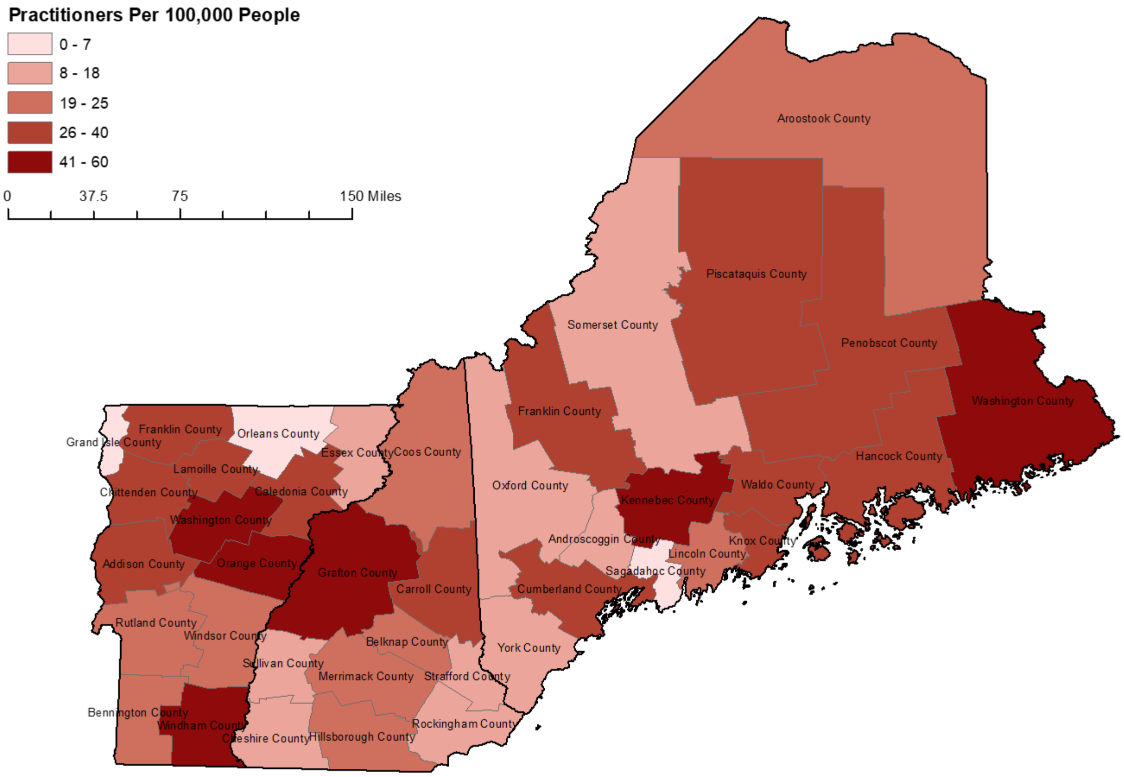

Figure 3.3: Population Density of Practitioners Authorized to Prescribe Buprenorphine

CHAPTER 4

DISCUSSION

Analysis of ecological data in the northern New England states of Maine, New Hampshire, and Vermont suggests that counties of lower SES experience greater rates of opioid overdose compared to counties of greater SES after controlling for county urbanicity and population density of practitioners capable of prescribing buprenorphine. It was also observed that counties that are classified as more metropolitan experience greater rates of opioid overdose compared to rural counties after controlling for county socioeconomic status and population density of practitioners capable of prescribing buprenorphine. Lastly, there was an association between the population density of practitioners capable of prescribing buprenorphine and opioid overdose rates after controlling for county socioeconomic status and urbanicity. However, the temporal sequence of this association cannot be determined within the confines of this analysis. Specifically, practitioners capable of providing treatment that is highly beneficial for recovery from opioid addiction and dependence are practicing where the need for such treatment is high. If the effectiveness of availability of buprenorphine treatment is to be determined, then an analysis designed to establish the temporal sequence of those measures appropriately should be considered.

The results of this study regarding the lowest two quartiles of county SES experiencing significantly greater rates of opioid overdose supports the body of evidence that has examined a similar association between specific macroeconomic measures such as unemployment, poverty, and education (Hollingsworth et al., 2017; Pear et al., 2019; Wright et al., 2014). Even when a comprehensive composite measure of these factors that is designed to quantify the county-level socioeconomic gradient is used, counties that are more socioeconomically disadvantaged experience greater rates of opioid overdose deaths. In contrast to the study by Stewart et al., the results of this analysis show that in Maine, New Hampshire, and Vermont counties, metropolitan counties experience greater rates of opioid overdose deaths compared to rural counties.

This analysis is subject to some limitations. First of which is the small sample size of counties used in the analysis. Being limited to 40 counties creates a 'budget' of how and what can be utilized in a regression analysis. Compromises were made to the specificity of variables, especially in the case of the measure used for county urbanicity which was initially comprised of 6 levels and was simplified to two levels for this analysis. Furthermore, there is a compromise in geographical specificity made due to the unit of analysis being the county-level. Counts of opioid overdose deaths through CDC wonder are only available to the county-level. Using this unit of geographic specificity is restrictive as it is unable to consider the potential variation in sub-county level regions. Within these three states, a metropolitan city within a county can be surrounded by rural areas; therefore, if analysis is conducted at the county-level, these areas are lumped together despite being quite different, a reflection of the modifiable area unit problem.

The usage of quartile categorization of the variable for county SES is a limitation that is necessary since it is a composite of multiple census measures. The values of the variable being a representation of this combination of census measures force the interpretation of the measure in its continuous form to be vague and uninformative. The stack ranking of the quartiles provides a means by which to make more informative comparisons. It is however still less specific due to assumed homogeneity within the quartiles and still more difficult to interpret compared to viewing each census measure individually.

Requesting opioid overdose data from CDC Wonder for the years 2015, 2016, and 2017 collectively, also poses a limitation as it restricts the ability to examine any potential changes between these three years in the counties within the sample. Because of the small population size in many counties in this region of the United States, the individual counts of opioid overdose in a single year may be small. However, the crude opioid overdose rate for that year may still be profound and of substantial interest within the context of this analysis. Therefore, the small counts will still be censored if data is requested for a single year and that data then be left out of the analysis and introduce bias. The grouping of the three years is necessary ensure each county within the region is represented in the analysis. Also, the analysis performed is ecological and does not provide for inference for individuals.

The results of this analysis are limited in its generalizability due to noted regional heterogeneity of the opioid epidemic in the United States as well as likely economic heterogeneity (Scholl et al., 2018). Due to this fact as well as the aforementioned limitations of this study, it is recommended that the results presented in this study are considered to be regional specific. Independent analysis of separate regions of the United States should be conducted to assess if similar associations are held in other regions of the country.

One notable strength of this analysis is its ability to use the National Cancer Institute's census tract-level socioeconomic status index to derive a means by which to compare the socioeconomic environment of various regions within northern New England. People live in areas defined by their specific environment and no two are exactly alike. Individually, socioeconomic status is clearly defined as a triad of occupation, education, income, and that at minimum two of these measures should be viewed together if SES is what is of interest (Liberatos et al., 1988). Individuals and the environments in which they live are complex, and no single variable should be used to define either. To appropriately examine an epidemic as wide-reaching and detrimental to a population as the opioid epidemic in the United States, efforts should be made to consider the coexistence of multiple factors in an environment and their combined influence on the state of the epidemic in that environment. Given the National Cancer Institute's census tract-level socioeconomic status index was not designed with substance abuse in mind, there may be improvements or alterations that would be made if a similar index were created with the express purpose of usage for area-level substance abuse research in the United States.

It is evident that the opioid epidemic is far from being resolved in the United States, and recent observations from law enforcement and public health agencies suggest that fentanyl poses a significant danger to public health and safety. Thus, public health intervention must be targeted towards the heightened risk presented by the incorporation of fentanyl into the illicit opioid market. Its potency and toxicity place users at extremely high risk for overdose and death.

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