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AN EXAMINATION OF COUNTY-LEVEL SUICIDE MORTALITY IN THE US: IS THERE A PROTECTIVE EFFECT OF LITHIUM IN THE ENVIRONMENT?

A Thesis in

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by

Gregory R. Cook

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The thesis of Gregory R. Cook was reviewed and approved by the following:

Stephen A Matthews
Liberal Arts Professor of Sociology, Anthropology, Geography & Demography
Thesis Advisor

Anthony C. Robinson
Director of Online Geospatial Education

ABSTRACT

Suicide is the 10th leading cause of death in the United States, has increased by 35% in the last 20 years and varies in how it impacts people by age, sex, race and ethnicity. (Hedegaard et al., 2020, "Increase in Suicide Mortality in the United States, 1999–2018") Significant variation is exhibited geographically in the suicide rate, with wide ranging changes shown across the continental United States.

Lithium, the third element on the periodic table of elements, has numerous uses in electronics, industrial products and in the form of lithium salts has been used as a mood stabilizer in the treatment of bipolar disorder and major depression since the 1940s. (Cade, 1949) Lithium is unique as a compound which has significant geographical and environmental variation, a clear impact on individual level behavioral health and a strong anti-suicidal effect. (Lewitzka, et al., 2015)

A small body of research, of less than 15 articles in the last 30 years, demonstrates support that environmental lithium, found in groundwater and consumed regionally, may produce a protective effect decreasing the suicide rate. However, the relationship between the two is poorly defined, the statistical methods used to analyze the data are of limited sophistication and may impact the results of the analysis, the geographical areas of study are finite and the effect size found is small.

In this thesis, we will seek to replicate this existing body of research over a larger geographical area comprising the continental United States, process the data sources using a more robust statistical methodology, determine if there is significant local versus global variation to this effect, seek clarification if a threshold exists at which lithium starts to impact the suicide rate and conclude whether there are other appropriate data sources of lithium available to study this topic.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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Chapter 1

Introduction

What is the relationship between Lithium and Suicide?

In the review of extant literature, it has been observed that increased concentrations of lithium in groundwater relates to a decrease in the suicide rate. While the cause is unclear, lithium has a known anti-suicidal effect (Lewitzka, et al., 2015) and is a commonly used medication for the treatment of bipolar disorder and major depression. (*Lithium Monograph for Professionals*) The relationship between lithium and the suicide rate may be best termed as a protective effect decreasing the suicide rate, rather than as a driving cause more strongly influencing suicide rates such as deaths of despair. (Case & Deaton, 2020) Potentially, there may be a threshold level of lithium consumption that must be achieved by a population to reach the protective effect (Palmer et al., 2019), in turn, this may explain some of the local variation of this effect.

Therefore, we wish to further the study of the relationship between lithium and the suicide rate, verify if we can replicate existing research, determine what regional variations exist across the continental United States and potentially expand the identified sources of usable lithium level data. Studying the relationship between lithium and the suicide rate traverses many fields; including but not limited to demography, public health, behavioral health, environmental science and physical geography. As such, the perspective of this thesis will be to study this issue from an interdisciplinary viewpoint with a focus on geography. Existing research notably lacks this focus, instead viewing the issue through the lens of public health or environmental science.

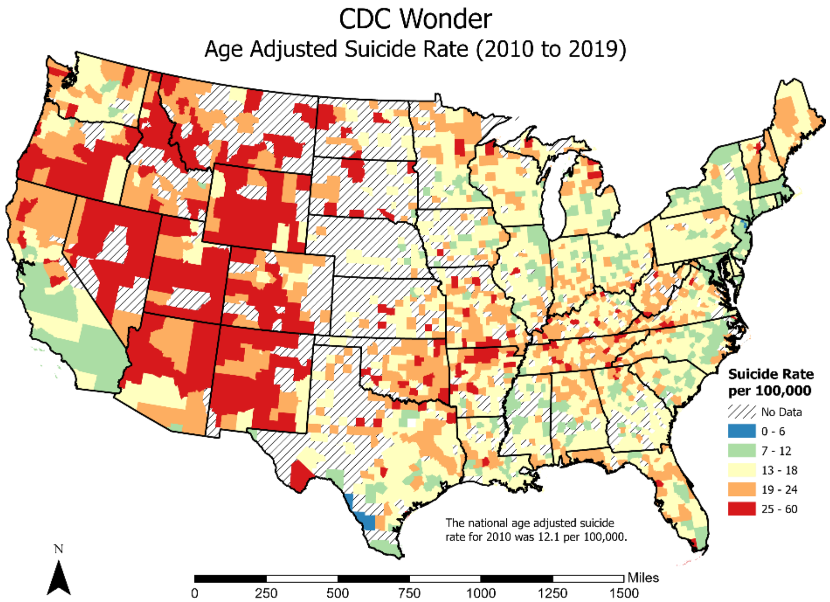


Figure **1-1**: 2010 to 2019 age adjusted suicide rate per 100,000 population based on data obtained from CDC Wonder. (*CDC WONDER*, n.d.)

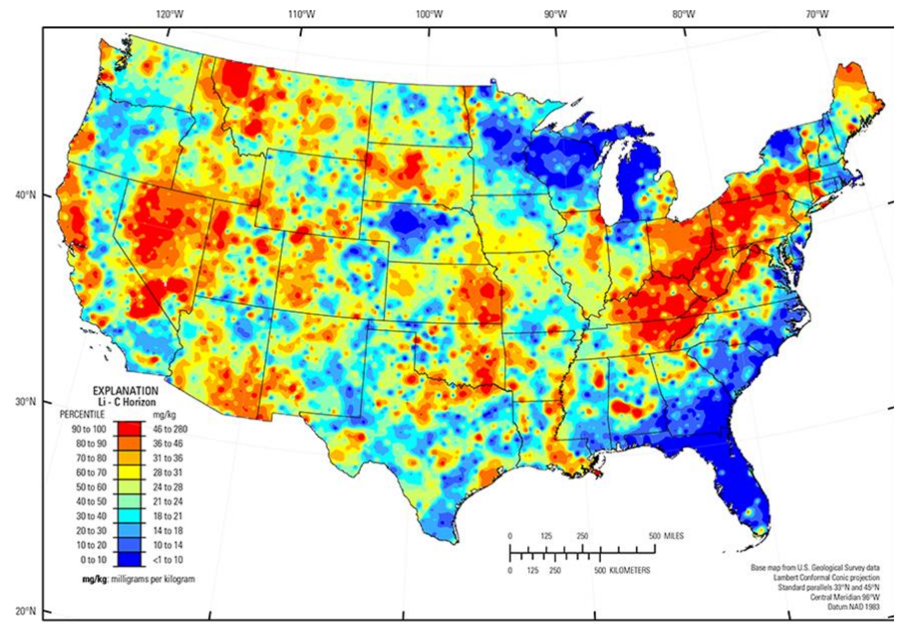


Figure **1-2**: Lithium levels in the C soil horizon in the continental United States. Soil level concentration of lithium is presented here as a similar map of water level lithium concentration is not known to be available. (*USGS Scientific Investigations Report 2017-5118: Geochemical and Mineralogical Maps, with Interpretation, for Soils of the Conterminous United States*, n.d.)

Suicide rates in the continental United States exhibit significant geographic variation as shown in Figure 1-1. Suicide is much higher among men than women, more rural than urban, affects older Americans more than younger Americans and may vary by race and ethnicity. Areas of interest on the above map include the high levels of suicide in the far western United States, the high levels surrounding the Appalachian mountain range, the high levels in Oklahoma, Arkansas and Missouri as well as the average to below average levels along the northeastern coast line and southern California. Of note, these are all examples of urban / rural and wealth divisions in the United States.

Lithium levels in the soil and water of the United States also vary geographically. Areas of note include the low levels of lithium concentration in the glaciated Midwest, the low levels along the Gulf and Atlantic coastal plain, the high levels of concentration in the Appalachian mountain range and high levels in the arid basins in Nevada. (*USGS Scientific Investigations Report 2017-5118: Geochemical and Mineralogical Maps, with Interpretation, for Soils of the Conterminous United States*, n.d.) These spatial concentrations do not exhibit a clear relationship between lithium levels and the suicide rate, but do prompt for regional investigation of areas of high lithium concentration and lower than expected suicide rates such the Appalachian mountain range, southern California and southern Michigan and Wisconsin.

Existing research surveying this relationship is limited and focused on specific geographic scales, analyzing areas equivalent in size to a US state and aggregating data to the level of a US county. Approximately 15 studies examining the relationship between lithium and the suicide rate have been completed in the last 30 years; they are distributed geographically around the globe with less than half completed in the United States. This thesis is based primarily around the work of Blüml et al. in Texas, Kabacs et al. in England and Palmer et al. in Alabama.

The geographical component of this question has been poorly accounted for in existing research; previous studies have used linear regression (Blüml et al., 2013) and Poisson regression.

(Kabacs et al., 2011) As Tobler's first law states "everything is related to everything else, but near things are more related than distant things" (A Computer Movie Simulating Urban Growth in the Detroit Region on JSTOR, n.d.), we assume that regional variation in lithium levels and the suicide rate will significantly impact the study of their relationship and needs to be appropriately accounted for in the regression analysis. We also assume that lithium's relation to the suicide rate will vary when analyzed locally versus globally, which the GWR analysis will help illuminate.

Regional variations in analysis are also limited in existing research, likely due to the sparse availability of comprehensive water quality datasets. Future work may have fewer limitations due to the adoption of EPA Unregulated Contaminant Monitoring Rule (UCMR 5), in March 2021, which requires public water systems (PWSs) in the United States to monitor lithium levels in their drinking water sources.

In the interim, this thesis will analyze the relationship between lithium and suicide rate using three nationally available datasets; the National Water-Quality Assessment Project (NAWQA) dataset, USGS National Geochemical Database (NGDB) for soil and the USGS Data Series 801 release. While it is unclear if soil data samples will represent a similar relationship between lithium in ground water and the suicide rate as shown in existing research, they are useful for this analysis as they are far more comprehensive spatially across the continental United States than the NAWQA dataset and represent a much larger set of samples, at more than an order of magnitude greater in scope.

What have we learned from different disciplines that informs the current understanding of suicide and environmental lithium?

As we have provided a brief overview of the limitations of existing research, now we need discuss the academic foundations of this work which are based around the concept of determinants of health; these are a “range of personal, social, economic, and environmental factors that influence health status”. (*Determinants of Health | Healthy People 2020*, n.d.) Determinants of health may be subdivided into more specific categories based on how they affect an individual such as social, economic or biologic determinants of health. Determinants of health may help describe larger socioeconomic health disparities between groups of people. An example of this would be Anne Case and Angus Deaton’s concept of Deaths of Despair, a framework to understand recent factors driving changes in the suicide rate.

How is this Thesis structured?

Effectively conducting this thesis requires defining the path through which to explore the complexities of lithium and suicide. For the first chapter of this thesis, we will review a background of current literature on suicide, lithium and the interactions between the two. What does the extant research define as the forces driving individuals to suicide? How does suicide impact American society and how has this relationship changed in the last 20 years? How does geography, race, ethnicity and sex impact suicide? What current trends are driving the increase in suicide and how will this change in the future?

Next, we will review a history of the element Lithium. What are its various uses as a compound? Why does it have a special relationship with mental health and suicide? Why has it been used for so long as a first line medication when treating bipolar disorder and treatment resistant depression? How does lithium vary geographically in the environment and how are individuals exposed to it? Why have the USGS and the EPA established monitoring levels for lithium in groundwater and what are these levels?

To conclude our review of existing literature, we will summarize the currently available research examining the protective effect of environmental lithium including its varied data, statistical and geographical limitations. We will discuss how the present research controls for social problems affecting suicide such as such as race and ethnicity, poverty and how this impacts the results of the research. Finally, we will analyze the statistical methods used in the current body of research.

For the second chapter, we will address the innovations proposed by this thesis compared to the existing research. This includes a geographic expansion compared to the existing studies from a regional to a national scale; a search for alternative lithium level data sources such as the USGS National Geochemical Database (NGDB) or the USGS Data Series 801 release and a replication of the 2013 Texas study by Blüml et al. We will conclude the second chapter by covering the specific hypotheses we expect to test with our data and methodologies.

Continuing on with the third chapter, we will review a summary of the data sources used to complete this study; discuss the methodology used to join, process and analyze each data source, suggest limitations to the data sources and how these limitations may impact the scope of this thesis. Next, we will move on to the fourth chapter, covering the results of this study, interpreting them and discussing their limitations. Finally, in the fifth chapter, we will conclude the thesis by discussing the numerous potential avenues for future research and synthesize the key points of this work.

Review of Literature

Suicide

Suicide has seen a dire increase in the 20th century as a cause of death, growing 35% between 1999 and 2018, from 10.5 deaths per 100,000 population to 14.2 deaths per 100,000 population. The suicide rate for men is much higher than the suicide rate for women, 3.7 times higher in 2018 with men rated at 22.8 deaths per 100,000 population and women rated at 6.2 deaths per 100,000 population. Currently suicide is the 10th leading cause of death in the United States. (Hedegaard et al., 2020, “Increase in Suicide Mortality in the United States, 1999–2018”)

In general, suicide is much higher for men than for women, more rural than urban, affects older Americans more than younger Americans and may vary by race and ethnicity. Suicide rates are highest among men 75+ and women aged 45 to 64. Racially suicide rates are highest among American Indians/Alaskan Natives and White non-Hispanics, with Native American reservations being particularly hard hit.

Suicide is driven by a variety of processes including lack of social capital, variations in race and ethnicity and variations by sex. (Dev & Kim, 2021) Lack of social capital may take several forms including community and familial support systems, access to health care and civic participation. Variations by race, ethnicity and sex are strongly influenced by the high suicide rates among non-Hispanic white men. Mental health and substance abuse problems are also primary drivers of suicidal behavior. (Bommersbach et al., 2021)

The Geography of Suicide

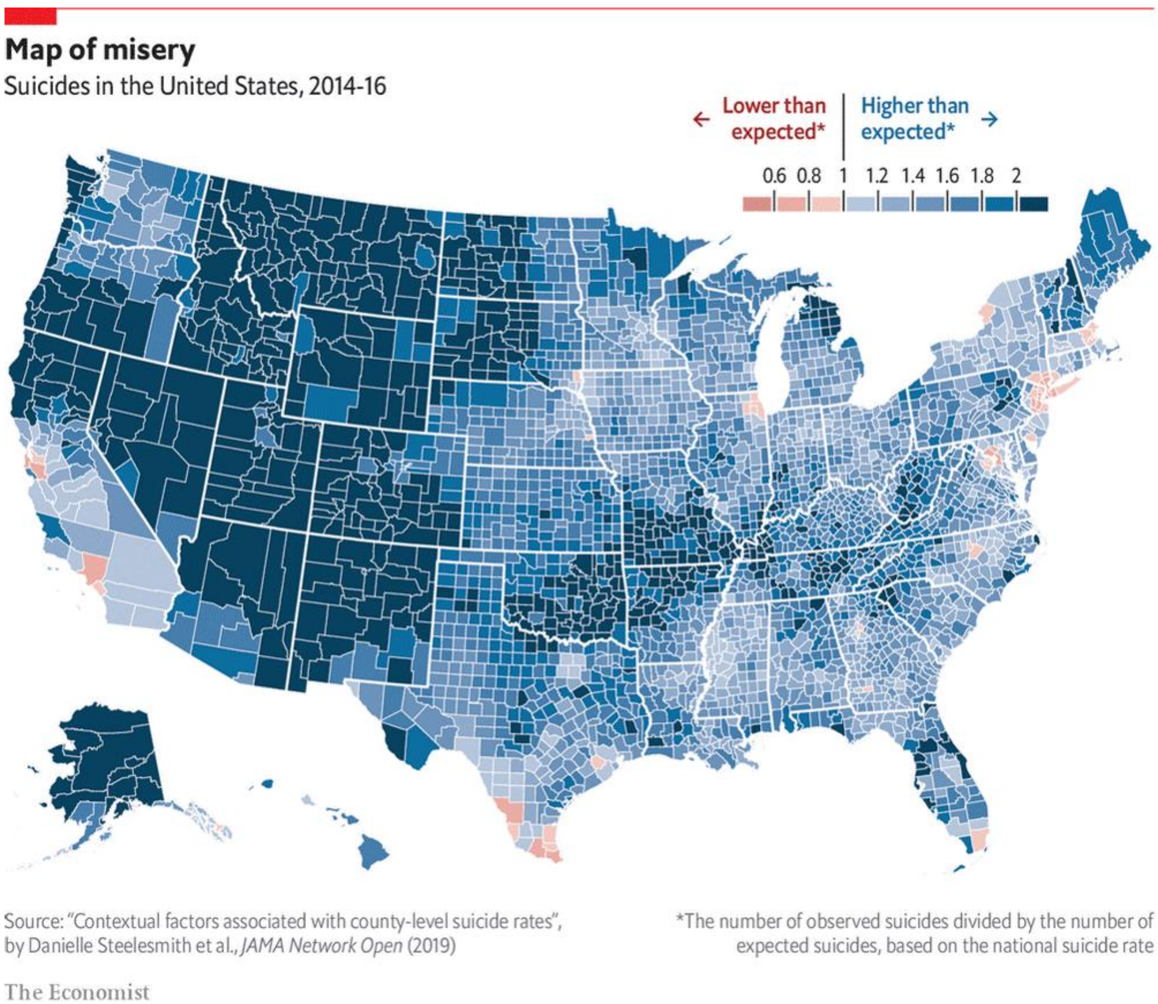


Figure **1-3**: Suicide rates in the United States from 2014 to 2016. ("Americas suicide rate has increased for 13 years in a row")

Deaths of Despair

Suicide is increasingly affecting subsets of the American population in different ways with significant deviations occurring in the suicide rate depending on age, sex, race, ethnicity, income, education and geography. Anne Case and Angus Deaton's Deaths of Despair and the Future of Capitalism (Case & Deaton, 2020) is an example of how the suicide rate is increasing for middle aged non-Hispanic whites with limited education in rural areas with limited economic opportunity. Case and Deaton categorize these increasing levels of death from suicide, drug overdoses and alcoholic liver disease as deaths of despair.

> "Our story of deaths of despair; of pain; of addiction, alcoholism, and suicide; of worse jobs with lower wages; of declining marriage; and of declining religion is mostly a story of non-Hispanic white Americans without a four-year degree."
>
> "The economic forces that are harming labor are common to all working-class Americans, regardless of race or ethnicity, but the stories of blacks and whites are markedly different."
>
> (Case & Deaton, 2020, p. 4)

Case and Deaton cite numerous examples of why this change in deaths of despair is affecting the suicide rate including, the opioid crisis, the decreasing economic ability in rural America, the decline of union membership and its associated well-paying jobs, the increasing divide in health between those with a bachelor's degree and those without and the breakdown of existing social communities such as marriage rates and church membership.

> "The increase in deaths of despair was almost all among those without a bachelor's degree. Those with a four-year degree are mostly exempt; it is those without the degree who are at risk. This was particularly surprising for suicide; for more than a century, suicides were generally more common among the educated, but that is not true in the current epidemic of deaths of despair."
>
> (Case & Deaton, 2020, p. 3)

Lithium

Lithium, the third element on the periodic table of elements, is best known for its use in rechargeable batteries, a technology that have been greatly refined over the last five decades. (Reddy et al., 2020) However, lithium has numerous other applications; it may be combined with aluminum and magnesium to create metal alloys with increased strength and lighter weight than their component metals. Compounds of lithium are used in industrial processes such as lithium oxide, lithium chloride, lithium bromide and lithium stearate. (*Lithium - Element Information, Properties and Uses | Periodic Table*, n.d.) Lithium hypochlorite is used as a sanitizer for water systems. (*Fact Sheet for Lithium Hypochlorite*, n.d.) The Lithium-6 isotope may be used in nuclear fusion to produce tritium with Deuterium–tritium fusion reaction. (*Fuelling the Fusion Reaction*, n.d.) Lithium salts are used to treat bipolar disorder and major depression. (*Lithium Monograph for Professionals*)

Human intake of lithium through drinking water is readily absorbed, whereas ingesting lithium through food is not fully absorbed. (Geochemistry and the Environment, 1974) Even though lithium is considered toxic for humans in large quantities and is readily absorbed through drinking water, lithium is not regulated in drinking water in the US. However, this is likely to change in the future because in March 2021, the EPA added lithium to the fifth proposed update for the Unregulated Contaminant Monitoring Rule (UCMR 5) with a minimum reporting level of 9 µg/L. (*US EPA*, 2021) The Safe Drinking Water Act (SDWA) requires public water systems to monitor and report to the EPA levels of contaminants listed on the UCMR. USGS has established similar Health Based Screening Levels (HBSL) for lithium: these are, 60 µg/L when drinking water is the only exposure source for a person to lithium and 10 µg/L in drinking water when other exposure sources are present. (*HBSL Home*, 2018)

Lithium's use as a Medication

Lithium salts have seen continuous use as a treatment for bipolar disorder since the 1940s (Cade, 1949) and are still used to treat occurrences of bipolar disorder and major depression that prove resistant to other treatments. (*Lithium Monograph for Professionals*) Lithium has a known anti-suicidal effect which has been studied since the 1970s. (Lewitzka, et al., 2015)

Effective therapeutic levels of lithium are much higher than the levels an average person would encounter in the environmental absorption or through consumption. Therapeutic levels of lithium target a blood concentration of 1.0 to 1.5 mEq/L serum level. Dosage depends on patient weight, age and sex and typically ranges from 300 mg to 900 mg daily. (Eskalith Prescribing Information, n.d.) 150 mg of lithium daily is the lowest reported effective therapeutic dose. (Parker et al., 2018)

Lithium is considered toxic at large dosage levels, *"Serum lithium levels should not be permitted to exceed 2.0 mEq/L during the acute treatment phase."* and patients on lithium therapy require consistent blood work to check for lithium intoxication.

> "The occurrence and severity of adverse reactions are generally directly related to serum lithium concentrations as well as to individual patient sensitivity to lithium, and generally occur more frequently and with greater severity at higher concentrations. Adverse reactions may be encountered at serum lithium levels below 1.5 mEq/L. Mild to moderate adverse reactions may occur at levels from 1.5 to 2.5 mEq/L, and moderate to severe reactions may be seen at levels of 2.0 mEq/L and above."
>
> (*Eskalith Prescribing Information*, n.d.)

Lithium does not have a known biological role (Geochemistry and the Environment, 1974) and the mechanisms for how it acts as a mood stabilizer and anti-suicidal agent are not established. However, numerous pathways have been examined as to how lithium interacts with brain chemistry including examples of genetic influence (McCarthy et al., 2010) and enzyme inhibition. (Diniz et al., 2013) (Ge & Jakobsson, 2018)

The Geography of Lithium

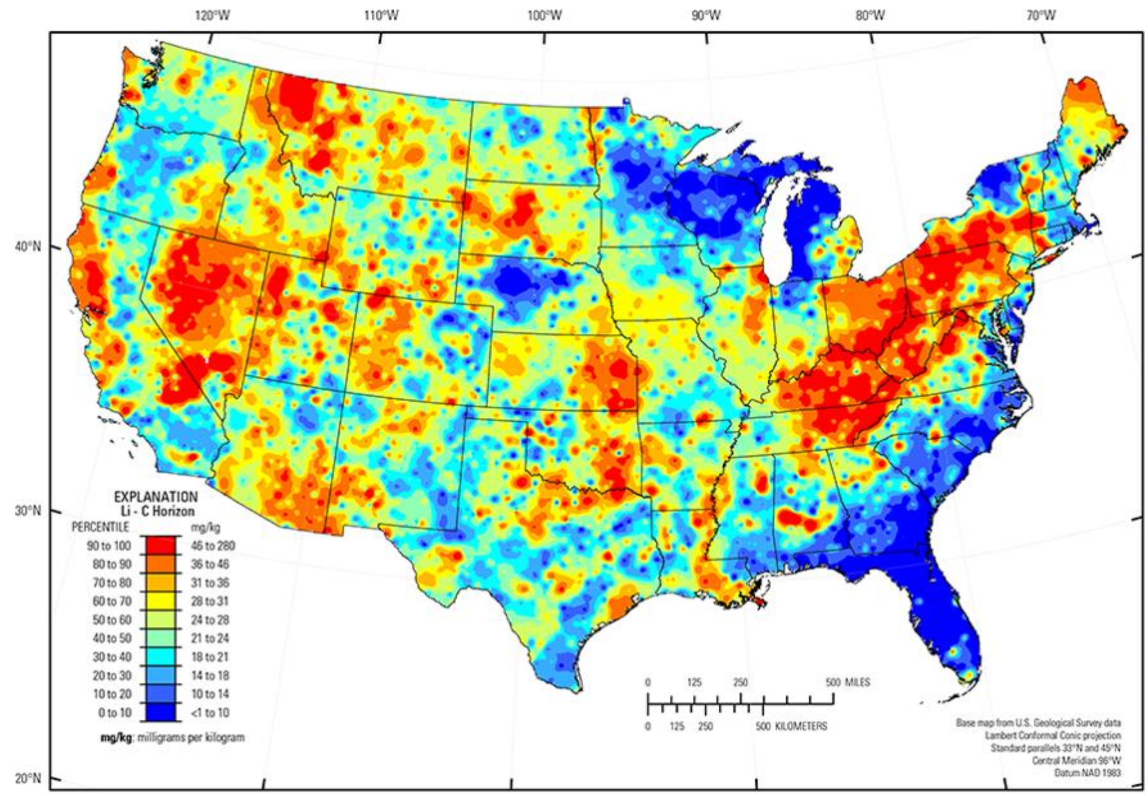


Figure **1-4**: Lithium levels in the C soil horizon in the continental United States. (*USGS Scientific Investigations Report 2017-5118: Geochemical and Mineralogical Maps, with Interpretation, for Soils of the Conterminous United States*, n.d.)

Lithium is naturally present in the Earth's crust at an estimated concentration of 41 mg/kg with the continental United States having an estimated 24 mg/kg in the C soil horizon. (*USGS Scientific Investigations Report 2017-5118: Geochemical and Mineralogical Maps, with Interpretation, for Soils of the Conterminous United States*, n.d.) Changes in lithium concentration between soil horizons do not vary significantly, but there are slightly higher concentrations in the C soil horizon due to lithium leaching into clay. Per USGS Scientific Investigations Report 2017-5118, the distribution of lithium in the soils of the United States is:

> "controlled, in large part, by the composition of underlying soil parent materials. High Li concentrations occur in soils developed on felsic rocks (granite and rhyolite) and alluvium sourced from similar rocks, for example within the Mojave Desert (USDA, 2006)."

> (USGS Scientific Investigations Report 2017-5118: Geochemical and Mineralogical Maps, with Interpretation, for Soils of the Conterminous United States, n.d.)

The impacts of glaciation on lithium per Figure 1-4 are immediately obvious, with northern Minnesota, Wisconsin, Michigan and New York showing low levels of lithium concentrated in the soil. Low levels of lithium concentration are also found in Florida and the Gulf Coast due to the underlying quartz–rich sedimentary rocks. Notably high levels of lithium are found in arid basins such as that covering the state of Nevada. High levels of lithium concentration are also found along the Northern Rocky Mountains and the Appalachian Mountain range.

Consumption of Lithium

Lithium is unlikely to be absorbed through the skin. (McCarty et al., 1994) Instead, lithium is primarily absorbed through the consumption of water or food. Lithium is not expected to bioaccumulate in the food chain. Plants will absorb lithium through the soil, though it depends on the specie as to whether this provides a beneficial or toxic effect. Tobacco is the best known plant that is tolerant of large levels of lithium in the soil. (*Geochemistry and the Environment*, 1974) However, per Aral & Vecchio-Sadus, lithium concentrations in plant foodstuffs vary widely:

> "from 0.01ppm (dry basis) in bananas to 55ppm in oats (Shacklette et al., 1978). Lithium is relatively toxic to citrus plants."
>
> (Aral & Vecchio-Sadus, 2008)

Table **1-1**: Typical concentration ranges of lithium in water, soil, the upper crust and the atmosphere.

	Fresh water (mg/L)	Seawater (mg/L)	Sediment (mg/kg)	Soil (mg/kg)	Earth's crust (mg/kg)	Atmosphere (ng/m 3)
Typical background concentration	0.07–40	170–190	56	3–350	20–60	2

(Aral & Vecchio-Sadus, 2008, p. 352)

Suicide and Lithium

Recent literature comparing the impact of lithium on the suicide rate in the United States is limited, but paints a consistent theme; a weak relationship exists between areas with higher levels of lithium in their water supply associating to a lower level of suicide for the region. However, the association is fragile and is decreased when studies attempt to account for social issues which impact the suicide rate such as race and ethnicity, poverty and the unemployment rate. Several articles on the topic are summarized below in Table 1-2.

Table **1-2**: Meta-analysis of recent studies surveying the association between the suicide rate and environmental lithium levels.

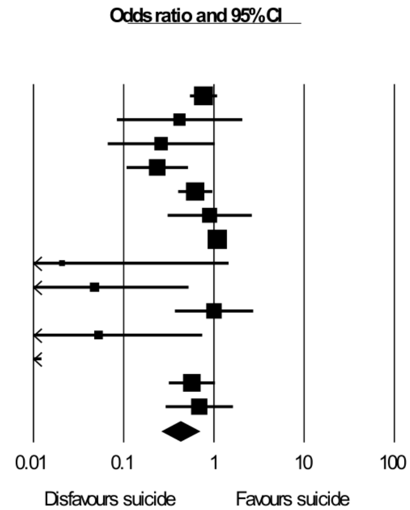
Study	Study Area	Lithium Values	Social Parameters	Statistical Method	Results
Blüml et al., 2013	Texas counties from 1999 – 2007 with 3,123 samples from public wells.	2.8 to 219 µg/L sample values.	Median household income, unemployment, population density, percent Hispanic, percent African American.	Poission regression.	Found a statistically significant association between mean lithium levels and the suicide rate.
Kabacs et al., 2011	Six counties comprising the East of England region in England. One sample per the 47 municipal subdivisions.	0.1 to 21 µg/L sample values.	Not accounted for.	Pearson's correlation coefficient (r) and bivariate scatter plots.	No association between the lithium levels and the suicide rate.
Palmer et al., 2019	15 selected Alabama counties in 2018 with 75 water samples from public spaces.	0.4 to 32.9 µg/L sample values.	Age, gender and poverty.	Linear and Poisson regression.	Inverse relationship between measured lithium concentration and suicide rate.
Barjasteh-Askari et al., 2020	Meta-analysis covering fourteen studies between 1972 and 2019.				13/14 studies found an association between lithium levels and the suicide rate.
Vita et al., 2015	Meta-analysis covering nine studies between 1990 and 2013.				13/14 studies found an association between lithium levels and the suicide rate.

Blüml et al. notes in their 2013 study that the statistical association found between the suicide rate and lithium levels is weak and may be impacted by the statistical methods used for analysis. Results across the studies are inconsistent based on sex, with some not examining sex. In general, a stronger association is found between the suicide rate for men and lithium levels. This is described in a meta-analysis from

Barjasteh-Askari et al. (2020) which shows that the association between the decrease in the suicide rate and the increase in lithium levels in the water supply are much stronger when examining the differences in suicide rate between the male and female sex.

Table **1-3**: Forest plot from Barjasteh-Askari et al., 2020 showing a meta-analysis of study results examining the relationship between lithium and the suicide rate.

Study name	Subgroup within study	Statistics for each study				
		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Pompili et al. 2015	Combined	0.77	0.54	1.08	-1.506	0.132
Dawson et al. 1972	Blank	0.42	0.08	2.05	-1.077	0.282
Giotakos et al. 2013	Blank	0.26	0.07	1.02	-1.938	0.053
Helbich et al. 2015	Blank	0.24	0.11	0.51	-3.625	0.000
Ishii et al. 2015	Blank	0.62	0.40	0.96	-2.146	0.032
Kabacs et al. 2011	Blank	0.90	0.31	2.62	-0.199	0.842
Knudsen et al. 2017	Combined	1.09	1.06	1.13	5.435	0.000
Liaugaudaite et al. 2017	Blank	0.02	0.00	1.45	-1.788	0.074
Ohgami et al. 2009	Blank	0.05	0.00	0.52	-2.490	0.013
Oliveira et al. 2019	Blank	1.00	0.37	2.72	0.007	0.994
Palmer et al. 2019	Blank	0.05	0.00	0.74	-2.182	0.029
Schrauzer and Shrestha 1990	Combined	0.00	0.00	0.01	-6.141	0.000
Shiotsuki et al. 2016	Blank	0.57	0.32	1.03	-1.874	0.061
Sugawara et al. 2013	Combined	0.69	0.29	1.62	-0.854	0.393
		0.42	0.27	0.67	-3.662	0.000



(Barjasteh-Askari et al., 2020, p. 239)

Greater levels of lithium in the water supply correspond with a decreased suicide rate, but it is unclear how this relationship changes with increased lithium concentration levels. None of the studies establish a consistent level or threshold of lithium required to cause a decrease in the suicide rate for the study area. Palmer et al. (2019) notes there may be a concentration threshold for the suicide prevention effect of lithium. Some support for this may be found in a Texas study from 1990 which only found a relationship between lithium and the suicide rate at concentrations between 70 to 160 µg/l. (Schrauzer & Shrestha, 1990) Kabacs et al.'s 2011 study, resulting in no association between the suicide rate and lithium levels, may also support this claim as much lower levels of lithium were reported in their study of the East of England than in comparable studies from different areas.

Chapter 2

Innovations and Hypotheses

Innovations Addressed

Several innovations are bought to this study which do not exist in the current literature. First, existing research comprises highly regional cross sectional studies, focusing on local areas, roughly the size of a US state. For this study, a national scale analysis was devised to examine the larger context of lithium levels and the suicide rate across the continental United States which still retaining the US county as the smallest unit of analysis.

Second, this study seeks alternative data sources for environmental lithium levels due to the lack of comprehensive data sources available for groundwater lithium samples. These data sources, the USGS National Geochemical Database: Soil and the USGS Data Series 801 release will be compared to samples from National Water-Quality Assessment to determine if they align to the existing body of research and may be suitable for use in future analysis.

Finally, this study seeks to establish a more robust statistical analysis of the relationship between environmental lithium and the suicide rate. This will be completed by analyzing the relationship using Geographically Weighted Regression to account for local versus global effects in the relationship. Social variables impacting the suicide rate will be controlled using the variables outlined in the 2013 study in Texas by Blüml et al.

Hypotheses

For the results of this thesis, we expect to replicate on a regional scale current research which describes a weak association between higher lithium levels and lowered suicide rates. In particular, we expect this effect to follow current literature and be most pronounced when examining the suicide rate for men. However, since this study takes a national focus on the continental United States and breaks from the regional focus of existing research, the association found in the existing research may only replicate on a regional basis and not across the entire study area.

It is less clear if the association between higher lithium levels and lowered suicide rates will hold true when controlling for social issues which drive the suicide rate such as race and ethnicity, poverty and the unemployment rate. Extant research suggests this association should hold true, but with a much weaker connection that is heavily influenced by the statistical analyses used to process the results. This work implements the social controls suggested in Blüml et al.'s 2013 study of lithium and suicide in Texas; with these variables accounted for in the work, we expect this association between the suicide rate and lithium to maintain on a local, but not global basis.

Since the present body of literature is focused on a regional scale, does the relationship between lithium and the suicide rate continue when analyzed on a national scale in the United States? If not, what regional variation is shown? Of particular interest may be areas of very high lithium levels such as the Appalachian mountain range, the Mojave Desert and the Great Salt Lake area. In turn, areas with very low lithium levels are also of interest, such as the Gulf and Atlantic coastal plain and the glaciated upper Midwest. (*USGS Scientific Investigations Report 2017-5118: Geochemical and Mineralogical Maps, with Interpretation, for Soils of the Conterminous United States*, n.d.)

Hypothesis H_1 While local studies have found some evidence of an association between lithium and suicide, we do not expect to find a statistically significant association in a national study. (Global model)

Hypothesis H_2 We expect controlling for social effects may significantly limit or eliminate the relationship between lithium and the suicide rate in some regions. (Local models)

Hypothesis H_3 We expect the association between lithium and the suicide rate to be spatially heterogeneous or non-stationary across the United States. (Local models)

What form does the relationship between lithium levels and the suicide rate take? Does accounting for a threshold limit change the relationship? These questions lead to an additional point for review, at what threshold would we expect lithium to exhibit a protective effect on the suicide rate? As an appropriate threshold is unclear, we will examine this using the higher 60 µg/L level of concern (*HBSL Home*, n.d.) set by the USGS for the NAWQA water quality dataset. An appropriate threshold for the USGS Geochemical Database: Soil or the USGS Data Series 801 release is less clear, though a lower level of 2.1 mg/kg/day is proposed for adverse health effects in humans by the EPA's CompTox dashboard. (*CompTox Chemicals Dashboard*, n.d.) As this level of toxicity is comparatively much lower than the 60 µg/L level established by the USGS and would include nearly all samples in the lithium soil level datasets, we will decline to offer a parallel threshold for the soil datasets.

How does controlling for social effects impact the relationship between lithium and the suicide rate? Existing research is inconsistent in how it controls for the social effects which drive suicide rates. For this thesis we have chosen to replicate the social control variables implemented in Blüml et al.'s Texas study from 2013, one of the most robust examples of statistical control shown in the literature. Each of these hypotheses will be tested using the data and methodology outlined in the next chapter.

Chapter 3

Data and Methods

Data sources used for this thesis are listed below in Table 3-1; data from the American Community Survey and CDC Wonder were chosen to align after the collection date for the lithium samples used in this work. We assume that lithium levels are relatively static over time and that any change in the lithium level for an area would not produce an immediate change in the suicide rate. As such, we wanted the suicide rate data and demographic data for this work to lag several years behind the lithium sample collection dates. Demographic data was collected from the American Community survey as a way to control for the impact of social variables on the suicide rate. Fields were chosen to align with the variables presented in Blüml et al.'s 2013 study in Texas. (Blüml et al., 2013)

American Community Survey 5 year estimates were chosen since they include estimates for the entire United States; 1 and 3 year estimates do not. (*Understanding and Using ACS Single-Year and Multiyear Estimates*, n.d.) GIS boundaries from IMUPS GIS were chosen from 2010 as all datasets either overlap the year or started collection after 2010. CDC Wonder suicide rate data was collected from 2010 to 2019; an attempt to collect a five year span to align with the American Community Survey data was discarded as a more limited range encountered significant issues with suppressed data due to the small number of suicide deaths over the timespan.

Table **3-1**: List of the data sources utilized in this work and the associated time span of data collection.

Dataset	Source	Time Span
Population Density (ALAND10 / DP05_0001E)	Calculated using 2015 ACS 5 Year Estimates for population and Tiger/Line ALAND10 value.	2011 to 2015
Percent Black or African American (DP05_0033PE)	2015 ACS 5 Year Estimates	2011 to 2015
Percent Hispanic or Latino (DP05_0066PE)	2015 ACS 5 Year Estimates	2011 to 2015
Unemployment Rate (S2301_C04_001E)	2015 ACS 5 Year Estimates	2011 to 2015
Median Household Income in the past 12 months (B19013_001E)	2015 ACS 5 Year Estimates	2011 to 2015
Percent High school education or higher (S1501_C02_014E)	2015 ACS 5 Year Estimates	2011 to 2015
Poverty Status (S1701_C03_001E)	2015 ACS 5 Year Estimates	2011 to 2015
Lithium Groundwater Samples	National Water-Quality Assessment	2013 to 2015
Lithium Soil Samples	USGS National Geochemical Database: Soil	1960s to Present
Lithium Soil Samples	USGS Data Series 801	2007 to 2013
Age Adjusted Suicide Rate	CDC Wonder	2010 to 2019
US County Boundaries	IPUMS NHGIS	2010
US State Boundaries	IPUMS NHGIS	2010
US National Boundaries	IPUMS NHGIS	2010

A comparison of the geographic distribution of the lithium data sources used in this work is found in Figure 3-1. None of the data sources, when aggregated to the county level, provide complete coverage of the continental United States. The USGS Data Series 801 release has the most expansive coverage, due to the project’s extensive usage of control points distributed across the continental United States. However, this results in an aggregation descrepenacy, where the control points provide adequate coverage across the scale of the United States, but do not align to points within every county boundary in the United States.

The USGS National Geochemical Database: Soil has the next most comprehensive coverage. Distribution of sample points within the database rely on submitted projects, so the number of sample points within an area may vary dramatically. As shown in Figure 3-1, the south eastern and mid-western United States has particularly poor sample coverage. This is due in part to the modifiable areal unit problem (MAUP) as many counties in the western United States are much larger in area than the south eastern and mid-western United States. Finally, the National Water-Quality Assessment Project (NAWQA) sample points convey very limited coverage of the United States, with most samples centered on the Gulf and Atlantic coastal plain with some samples across the Midwest and the Pacific coast.

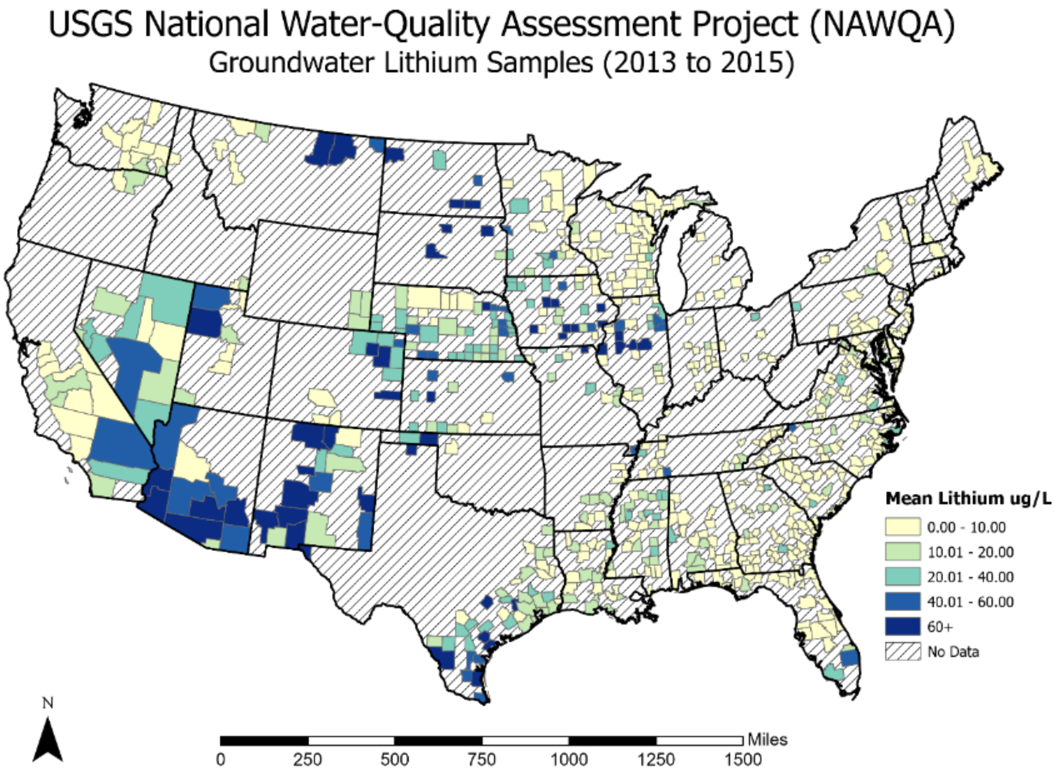
Table **3-2**: Quantile ranges for each of the Lithium datasets.

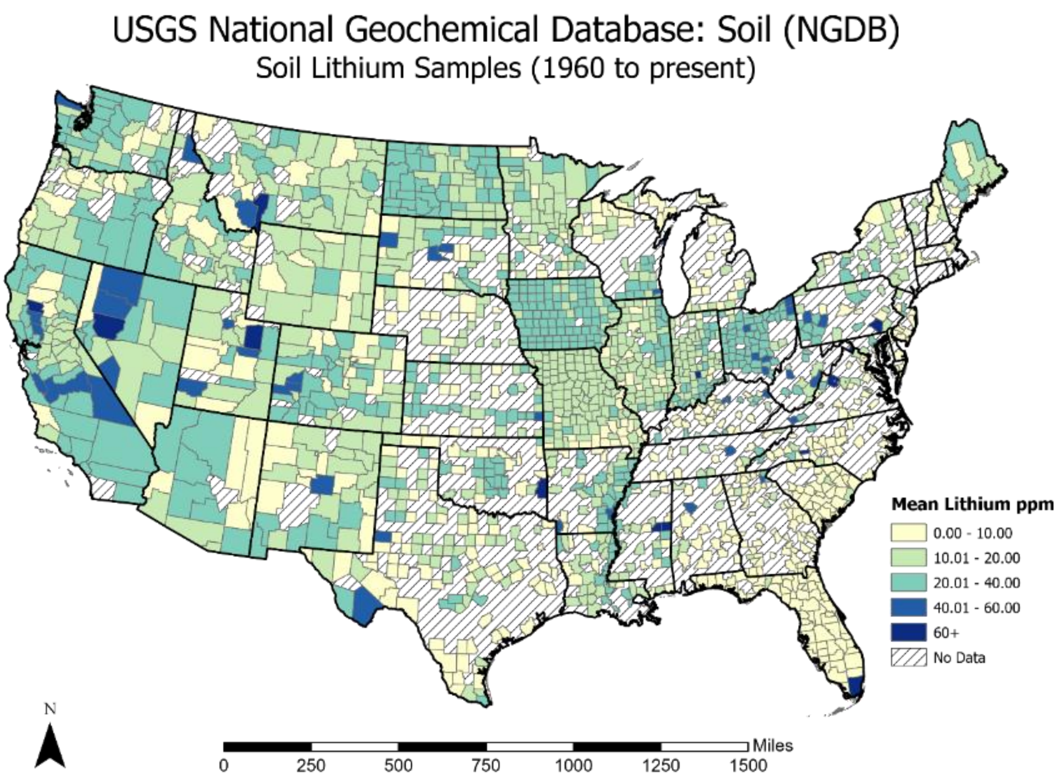
	NAWQA	USGS801	USGSNGDB
Low	4.05	6	10.5
Medium	14.36	25	19.6
High	929	123	2050

Table **3-3**: Count of counties within the low, medium and high quantile range for their associatded lithium data source. Sample size of 284 counties. Note that the datasets represent different units. The NAWQA dataset has samples in µg/L and the soil datasets have samples in mg/kg.

	NAWQA	USGS 801	USGSNGDB
Low	88	20	111
Medium	90	134	87
High	106	130	86

Quantile ranges for the lithium concentrations levels for each dataset were developed as shown in Table 3-2. 284 counties overlap between the three datasets and were compared in Table 3-3; the USGS 801 Series data release is a notable outlier in this analysis with limited samples


USGS National Water-Quality Assessment Project (NAWQA)
Groundwater Lithium Samples (2013 to 2015)
Mean Lithium ug/L
0.00 - 10.00
10.01 - 20.00
20.01 - 40.00
40.01 - 60.00
60+
No Data
N
Miles
0
250
500
750
1000
1250
1500


USGS National Geochemical Database: Soil (NGDB)
Soil Lithium Samples (1960 to present)
Mean Lithium ppm
0.00 - 10.00
10.01 - 20.00
20.01 - 40.00
40.01 - 60.00
60+
No Data
N
Miles
0
250
500
750
1000
1250
1500

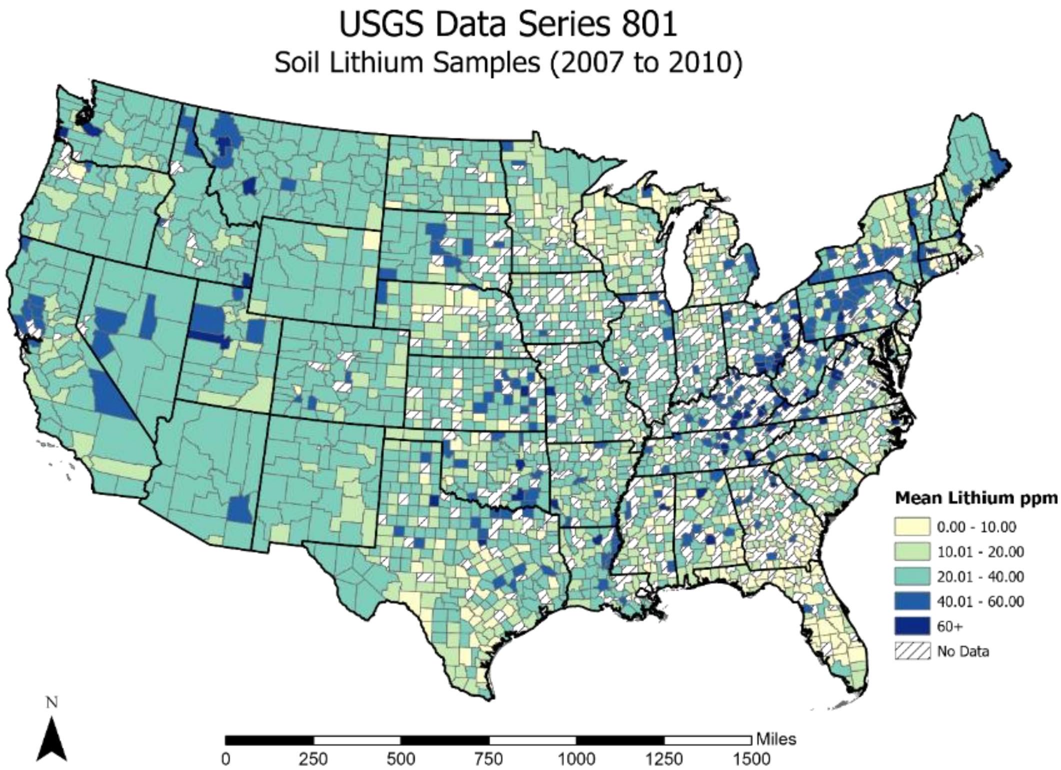


Figure **3-1** : Comparison of the distribution of lithium values across the three lithium datasets used in this work.

falling in the low category. It is unclear why this is the case, but as the USGS 801 Data Series release is the most spatially representative dataset, the assumption would be that the 284 overlapping counties are not representative samples of their associated lithium data sources.

Limitations of the Data Sources

Numerous issues with the data sources limit the scope of research conducted for this thesis; most datasets have spatial and temporal coverage limitations, which may be further aggravated when aggregated to the county scale. Additional datasets have data suppression and estimate concerns; in these cases non-viable samples were removed from the study. Of the three lithium datasets used in this thesis, the NAWQA water quality samples and the NGDB and Data

Series 801 soil samples, none provide comprehensive spatial coverage of the continental United States when aggregated to the county scale. The NAWQA water quality samples are notably lacking in this regard, covering only 676 of the 3,100 counties used in the thesis. In turn, the USGS NGDB data source covers 1,724 counties and the USGS Data Series 801 release covers 2,197 counties respectively.

A unique issue which affects the NGDB soil quality samples are limit of detection errors (LOD); approximately 1/5th of the NGDB soil samples were coded as negative values representing that the method used to determine the sample value was not sensitive enough to return an accurate sample value. USGS makes several recommendations on how to process these data points to make them usable for a study (*Frequently Asked Questions Concerning NURE HSSR Data*, n.d.), but doing so is not straightforward. Due to the added difficulty of classifying these samples in a defensible manner, they were removed from the study.

Several issues impact the CDC suicide rate data including time scale coverage and suppressed values. Data for deaths due to suicide was collected from the CDC Wonder data portal for the years spanning 2010 to 2019. However, even collecting a decade of suicide rate data does not provide comprehensive coverage of the continental United States at the county scale. CDC Wonder suppresses results when "data cells [contain] fewer than 10 case counts…" (Tiwari et al., 2014). This particularly impacts attempts to split the suicide rate data by sex; of the 3,100 counties included in the dataset only 2,331 counties contained suicide rate data for all deaths, 2,148 counties contained suicide rate data for male deaths and 892 contained suicide rate date for female deaths. Data suppression issues in the CDC Wonder dataset may be processed to generate valid count data for suppressed regions, but similar to the level of detection issues present in the NGDB data source, this is a non-trivial process. As such, suppressed areas in the CDC Wonder dataset were removed from this study.

Data obtained from the American Community Survey has similar data limitations; only the 5-year ACS estimates contain complete coverage of the continental United States; 1-year and 3-year estimates only survey geographic areas meeting set population thresholds. (*Understanding and Using ACS Single-Year and Multiyear Estimates*, n.d.) Though rare, data from the ACS may also be suppressed in cases where the population of an area is very small.

Finally, much of the scope of this thesis is dictated by data limitations from the various lithium level datasets. While we are studying the continental United States, none of the lithium level data sources available allow complete spatial coverage when aggregated to the county level. Additionally, the number of overlapping counties between each dataset is limited increasing the difficultly of making direct comparisons between each lithium dataset. As such, the scope of this work will be maintained at the national scale, comparisons between lithium data sources will be made when possible and analysis of the local models produced by each data source will be combined in effort to expand the spatial coverage of the results of this work.

Methods

Various data sources were used in this work as outlined in in Table 3-1; each of these data sources were aggregated together to facilitate analysis. National county level boundaries were extracted from the IPUMS GIS service hosted by the University of Minnesota. (IPUMS NHGIS | National Historical Geographic Information System, n.d.) Data from the American Community survey was obtained at county level geography and was joined to the IPUMS GIS data layer based on the common GEOID defined by the census. ("Understanding Geographic Identifiers (GEOIDs)")

Age adjusted suicide rate data suicide rate data was obtained from the CDC Wonder portal based on the underlying cause of death ICD10 codes shown in Table 3-2. As the suicide rate data was also obtained at the county level, this was joined to the IPUMS GIS data layer based on the common GEOID. Lithium sample points from the National Water-Quality Assessment (NAWQA), the USGS National Geochemical Database: Soil and the USGS Data Series 801 release were aggregated to the county level as an average value for each dataset. Missing values for each data source were coded to a -9999 value.

Table **3-4**: Underlying cause of death ICD 10 codes used to represent deaths from suicide. Age adjusted suicide rate data was extracted from the CDC Wonder portal based on these codes. (Hedegaard et al., 2020, "Increase in Suicide Mortality in the United States, 1999–2018")

ICD 10 code
U03
X60–X84
Y87.0

The resulting dataset was then split into separate shapefiles based on the lithium data source, male versus all suicide rates and whether or not the lithium source values would be controlled by demographic variables; these datasets are outlined below in Table 3-5.

Table **3-5**: Model runs generated for this work. Models with social controls applied through demographic variables are highlighted in grey.

ID	Lithium Data Source	Suicide Type	Sample Size
NAWQA-001	National Water-Quality Assessment	All	515
NAWQA-002	National Water-Quality Assessment	All	515
NAWQA-003	National Water-Quality Assessment	Male	489
NAWQA-004	National Water-Quality Assessment	Male	489
NAWQA-005	National Water-Quality Assessment Samples >= 60µg/L	All	31
NGDB-001	USGS National Geochemical Database: Soil	All	1316
NGDB-002	USGS National Geochemical Database: Soil	All	1316
NGDB-003	USGS National Geochemical Database: Soil	Male	1204
NGDB-004	USGS National Geochemical Database: Soil	Male	1204
USGS801-001	USGS Data Series 801	All	1641
USGS801-002	USGS Data Series 801	All	1641
USGS801-003	USGS Data Series 801	Male	1641
USGS801-004	USGS Data Series 801	Male	1641

To better account for geographical variations in the relationship between environmental lithium and the suicide rate, this work will use Geographically Weighted Regression (GWR). GWR accounts for geographical variation in the regression model by "allowing the relationships between the independent and dependent variables to vary by locality." (*Geographically Weighted Regression | Columbia Public Health*, n.d.) This provides several advantages over the existing uses of Poisson regression and linear regression in the extant research. First, it is a more robust statistical method which allows examining both a local and global context to the studied relationship. Second, it allows the relationship to be mapped since it generates local models. Finally, it allows examining whether the variables in the model are nonstationary across space indicating global significance.

Each shapefile was then processed using Geographically Weighted Regression (GWR) using the MGWR tool produced by the Arizona State University Spatial Analysis Research Center. (Oshan et al., 2019) An initial bandwidth was determined for each lithium source by processing a GWR using a Golden Section search for the total suicide rate using only the lithium source and an intercept as explanatory variables.

> "The Golden Section search finds the optimal value for the bandwidth by successively narrowing the range of values inside which the optimal value exists and comparing the optimization score of the model for each—returning the value which has the lowest score."
>
> (Li et al., n.d.)

The derived bandwidth from the Golden Section search was then used to process any further GWR models using that lithium data source; the values of which may be seen below in Table 3-6.

Table **3-6**: Bandwidths determined by Golden Section search for each lithium data source.

Lithium Data Source	Number of Counties	Bandwidth
National Water-Quality Assessment	515	46
USGS National Geochemical Database: Soil	1316	46
USGS Data Series 801	1641	56

Chapter 4

Results and Interpretation

Results

A total of thirteen model runs were conducted for this work; five of the thirteen model runs show statistical significance at the 95% confidence level globally on both the p and t values where p is less than or equal to 0.05 and t is less than or equal to -1.96 or t is greater than or equal to 1.96; three of the statistically significant models for the total suicide rate are listed below in Table 4-1, corresponding to models NAWQA-001, NAWQA-002 and USGS801-001. For a full list of the models run for this work see Appendix C.

Two of the three models, NAWQA-001 and USGS801-001 correspond to the models where only lithium is included as an explanatory variable, as such their return of statistical significance is unsurprising as no other variables are being controlled for in the Ordinary Least Squares model (OLS). These model runs were never intended to be a full analysis, merely an attempt to more fully examine lithium's specific impact as a variable on the suicide rate. USGS801-001 statistical significance is surprising, but the Adj. R2 shows that its ability to explain the variation in the suicide rate is extremely limited, at 0.010.

Table **4-1**: Global Model OLS results for the model runs examining the total suicide rate, both male and female, for a county. Models with social controls applied through demographic variables are highlighted in grey.

ID	Sample Size	Adj. R2	Lithium t	Lithium p	Significant?
NAWQA-001	515	0.033	4.322	0.000	✓
NAWQA-002	515	0.445	2.161	0.031	✓
NAWQA-005	31	0.493	0.082	0.935	
NGDB-001	1316	0.000	-0.774	0.439	
NGDB-002	1316	0.449	-1.172	0.241	
USGS801-001	1641	0.010	4.094	0.000	✓
USGS801-002	1641	0.449	0.775	0.439	

NAWQA-002 is the sole outlier here, showcasing both statistical significance and inclusion the demographic variables used for social control derived from Blüml et al's. 2013 study in Texas. A more in depth view at the global OLS model results for NAWQA-002 is shown in Table 4-2 below. Nearly all of the variables in the OLS model returned a statistically significant result; these include Population Density, Percent Black or African American, Percent Hispanic or Latino, Unemployment Rate, Median Household Income, Poverty Status and the NAWQA Lithium groundwater sample values. Percent High School Education or Higher is the notable outlier in the NAWQA-002 model run, a result at odds with the other statistically significant model runs.

The t values for the statistically significant model variables show that they are impact the suicide rate in differing directions. Population Density, Unemployment Rate and the NAWQA Lithium samples have a positive impact, lowering the suicide rate whereas Percent Black or African American, Percent Hispanic or Latino, Median Household Income in the Past 12 months and Poverty Status have a negative impact, increasing the suicide rate. How strong these relationships are is less clear in the global model, but may be examined in the local GWR models through the beta coefficient value.

Table **4-2**: Ordinary Least Squares (OLS) model results for the NAWQA-002 model run. Sample size contains 515 counties.

Variable	Est.	SE	t(Est/SE)	p-value
Intercept	0	0.033	0	1
Population Density (ALAND10 / DP05_0001E)	0.408	0.034	11.846	0
Percent Black or African American (DP05_0033PE)	-0.396	0.049	-8.129	0
Percent Hispanic or Latino (DP05_0066PE)	-0.116	0.048	-2.433	0.015
Unemployment Rate (S2301_C04_001E)	0.107	0.047	2.29	0.022
Median Household Income in the past 12 months (B19013_001E)	-0.392	0.064	-6.086	0
Percent High school education or higher (S1501_C02_014E)	0.064	0.054	1.198	0.231
Poverty Status (S1701_C03_001E)	-0.157	0.075	-2.091	0.037
NAWQA Lithium Groundwater samples	0.077	0.036	2.161	0.031

Table **4-3**: Comparison of the Ordinary Least Squares (OLS) model results for the NAWQA-002, NGDB-002 and USGS801-002 model runs.

	NAWQA-002				NGDB-002				USGS801-002			
Variable	**Est.**	**SE**	**t(Est/SE)**	**p-value**	**Est.**	**SE**	**t(Est/SE)**	**p-value**	**Est.**	**SE**	**t(Est/SE)**	**p-value**
Intercept	0	0.033	0	1	0	0.021	0	1	0	0.018	0	1
Population Density (ALAND10 / DP05_0001E)	0.408	0.034	11.846	0	0.467	0.022	21.147	0	0.452	0.019	23.86	0
Percent Black or African American (DP05_0033PE)	-0.396	0.049	-8.129	0	-0.309	0.025	-12.316	0	-0.343	0.022	-15.749	0
Percent Hispanic or Latino (DP05_0066PE)	-0.116	0.048	-2.433	0.015	-0.062	0.027	-2.278	0.023	-0.105	0.023	-4.519	0
Unemployment Rate (S2301_C04_001E)	0.107	0.047	2.29	0.022	0.12	0.028	4.243	0	0.134	0.025	5.414	0
Median Household Income in the past 12 months (B19013_001E)	-0.392	0.064	-6.086	0	-0.352	0.038	-9.346	0	-0.276	0.032	-8.529	0
Percent High school education or higher (S1501_C02_014E)	0.064	0.054	1.198	0.231	0.131	0.033	3.937	0	0.097	0.028	3.432	0.001
Poverty Status (S1701_C03_001E)	-0.157	0.075	-2.091	0.037	-0.073	0.043	-1.705	0.088	-0.004	0.037	-0.118	0.906
Lithium Samples	0.077	0.036	2.161	0.031	-0.025	0.021	-1.172	0.241	0.015	0.019	0.775	0.439
	Sample Size : 515 Counties				Sample Size : 1316 Counties				Sample Size : 1641 Counties			
	Adj. R2: 0.445				Adj. R2: 0.449				Adj. R2: 0.449			

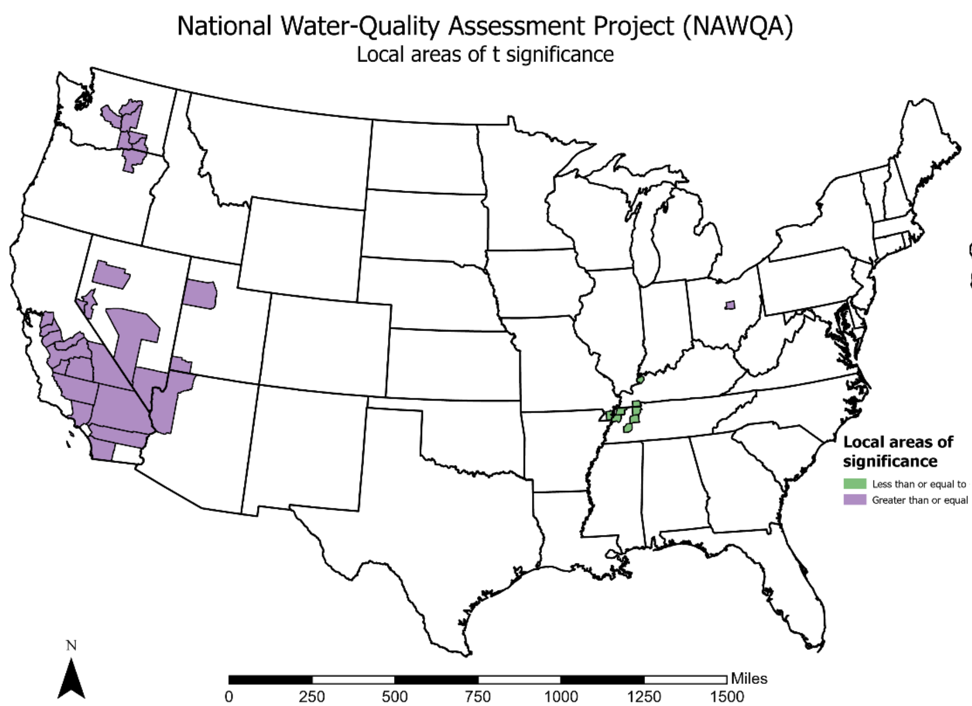


Figure **4-1**: Map of local areas of t significance for the NAWQA-002 model run.

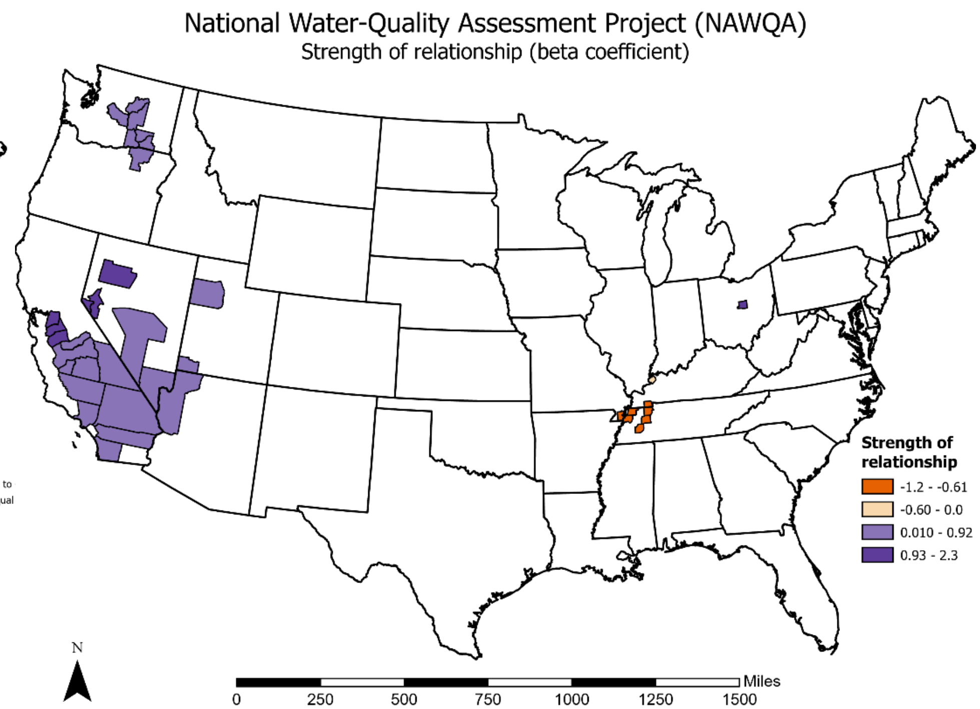


Figure **4-2**: Map of the beta coefficient values for local areas of t significance for the NAWQA-002 model run.

As this thesis is primarily concerned with the local effects of environmental lithium, now let us examine the results of the local GWR models for the NAWQA-002 model run. Displayed below in Figure 4-1 is a map of the t values of the local GWR model results for the NAWQA-002 model run. Areas highlighted in green represent t values of less than or equal to -1.96 where lithium sample values correlate to an increase in the suicide rate. Areas highlighted in purple represent t values of greater than or equal to 1.96 where lithium sample values correlated to a decrease in the suicide rate.

Figure 4-2 relates to Figure 4-1 by showing the strength of the relationship in areas of statistical significance for the NAWQA-002 model run. Areas highlighted in purple represent a positive relationship and areas highlighted in red represent a negative relationship with lighter shades representing a weaker relationship. The relative variation in the strength of the relationship displayed across the map is limited, but there is a clear divide in the positive relationship shown in California between the northern and southern halves of the state.

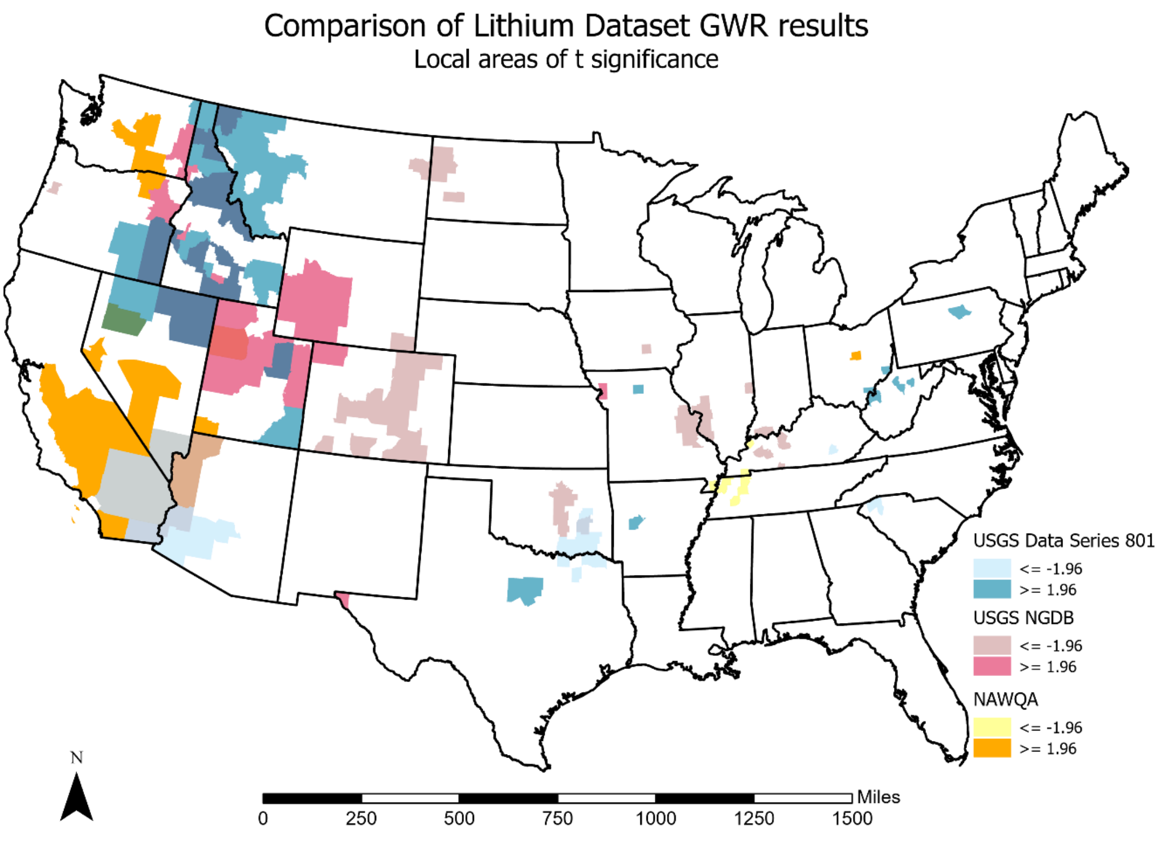


Figure **4-3**: Map of local GWR results for all three lithium datasets utilized in this thesis.

Figure 4-3 listed above furthers the examination of local areas of significance within each lithium dataset. Areas in blue represent counties where the USGS Data Series 801 dataset shows local statistical significance, red for the USGS NGDB dataset and yellow for the NAWQA Water Quality dataset. Lighter shades represent negative statistical association while darker shades represent positive statistical association. Areas of overlap between all of the datasets result in a mixed grey hue. Particularly notable within the map is the area of overlap between all three datasets in southern California. Other states in the west, such as Washington, Oregon, Idaho, Montana, Nevada and Utah demonstrate areas where overlap in statistical significance between at least two of the three lithium datasets occurs. Note that none of the datasets used to derive this map present complete geographical coverage of the continental United States, so only a limited view of the impact of lithium on the suicide rate is presented here.

Interpretation

Results from this work either align or break from the hypotheses posed in Chapter 2 based on the sources of the lithium data. For hypothesis H_1, we accept it for the USGS National Geochemical Database: Soil dataset and the USGS Data Series 801 release dataset as the global OLS models for these datasets shown in Table 4-1 do not show statistical significance when controlling for social variables. Surprisingly, however we can reject hypothesis H_1 for the NAWQA water quality dataset as that dataset does show statistical significance with the global OLS model.

In turn, we can accept hypothesis H_2, as all of the lithium data sources showed local statistical significance when controlling for social variables. As demonstrated in Figure 4-3, significant local areas of significance occur within each of the three lithium datasets examined in this thesis. Some evidence is given that some of the areas of significance overlap spatially, which may support usage of the USGS National Geochemical Database: Soil dataset and the USGS Data

Series 801 release as potential sources of lithium samples for furthering the examination of the relationship between lithium and the suicide rate.

Finally, we can accept hypothesis H_3, as Figure 4-3 demonstrates that, while there are a few clear patterns in the relationship between lithium and the suicide rate, the overall result is a wide variance of both positive and negative relationships across the continental United States.

How does the model fit these datasets?

Demographic variables derived from the Blüml et al's. 2013 study in Texas may not be the best fit with these data sources when examined through the global OLS models. The global adjusted R2 value shows that it explains between 44.5% and 44.9% of the variation in the total age adjusted suicide rate and 25.9% to 44.1% of the variation in the male only age adjusted suicide rate. When comparing the global adjusted R2 values between the models including all suicide versus the male suicide rate, the R2 values drop substantially indicating that this data fit is worse for modeling the male suicide rate than the suicide rate for all.

However, when examining the GWR models for local fit, substantial regional variation was found, with many areas found to have significantly higher fit than what was demonstrated in the global OLS models. As shown in Figure 4-4 below, local R2 for the USGS Data Series 801 ranges from 0.346 to 0.949 with extremely strong model fit shown on the Pacific and Atlantic coasts as well as portions of the upper Midwest. The Data Series 801 model was used for this example since it has the most complete geographic coverage within the continental United States.

Trends influencing the fit of this model are unclear, but some evidence of a divide between rural and urban areas is shown in Figure 4-4. Variables such as Percent High School Education or Higher and Poverty Status may also be impacting the local fit of the model as they are shown to be the least likely to be statistically significant across the model runs.

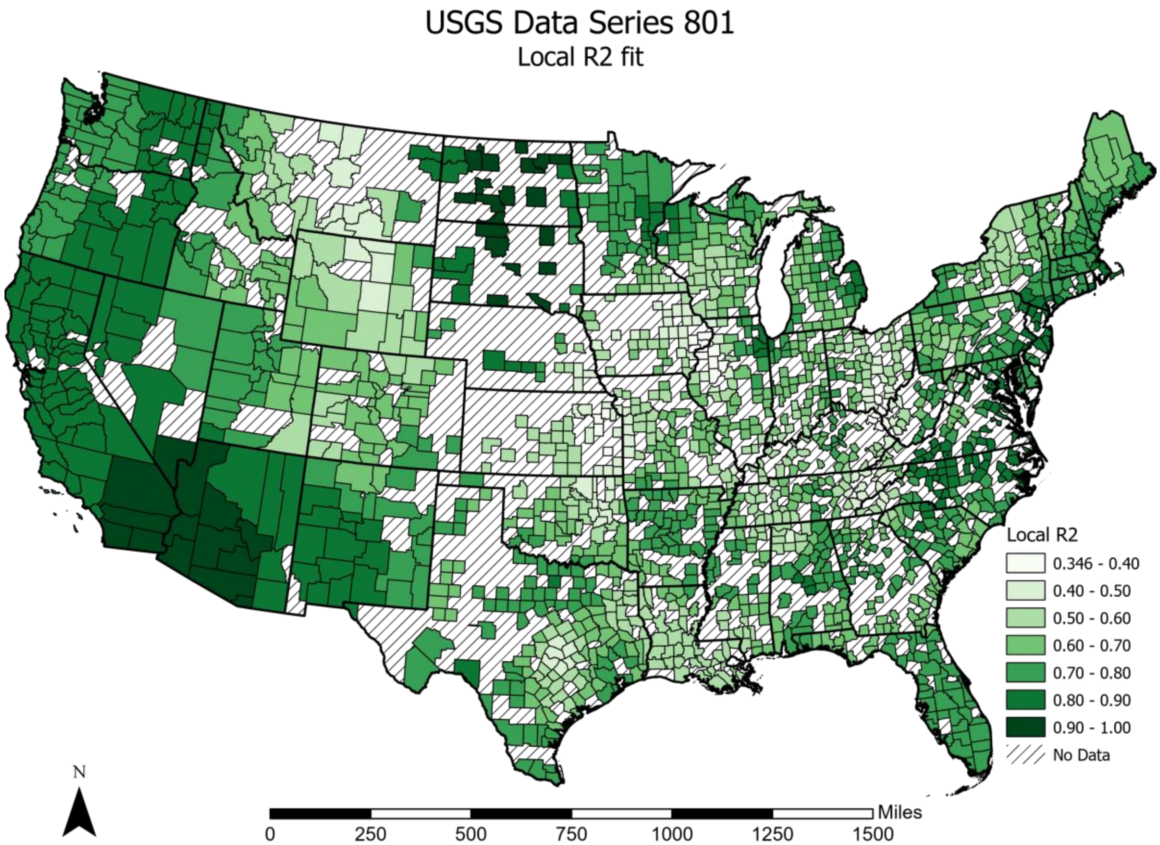


Figure **4-4**: Map of the local R2 model fit in the USGS Data Series 801 release. Examples of the R2 model fit for other datasets used in this work may be found in Appendix D.

Are lithium soil samples appropriate for this analysis?

The global OLS model would not support utilizing the lithium soil samples as an appropriate data set for analyzing the relationship between environmental lithium and the suicide rate as only the NAWQA dataset was statistically significant and represents a non-negligible R2 value. In turn, while the global OLS model does not demonstrate statistical significance, the local GWR models indicate that specific areas of the United States do demonstrate statistical significance between the soil lithium datasets and their association to the suicide rate. As shown in Figure 4-3, southern California and portions of the western United States demonstrate overlapping statistical significance between the three lithium datasets. As the NAWQA dataset aligns with extant research, this may lend some credence towards the soil lithium datasets being suitable for local analysis.

Numerous reasons may support the differences shown between the NAWQA water quality dataset and the soil lithium datasets. The soil datasets, the National Geochemical Database: Soil and the USGS Data Series 801 release represent an order of magnitude smaller sample sizes than the NAWQA dataset as they are recorded in mg/kq values whereas the NAWQA dataset is recorded in µg/L. Water levels of lithium and soil levels of lithium may also not be meaningfully similar in a geographic area.

Lithium does not absorb through skin contact (McCarty et al., 1994) so it must be consumed in some manner to have an effect on an area's populace. In this case, water samples may represent a more accurate level of exposure to lithium in a geographic area than soil samples as lithium consumption from soil sources would primarily be consumed through food grown in a local area. Locally grown food sources are increasing in the United States, but still represent an infrequent source of food for the majority of Americans. (*Improving Fruit and Vegetable Consumption: Use of Farm-to-Consumer Venues Among US Adults*, 2011) In turn, approximately 12% of American households were served by well water in 2010 (Johnson et al., 2019) and in 2007 approximately 286 million Americans had access to a public water system. (*FACTOIDS: Drinking Water and Ground Water Statistics for 2007*, 2008) This indicates that a local population is much more likely to be consuming local water sources than local soil sources.

Further analysis is needed to resolve this question, but the soil datasets used in this work may be suitable at least for local level analysis of the relationship between environmental lithium levels and the suicide rate.

Are areas exceeding 60 µg/L concentrations of lithium showing a stronger association to the suicide rate?

It was expected that areas of lithium concentration 60 µg/L in the NAWQA dataset may be more likely to show a statistically significant relationship between lithium levels and the suicide rate due to passing a threshold for high levels of lithium to be consumed by a local population. In this work, this corresponded to the NAWQA-005 model run which did not show statistical significance in the global OLS model, shown below in Table 4-4.

Table **4-4**: Ordinary Least Squares (OLS) model results for the NAWQA-005 model run. Sample size contains 31 counties.

Variable	Est.	SE	t(Est/SE)	p-value
Intercept	0	0.13	0	1
Population Density (ALAND10 / DP05_0001E)	0.806	0.169	4.757	0
Percent Black or African American (DP05_0033PE)	0.095	0.152	0.626	0.531
Percent Hispanic or Latino (DP05_0066PE)	0.601	0.335	1.795	0.073
Unemployment Rate (S2301_C04_001E)	0.096	0.168	0.57	0.568
Median Household Income in the past 12 months (B19013_001E)	-0.07	0.218	-0.318	0.75
Percent High school education or higher (S1501_C02_014E)	0.676	0.27	2.504	0.012
Poverty Status (S1701_C03_001E)	-0.234	0.298	-0.783	0.434
NAWQA Lithium Groundwater samples	0.013	0.162	0.082	0.935

This was an unexpected result, but several key issues may help explain it. Areas exceeding lithium concentrations of 60 µg/L are extremely limited in the NAWQA dataset, representing only 31 of the 515 counties present in the dataset. Many of these counties are in the rural south western United States and a plurality represent counties with extremely high suicide rates at double or triple the national average. Finally, the value of 60 µg/L may not represent an accurate threshold value for this relationship since it was based on published toxicity levels from the USGS. A better method to determine a threshold value may be to develop a consumption index for lithium and examine where minimum consumption levels might be exceeded to display an anti-suicidal effect.

Is the relationship between lithium and male suicide stronger than lithium and all suicide?

Based on the existing body of research surveyed as part of the literature review for this work, a stronger level of statistical significance would be suggested when examining the relationship between male suicide and the lithium rather than the total suicide rate for an area. For the models examining the male suicide rate in this work, only the NAWQA-003 model run reported statistical significance, it did not control for demographic variables influencing the suicide rate and reported a lower t value than the equivalent model run examining the total suicide rate, NAWQA-001. This was an unexpected result since it contradicts examples in the research such as Barjasteh-Askari et al.'s meta-analysis from 2020.

In what ways does this study align or depart from the results found in existing research?

Both the Texas study in 2013 by Blüml et al. and the 2019 study in Alabama by Palmer et al. showed global statistical significance in the relationship between lithium and the suicide rate. The work in Texas reported a global R2 of 0.92, with a p of <0.01*** with a Poisson regression model; in turn, the Alabama study reported $r = -.6286$ and $p = .0141$. As shown in Figure 4-3, limited statistical significance is shown in the local model results for this work in Texas and none is shown in Alabama.

In Texas, the model for the USGS National Geochemical Database shows positive statistical significance for El Paso County and the model USGS Data Series 801 release shows positive statistical significance for Eastland, Erath, Hood, Stephens, Palo Pinto and Parker Counties. In turn, negative statistical significance is shown for Grayson, Hunt, Lamar and Red River Counties.

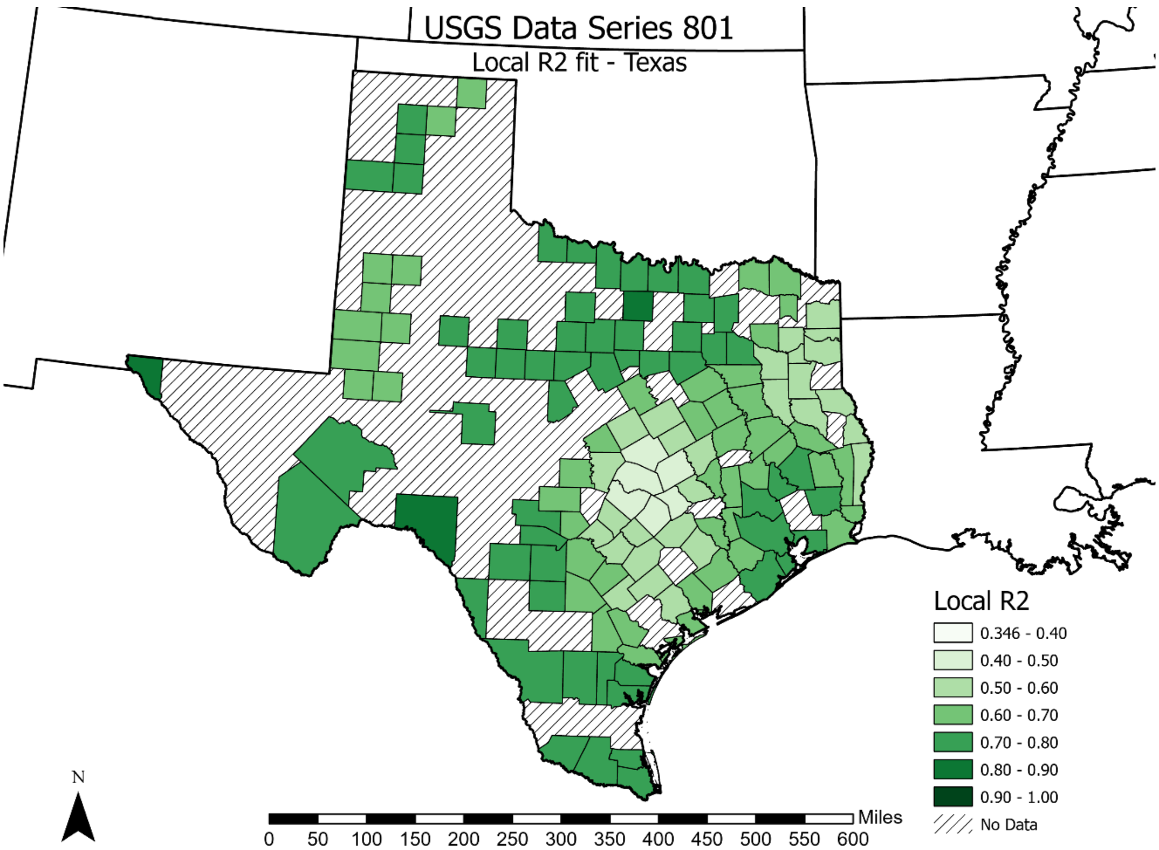


Figure **4-5**: Map of the local R2 values demonstrating model fit in Texas from the USGS Data Series 801 release.

Figure 4-5 shows that the fit for this model varies geographically in Texas, with the weakest fit shown in central Texas. Bastrop, Bell, Milam, Travis and Williamson counties are the clear center of this trend, reporting the lowest R2 values on the map in the 0.40 to 0.50 range. In comparison to the statistically significant local counties in Texas; Eastland, Erath, Hood, Stephens, Palo Pinto and Parker, these counties in Central Texas have an inversed relationship in the model to the unemployment rate. In most Texas counties, including the statistically significant ones for this model, the unemployment rate results in a high, though not always statistically significant negative t value. In Central Texas, these values are inversed with each county showing a statistically significant positive t value for unemployment rate.

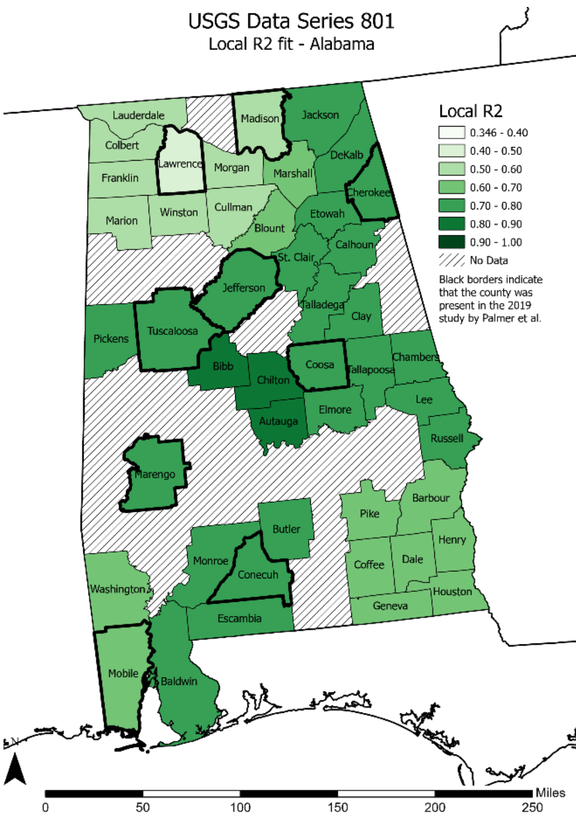


Figure **4-6**: Map of the local R2 values demonstrating model fit in Alabama from the USGS Data Series 801 release.

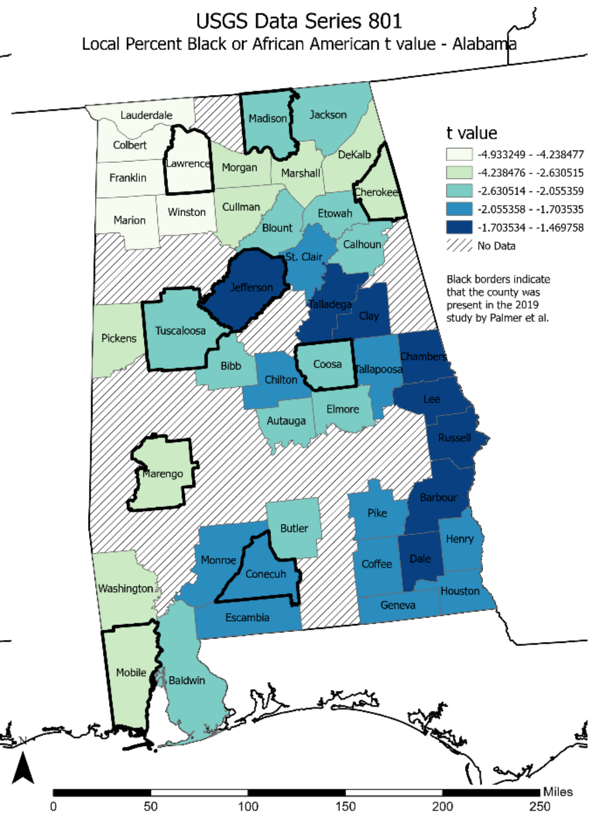


Figure **4-7**: t values for Percent Black or African American in Alabama from the USGS Data Series 801 release.

In Alabama, Figure 4-6 shows that model fit is generally very high with the lowest R2 reported in northwest Alabama centering on Lawrence County and the surrounding area. The cause of this in Alabama is less clear; it is unlikely to be the similar to the unemployment rate as shown in Texas as only Winston County reports a statistically significant positive t value for that variable. One driving portion of this trend is shown in Figure 4-7; almost the entirety of the state of Alabama in this model indicates the variable for Percent Black or African American has a statistically significant negative t value. But this relationship is particularly pronounced in the northern parts of Alabama with Lawrence County and surrounding counties reporting t values of less than or equal to -4.

What are the primary drivers of the suicide rate shown in this model?

It is clear that lithium is not a primary driver of the suicide rate; from this work the strongest variables decreasing the suicide rate are Population Density and the Unemployment Rate while Percent Black or African American, Percent Hispanic or Latino and Median Household Income are variables generally related to an increase in the suicide rate. Of course, these variables have local spatial variation as shown in the local models from Geographically Weighted Regression. Maps produced to show this spatial variation against the USGS Data Series 801 release are listed in Appendix E.

Limitations of the Results

Data limitations continue to impact this work; the highest quality data across each of the available lithium datasets is in the southeast continental United States. Unfortunately, this represents regions with very low levels of lithium concentration due to the Gulf and Atlantic coastal plain. In turn, these areas are not represented in the results of this work since they do not show a statistically significant association to environmental lithium concentrations. In future works, it would be helpful to have more lithium samples available in areas not well represented in the current lithium data sources such as the Midwest, the Appalachian mountain range and the west coast. Since geographical coverage is limited across the three lithium datasets, it notably restricts the local model results found in the key outcome of this work, Figure 4-3.

Model fit for this work shows significant geographical variation, with some areas showing extremely strong fit with R2 values greater than 0.8; in turn, some areas show poor fit with R2 values less than 0.4. Determining which variables are reducing the model fit and seeking alternative data sources with better fit would help improve the model.

Chapter 5

Future Research and Conclusion

Future Research

Now that we have discussed the results of this thesis, what future applications are available when studying the relationship between lithium and the suicide rate? Data limitations have been a consistent hindrance throughout the completion of this thesis. In particular, groundwater samples of lithium levels are extremely limited compared to soil samples. Lindsey et al. (2021) developed an extensive groundwater and well sample dataset for the continental United States which includes the NAWQA 2013 to 2015 data releases utilized in this thesis. Reexamining the content of this thesis using this more comprehensive dataset may provide better insight into where the values of soil level and water level lithium samples diverge across the continental United States.

Released information from the USGS Data Series 801 dataset is a substantial trove of geochemical information for the continental United States and includes collected samples on nearly half of the periodic table of elements. Examining the relationship between the suicide rate and other elements in the periodic table of elements is a direct expansion of the work completed in this thesis. Of particular interest may be to examine elements with known health effects and toxicity such as arsenic (As), mercury (Hg), thallium (Tl) and lead (Pb).

The relationship between lithium levels in groundwater and the suicide rate espoused in the reviewed literature may support behavioral health benefits of lithium consumption below the known lowest therapeutic dosage of 150 mg daily. (Parker et al., 2018) Further longitudinal studies of the effects of small doses of lithium on a population may help clarify this relationship. While lithium is not expected to bioaccumulate, it may also be of interest to examine tobacco products for lithium levels to see if habitual tobacco users are ingesting any notable quantity of lithium through their tobacco usage. A cursory glance of several (Guttuso, 2019) studies (Houas et al., 2016) seem to indicate that high levels of lithium in tobacco products have been noted.

Rather than aggregating this analysis to the county level, a variety of other data sources could have been used; one example are Health Service Areas used by the CDC and other federal agencies. (*Health Service Areas (HSAs) - Small Area Estimates | SRP/DCCPS/NCI/NIH*, n.d.) If granular enough lithium sample data was available, larger scale analysis could be completed in certain areas of the United States. Colorado is one such possible area as it provides access to suicide rate data at the census tract level (*Suicide Mortality Rate (Census Tracts)*, n.d.). CDC Places also provides census tract level suicide rate data for the 500 largest cities in the United States through the 500 Cities Project. (*500 Cities Project*, 2020)

The statistical analysis used in this work may be more appropriately analyzed using Semi-parametric Geographically Weighted Regression (SGWR) instead of Geographically Weighted Regression.

> "A semi-parametric model mixes terms of geographically varying/local coefficients and fixed/global coefficients.... By fixing some effects as global rather than local, we can reduce the complexities of local relationships. This, in turn, may enhance the readability of geographically varying relationships, as well as the predictive performance of the model. Importantly, it also enables model comparisons, which we can use to determine which explanatory effects on the response variable are fixed globally and which vary geographically in GLM."
>
> (Nakaya, 2015)

When it is known that part of a model has both global and local effects, SGWR allows maintaining some variables as a fixed global value to better explore the local effects of other variables. The model structure used for this work is based on the work from Blüml et al.'s 2013 study in Texas. Several of the variables used by that model appear globally significant and non-stationary across all of the statistically significant model runs and may be better represented by an

SGWR model. Of particular interest would be the variables for Percent Black or African American, Median Income and Population Density.

As discussed above, a multitude of potential future research exists for this topic, much of which would benefit from more detailed lithium level datasets and more robust statistical analysis. Future work focusing on global versus local models would also help to further clarify the spatial component to the relationship between lithium and the suicide rate.

Conclusion

It has been demonstrated in this work that environmental lithium is not a primary driver of the suicide rate. However, it is also clear that environmental lithium does explain a portion of the suicide rate and while this effect is limited, it is not negligible and maintains a unique place in the story of suicide as an environmental and biologic impact. This work has sought to provide additional support to the extant body of literature describing the relationship between lithium and the suicide rate, has replicated existing research on a national rather than regional scale, has found significant regional variations in the relationship between lithium and the suicide rate across the continental United States and has outlined several potential use cases for soil lithium data sources in place of water lithium data sources.

Lithium soil samples appear to show some validity for use in examining local relationships between lithium levels and suicide. Better methods to compare soil lithium datasets to water lithium datasets are needed to assess whether they represent meaningfully similar concentration levels in the same geographic area. Further work is needed to determine how and when lithium is consumed by a local population to determine if they are truly consuming lithium from local sources.

Threshold levels for lithium are still unclear and this work provides little further clarification of this relationship beyond that it does not appear to exist when examined using the NAWQA water quality dataset. Comparisons to prior works are also not as clear as desired since previous work does not examine this relationship through a geographic context and show maps of local models. Finally, data limitations do significant impact the results of this work and expanded coverage of lithium data samples across the continental United States would help further clarify the relationship between lithium and the suicide rate.

Appendix A

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Appendix B

Examination of Lithium Data Sources

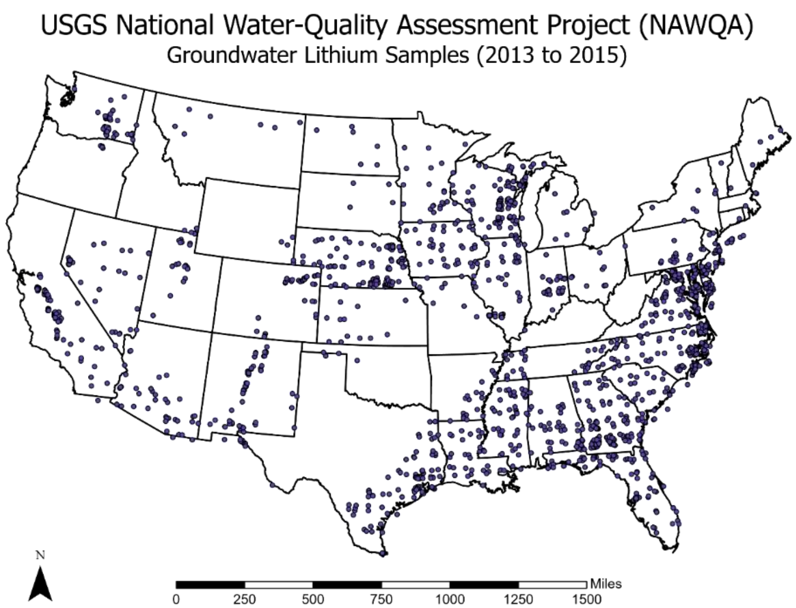

Figure **B-1**: Point locations of groundwater lithium samples in the continental United States from the National Water-Quality Assessment Project (NAWQA) collected between 2013 and 2015. Note that the largest concentration of samples is along the Gulf and Atlantic coastal plain.

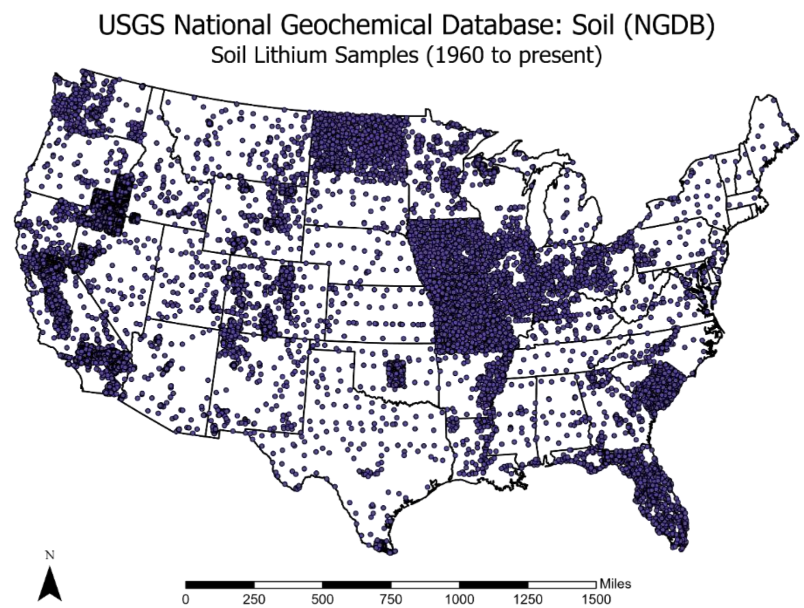

Figure **B-2**: Point locations of soil lithium samples in the National Geochemical Database (NGDB) in the continental United States from 1960 to the present day.

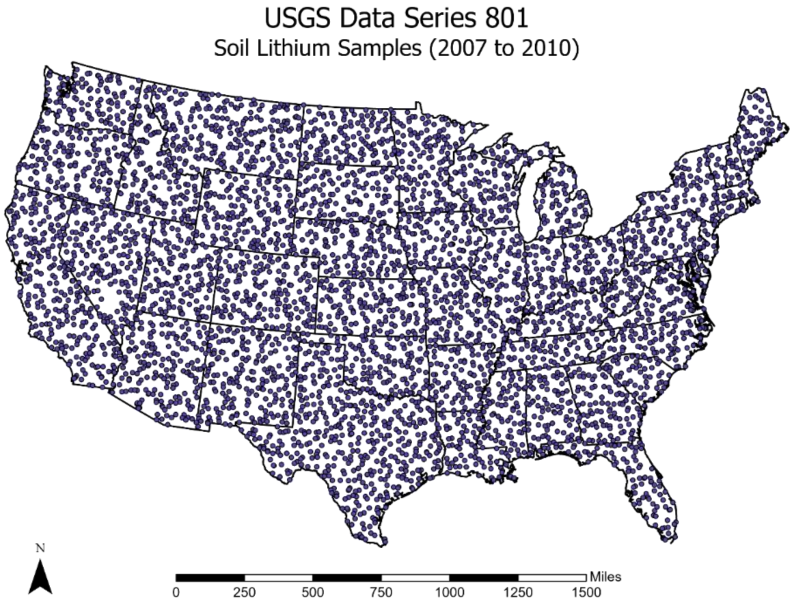

Figure **B-3**: Sample collection sites for the USGS Data Series 801 dataset. Note the relative uniformity of the sample sites across the continental United States compared to the other datasets used in this work.

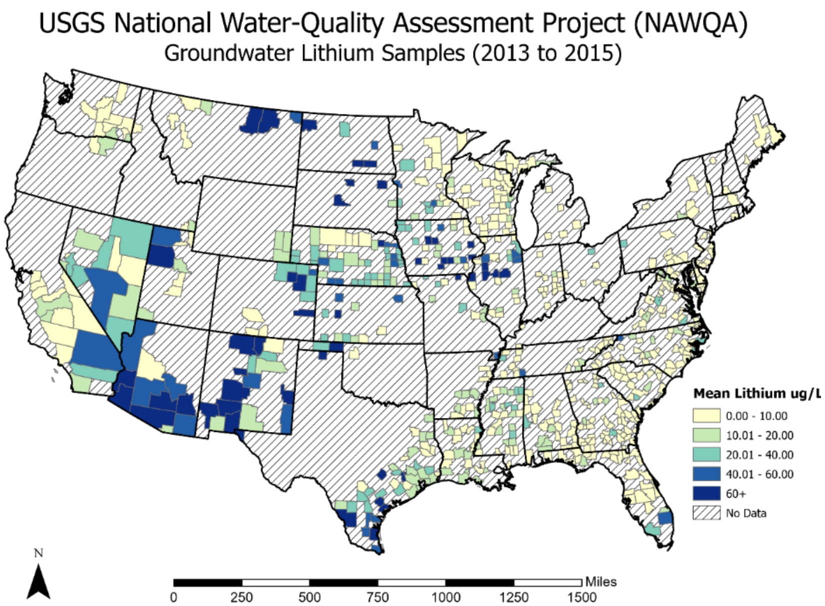

Figure **B-4**: County level aggregations of groundwater lithium samples in the continental United States from the National Water-Quality Assessment Project (NAWQA).

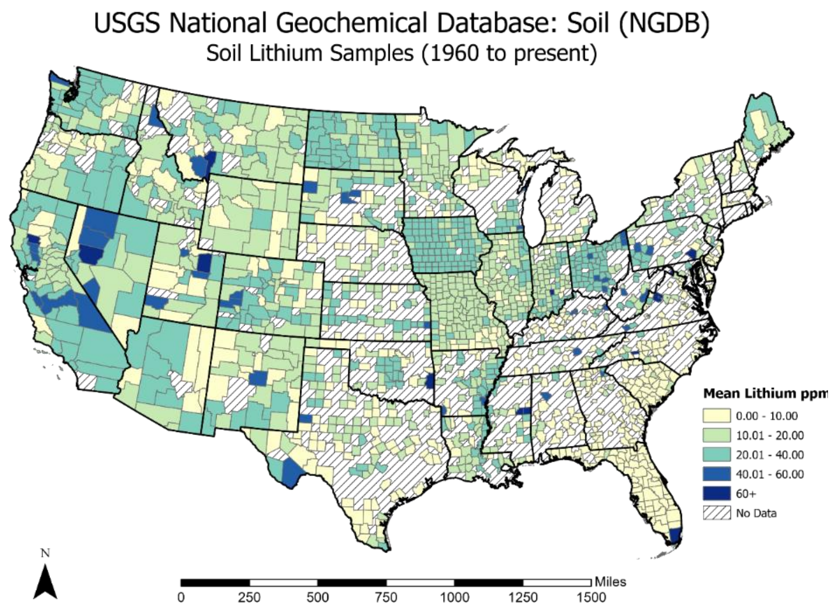

Figure **B-5**: County level aggregations of soil lithium samples in the continental United States from the National Geochemical Database (NGDB).

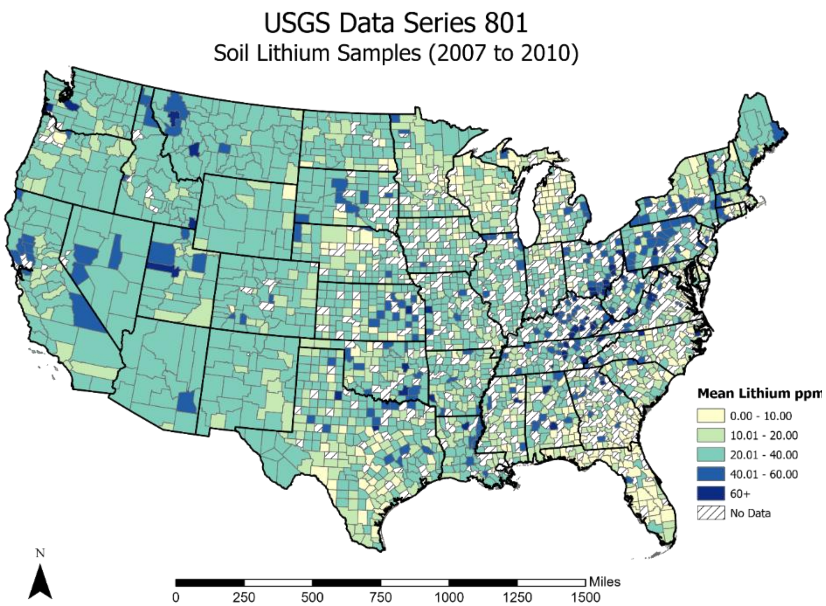

Figure **B-6**: County level aggregations of soil lithium samples in the continental United States from the USGS Data Series 801 dataset.

Table **B-1**: Descriptive statistics for each of the lithium data sources in this work.

National Water-Quality Assessment Project (NAWQA) Lithium Samples	
Mean	21.6801478
Standard Error	2.107590934
Median	7.683333333
Mode	0
Standard Deviation	54.79736427
Minimum	0
Maximum	928.1666667
Count	676

National Geochemical Database (NGDB) Lithium Samples	
Mean	17.58801412
Standard Error	1.215984905
Median	14.26136364
Mode	0
Standard Deviation	50.4890053
Minimum	0
Maximum	2050
Count	1724

USGS Data Series 801 Lithium Samples	
Mean	25.63563319
Standard Error	0.312611157
Median	24
Mode	21
Standard Deviation	14.6527622
Minimum	0
Maximum	123
Count	2197

Appendix C

Summary of OLS model results

Table **C-1**: Summary of all OLS model results. (Global)

ID	Suicide	Sample Size	Adj. R2	Lithium t	Lithium p	Significant?
NAWQA-001	All	515	0.033	4.322	0	✓
NAWQA-002	All	515	0.445	2.161	0.031	✓
NAWQA-003	Male	489	0.023	3.56	0	✓
NAWQA-004	Male	489	0.394	1.443	0.149	
NAWQA-005	All	31	0.493	0.082	0.935	
NGDB-001	All	1316	0	-0.774	0.439	
NGDB-002	All	1316	0.449	-1.172	0.241	
NGDB-003	Male	1204	0	-0.937	0.349	
NGDB-004	Male	1204	0.441	-1.35	0.177	
USGS801-001	All	1641	0.01	4.094	0	✓
USGS801-002	All	1641	0.449	0.775	0.439	
USGS801-003	Male	1513	0.01	3.99	0	✓
USGS801-004	Male	1513	0.428	0.983	0.326	

Table **C-2**: NAWQA-001 OLS model results including all suicide, but not including demographic variables. (Global)

Variable	Est.	SE	t(Est/SE)	p-value
Intercept	0	0.043	0	1
NAWQA Lithium Groundwater samples	0.187	0.043	4.322	0

Table **C-3**: NAWQA-002 OLS model results including all suicide and demographic variables. (Global)

Variable	Est.	SE	t(Est/SE)	p-value
Intercept	0	0.033	0	1
Population Density (ALAND10 / DP05_0001E)	0.408	0.034	11.846	0
Percent Black or African American (DP05_0033PE)	-0.396	0.049	-8.129	0
Percent Hispanic or Latino (DP05_0066PE)	-0.116	0.048	-2.433	0.015
Unemployment Rate (S2301_C04_001E)	0.107	0.047	2.29	0.022
Median Household Income in the past 12 months (B19013_001E)	-0.392	0.064	-6.086	0
Percent High school education or higher (S1501_C02_014E)	0.064	0.054	1.198	0.231
Poverty Status (S1701_C03_001E)	-0.157	0.075	-2.091	0.037
NAWQA Lithium Groundwater samples	0.077	0.036	2.161	0.031

Table **C-4**: NAWQA-003 OLS model results including male suicide, but not including demographic variables. (Global)

Variable	Est.	SE	t(Est/SE)	p-value
Intercept	0	0.045	0	1
NAWQA Lithium Groundwater samples	0.159	0.045	3.56	0

Table **C-5**: USGS801-001 OLS model results including all suicide, but not including demographic variables. (Global)

Variable	Est.	SE	t(Est/SE)	p-value
Intercept	0	0.025	0	1
USGS801 soil samples	0.101	0.025	4.094	0

Table **C-6**: USGS801-003 OLS model results including male suicide, but not including demographic variables. (Global)

Variable	Est.	SE	t(Est/SE)	p-value
Intercept	0	0.026	0	1
USGS801 soil samples	0.102	0.026	3.99	0

Appendix D

R2 model fit for each lithium data source

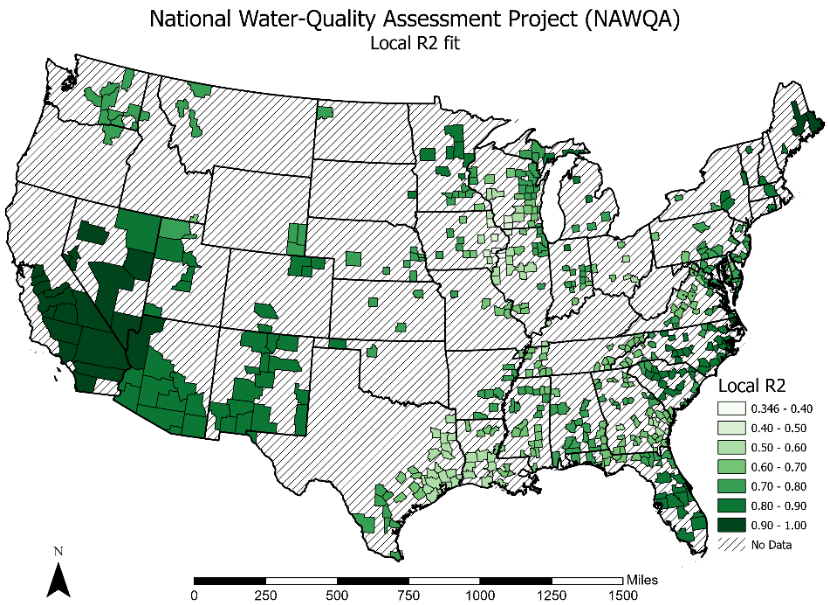

Figure **D-1**: R2 model fit for the National Water-Quality Assessment Project (NAWQA) data set. This map corresponds to the NAWQA-002 model run.

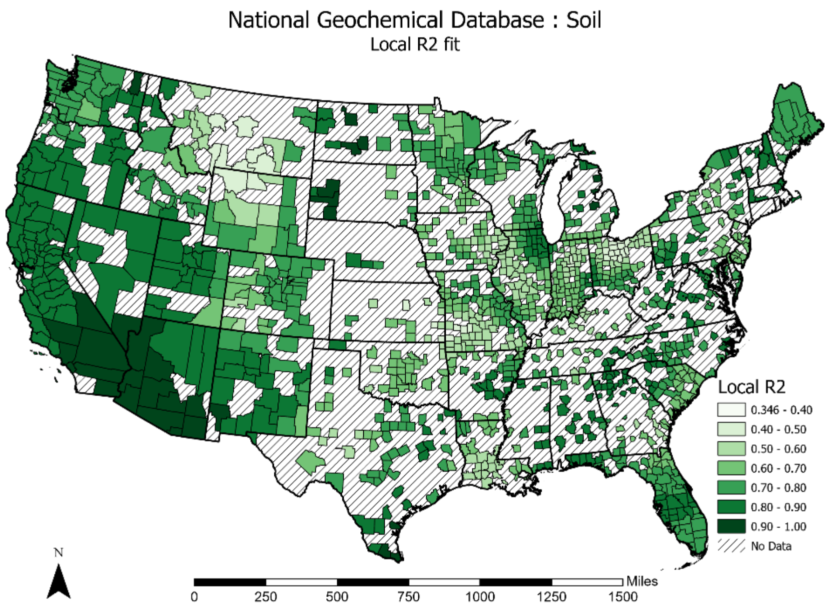

Figure **D-2**: R2 model fit for the National Geochemical Database (NGDB) data set. This map corresponds to the NGDB-002 model run

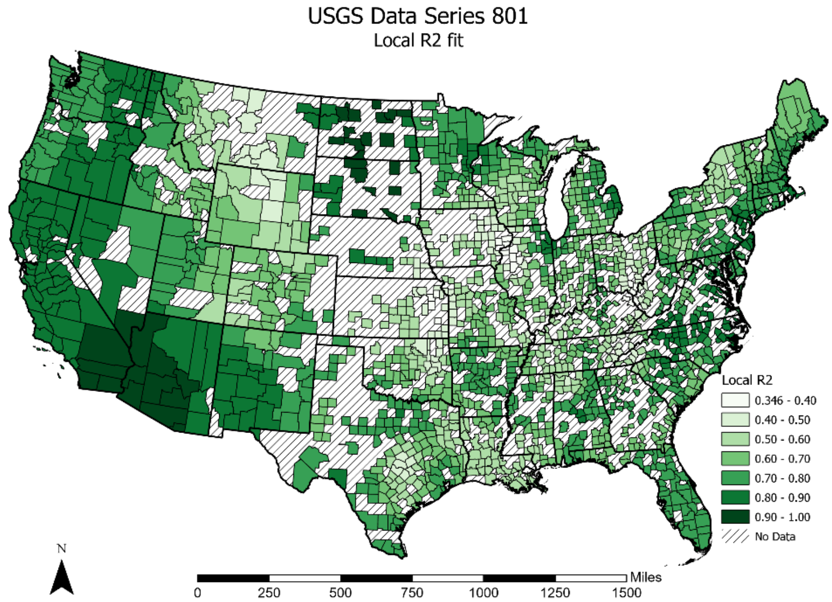

Figure **D-3**: R2 model fit for the USGS Data Series 801 release. This map corresponds to the USGS801-002 model run.

Appendix E

Driving variables impacting the suicide rate

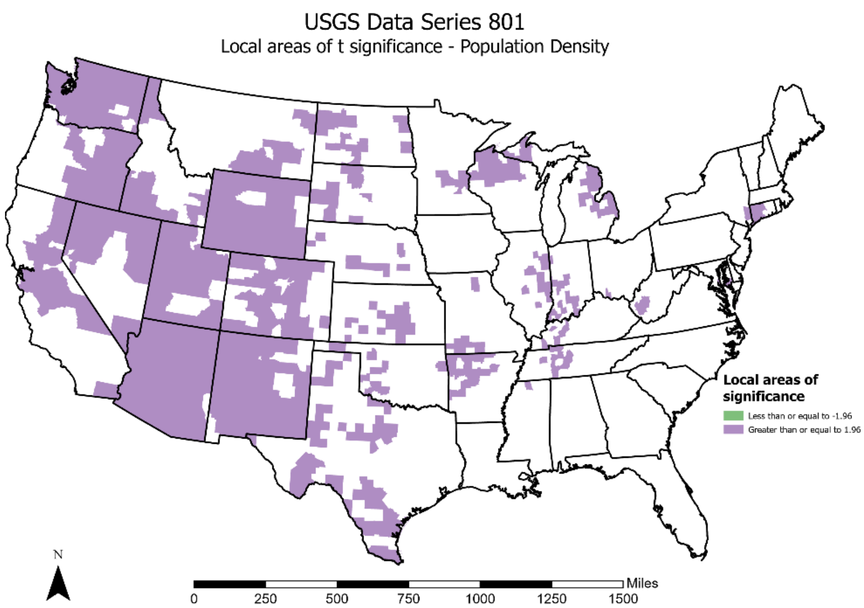

Figure **E-1**: Local areas of t significance for the Population Density variable for the USGS Data Series 801 model.

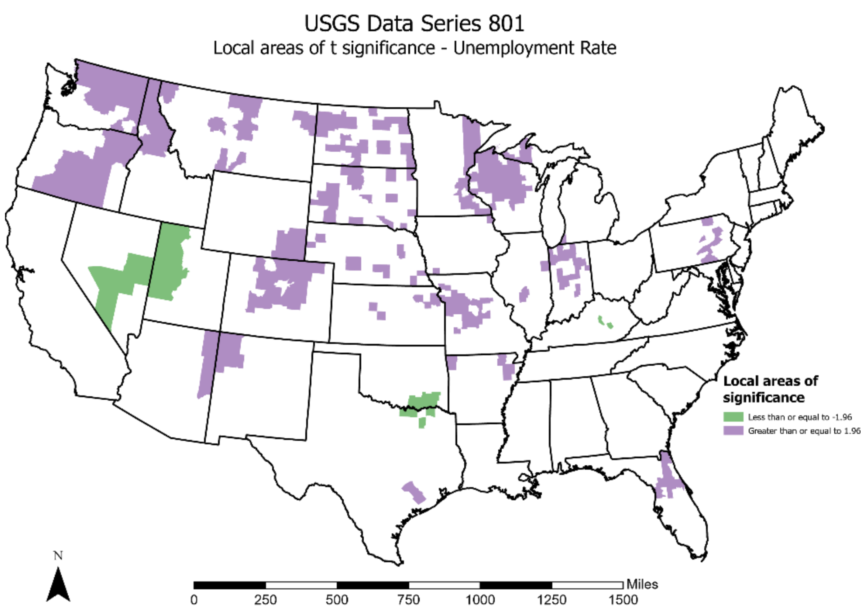

Figure **E-2**: Local areas of t significance for the Unemployment Rate variable for the USGS Data Series 801 model.

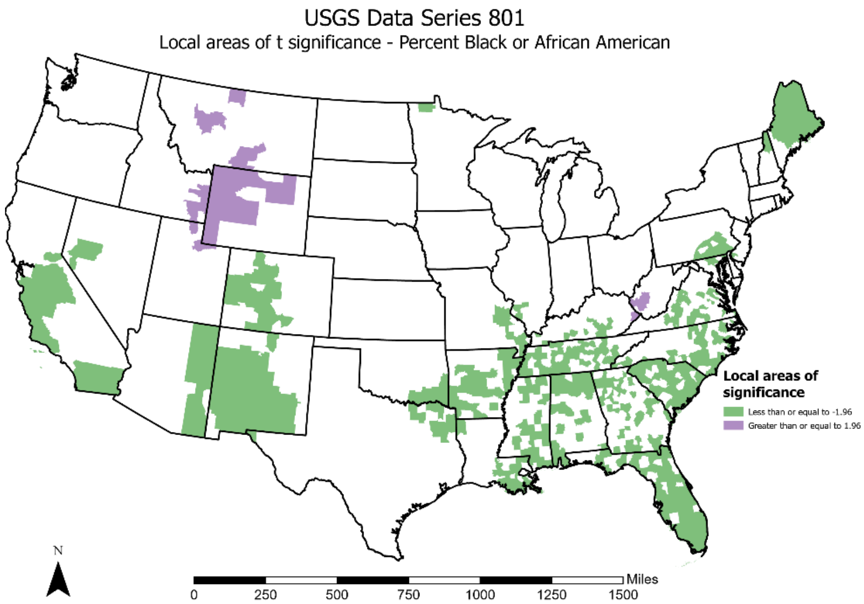

Figure **E-3**: Local areas of t significance for the Percent Black or African American variable for the USGS Data Series 801 model.

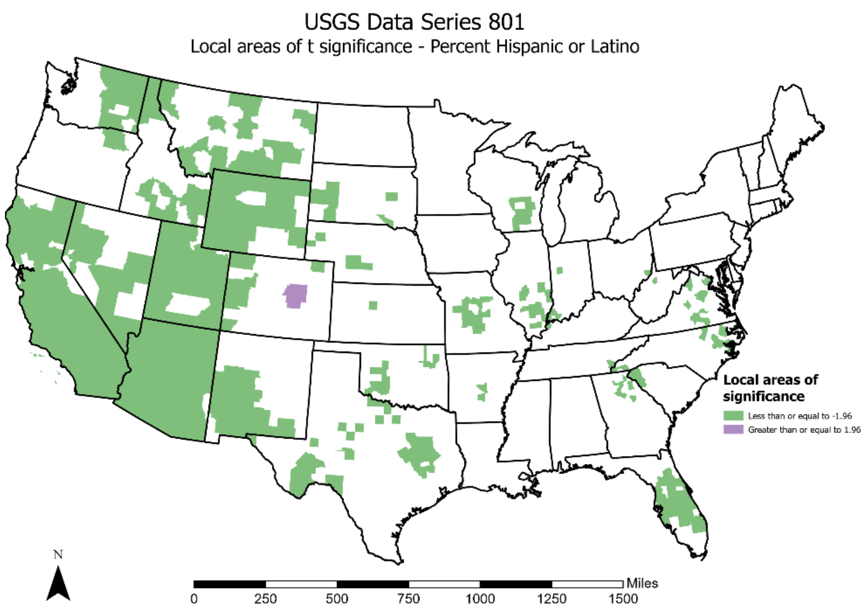

Figure **E-4**: Local areas of t significance for the Percent Hispanic or Latino variable for the USGS Data Series 801 model.

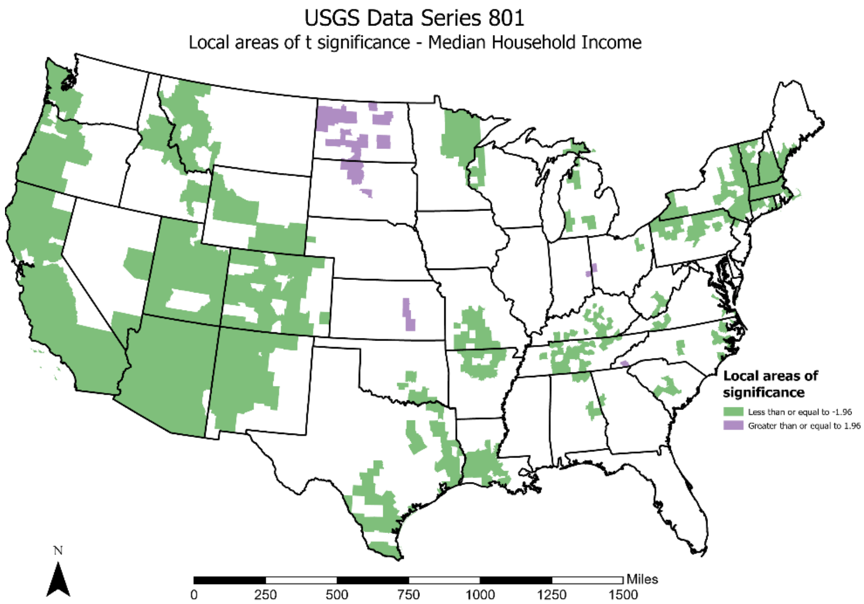

Figure **E-5**: Local areas of t significance for the Median Household Income variable for the USGS Data Series 801 model.