

2014

Preliminary multifactorial analysis of Parkinson's disease

Max James Miller

Louisiana State University and Agricultural and Mechanical College

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PRELIMINARY MULTIFACTORIAL ANALYSIS OF PARKINSON'S
DISEASE

A Thesis

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Master of Science

In

The Department of Environmental Science

By
Max Miller
B.S., Tulane University, 2012
May 2014

ACKNOWLEDGEMENTS

I cannot express enough thanks to my committee for their continued support and encouragement: Dr. Vincent Wilson, my committee chair; Dr. Martin Hugh-Jones and Dr. James Diaz. I offer my sincere appreciation for the learning opportunities provided by my committee.

My completion of this project could not have been accomplished without the support of Dr. Raoult Ratard, Dr. Susanne Straif-Bourgeois, and Mr. Hampton Peele– thank you for offering helpful suggestions with my data, tables, and figures. Thanks to my parents as well, Cathi and Craig Miller. You have been amazing role models and a true inspiration in my life. I could not have completed my research without you.

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ABSTRACT

Neurodegenerative disorders affect millions of Americans every year. Incidence increases as the human population ages. Parkinson's Disease, a neurodegenerative disorder in the dopaminergic system of the basal ganglia, causes deterioration of movement as the disease progresses. Researchers have attempted to figure out what causes PD and are currently examining it as an environmental disease.

This study examined PD as an environmental disease using a multifactorial approach. Methods included 1) utilization of hospital and mortality records in order to investigate a relationship between occupation and PD 2) using ArcGIS 10.2 technology to examine the spatial components of PD 3) conducting Chi-Square tests and other statistical tests in order to determine the validity of the approach.

The findings of this study identified that no factor singlehandedly was responsible for increased PD hospitalization or mortality. Furthermore, this study concludes that many factors in combination may contribute to increased PD hospitalization and/or mortality.

INTRODUCTION

Parkinson's disease is a central nervous system disorder that causes a deterioration of the dopaminergic system in the basal ganglia (Braak and Del Tredici 2008). Some of the disease's symptoms include shaking, rigidity, slowness of movement, and difficulty with walking (Lang and Lozano 1998). Parkinson's disease is more common in the elderly, with a peak age of onset of 65 years. However, early onset of PD (generally defined as younger than 40 years of age) can occur (Dick 2006). Diagnosis of PD has proved to be a challenge in the clinical setting. Neurologists fail to identify non-motor symptoms of PD in over 50 percent of consultations and sleep disturbance is not observed in over 40 percent of PD patients (Shulman et al. 2011). Common reasons for admission to the hospital for PD include falls, dementia, and hallucinations (Findley 2003). Due to a lack of a medical device to identify PD, medical professionals are currently developing screening questionnaires in order to improve the efficiency of diagnosis in a clinical setting. The NMSQuest International Group created a 30 item questionnaire to be used by the PD patient/caregiver as a screening tool (Chaudhuri 2006). Neuropathological examinations, the gold standard for PD identification, has been incorrect in over 20 percent of cases performed postmortem (Hughes et al. 1993). Continuing to develop instruments for identifying PD would help to improve individualized and integrated delivery of care (Chaudhuri 2004).

It has baffled researchers that PD can dramatically impair basic coordination while not depleting memory or any other part of the brain. While there are several components that may contribute to the onset and prevalence of PD, we chose to investigate the disease from an environmental perspective. More specifically, we used an ecological-based study. This type of study is often used to study potential causal associations between multiple variables or exposures

(Tu and Ko 2008). Ecological studies are particularly useful when alternative study designs are not possible (Tu and Ko 2008). Researchers have used ArcGIS as a tool to estimate pesticide exposure data. In the central valley of California using PUR (pesticide usage report) data as an exposure measurement, researchers discovered that when both Paraquat and Maneb are applied within 500 meters of the home, there was a dramatic increase in risk of developing PD (Costello et al. 2009). A similar study was conducted in the same area of California that examined the association between well-water consumption and PD. The case-control study determined individuals consuming well-water with 8 or more water-soluble pesticides were at increased risk for developing PD (Gatto 2009). Both of the aforementioned studies suggest that causation of PD is not due to a single etiological agent such as one pesticide, but more likely a combination of neurotoxic exposure events.

The present work attempts to discern potential exposures and causation of PD in the State of Louisiana. A multifactorial ecological analysis of PD was performed using ArcGIS 10.2 thematic and land use maps while incorporating geocoding techniques in order to identify geographic areas of concern in the state of Louisiana. Hospitalization and mortality records were obtained from the Louisiana Department of Health to document cases and deaths related to PD. The proximity to a particular industry or industries, alone and in combination, were investigated to determine associated increased the risk of PD among residents of Louisiana. These studies have provided interesting complexities and potential leads to the causation of PD.

REVIEW OF LITERATURE

The causes of PD are not completely understood. For this reason, we decided to examine the literature under the assumption that many factors may contribute to the onset and prevalence of PD. In rare cases, Parkinson's disease is a familial syndrome but in most cases, the genetic component of the disease is unknown. Although causal genetic variants in several genes (parkin, alpha-synuclein, DJ-1, PINK1, and LRRK2) have been identified, the overall prevalence of PD is largely unaffected by these rare genetic risk factors (Lucking et al. 2006). Reduced blood progranulin (GRN) levels might be associated with increased risk of developing PD by pathogenic factors different from rs5848 and rs646776 polymorphisms, but needs a much larger set of patients to confirm this relationship (Mateo et al. 2013). In previous familial studies, researchers have examined the relationship between pesticide use and PD using affected sibling pairs (Qing et al. 2009). Few family based studies with non-sibling pairs have been conducted over the past several decades. Many studies have investigated the relationship between pesticide use and PD in unrelated individuals (Hancock et al. 2008). Individuals with no family history of PD are more susceptible to direct pesticide exposure than individuals with family history of PD (Hancock et al. 2008).

Although the mean age of diagnosis is 65 years old, about 5 percent of cases are considered early onset (meaning the patient is <40 years of age) (Lees and Tamas 2009). Many identified cases of early onset, autosomal-recessive PD can be attributed to genetics and are considered a familial syndrome (Sironi et al. 2013). In rare cases of early onset PD, two autosomal dominant point mutations (A30P and A53T) are found in the gene encoding alpha-synuclein (Polymeropoulos 1997). Early onset PD is poorly understood. Due to the lack of

frequency in cases, it is difficult to perform studies that measure an association between early onset PD and the environment.

In western populations, the incidence of PD is greater in men than in women, although researchers report a high level of heterogeneity (Taylor et al. 2007). Men also tend to be younger at symptom onset with a more severe motor deterioration than women (Haaxma et al. 2007). The cause for gender-related differences in PD is largely unknown, but endocrine factors may be a contributing factor (Lyons et al. 1998). Epidemiologic-based studies suggest age at menopause may have a significant influence on the development of PD with respect to age (Ragonese et al. 2004). Researchers have explored estrogen as a potential therapy for women with PD. Estrogen has been shown to improve motor function and motor fluctuations in women with PD (Tsang et al. 2000). Estrogen may activate the mitogen-activated protein kinase pathway to provide neuroprotection against PD (Singer et al. 1999). An incidence study of PD was performed as part of the Rotterdam study in 1995 (Breteler et al. 1996). Researchers did not find a significant difference in incidence PD for male and female subjects of ages 55 years and older (Breteler et al. 1996). However, this subpopulation does not include potential early-onset PD patients, reflecting a potential age-bias. The reason for increased risk of incidence PD amongst males is unknown (Wooten et al. 2004). Higher incidence of PD amongst males may be related to occupation. Studies have cited male-dominated professions such as farming, welding, and paper mill workers as individuals with a greater risk of developing PD.

Data regarding the relationship between race and PD is inconsistent and controversial (Van den Eeden et al. 2003). Utilizing hospitalization data alone may not provide an accurate representation of the total population with the disease (Van den Eeden et al. 2003). A meta-analysis performed by researchers on individuals with African ancestry suggests that PD is less

prevalent in individuals of African origin compared to those of Caucasian descent (McInerney et al. 2004). Health disparities researchers have suggested that PD may be underdiagnosed in minority populations and that PD may be one of many chronic diseases in which racial minorities receive inadequate treatment (Cohen 2003). While access to healthcare and socioeconomic status may play role in PD diagnosis and treatment, it is not reasonable to assume racial injustice is occurring with PD patients. Incidence and/or prevalence of PD amongst different races may be a result of genetics. In New Orleans, medical records over a decade (1959-1969) were examined in a charity hospital where 75 percent of the patients are black (Paddison and Griffith 1974). Using only patients with unequivocal evidence of PD, the researchers found that there were nearly 7 times as many Caucasian PD patients as black PD patients (Paddison and Griffith 1974). Not including factors such as age and gender, this study suggests African Americans may be at lower risk for PD than Caucasian individuals. A worldwide review regarding the occurrence of PD cited that Asian and black African populations have the lowest prevalence rates of the disease (Zhang et al. 1993). Race may play a role in prevalence and incidence of PD, but it is unlikely that this factor operates on its own. Further examination of race as it relates to PD need to include factors including gender, age, and socioeconomic status.

Due to the largely unexplored nature of genetics as it relates to Parkinson's disease, researchers have postulated that Parkinson's may be an environmental disease. Case reports and experimental and epidemiological research has suggested that pesticides may play a key role in the etiology of Parkinson's Disease (Ritz and Yu 1999). After World War II, agricultural use of pesticides became widespread (Ecobichon 1994). Agricultural use of pesticides can have detrimental health effects if residues are present. Parkinson's disease has been reported to occur

at high rates among farmers and in rural populations, contributing to the hypothesis that agricultural pesticides may be causal agents. A series of studies performed in the Central Valley of California suggest that pesticides such as Rotenone, Paraquat, and Maneb all cause neurodegeneration leading to Parkinson's disease.

Exposure to pesticides may occur directly or indirectly. A potentially important vehicle for pesticide exposures is by ingestion of contaminated drinking water. Pesticides are not unique to the area in which they are applied, as these toxic agents have the potential to move from their original application site. Private water wells may be at greater risk for pesticide exposure than public water systems because they are not subject to the same regulations and thus are not similarly monitored. A study examining this relationship, using California pesticide use reporting (PUR) data and an ArcGIS-based exposure assessment tool, found that consumption of drinking water from private wells suspected to be contaminated with diazinon, methomyl, chlorpyrifos, propargite, or dimethoate was associated with an elevated risk of PD (Gatto 2009). This study employed methods that are less subject to bias than previous studies, which relied on subjects' recall of their own pesticide use to estimate exposure. However, exceedingly high odds ratios were only observed when possible well-water exposure was contaminated with more than 8 different pesticides. These findings make it difficult to ascertain the source of the contamination.

Paraquat has been reported in association with Parkinson's disease, but results are inconsistent because few studies include exposed cases (Tanner et al. 2011). The ability of Glutathione transferases to provide cellular protection against oxidative stress has made them a subject of recent research (Goldman et al. 2012). Individuals lacking GSTT1 (Glutathione S-Transferase 1) may be at increased risk for developing Parkinson's disease via exposure to Paraquat; however, replication of this study is needed (Goldman et al. 2012). Maneb is a

wettable and flowable power that has been used in agricultural settings and golf courses in the 1990s and 2000s (Roberts and Reigart 1999). Although Maneb is no longer in use, exposure to Maneb alone has been associated with increased risk as much as 4 to 6 fold in subjects younger than 60 years old (Costello et al. 2009). Furthermore, these researchers found that when both Paraquat and Maneb are applied within 500 meters of the home, there was an increased risk of PD by 75% (Costello et al. 2009). Paraquat and Maneb, both potent mucosal irritants, can lead to degeneration of the substantia nigra, cause dopaminergic depletion, and reduce tyrosine hydroxylase and dopamine transporter immunoreactivity (Thiruchelvam et al. 2003). Chronic exposure to Paraquat and Maneb may have synergistic effects when individuals are exposed to both of these potent toxins simultaneously.

Exposure to the pesticide Rotenone can produce symptoms of PD, namely behavioral and neuropathologic features, in some rodent models through chronic systemic inhibition of mitochondrial complex I (Costello et al. 2009). MPTP, a pro-toxin that produces PD in humans, can be metabolized into MPP⁺ and inhibits complex I at the electron transport chain. The selectivity of MPP⁺ for dopaminergic neurons is due to the fact that it is an excellent substrate for the dopamine transporter, and accumulates preferentially in cells that transport dopamine (Betarbet et al. 2000).

Symptoms similar to PD have been reported due to chronic occupational exposure via manganese toxicity (Ferraz 1988). Manganese exposure at excessive levels is toxic to the Central Nervous System (CNS), despite its essentiality to the human body (Sidoryk 2013). Many studies focusing on the role of manganese in idiopathic PD fail to consider manganism, a parkinsonian syndrome (Park 2013). Using x-ray fluorescence microscopy, selective trace metal dopaminergic neurons that play a pivotal role in PD onset are more prone to manganese accumulation than

other neurons. Manganese accumulation often occurs when iron concentrations are low (Ducic 2013). Because the aforementioned condition is not always present in PD patients, the literature regarding low iron levels as it relates to the disease remains inconclusive. Occupations such as welding have been associated with cognitive, psychological, motor, and sensory effects from manganese exposure (Sjogren 1996). Due to methodological limitations such as a lack of blood-Mn determinations in studies concerning manganese as it relates to Parkinson's, the research is controversial (Antonini 2006).

Louisiana has 13.9 million acres of forests and 3.6 million cords of pulpwood are cut annually in order to support the paper industry (doa.louisiana.gov). A case-control study performed on 255 paper mill workers chronically exposed to the fungicide diphenyl reported a small cluster of 5 PD cases, indicating a potential for elevated susceptibility to the disease (Wastensson 2006). In our study, using ArcGIS 10.2 geocoding techniques to assess clustering of PD mortality patients, we found an unusually high occurrence of deaths in Morehouse Parish in Louisiana. This is an area where International Paper Company employed 3.34 percent of the entire parish population as of 2008 (internationalpaper.org). Despite limited data, we investigated the association between paper mill locations and PD death locations in Louisiana using ArcGIS 10.2 as well as hospitalization and mortality records obtained from the Louisiana Department of Health.

At the moment, human data is insufficient to support the claim that these pesticides are contributing to neurodegeneration. Therefore, it is critical to begin the process of understanding the possible environmental factors associated with the incidence and prevalence of PD. Many pesticides leave residues or have measurable concentrations that exist in plants, are bioaccumulated in various animals, and have presence in air or groundwater. The state is the

nation's third largest producer of rice, twelfth largest producer of cotton, and accounts for twenty percent of all sugar grown in the United States (LSU Ag 2013). Because of the high production of the three aforementioned crops, it is important to target prevalent exposures to pesticides in Louisiana. The most logical occupational exposure with regards to agricultural pesticide use is farming. Limitations in our hospital data set forced us to search amongst the listed occupations in mortality records from 1999-2012 provided by the Department of Health. Due to a limited amount of farmers and lack of pesticide reporting data, we could not reach a conclusion that farmers were at increased risk for PD. Although we did not find evidence of high risk for amongst farmers for PD in Louisiana, it is important to note that further investigation using pesticide reporting data may provide noteworthy results.

Methodological limitations have raised questions regarding the validity of research involving the relationship between agricultural pesticide use and Parkinson's Disease. Reliance on self-reporting and recall of chemical usage in previous studies cause vulnerability to differential recall bias and information bias (Seidler et al 1996). To alleviate concerns of these biases, we did not use any survey or self-reporting data. Using listed occupations from our mortality records combined with ArcGIS geocoding practices to provide a spatial component, we found that individuals working in paper mills may be at increased risk for PD development. Researchers in Sweden found a cluster of five cases of PD among paper mill workers exposed to the fungicide diphenyl (Wastensson et al. 2009). Because pesticide data is not readily available in Louisiana, ArcGIS may be an effective way to estimate exposure using proximity to industries with toxic agents such as paper mills. We investigated whether proximity to paper mills increased the risk of incident PD among residents of Louisiana, a state that has 11 parishes with paper mills.

MATERIALS AND METHODS

At the beginning of the project, the method of choice was a case-control study. It seemed logical to choose a disease unrelated to PD (e.g. stomach cancer) that would act as a valid control group to compare to PD. However, data regarding another disease unrelated to PD was unavailable. This modification occurred after odds ratios had already been calculated to assess risk in a given area using 2010 United States Census data as the individuals in the control group. I later realized that this was an inappropriate control group. While the approach had to be modified later, the data obtained was still vital to the multifactorial analysis. This is important to mention at the beginning section, as some of the data that follows was obtained using a case-control approach.

An ecological study was performed in addition to examining PD prevalence by perceived risk with the data. Ecological studies are important tools for examination of a relatively new hypothesis. These types of studies focus on the comparison of groups rather than individuals (Morgenstern 1995). Although data was available on the individual level via hospital records and mortality records, it was not possible to provide an adequate exposure measurement. Due to a limited amount of knowledge on the causes of PD on the individual level, an ecological approach to studying the disease appeared to be a more promising approach. All ecological studies are subject to a bias known as the “ecological fallacy,” which is the idea that an association made at the aggregate level may not be applicable on the individual level (Tu et al. 2008). However, it may be dangerous to assume that individual patients are unaffected by the neighborhood in which they live or the setting in which they are treated. This is known as the “individualistic fallacy,” and avoidance of this bias may offset issues observed in the ecological fallacy (Alter et al. 1999).

The study was performed in two directions: prospectively and retrospectively. The data was obtained from the Department of Health and Hospitals: Office of Public Health. For the prospective component, the study started by examining hospital clinical records of individuals with PD from the years 1999-2012, obtained a unique identifier (in the form of a randomized ID number) for each patient, and determined how many of these individuals appeared in the death certificates. Three codes were used in the hospitalization record to indicate that the patients had PD (Parkinson's Disease, Paralysis Agitans, and Secondary Parkinsonism). These codes were used to extract records of hospitalization. The extraction was made on DxMain, Dx01, Dx02, Dx03, up to Dx08. Most records had a Parkinson code in DxMain but some had other codes in DxMain and PD code in Dx02 or the other remaining Dx cells. De-duplication was performed by the Department of Health prior to distribution of the hospital records. The de-duplication was a two-step process. The total number of patients prior to de-duplication was 51, 667. First, it was necessary to eliminate duplicate hospitalizations: those who had the same last name, first name, date of birth, social security numbers and admission date. After subtracting the duplicate hospitalizations, our patient total was 48, 573. The second component eliminated those who had the same last name, first name, date of birth, and social security numbers to keep a non-duplicated count of patients. After eliminating duplicate patients, the total number of patients was 23, 690. It was realistic to assume 23, 690 patients had PD at any given time from 1999-2012. It is estimated that as many as one million Americans live with PD, meaning that there is a 0.3 percent prevalence, or 300/100,000 persons when including the total population (Stickland et al. 2004). When incorporating the U.S. Census Bureau's 2000 and 2010 data and extrapolating this to Louisiana, this would mean 13,504 person have PD. It is estimated that 60,000 Americans are diagnosed with PD each year (20/100,000 population), and this number does not reflect the

thousands of cases that go undetected (Van den Eeden et al. 2003). Extrapolating those numbers to Louisiana would mean that roughly 1,000 new cases develop each year. Using the data which included 23,690 PD patients hospitalized over a period of 14 years means an average of 1,700 patients are hospitalized per year. Considering that there are 13,504 persons living with PD in Louisiana at any time, it would mean that 10% of persons living with PD are hospitalized every year, which seems to be realistic.

The retrospective study was in the reverse direction, starting with the deaths with PD and searching for those individuals in the clinical records. For both the prospective and retrospective studies, it was critical to obtain information regarding the patient's occupation and/or job title. This data allowed us to more accurately assess any biases in the two medical datasets, and whether a patient's job contributed to his/her onset of PD. In addition, the patient's occupation and/or job title may be indicative of their potential exposure to toxic agents (i.e. a patient who is a paper mill worker may directly handle diphenyl, thereby increasing their exposure levels).

The hospitalization data was stratified by age, race, gender, and parish. However, without occupations present as well as street addresses, the hospitalization data was not as useful for the ecological study. In order to best assess perceived risk of PD as it relates to certain occupations and/or specific locations, it was necessary to use data that had both occupations and street addresses. For the remaining portion of the methods section, mortality records were used for all rate calculations and ArcGIS 10.2 thematic maps.

Before examining patients' occupations, it was critical to analyze the data at the parish level. This portion of the study started by tallying the total number of deaths for all 64 parishes in the state of Louisiana. After the total number of deaths for each parish was calculated, it was important to compute a mortality rate for each parish. Calculating mortality rates provided a

more useful indicator in order to identify potential exposure areas of concern. Using United States Census data from 2010 as the denominator, a crude mortality rate for each Louisiana parish was compiled.

The data was then organized by age groups in 5 year increments. The groups started at Age 35 and younger, then progressed in 5 year increments until the maximum age was reached at 100 years. It was expected that as age increased, risk of PD death would also increase. The focus of this age stratification was to identify early onset cases (defined as younger than 40 years).

The mortality data was then stratified by occupation. Due to the lack of occupational data in the hospitalization records, they were not used in this portion of the analysis. In order to better categorize and consolidate the dataset, the patients' self-reported identification of industry was also assessed. After taking this into consideration, 31 occupations were individually assessed by compiling the total number of deaths for each respective occupation. An odds ratio was then calculated in a 2x2 table for all 31 occupations with the following parameters: 1) whether the patient lived in the parish of focus defined as "Parish." The comparison group was the remaining patients from the mortality records defined as "Non-Parish." 2) determining whether the patient was "exposed" or "non-exposed." Exposure was defined by whether patient had died with PD with the occupation of interest. Non-exposure was defined as the individuals alive, without PD, not in the occupation of interest, and in the remaining 63 parishes. This was a useful tool for deciphering which professions were most at risk for death with PD. ArcGIS 10.2 was then used to create a thematic map that demonstrated the different risk levels association with each occupation. In order to create the thematic map, the 2010 Microsoft Excel file with the 2x2 tables was converted into a comma-delimited (CSV) Microsoft Excel format.

This file was then joined with a file containing boundary lines for each Louisiana parish using the “Joins and Relates” function in ArcGIS 10.2.

After determining which professions to carefully examine, a comparison of Interstate 10 and Interstate 20 was performed. I set up 2x2 tables for all occupations in the major parishes bordering I-10 and I-20 (Calcasieu, Orleans, Caddo, and Morehouse, respectively) with the following parameters: 1) whether the patient lived in the parish of focus defined as “Parish.” The comparison group was the remaining patients from the mortality records defined as “Non-Parish.” 2) determining whether the patient was “exposed” or “non-exposed.” Exposure was defined by whether patient had died with PD in the parish of focus. Non-exposure was defined as the individuals alive, without PD, and in the remaining 63 parishes. This data was presented as an odds ratio. A thematic map was then constructed using ArcGIS 10.2 to provide a visual of the varying levels of risk associated with each respective Interstate Highway. To find a description on the development of the thematic map, see the paragraph above.

Because of the findings regarding specific occupations that will be further expanded upon in the results/discussion section, a chi-square test was conducted that measured an association between zip codes with paper mills and a weighted average of deaths in each respective zip code. The death rates were compiled for each zip code in Louisiana using 2010 Census Data for zip codes (total deaths from Parkinson’s/zip code population). Next, a weighted average was calculated for all 512 zip codes in the state. The average death rate for the state of Louisiana due to Parkinson’s per zip code (according to the mortality records of PD) is 0.11%. Afterwards, each zip code with a paper mill located in it was examined that had either above a 0.25% WA (weighted average) and one below 0.11% WA. The goal was to discard about 1/3 of the data set (between .11% and .249%, which ended up being 176 zip codes, or 34.3% of all zip codes). That

portion of the dataset was eliminated in order to highlight the highest death rates while incorporating the lower death rates. For the analysis, 336 zip codes were examined which met this requirement: 1) Death Rate for “above” category had to exceed a weighted average of 0.25% and below had to be lower than 0.11%. This helped to eliminate the middle portion of the dataset.

Due to a lack of direct exposure data, an individual’s proximity to potentially toxic industries was considered the best method for ecological assessment. Because the hospitalization records did not have street addresses, mortality records with individuals’ street, parish, and zip codes were used. ArcGIS 10.2 was used to geocode addresses. Geocoding is the process of transforming a location—in this case, an individual’s street address—to a location on the earth’s surface (Esri.com). In order to geocode the 5,519 mortality records, the Microsoft Access 2010 database was converted into a comma delimited (CSV) file in Microsoft Excel 2010 and uploaded into ArcGIS 10.2. Addresses were automatically geocoded to Louisiana TigerLine files. However, many addresses were unable to automatically geocode due to misspellings of the address or entrance of a wrong zip code. Additional modification was applied to certain addresses (example: 3521 Ninth Street modified to 3521 9th Street). 92 percent of the 5,519 mortality cases were able to be geocoded. The reasons the remaining 8 percent failed to geocode was due to a complete lack of a street address (only a parish of death given, 376 patients) or the address given was out of state (49 patients). In the maps containing the geocoded addresses, industrial locations were then geocoded (e.g. paper mill locations). These locations were geocoded in order to determine if there was a spatial component to a potentially toxic industry as it relates to PD.

Additionally, the geocoded maps were plotted against NASS (National Agricultural Statistics Service) data to examine residential addresses and their proximity to cotton, rice, and sugarcane crop data.

RESULTS

HOSPITALIZATION RECORDS

Figure 1 indicates that as age increases, diagnosis with PD increases. The average age for hospitalization was 76.3 years of age. The hospitalization data suggests that being diagnosed with early onset PD (<40 years of age) does not seem to be a primary area of concern at first glance. Early onset PD incidence in the United States has been estimated at 1.5/100,000 persons (Roze 2006).

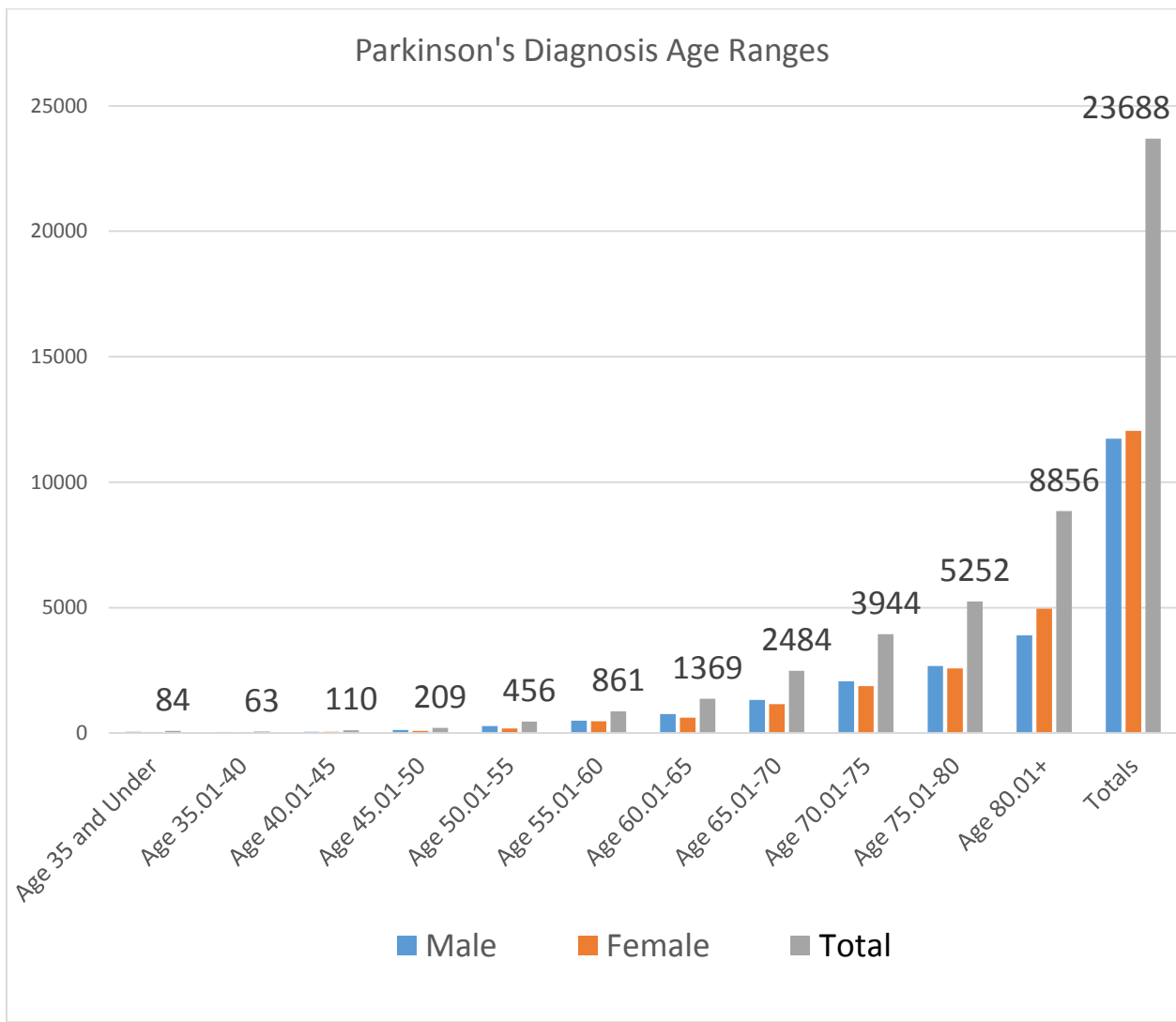


Figure 1 A bar graph examining PD diagnosis by age in 5 year increments

It is important to note that in this study, no time interval for early onset PD incidence was given. In Louisiana, early onset PD incidence is 3.24/100,000 persons over the 14 years of hospitalization data (95% CI, 2.97-3.50). After extracting the data and calculating a hospitalization rate per 100,000 individuals in the state based on 2010 United States Census data, residents of Louisiana may be at increased risk for early onset PD. Of all the age groups, the interval with the highest hospitalization total is the age category exceeding 80. The total number of females diagnosed with PD slightly exceeds the total number of males diagnosed with disease across all age categories (12,048 females to 11,740 males, respectively).

Figure 2 is a bar graph compiling hospitalizations of PD for the top 15 parishes in terms of total number of diagnosed patients. The Out of State category had 3,378 patients, all of whom either had parish data in the hospital records that was classified as “missing” or “out of state”. These patients were not incorporated into the total numbers for PD hospitalizations by parish. Many of the parishes with the highest number of hospitalizations also had the highest number of people living in that parish according to the 2010 United States Census data. This highlights the importance of considering total parish population when examining Figure 1. There was not a significant difference in lifespan per parish.

Figure 3 examines the odds ratios per parish in Louisiana. No parish in Louisiana had a complete absence of hospitalizations. These odds ratios incorporated 2010 United States Census data. 25 of 64 Louisiana parishes had odds ratios exceeding 1.0. Five of these parishes had odds ratios exceeding 1.5. The reason for calculating odds ratios was to determine whether there was a spatial component as it relates to PD. Parishes located near cities exceeding a total population of 100,000 individuals do not appear to be at a dramatically increased risk for hospitalization due to PD. All 5 parishes with odds ratios exceeding 1.5 had total parish

populations under 40,000 individuals. Looking at the map from a spatial perspective, there appears to be more odds ratios exceeding 1.0 in the northern half of the state than the southern half.

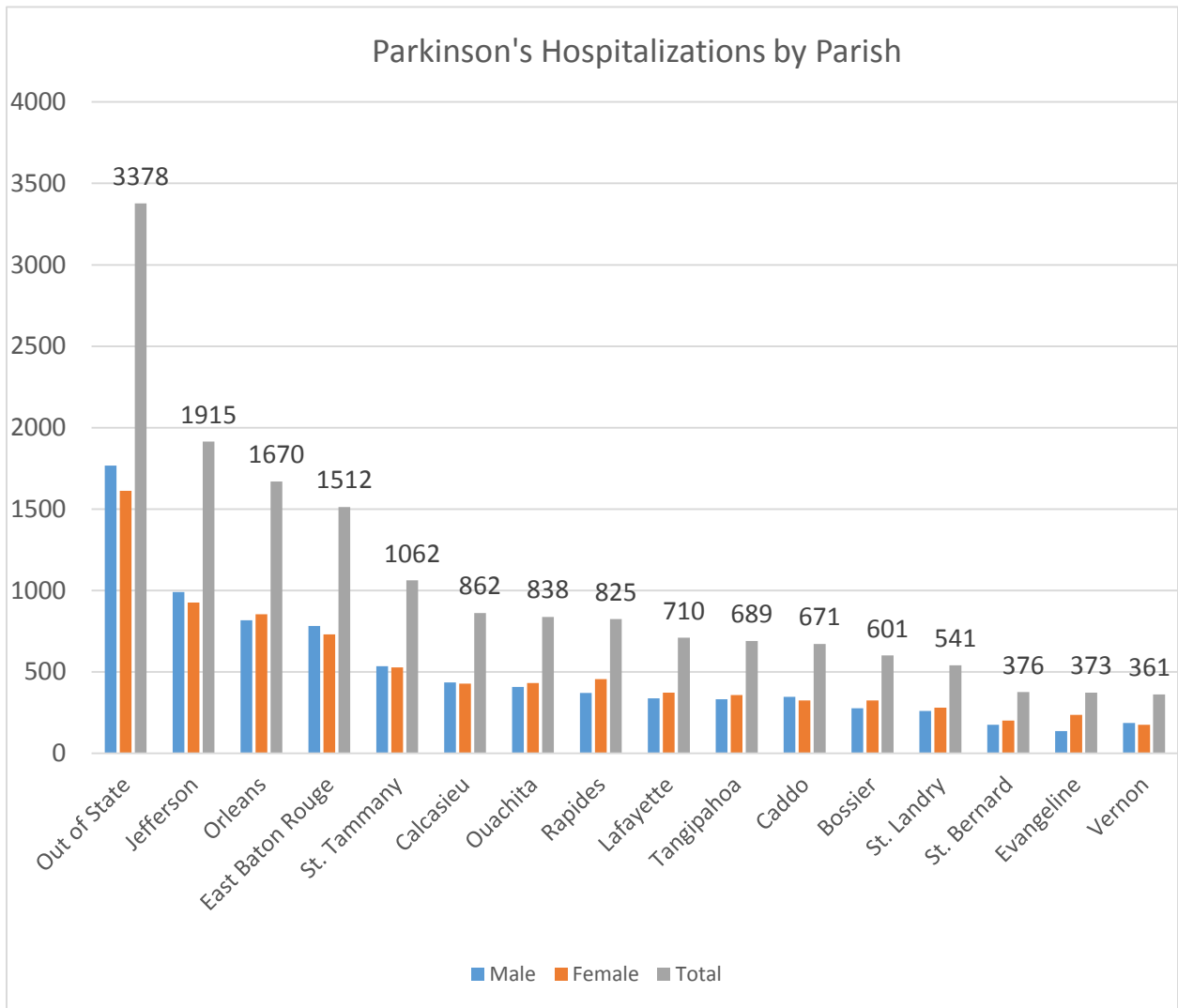


Figure 2 A bar graph examining PD hospitalizations by parish in Louisiana

Hospitalization Odds Ratios per Parish

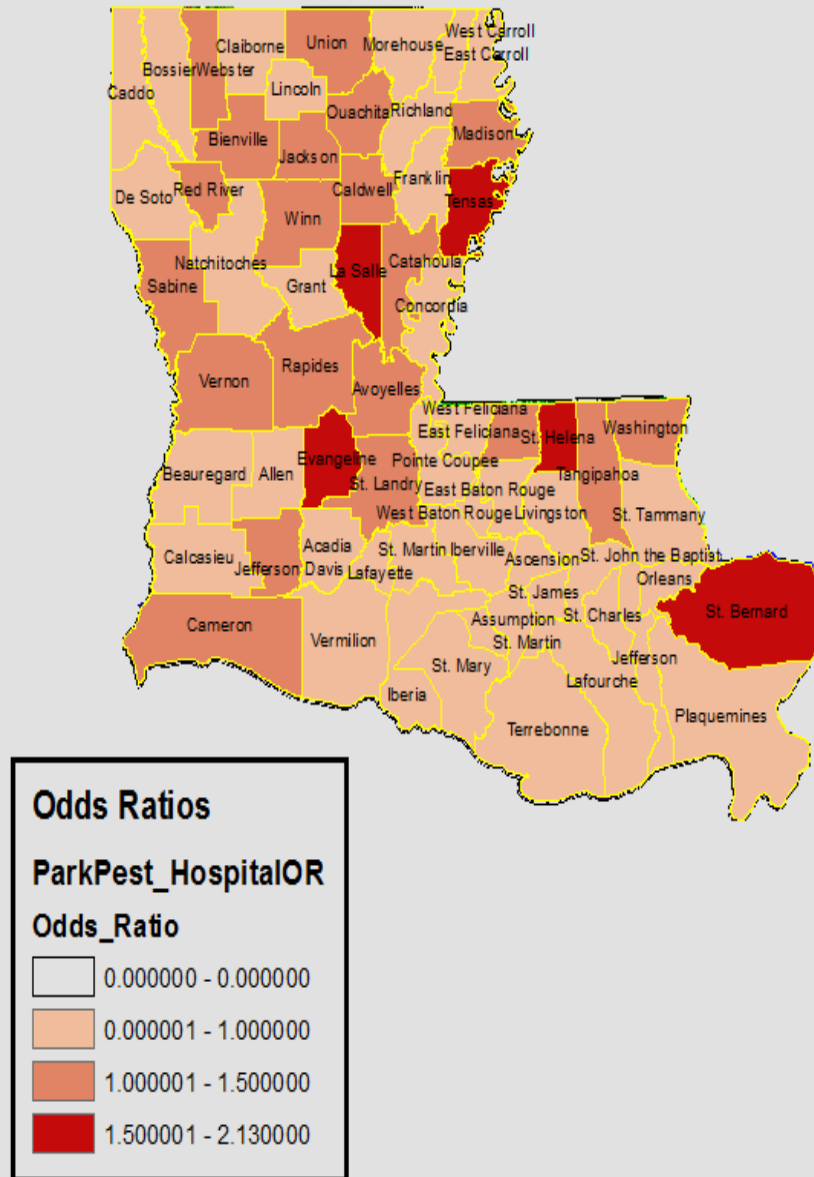


Figure 3 Thematic Map of Hospitalization Odds Ratios per parish in Louisiana

MORTALITY RECORDS

With 5,519 mortality records, the data was first categorized according to age groups using the same age increments as the hospitalization records. The average age of death with PD was 80.2 years old. Like the hospitalization data suggested, age increased the risk for death associated with PD for both men and women. Figure 4 examines risk for mortality in 5 year increments. The average life expectancy for a United States citizen is 78.7 years of age (CDC). Nearly 75 percent of all patients who died with PD were over the age of 78.7. Less than 1 percent of the mortality records died before the age of 40 (the suggested age barrier for early onset PD). The total number of males who died with PD outnumber the total number of females who died with PD (3,082 total males to 2,437 females, respectively). It is also important to note that 89.2% of the dataset died with PD after the age of 70.

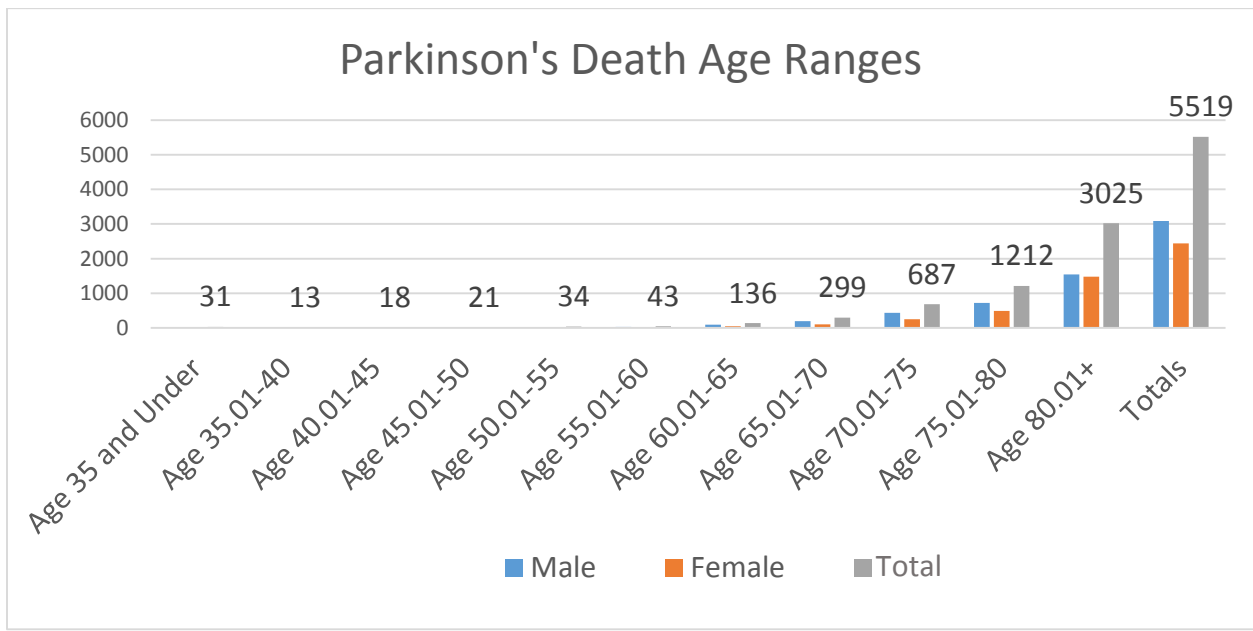


Figure 4 A bar graph examining mortality with PD in 5 year increments

Like the hospitalization records, an analysis of PD deaths per Louisiana parish was performed using the mortality records. Figure 5 is a subset of the data that displays the top 16 parishes in terms of total deaths. Similar to the hospitalization records, the hospital death totals were strongly associated with the total parish population. The 5 parishes with the highest number of deaths all had parish populations exceeding 100,000 individuals according to the 2010 United States Census data. Figure 6 provides a more visually descriptive thematic map that uses the total deaths per parish and the 2010 U.S. Census data per parish as a denominator to obtain a total death rate for each parish in Louisiana. The average death rate per parish for the State of Louisiana was 0.11%. Using 4 different classifications, the thematic map separates complete absence of death (0.00%) from a low (0.01-0.11%), medium (0.11-0.15%), and high (0.15% and above) death rates. No parish in the state of Louisiana had a complete absence of death. 31 parishes were categorized as a “low” death rate. Twenty-five parishes fell under the “medium” death rate category. The “high” death rate category contained the remaining 8 parishes in Louisiana (Morehouse, Madison, Caddo, Winn, St. Bernard, Point Coupee, Bienville, and Beauregard parishes, respectively).

MORTALITY RECORDS- OCCUPATIONAL ANALYSIS

Figure 7 presents a comparison of individuals in the oil industry with PD compared with individuals of other occupations. Individuals with odds ratios exceeding 2.0 are concentrated towards the southern portion of Louisiana. Individuals in the middle and northern portion of the state appear to be at no risk, or marginally increased risk when compared to the southern portion. Twenty-five parishes in the state have a complete absence of risk. Twenty parishes have odds ratios between 0.01 and 1.0, meaning they are at decreased risk or a non-increased risk of dying

with PD. The remaining nineteen parishes have odds ratios between 1.01 and 4.46, meaning all have an increased risk of dying with PD when compared to the rest of the parishes in the state.

Figure 8 demonstrates how many farmers died with PD in all 64 Louisiana parishes. Odds ratios were compiled for each of the parishes, but only 1 parish (Tangipahoa) was found to be at increased risk for PD. The other 63 parishes had a complete absence of risk or odds ratios near 1.0.

Figure 9 provides an example of how the odds ratios were compiled. These did not incorporate the 2010 United States Census data, but compared farmers within the dataset. Tangipahoa parish had the highest number of total farming mortalities at 10 individuals. Without adequate exposure measurement, it is difficult to definitively conclude whether these results are significant or due to chance.

The results of the geocoded addresses are provided in Figure 10. Additionally, NASS (National Agricultural Statistics Service) data was incorporated into the map in order to determine if there was clustering near the crop acreage for cotton, rice, and sugarcane. The northeast portion of the state has little to no clustering near the crops grown in that area (primarily a cotton region of the state). The northwest corner of the state has a high number of geocoded addresses, which appears to be independent of crop coverage. When examining the middle of the state, clustering occurs around the city of Alexandria in Rapides parish. Similar to the northwest portion of Louisiana, this increase in the number of cases is not highly associated with the 3 aforementioned crops. The southeastern portion of the state contains a large number of cases concentrated around Lake Pontchartrain. In the discussion, I will further expand on the possible relationship between PD mortalities and water. The southernmost pocket of the state in Lafayette parish has a high degree of clustered cases. Rice and sugarcane are grown on either

side of the parish and may have a potential relationship to this high concentration of PD mortalities.

Like Figure 10, Figure 11 displays the geocoded PD mortalities. The red triangles displayed the locations of paper mills in order to assess whether proximity to the mills had a correlation to death with PD. Both the mortalities and paper mills were geocoded to TigerLine files from 2006. Caddo, East Baton Rouge, and Ouachita parishes have significant clustering and a paper mill present. However, I believe the high number of deaths due to PD is attributed to the significant populations in these areas. If a relationship existed between paper mills and mortality with PD, it is expected that clustering would occur in any parish with a paper mill present. In this map, this is clearly not the case.

After compiling death rates for each zip code in Louisiana, a chi-square test (results shown in Figure 12) was performed in order to determine whether a significant difference in mortality existed between zip codes with paper mills present. The middle portion (approximately one-third) of the dataset was eliminated to highlight the more extreme rates. Deaths rates over 0.25% were categorized as “high” death rates while below 0.11% were considered “low” death rates. The weighted average of the entire dataset was slightly above 0.11%. The uncorrected p-value indicated that results were significant and that a difference in death rates existed between parishes with and without paper mills. Additionally, once the results were corrected, the p-value remained significant (below .05). From these results, it remains possible that there is a correlation between proximity to paper mills and death with PD. However, more studies need to be performed in order to provide conclusive evidence of this notion.

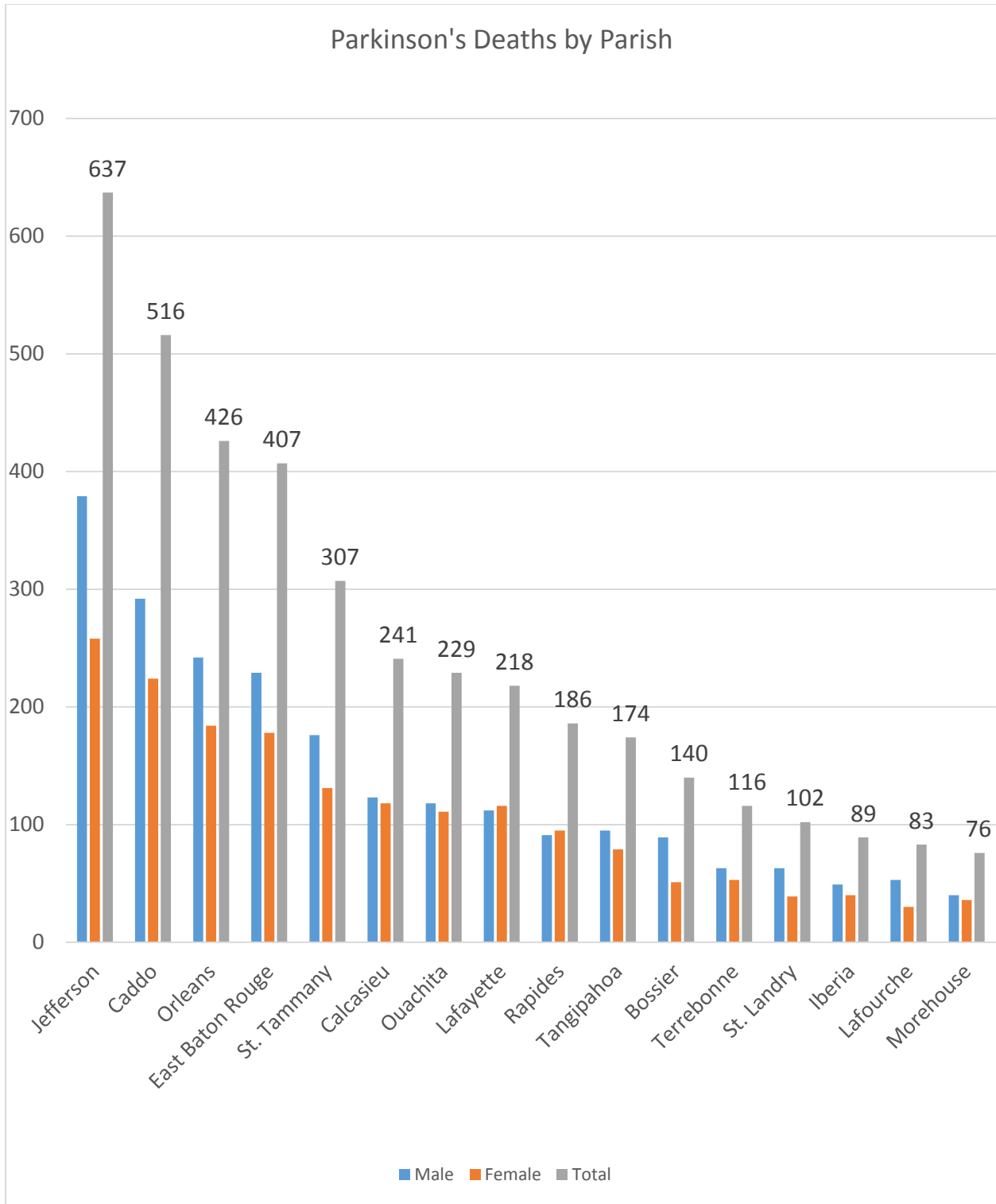


Figure 5 A bar graph documenting PD deaths per parish in Louisiana

Louisiana Death Rate per Parish (Using 2010 United States Census Data)

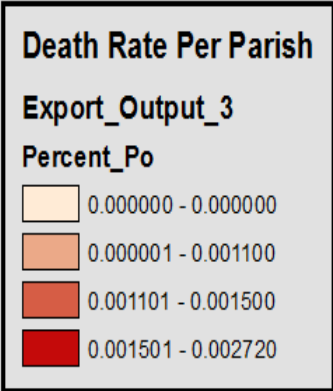
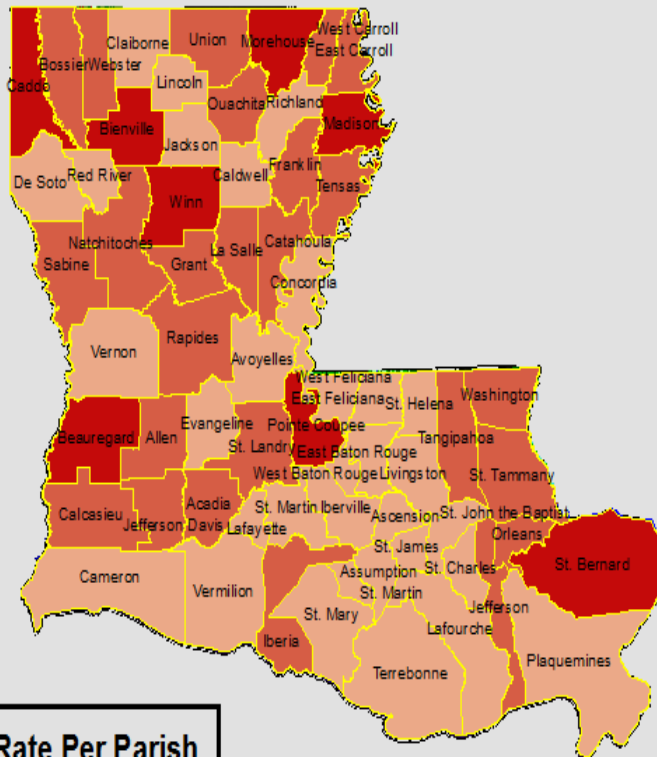


Figure 6 Thematic Map of Death Rate per Parish in Louisiana

Odds Ratios for Oil Industry Workers

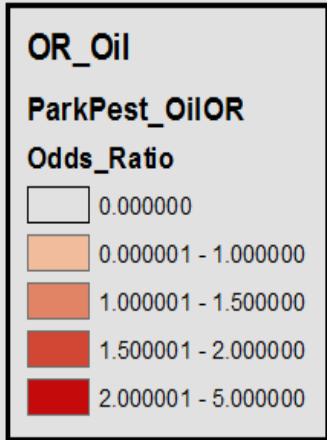
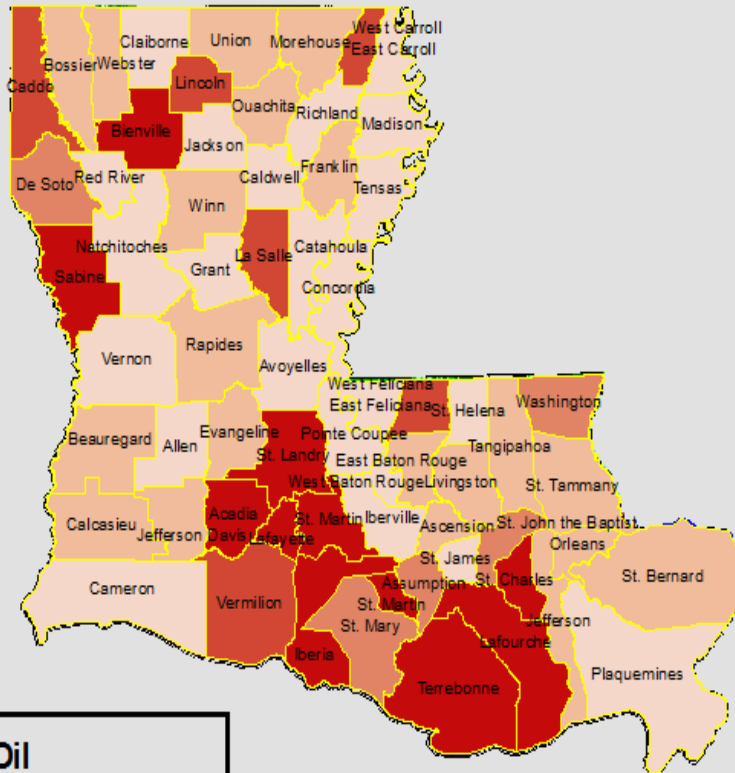


Figure 7 Thematic Map of odds ratios per parish of PD individuals listing oil as occupation

Total Mortality by Parish for Farmers

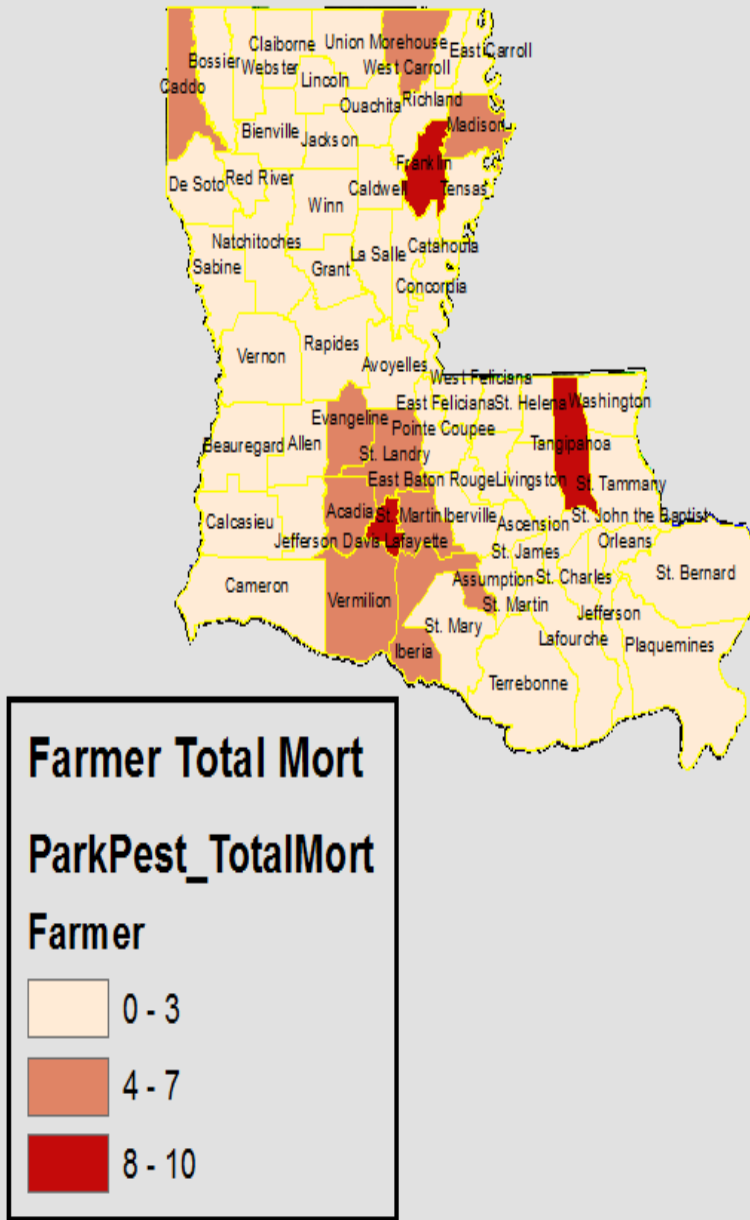


Figure 8 Thematic Map tallying total deaths with PD for the farming occupation

	Farmer	Non-Farmer	Totals
Tangipahoa	10	164	174
Non-Tangipahoa	120	5225	5345
Totals	130	5389	5519
Odd's Ratio= 2.654979675			

Figure 9 Odds ratio calculation table for farmers in Tangipahoa parish

Crop Distribution and Geocoded Addresses

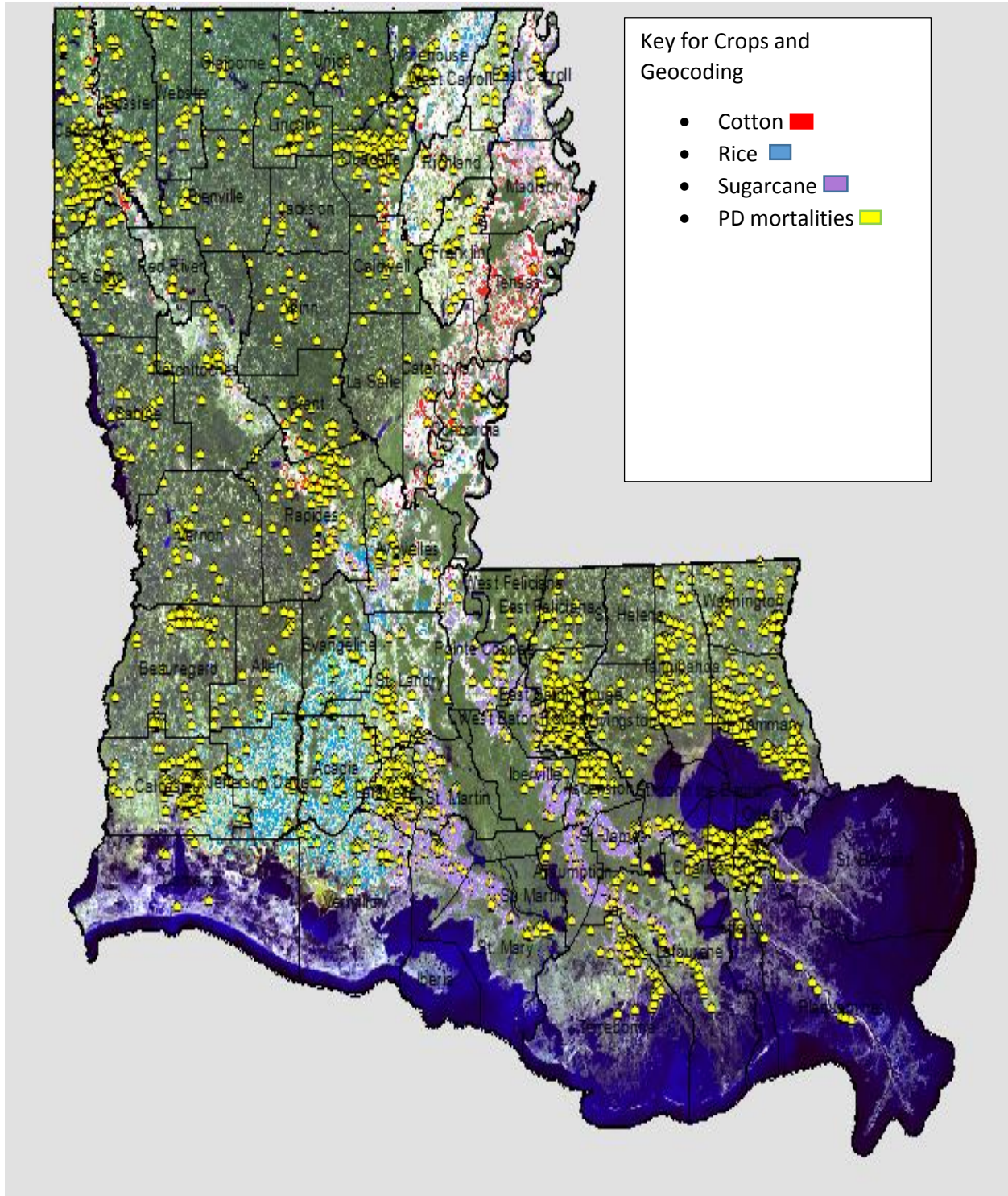


Figure 10 NASS Crop data (Cotton, Rice, Sugarcane) plotted against Geocoded Addresses

Paper Mills and PD Mortalities

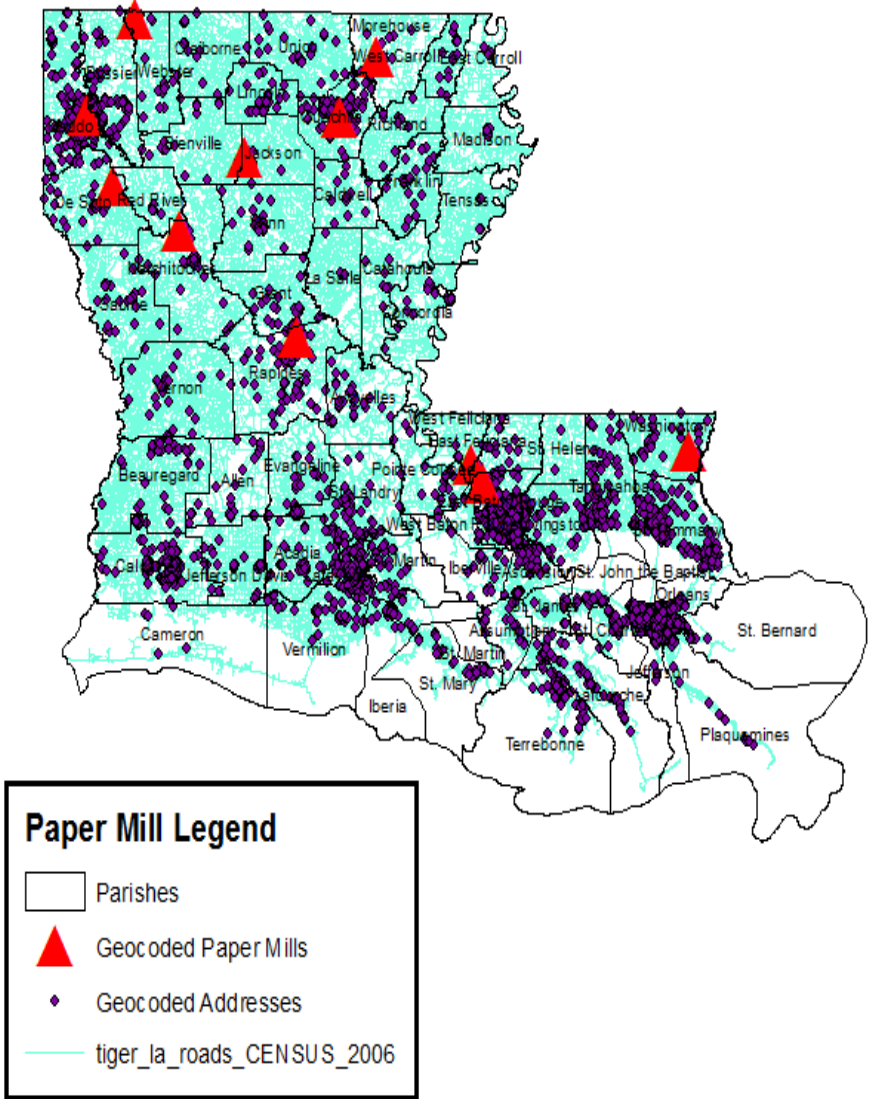


Figure 11 Map displaying PD deaths and Paper Mill locations in Louisiana

Figure 13 examines total PD mortality attributed to the occupation listed as homemaker/housewife. All 1,261 deaths in this category were female. In this figure, it is clear that the parishes with the highest total populations also have the highest number of deaths. However, many of the parishes with the highest death totals are concentrated in the southern portion of the state.

	Above 0.25% WA	Below 0.11% WA	Totals
Paper Mill	3	5	8
No Paper Mill	31	297	328
Totals	34	302	336

	Chi-Square Value	2 Tailed P-Value
Uncorrected	6.7553	0.0093480745
Mantel-Haenzsel	6.7352	0.0094540011
Corrected	4.0233	0.0448759954

Figure 12 Results from the Chi-Square Analysis regarding Paper Mill locations and PD deaths

Homemaker/Housewife Total Mortality

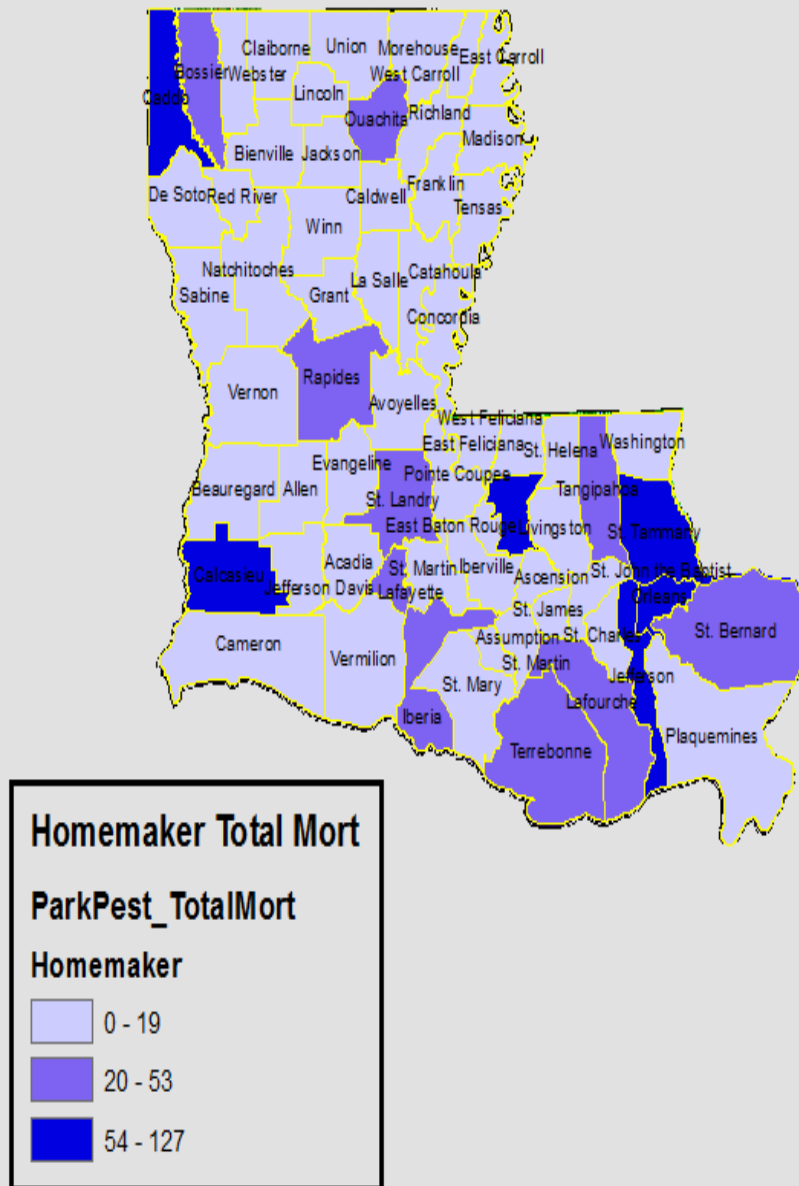


Figure 13 A Thematic Map Displaying Total Homemaker/Housewife Mortality

MORTALITY AND HOSPITAL RECORDS- EXAMINATION OF AREA

Hospitalization and mortality rates per 100,000 persons were calculated in Figures 14 and 15 to examine rates at the “city level” rather than parishes. “City level” was determined by the following parameters 1) the “city” contained 3 parishes, all adjacent to one another and 2) the combined population of the 3 parishes had to exceed 100,000 individuals. The following parishes were included in the assessment in the parenthesis for each “city” 1) Alexandria (Rapides, Grant, Avoyelles), 2) Baton Rouge (Ascension, East Baton Rouge, West Baton Rouge), 3) Lafayette (Acadia, Lafayette, St. Landry), 4) Lake Charles (Beauregard, Calcasieu, Jefferson Davis), 5) Mid-State (Natchitoches, Sabine, Vernon), 6) Monroe (Morehouse, Ouachita, Union), 7) New Orleans (Jefferson, Orleans, St. Charles), 8) North Shore (St. Tammany, Tangipahoa, Washington) and 9) Shreveport (Bossier, Caddo, De Soto). The average hospitalization rate for individuals with PD for the state of Louisiana was 523 per 100,000 persons (95% CI, 516-530). The highest hospitalization rate for individuals with PD of any “city” was Mid-State at 612 per 100,000 persons (95% CI, 567-657). This was an unexpected result, as the Mid-State area had the lowest total population of all the 9 “cities” in the assessment. Only 3 “cities” exceeded the average hospitalization rate of Louisiana for individuals with PD. These 3 “cities” had the 3 lowest total populations in the assessment. The average mortality rate for individuals with PD for the state of Louisiana was 122 per 100,000 persons (95% CI, 119-125). Figure 15 indicated that the “city” with the highest mortality rate for individuals with PD was Shreveport at 174 per 100,000 persons (95% CI, 161-187). Six of the nine “cities” assessed were above the average mortality rate for individuals with PD for the state Louisiana. When comparing Figure 14 to Figure 15, only 4 of the 9 “cities” had rates that were either similarly above or below the average rate in Louisiana for both figures (Alexandria, Baton Rouge, Lafayette, and Monroe,

respectively). It was surprising that over half of the “cities” did not have rates similarly above or below the average rate for Louisiana in both figures. In terms of average hospitalization and mortality rates per 100,000 in the state of Louisiana, Baton Rouge has the lowest rates in both categories. Based on this, it is reasonable to assume that Baton Rouge has the lowest risk for hospitalization or death attributed to PD of any of the 9 “cities” examined. Because Monroe had the 3rd highest hospitalization rate per 100,000 and 2nd highest mortality rate per 100,000 persons, it can be concluded that Monroe has the highest risk for hospitalization or death attributed to PD of any of the 9 “cities” examined.

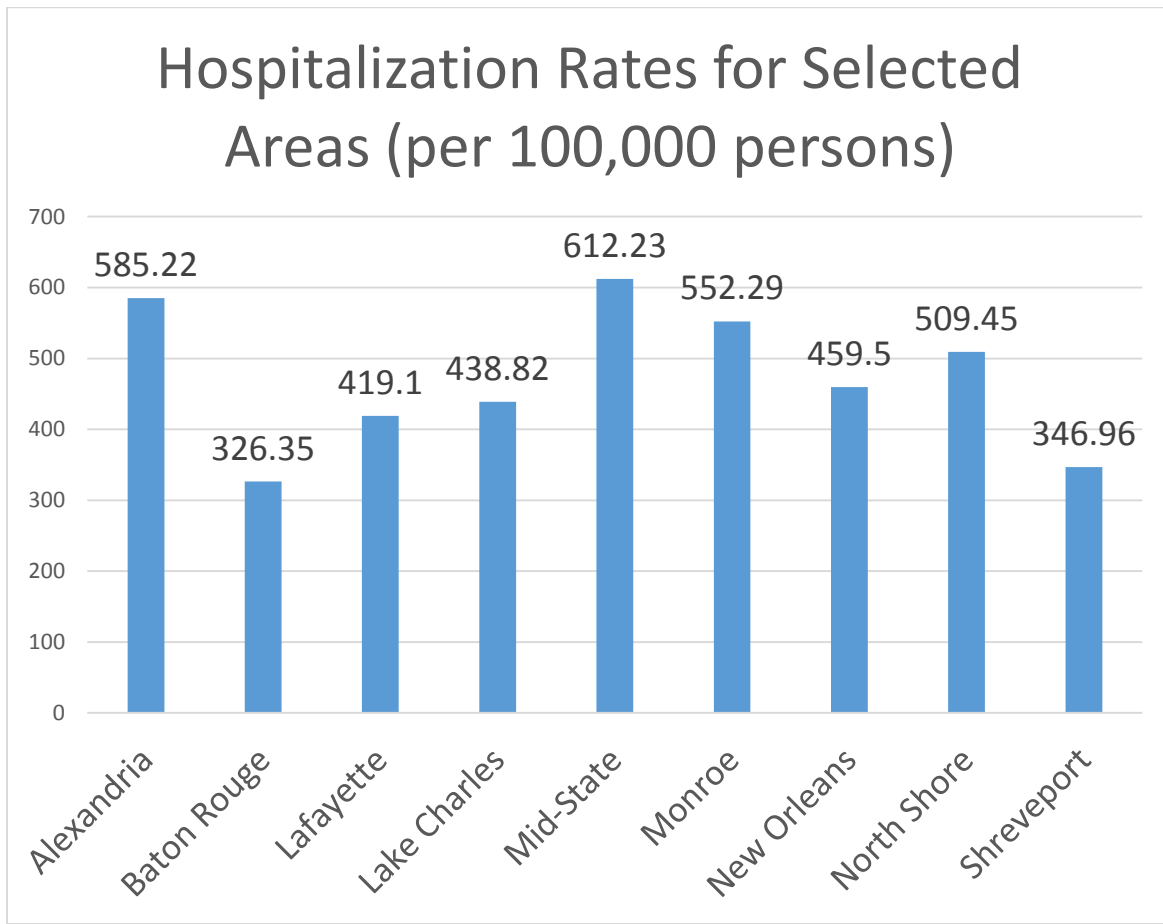


Figure 14 A bar graph documenting hospitalization rates per 100,000 with a focus on area.

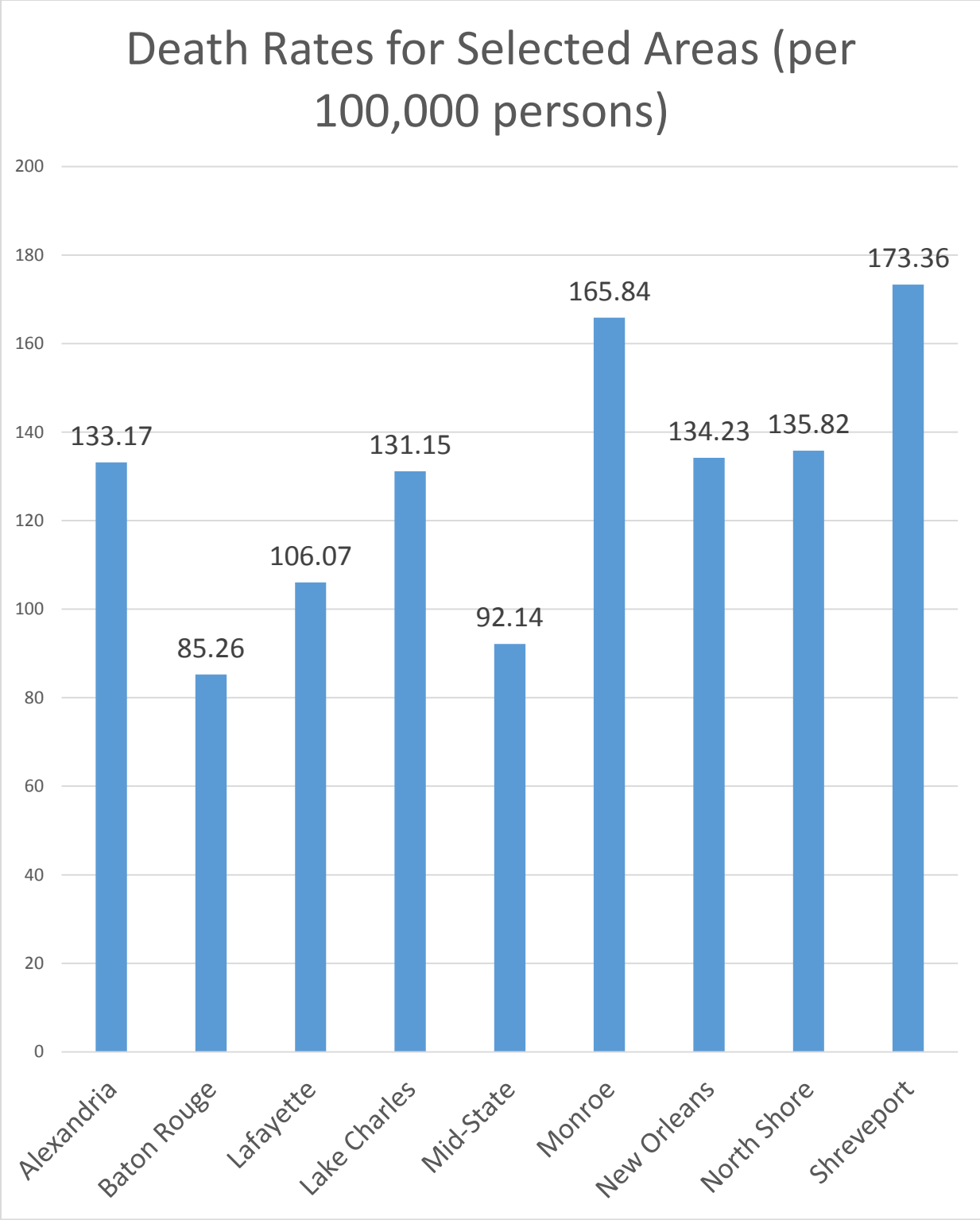


Figure 15 A bar graph documenting mortality rates per 100,000 with a focus on area.

DISCUSSION

The results suggest that many occupations and toxic agents contribute to both PD hospitalization and mortality. The possibility of a single exposure contributing to the etiology of PD cannot be ruled out. However, the results indicate that a multifactorial approach to examining PD can aid researchers in adding or subtracting causative factors. Geography appears to play a key role in the etiology of PD. The use of ArcGIS as a tool to evaluate spatial distributions is critical in examining PD as an environmental disease. Performing studies at an area level rather than an individual one appears to contradict the notion that exposure to one pesticide or toxic agent alone contributes significantly to the etiology of PD. In the occupational assessment, it is important to note that calculating the Standard Mortality Ratio (SMR) would have been a more effective way to analyze this data if the dataset included how many years an individual was employed at their workplace. However, without any knowledge regarding longevity of employment at a particular occupation, it was not possible to calculate the aforementioned ratios.

While there are many correlative factors associated with PD, the results indicate that no single factor directly causes PD. Moreover, it appears that there may be synergistic effects amongst multiple exposures that may be contributing to the onset, incidence, and prevalence of PD. Based on hospitalization records, the results suggest that early onset PD may be a problem in the state of Louisiana. The early onset incidence rate of PD per 100,000 persons in Louisiana is over twice the national average of the United States (3.24 to 1.50, respectively). However, it is important to note the national average of incidence for early onset PD per 100,000 persons is merely an estimation, which compromises its validity as a true rate (Roze 2006). The key motor symptoms of PD remain undertreated and unrecognized (Chaudhiri 2006). The incidence rate of 1.5 per 100,000 persons for the United States may be a gross underestimation of the true rate.

There may be a wide variety of reasons for underdiagnosis of early onset PD. Researcher Leslie Findley studied over 20,000 patients with and without PD and compared their healthcare costs. Cost of healthcare may be a prohibitive factor in the diagnosis of early onset PD, as patients of lower socioeconomic status may not be able to explore the option of seeking treatment for motor function disorders like PD. Patients without PD paid a total annual direct cost of \$11, 247 compared to \$23,101 for patients with PD (Findley 2007). Additionally, screening tools for PD are in their infant stages scientifically, as the first NMS (non-motor symptom) screening questionnaire was developed in 2006 (Chaudhuri et al. 2006). It is reasonable to assume that different medical institutions in the United States vary in their diagnostic practices for recognizing early onset PD. Therefore, early onset PD symptoms may be more or less prevalent depending on an individual's geography. As expected, the category exceeding 80 years of age had the highest number of total individuals hospitalized with PD. Most neurodegenerative diseases increase in risk with an increase in age.

When the hospitalization records were broken down by parish, it was assumed that the parishes with the highest total populations would be the most likely to have the highest total number of patients with PD. This was not always the case. Examining the top 4 parishes in terms of total patients hospitalized with PD, all of them had one common denominator: location near a major water source (the Mississippi River and Lake Pontchartrain, respectively). Private wells suspected to be contaminated with various pesticides were associated with elevated risk of PD in California (Gatto et al. 2009). While the Mississippi River and Lake Pontchartrain may be contaminated with pesticides, it would be difficult to pinpoint either the source of this problem or quantify exposures. The study performed in California found that risk for PD was higher when exposed to more than 4 organophosphate pesticides and more than 8 water soluble pesticides

(Gatto et al. 2009). The Mississippi River touches 11 different states in the U.S., all of which have industry located near the river banks. It is possible that agricultural runoff also plays a role in the development of PD in Louisiana. The state contains the drainage basin into the Gulf of Mexico (making it the southernmost state through in which the Mississippi River runs), therefore making it susceptible to receiving contamination from the other 10 states that border the Mississippi River. Three out of the 4 parishes with the highest number of hospitalization (Orleans, Jefferson, and St. Tammany, respectively) are located on Lake Pontchartrain. Lake Pontchartrain, a brackish water lagoon located north of New Orleans, experiences annual variations in salinity as high as 8 ppt (parts per thousand) (Sikora and Kjerfve 1985). A study on a harpacticoid copepod demonstrated a significant statistical interaction between salinity and pesticide exposure on the copepod's survival (Staton et al. 2002). Based on the two aforementioned pieces of information, it is possible that exposure to other contaminants associated with brackish water in addition to pesticides may play a role in the etiology of PD.

The map highlighting the odds ratios for hospitalizations attributed to PD (see Figure 3) suggests that the northern half of Louisiana may be at more risk for PD than the southern half of the state. With many data limitations, odds ratios were compiled to calculate a crude estimate for further investigation into potential geographical risk factors for PD. It was later recognized that odds ratios were the incorrect way to provide estimates and in hindsight, a chi-square test would have been a more appropriate form of calculation given these circumstances. Without a valid control group (i.e a group of individuals with an unrelated disease such as hepatocellular carcinoma), odds ratio compilation fails to indicate whether a given population is at increased risk for hospitalization with PD. When a nominal predictor variable and a nominal response variable are present, a chi square test is an appropriate statistic (Lehman et al. 2013). With a

nominal predictor variable of Louisiana geographic region (more specifically, parish) and a nominal response variable of hospitalization with PD, a chi square test would have provided a more accurate statistical association than a compilation of an odds ratio. Thus, it is difficult to recognize any associations between hospitalizations with PD and geographic risk factors based on the parish Odds Ratio analysis (see Figure 4).

Like the hospitalization records, the mortality records indicate that as age increases, risk of death with PD increases. However, unlike the hospitalization records, the mortality records indicate that residents of Louisiana are not at increased risk for early complications from PD (in this case, death). This may be attributed to access to healthcare or drug induced treatments for PD. Levodopa, a common drug used to treat PD by slowing dopaminergic cell death, may increase lifespan by 5 years in younger patients (Clarke 1995). With early onset PD appearing to be an issue (see Figure 1), early clinical diagnosis of PD in Louisiana may increase lifespan by administering Levodopa to these young patients. However, this dataset has its limitations. As patients age, it becomes increasingly difficult to attribute mortality to PD. Older patients with PD become less mobile and at increased risk for aspiration (Hely et al. 1999). This subjects the older patients to pneumonia, the most frequent cause of death in patients with PD (Wermuth et al. 1995). Additionally, death certificates are not always satisfactory ways of evaluating the clinical picture (Hoehn and Yahr 2012). The underlying cause provided on the death certificate must be evaluated in conjunction with the mode of dying and the immediate cause of death. Because the majority of patients die with PD and not from the disease, it is critical to evaluate all of the aforementioned information collectively. Unfortunately, the 5,519 mortality records were not evaluated with this approach due to limitations in accessibility of clinical records. For future

studies, it is important to evaluate all diseases that may be associated with PD in order to be more definitive in discerning cause and effect.

When broken down by parish, the mortality records indicated that larger total populations have more deaths associated with PD. The 5 parishes with the highest number of deaths with PD all had total populations exceeding 100,000 individuals according to the 2010 U.S. Census Data. Four out of these 5 parishes are located near the Mississippi River and Lake Pontchartrain, much like the hospitalization records. After evaluating these mortality records by parish, occupational related data was examined. The data (see Figure 6) demonstrated that many individuals who died with PD and listed their occupations as oil-related work were concentrated in the southern portion of Louisiana. According to the USGS (Marsalis et al. 2000), 24 out of the 30 crude oil refineries operate in the southern half of Louisiana. Studies have suggested a relationship between manganese, an abundant element in the oil and gas industry, and PD (Jankovic 2001). Neurologic toxicity from manganese exposure was first documented in 1837 when five workers in a manganese ore grinding plant in France developed a variety of symptoms such as low-volume speech, drooling, and loss of facial expression (Couper 1837). Even after being removed from the environment for 7 years, 2 of these 5 workers complained of uncharacteristic abnormalities in gait (Couper 1837). In one study, 46 percent of workers with alleged occupational exposure to manganese showed changes in the globus pallidus with no other neurological symptoms (Kim and Yang 1999). There may be a relationship between individuals in the oil industry and mortality with PD via chronic manganese exposure. However, without adequate exposure data, it is not possible to definitively conclude that manganese is an etiological element responsible for individuals' mortality with PD in the oil industry.

In a meta-analysis examining 12 separate studies regarding farming and its relationship to PD, the researchers found that farming or living on a farm can significantly increase the risk of getting PD (Priyadarshi et al. 2001). However, 2 studies in the analysis reported a negative association between farming and PD (Semchuk et al. 1991, Chan et al. 1998). These two studies were performed in countries outside the United States: Canada and China, respectively. Different farming practices may have played a role in a decreased risk in PD rates. Agricultural pesticides have been associated with increased PD mortality in the United States (Ritz and Yu 1999). Therefore, differential pesticide use between the United States and other countries may be the contributing factor to increased rates of PD in the U.S.

In the present work, a large absence of mortality in farmers with PD was noted (see Figure 7). Because of data limitations, exposures could not be assessed in agricultural regions of Louisiana. When investigating a relationship between farming and PD, it is critical to have exposure data such as types and quantities of pesticides used on the farms and acreage of these farms. While mortality in a given parish may be low, it is possible that one or a few farmers control most of the farm acreage. Studies documenting a positive relationship between agricultural pesticide use and PD (Costello et al. 2009) relied on PUR (Pesticide Use Reporting) data and land use maps to estimate potentially hazardous exposures. Such data was not readily available in the state of Louisiana. The only parish in Louisiana with a significantly increased risk was Tangipahoa parish. Tangipahoa parish is the host of Ponchatoula Strawberry festival (Carmon 2007) and is Louisiana's leading producer of strawberries (LSUAgCenter 2012). Bromomethane is a commonly used pesticides on strawberries (Wilhelm and Paulus 1980). Quantitative evidence linking bromomethane exposure and negative neurotoxic effects is limited (United States Department of Health and Human Services (1992). There is no evidence linking

pesticides used on strawberries and increased risk of PD development. Therefore, without adequate exposure data, evidence remains inconclusive regarding association between farming and increased risk of PD in Louisiana.

Analyses of the NASS crop cover data and geocoded residential addresses from the PD mortality records did not provide clear answers. Paraquat, a pesticide known to be associated with increased risk of PD (Gatto et al. 2009), is applied to cotton in Louisiana. Aerial application of paraquat was found to be non-toxic to pilots, ground-crew members, and downwind bystanders in a California study on cotton (Chester and Ward 1984). Atrazine is an extensively-used herbicide and virtually the entire production volume is released to the environment as a result of agricultural practices (United States Department of Health and Human Services 1992). In addition to paraquat, atrazine is a commonly used herbicide on cotton (Zablotowicz 1970). Human data is insufficient to support a claim that there is a relationship between atrazine and increased risk of PD. However, a study performed on rats suggests that exposure to atrazine decreases dopamine levels by interfering with vesicular storage and/or cellular uptake of dopamine (Filipov et al. 2007). It is not yet possible to definitively link atrazine exposure and increased risk of PD but more research may provide fruitful information regarding this relationship. While rice and sugarcane crops are sparsely distributed throughout the northern half of Louisiana, the majority of these crops' acreage is concentrated in the southern part of the state (see Figure 10). A cluster of PD mortalities exists in Lafayette parish between a significant amount of rice and sugarcane crop coverage, respectively. It is possible that indirect exposure to both of these crops simultaneously have a relationship to PD mortality. However, it is more likely that the clustering of cases in Lafayette parish is attributed to a high total population. Significant amount of clustering was observed near two major water sources in Louisiana: the

Mississippi River and Lake Pontchartrain, respectively (see Figure 10). Also, significant sugarcane crop coverage exists on the banks of the Mississippi River across from East Baton Rouge parish, an area with a high number of PD mortalities. Like cotton, atrazine is also used on sugarcane (United States Department of Health and Human Services 1992). Atrazine was one of the most frequently detected pesticides in surface water in a study performed in south Florida canals from 1991 to 1995 (Miles and Pfeuffer 1996). While water treatment facilities may eliminate a majority of pesticides present in public drinking water, this information further demonstrates the need to investigate atrazine as a potential risk factor for PD. When examining Lake Pontchartrain and PD mortalities, it is important to note that many of the geocoded deaths are concentrated in close proximity to the lake itself. This may be a function of where a majority of the respective parish's total population resides; however, there is a noticeable decrease in mortalities as distance away from Lake Pontchartrain increases. Lake Pontchartrain is one of the southernmost bodies of water accumulating drainage from the Mississippi River. Researchers demonstrated that PD risk increases when exposed to more than 2 pesticides (Gatto et al. 2009). Combining the two aforementioned statements, it is reasonable to hypothesize that individuals residing near Lake Pontchartrain may be at increased risk of PD mortality because of multiple toxic agents flowing from northern areas via the Mississippi River.

The Mississippi River also has two naval bases that are located on it: NSA New Orleans and JRB New Orleans. Naval ships frequently paint with a lead-based paint (McCallum 1963). Although some mechanisms by which lead exerts its neurotoxic effects are not well understood, it is well documented that is harmful to the central nervous system (Silbergeld 1992). A study examining lead and its neurotoxic effects determined that chronic occupational exposure to lead (>20 years) was associated with PD (Gorell et al. 1999). While a relationship between lead-based

paints used in naval shipyards and PD prevalence has not been documented, it is possible for these workers, depending on longevity of employment, to be at increased risk for PD.

Although there is limited evidence suggesting a link between paper mills and PD, significant amount of clustering occurs in 3 parishes containing paper mills (see Figure 11). Without adequate exposure data, it is not possible to conclude whether a toxic agent affiliated with paper mills is contributing to PD mortality. Diphenyl (or biphenyl) has been implicated as a chemical associated with paper mills that may be contributing to PD mortality (Wastensson et al. 2006). Diphenyl was originally a chemical added to plastics that made them difficult to burn (United States Department of Health and Human Services 1992). Neurotoxic effects of diphenyl have been primarily evidenced by orally dosed laboratory animals (United States Department of Health and Human Services). More human based evidence is needed before concluding that diphenyl exposed paper mill workers are at increased risk for PD mortality. The chi-square analysis performed demonstrates that there is a significant difference in PD mortality between zip codes with paper mills and zip codes without paper mills ($P < .05$) (see Figure 11). However, this analysis alone does not provide sufficient evidence that paper mills are indirectly contributing to PD mortality in every zip code with a paper mill. Epidemiological evidence suggests that work history in paper/lumber mills may be associated with an increased risk of PD (Dhillon et al. 2008). This study demonstrated a need for more long term studies examining the relationship between paper mill employment, associated chemicals and pesticides and PD.

The homemaker/housewife relationship to PD is not cited in the literature. It is a difficult occupation to assess, as it is not clear as to the nature of the profession. A significant number of mortalities were in this category. There may be toxic agents in the home that are associated with

PD. However, it is not appropriate at this time to make any assumptions as to why this total mortality number was exceedingly high.

While they are an outcome of normal aerobic cellular metabolism, excess amounts of free radicals may lead to neurodegeneration (Uttara et al. 2009). Natural resources such as radon produce free radicals and release them into the environment (Uttara et al. 2009). Although less than 1 percent of homes have radon levels that require owners to take immediate action, chronically breathing it in is dangerous (Merrill 1994). The relationship between excess free radical production attributed to radon and PD has not been determined. However, it may be worth investigating this relationship as it relates to Louisiana.

Hospitalization for PD and mortality rates associated with PD per 100,000 persons were analyzed. It is important to note that only 2 of the 9 areas were above the state averages for both hospitalization and mortality rates (Alexandria and Monroe, respectively) (see Figures 14 and 15). It is difficult to definitively pinpoint the reason behind these rates. A factor that may play a role is access to adequate health care. For the hospitalization rates, it is possible that PD is underdiagnosed in areas with rates lower than the average for the entire state of Louisiana. This may play a role when assessing PD mortality rates per 100,000, as a number of individuals may die with PD that are not accounted for. A majority of the areas in the assessment were inconsistently above or below the state average per 100,000 persons between the hospitalization and mortality records. Areas above average for hospitalization records but below average for death records may be attributed to migration to better health care. In other words, an individual may be hospitalized in a given area but die in a different one. Likewise, an area below the state average for hospitalization but above average for mortality may also be attributed to health care. Individuals may seek care from nursing homes in adjacent parishes or may seek help from family

members in parishes outside of the one in which they were hospitalized. All 64 parishes were not included in this regional assessment. Parishes not examined in this assessment may prove to be areas of concern and may need to be investigated further.

When combining data from this multifactorial analysis, it should be noted that no factor alone contributes to the onset, progression, hospitalization, or mortality attributed to PD. In fact, evidence suggests that synergy may exist within industry. Due to a large amount of clustering and high hospitalization and mortality rates in major cities, it is possible that exposure to a number of toxic agents may put individuals at increased risk for PD. Future studies should pay careful attention to the issue regarding geography and its relationship to PD. Proximity to multiple potentially hazardous industries may further the hypothesis of PD as a multifactorial disease. Familial PD is not highly prevalent, which furthers the idea of PD as an environmental disease (Ward et al. 1983). More ecological studies may provide more clues to factors that contribute to PD. A significant number of data limitations prohibited more exposure-based assessments in this multifactorial analysis. Obtaining PUR (Pesticide Use Reporting) data may strengthen the notion that agricultural pesticides increase risk of PD. Water quality data also may play a role in discovering which toxic agents are most heavily associated with PD. Other potential factors that should be examined in future multifactorial analyses include SES (socioeconomic status) and access to health care. Because there is a lack of consensus in the literature as to the factors causing PD, it is imperative to use more multifactorial approaches that incorporate experts from a variety of fields to better understand this disease contributing to a decrease in quality of life for millions of people in the United States.

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VITA

Max Miller, a native of Katy, Texas, received his bachelor's degree at Tulane University in New Orleans, Louisiana in 2012. Thereafter, he went to pursue his master's degree in Baton Rouge, Louisiana at Louisiana State University in the School of the Coast and the Environment in August of 2012. He expects to receive his master's degree in May 2014 and will matriculate to Louisiana State University Health Sciences Center to pursue a master's degree in Public Health.