

# AN EPIDEMIOLOGIC ANALYSIS OF SARCOIDOSIS IN NORTH CAROLINA

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## ABSTRACT

Sarcoidosis is a rare, complex inflammatory chronic condition that commonly affects the lymphatic system and the lungs. The clinical course of sarcoidosis can vary from acute to progressively chronic conditions including organ dysfunction, other comorbidities and even death. The etiology of sarcoidosis remains largely unknown and there is no cure. Risk factors includes being African American or black race, low socio-economic status, unhealthy lifestyle behavior, and a history of environmental/occupational exposures to antigens. In the U.S., the mortality rate of sarcoidosis is 10 to 11 times higher among African Americans compared to whites. North Carolina (NC) ranks fourth in the nation with the highest sarcoidosis mortality rates. Despite these facts, little published research is available, and no studies have explored the epidemiology of sarcoidosis mortality of NC using a population-based approach. Sarcoidosis in NC is an important public health concern that needs to be further investigated.

The overarching aims of this project were to examine sarcoidosis mortality using an applied, public health practice approach. The primary objectives of this study were multifaceted, including, 1) synthesizing relevant literature to examine the relationship between increased risk of physician diagnosed sarcoidosis and exposures to respirable particles; 2) detecting spatial

clusters or hotspots of sarcoidosis deaths; 3) evaluating sarcoidosis mortality risk factors and their spatial-temporal distribution in NC; 4) determining common demographic and clinical characteristics among sarcoidosis patients in the East Carolina University Sarcoidosis Patients Registry (ECUSaR); and 5) developing information brochure for ECUSaR .

Systematic review and meta-analysis were used to synthesize literature and examine the association between exposure to respirable particles and physician diagnosed sarcoidosis. Spatial distributions of sarcoidosis mortality risk factors, County-level analysis of sarcoidosis mortality clustering, and outlier analysis were performed. To assess the factors associated with observed spatial temporal mortality patterns, a multivariate linear regression model with region, percent of Africa Americans, percent of people working in nature, percent of obese adults and average annual ambient PM<sub>2.5</sub> as predictor variables was conducted. Descriptive statistics were conducted to explore sociodemographic and clinical characteristics of sarcoidosis patients in ECUSaR.

Although the pooled risk estimated from meta-analysis showed an increase in risk among those exposed to respirable particles compared to the unexposed (odds ratio (OR)=2.18, 95% confidence interval (CI) =0.79 – 5.79), the estimated risk was not statistically significant. Eastern NC had higher sarcoidosis mortality rate (1.16 per 100,000) compared to Piedmont (0.49 per 100,000) and Western (0.32 per 100,000) regions. Statistically significant sarcoidosis mortality clusters were detected in Eastern NC with p-value <0.001 for Global Moran's I. Similarly, associated sociodemographic (percent of African Americans, p-value <0.001, percent of obese adults, p-value <0.001) and environmental (percent working in nature, p-value <0.001) sarcoidosis risk factors were more prevalent in Eastern NC compared to Piedmont and Western regions. Region and percent of African American population were statistically significant predictors of sarcoidosis mortality. Results from the ECUSaR registry identified that most

patients were of African American (85.4%) decent, and females accounted for 67.5% of all patients. Body mass index (BMI) was higher among females than males (median =33, Q1 (25<sup>th</sup> percentile) = 27.6 and Q3 (75<sup>th</sup> percentile) = 39.1 and median =29, Q1= 24.6 and Q3 = 32.2, respectively). Approximately 42% of patients had restricted lung function which was indicative of majority of patients (>95 %) presenting with pulmonary sarcoidosis.

This dissertation advances the field of public health by describing the epidemiology of sarcoidosis mortality, associated risk factors, demographic, spatial, temporal, and clinical characteristics of sarcoidosis in NC. Evidently, Eastern NC region disproportionately bears the largest sarcoidosis mortality burden in the state. This disproportionality could be explained by the prevalence of associated sociodemographic and environmental risk factors in the region. More robust studies that are directed towards uncovering and explaining the patterns that this study has identified may help understand better and develop strategies to minimize sarcoidosis burden in the region.



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In Partial Fulfillment of the Requirements for the Degree

Doctor of Public Health

by

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## **DEDICATION**

I would like to genuinely dedicate my dissertation to my loving and supportive family, my son, my mother, and siblings. A special feeling of gratefulness to my mom for her unwavering support and words of encouragement and constant push for tenacity throughout my academic journey. I also dedicate this dissertation to my friends who have continuously sent their words of support and encouragement throughout the process.

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6-Minute Walk Distance (6MWD) .....	87
ADP-ribosylation factor-like GTPase 11 - ARL11.....	51
body mass index - BMI .....	38
Centers for Disease Control and Prevention, Wide-ranging ONline Data for Epidemiologic Research - CDC WONDER.....	20
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## CHAPTER 1: INTRODUCTION

Sarcoidosis is a rare, inflammatory multisystem condition characterized by the presence of noncaseating granulomas in affected organs (Liu et al., 2016). In over 90% of sarcoidosis cases, the most common bodily organs affected are the lungs (ATS, 1999). Other organs commonly involved includes the eyes, skin, liver, and extra-thoracic lymph nodes (Baughman et al., 2001; Judson et al., 2012). While several risk factors associated with granulomatous diseases have been identified, causative factors that influence sarcoidosis continues to remain speculative. In environmental studies, exposures to mycobacterium and certain species of fungi through inhalation have been shown to increase the development of granulomatous inflammation (Ehlers & Schaible, 2013; Zumla & James, 1996). In another study of environmental and occupational exposures, Judson indicated an increased risk of sarcoidosis and inhalation of bioaerosols, respirable dust, and metals (Judson, 2020).

Globally, the prevalence rate of sarcoidosis is estimated at 12.5 cases per 100,000 persons, and ranging between 3-10 cases per 100,000 in European populations to 35-80 cases per 100,000 among African American populations (Orphanet, 2019). Over the past few years, several studies have highlighted increasing sarcoidosis-related mortality (Hanley et al., 2011; Kearney et al., 2019; Swigris et al., 2011; Yoon et al., 2018).

Over the past decade, emerging clinical research studies have provided increased knowledge on this topic. Nevertheless, the etiology of the disease remains largely speculative. Several health researchers provide suggestive evidence that environmental/occupational exposures are major risk factors related to the pathogenesis of the disease, but many questions remain. The continuing upward trend in sarcoidosis deaths are an important public health topic. Whether these increases are due to improvements in identification, diagnosis, and/or severity of

environmental or occupational exposures needs to be further explored.

In Summary, while sarcoidosis is an important public health topic, more research is needed to better understand this disease and associated risk factors. The use of applied epidemiology and other public health surveillance techniques is beneficial for detecting mortality clusters, assessing trends, and evaluating population health. Results from this research may provide public health officials and healthcare providers increased knowledge and understanding while serving as a springboard for more in-depth, future studies.

### **Study Significance**

NC is among the leading states with the highest number of individuals with physician diagnosed sarcoidosis, ranking fourth in the highest age-adjusted mortality rates of sarcoidosis deaths in the nation. The Eastern rural region of NC is an ideal area to explore the epidemiology of sarcoidosis. This region suffers from tremendous health disparities, which include the highest percent of the African American population in the state, a high poverty rate, and a large percent of low wage jobs (i.e., agriculture and manufacturing) that may increase risk of environmental and occupational exposures (*Center for Health Disparities*, n.d.; NCDHHS, 2018; NCIOM, 2020). Given these potential risk factors, there has been little epidemiologic related research to evaluate the spatiotemporal trends of sarcoidosis deaths in NC.

In 2018, the East Carolina University Sarcoidosis Patients Registry (ECUSaR), longitudinal registry was created with the purpose of gathering data to learn more about the disease. The registry database includes demographic, clinical and radiographic, and other patient data and information. The ECUSaR registry database has not been fully explored to examine patient demographics and associations with patients clinical characteristics. A descriptive study to analyze this data could provide meaningful results on the demographic and

clinical characteristics of patients served in the clinic so that clinicians are better informed about offering available therapies, improving the quality and efficiency of care, and improving the quality of life of patients.

Most published findings on sarcoidosis have focused primarily on factors related to either clinical aspects or underlying mechanisms of the disease. Given that this type of research is of critical importance and offers tremendous benefits in establishing causation, there has been little in the published research that has evaluated sarcoidosis and possible risk factors from a public health surveillance approach. By taking an applied public health approach and using tools such as GIS to examine spatial-temporal trends may offer public health epidemiologists, clinicians, and researchers an increased understanding of the morbidity and mortality of this disease across NC. Findings of this research begin to lay the groundwork for more in-depth epidemiologic studies to investigate possible risk factors, while also providing groundwork for increased screening and early diagnosis for better health outcomes among high-risk groups through public awareness campaigns.

While African Americans or Blacks are at the highest risk of developing sarcoidosis, they also comprise most of the patients seen in ECU sarcoidosis clinic. Patients seen at the clinic often arrive and are diagnosed in late stages and are unaware of the disease. Eastern NC being largely rural and underserved, significant health disparities such as poverty, lack of access to care, and poor housing so it is important for African Americans and other high-risk populations to be fully aware of the ECU sarcoidosis clinic and the services provided. Identifying unique characteristics associated with sarcoidosis among patients seen in the clinic can assist with improved public health awareness by developing and distributing communication marketing materials (e.g., brochures, website) to targeted populations and areas. Providing information on

the ECUSaR to targeted audiences can raise health awareness and help to educate and inform high risk groups, thus increasing the number of patients screened at the ECU Sarcoidosis clinic to enhance early diagnosis.

### **Study Goal and Objectives**

This dissertation research will evaluate sarcoidosis through the lens of public health with the following specific aims, as follows; 1) synthesizing relevant literature to examine the relationship between increased risk of physician diagnosed sarcoidosis and exposures to respirable particles; 2) detecting spatial clusters or hotspots of sarcoidosis deaths; 3) evaluating sarcoidosis mortality risk factors and their spatial distribution in NC; 4) determining common demographic and clinical characteristics among sarcoidosis patients in the East Carolina University Sarcoidosis Patients Registry (ECUSaR); and 5) developing an information brochure for ECUSaR To carry out these aims, the objectives and research questions (RQ) are as follows.

1. To critically review the literature and construct a meta-analysis to evaluate the risk of developing physician diagnosed sarcoidosis following exposure to respirable particles.

RQ 1: Does exposure to respirable particles increase the measured risk estimate of physician diagnosed sarcoidosis?

2. To investigate and identify sarcoidosis mortality clustering in NC between the years 2000 to 2018 and associated social determinant risk factors.

RQ2: What spatial cluster patterns exist in sarcoidosis mortality in NC between 2000 and 2018?

RQ3: What social determinant of health were associated with sarcoidosis mortality in NC between 2000 and 2018 and was there an overlap between these factors and sarcoidosis mortality clusters?

3. To examine and describe key sociodemographic and clinical characteristics of sarcoidosis patients in the East Carolina University, Sarcoidosis Registry (ECUSaR).

RQ 4: What are the primary demographic characteristics and clinical features among patients and individuals in the ECUSaR database?

### **Theoretical Framework**

The ecosocial theory served as the theoretical framework and approach for this study. Ecosocial theory is a multi-level dynamic perspective, that was first introduced in 1994 to express the evolving and intertwining dimensions of disease patterns and disease distribution. This theoretical framework expresses the importance of interactive systems between host, the environment and social context withing which population health revolves (Krieger, 1994; “Prisoners of the Proximate,” 2017; Susser & Susser, 1996). The theory seeks to guide researchers in generating integral principles to guide epidemiological inquiry and action.

Ecosocial theory fosters examination and analysis of changing population health patterns, disease, and wellbeing in lieu of biological, ecological, and social organization (Krieger, 2001). In this study, the theory guided the identification of sarcoidosis mortality patterns in NC. Additionally, the study sought to explore associated risk factors as identified in literature which ranges from biological, social, and ecological. Focusing on the objective of the study, the ecosocial approach allowed both social and ecological formulation of disease perspectives while integrating biological concepts to better understand the perspectives of sarcoidosis in NC. Using this framework, some of the important epidemiological constructs explored included racial predisposition, socioeconomic sarcoidosis risk factors, environmental hazards and predispositions, social constructs, and access to care.

## CHAPTER 2: LITERATURE REVIEW

### History of Sarcoidosis

The clinical definition of sarcoidosis dates back about one and a half centuries ago. The first clinically diagnosed sarcoidosis case was a 58-years-old coal worker at the Blackfriars Hospital for Diseases of the Skin in London (Spagnolo, 2015a). The patient visited Dr. Jonathan Hutchinson, who is described as a very distinguished medical consultant of all times (Spagnolo, 2015a). The patient complained of purple skin plaques on the hands and legs that had developed over two years. In the following years, Hutchinson observed more similar cases and described the lesions as a “form of skin disease which has – hitherto escaped special recognition” (Sharma, 2005). During this time, sarcoidosis was considered a dermatological curiosity, probably because the cases presented had characteristics of cutaneous sarcoidosis (Sharma, 2005).

In 1889, a French dermatologist, Ernest Besnier, described purplish swellings on a patient's ears, nose, and fingers which he called “lupus pernio” (Spagnolo, 2015). About 10 years after, a Norwegian dermatologist, Caeser Boeck, described a patient with “multiple benign sarkoid of the skin” and related it to Hutchinson’s “Mortimer’s malady”. Boeck described the lesions as sarcoid due to their resemblance to sarcoma (Spagnolo, 2015). Boeck also described the granulomatous histology of the disease. He published other works that described other forms of the disease involving the lungs, bone, lymph nodes, spleen, conjunctiva, and nasal membrane (Hem, 1999).

Over the following years, the disease gained considerable attention across Europe. There emerged several other sarcoidosis pioneers during those times but the most elucidative and was a clinical medicine professor at the University of Amsterdam (Sharma, 2005). In the 1940s,

Scadding and S. Sherlock at the Hammersmith Hospital in London developed a liver biopsy that became a valuable technique in diagnosing sarcoidosis before bronchoscopy replaced it (Sharma, 2005). In 1953, the ebullient internist and medical historian D.G. James made sarcoidosis a household name when he started the sarcoidosis clinic at the North London hospital which attracted sarcoidologists from across the world (Sharma, 2005). In 1958, D.G. James organized the first sarcoidosis international conference in London.

During the initial stages of understanding the disease, sarcoidosis was considered a dermatologic condition until the discovery of a chest roentgenogram which allowed investigation of lung involvement. Later, the multisystem nature of sarcoidosis was described. Despite the lung being the predominant site of involvement, today it is known that sarcoidosis can affect virtually any organ (Costabel & Hunninghake, 1999; Spagnolo, 2015). The development of noncaseating granulomas is the histologic hallmark of sarcoidosis diagnosis. It is hypothesized that granulomas form in response to pathogens, to limit inflammation, and to protect surrounding tissue (Baughman et al., 2011; Spagnolo, 2015). This inflammation is what causes the deformation of organ structure, tissue injury, and irreversible fibrosis in severe forms of the disease (Bonham et al., 2016).

Advances in immunological, molecular biology, and genetic techniques have led to a better understanding of the disease. Today, a consensus has been achieved that describes sarcoidosis as a disease that results from exposure of genetically susceptible individuals to antigens that trigger a Th1-type cellular immune response with the formation of noncaseating granulomas (Moller et al., 2017). The skin, lungs, and eyes are organs that are in regular contact with environmental agents that could trigger such immunological responses that lead to the development of sarcoidosis. Several studies have suggested that airborne antigens induce an

exuberant immunologic response that results to the immunopathogenesis of sarcoidosis (Moller et al., 2017; Newman et al., 1997; Noor & Knox, 2007; Spagnolo et al., 2008; Spagnolo & Grunewald, 2013; Zissel, 2014).

Today, the etiology and pathogenesis of sarcoidosis remain unknown. This is suggestive of the complexity in terms of exposure and genetic perspectives of sarcoidosis (Moller et al., 2017). Similarly, there are no definitive skin, blood, or imaging diagnostic findings for sarcoidosis. Its diagnosis requires a combination of suggestive clinic and radiological findings, presence of noncaseating granulomas on tissue biopsy, and exclusion of other known causes of granulomatous inflammation (Crouser et al., 2020; “Statement on Sarcoidosis,” 1999)

### **Clinical definition and diagnosis**

Sarcoidosis is a rare disease condition that is characterized by the aberrant formation of granulomas (cellular clumps involved in immune responses and inflammation) in different organs or tissues (Flavell, 2020). International Classification Disease Codes 10 (ICD-10) for sarcoidosis is D86, unspecified sarcoidosis D86.9, sarcoidosis of the lung is D86.0, sarcoidosis of the lymph node is D86.1 and sarcoidosis of other sites is D86.8 (CDC, 2020). There is no definitive diagnostic test for sarcoidosis. The disease can be detected incidentally by chest radiographic abnormalities such as bilateral hilar adenopathy and or reticular opacities before the development of symptoms (“Statement on Sarcoidosis,” 1999). Common presenting respiratory symptoms include cough, dyspnea, and chest pain. These symptoms are frequently accompanied by fatigue, malaise, fever, and weight loss (Judson et al., 2012). Sarcoidosis most frequently involves the lung, but up to 30 percent of patients present with extra-thoracic manifestations of sarcoidosis (James & Judson, 2020; Judson et al., 2012). Diffuse interstitial lung disease with or without mediastinal and hilar lymphadenopathy is the classic pulmonary manifestation of

disease; other less common pulmonary manifestations include pleural thickening and pulmonary hypertension (Judson et al., 2012). The extra-pulmonary manifestations of sarcoidosis involve the heart, nervous system, skin, lymph nodes, eyes, and organs of the digestive system (Judson et al., 2012).

When sarcoidosis is highly suspected the clinician must include these three important features for diagnosis: compatible clinical and radiographic manifestations, exclusion of other diseases such as mycobacterium tuberculosis infection or other fungal infection that may present comparably, and histopathologic detection of noncaseating granulomas (“Statement on Sarcoidosis,” 1999). A comprehensive initial evaluation of the suspected organ should be performed in all patients with suspected sarcoidosis. The purpose of this initial evaluation is to obtain supplementary information supporting the diagnosis of sarcoidosis while eliminating differential diagnoses, characterize the severity of pulmonary impairment, and identify extrapulmonary organ involvement that may be amenable to biopsy or require immediate therapy (Crouser et al., 2020). Indicated aspects of the assessment include a detailed history of presenting illness including occupational and environmental exposures. A clinician should conduct a thorough physical examination especially noting any skin lesions.

The next steps of diagnosis include imaging and laboratory tests. With lung involvement occurring in over 90 percent of sarcoidosis patients (Crouser et al., 2020), pulmonary imaging plays an essential role in the diagnosis of sarcoidosis. Initial imaging includes a chest radiograph, which may be followed by high-resolution computed tomography (HRCT) (Crouser et al., 2020). Typical chest x-ray findings include mediastinal and bilateral hilar adenopathy which may occur with or without lung parenchymal opacities (Judson, 2015; Spagnolo et al., 2011). HRCT scan of the chest is typically obtained to evaluate abnormalities seen on a chest

radiograph and/or to evaluate unexplained dyspnea or cough in a patient with a clear chest radiograph (Spagnolo et al., 2011; “Statement on Sarcoidosis,” 1999). HRCT can detect parenchymal and mediastinal abnormalities that are not seen on a plain chest radiograph (Lynch, 2003; Spagnolo et al., 2011). Lung parenchymal findings on HRCT are varied and include normal, diffuse reticular, nodular, or ground-glass opacities, focal consolidation, and fibrocystic scarring (Lynch, 2003; Shaikh et al., 2020; Spagnolo et al., 2011). These findings usually predominate in the vascular interstitium and along the bronchovascular bundles near the fissures (Lynch, 2003; Spagnolo et al., 2011). Other tests that are employed to assess for severity of respiratory disease and to monitor the course of disease with sequential measurements include pulmonary function tests (PFTs).

PFTs include spirometry, lung volumes, diffusing capacity for carbon monoxide (DLCO), and six-minute walk test (6MWD) (Crouser et al., 2020). However, PFTs are not a reliable means of detecting lung parenchymal sarcoidosis (HRCT is preferred instead) nor do they provide an accurate estimate of the extent of parenchymal disease (Crouser et al., 2020). Additionally, imaging tests such as fluorine-18-fluorodeoxyglucose-positron emission tomography may be used to identify extrapulmonary lesions and has arguably been reported to be better than earlier imaging techniques such as <sup>67</sup> Gallium scintigraphy due to its high resolution images that helps in detection of even smaller lesions (de Prost et al., 2010; Nishiyama et al., 2006). Magnetic resonance imaging (MRI) scan is also used in the evaluation of extrapulmonary sarcoid, such as cardiac sarcoidosis and neurologic sarcoidosis (Crouser et al., 2020).

Bronchoscopy with bronchoalveolar lavage, endobronchial biopsy, transbronchial biopsy and endobronchial ultrasound (EBUS) guided biopsy of the mediastinal and hilar lymph nodes

are traditional methods for the diagnosis of sarcoidosis. Transbronchial lung biopsy has a relatively high yield (50 to 75 percent) among patients suspected of having sarcoidosis based on compatible lung parenchymal findings on HRCT (e.g., beaded or irregular thickening along the bronchovascular bundles) (Descombes et al., 1997); however EBUS biopsy of the mediastinal lymph nodes has emerged as the bronchoscopic diagnostic procedure of choice (von Bartheld et al., 2013). The specimens obtained should be sent for culture and histologic stains for acid-fast bacilli and fungi to rule out *Mycobacterium tuberculosis* and other fungal infections respectively (Descombes et al., 1997).

Laboratory tests employed in the diagnosis of sarcoidosis include complete blood count, liver function tests, blood urea nitrogen, creatinine, glucose, electrolytes, serum calcium, and urinalysis (Crouser et al., 2020; Judson, 2008). Serologic testing for HIV infection should be considered when assessing a patient for sarcoidosis. Inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein are nonspecific measures of inflammation and are variably obtained (Judson, 2008).

### **Organ Manifestations of sarcoidosis**

Sarcoidosis is a systemic condition and can affect any organ in the body. A patient can have one or multiple organs inflamed by sarcoidosis at the same time. The most common presentation of sarcoidosis affecting over 90% of sarcoidosis patients involves the lungs and is therefore referred to as pulmonary sarcoidosis (Rao & Dellaripa, 2013). Sarcoidosis affecting other body organs is referred to as extrapulmonary sarcoidosis. Some of the common organs involved in extrapulmonary sarcoidosis include the eyes, skin, heart, extra-thoracic lymph nodes, brain, and spinal cord. Patterns of organ involvement vary by region. In Japan, ocular (involving eyes) and cardiac (involving the heart) are the most common extra-pulmonary organ

manifestations. In northern Europe, erythema nodosum (involving the skin) and joint symptoms are the most common manifestations observed (Pietinalho et al., 1995). In the US, the most commonly observed extrapulmonary manifestations involve the skin, eyes, and joints (Rybicki et al., 1997).

**i. Pulmonary Sarcoidosis**

Patients with pulmonary sarcoidosis may be asymptomatic or may develop a dry cough, chest discomfort, or dyspnea. A chest radiograph from a pulmonary sarcoidosis patient may show abnormalities which may be categorized into four stages as shown in Figure 1 (Criado et al., 2010). Laboratory testing although not specific for sarcoidosis may indicate increased levels of serum angiotensin-converting enzyme. Similarly, patients may show an increased ratio of CD4+/CD8+ in their bronchoalveolar lavage fluid which is considered a moderately specific test for sarcoidosis diagnosis (Rao & Dellaripa, 2013). Diagnosis is however confirmed by transbronchial or EBUS biopsy showing the presence of noncaseating epithelioid granulomas (Costabel, 1997; “Statement on Sarcoidosis,” 1999).

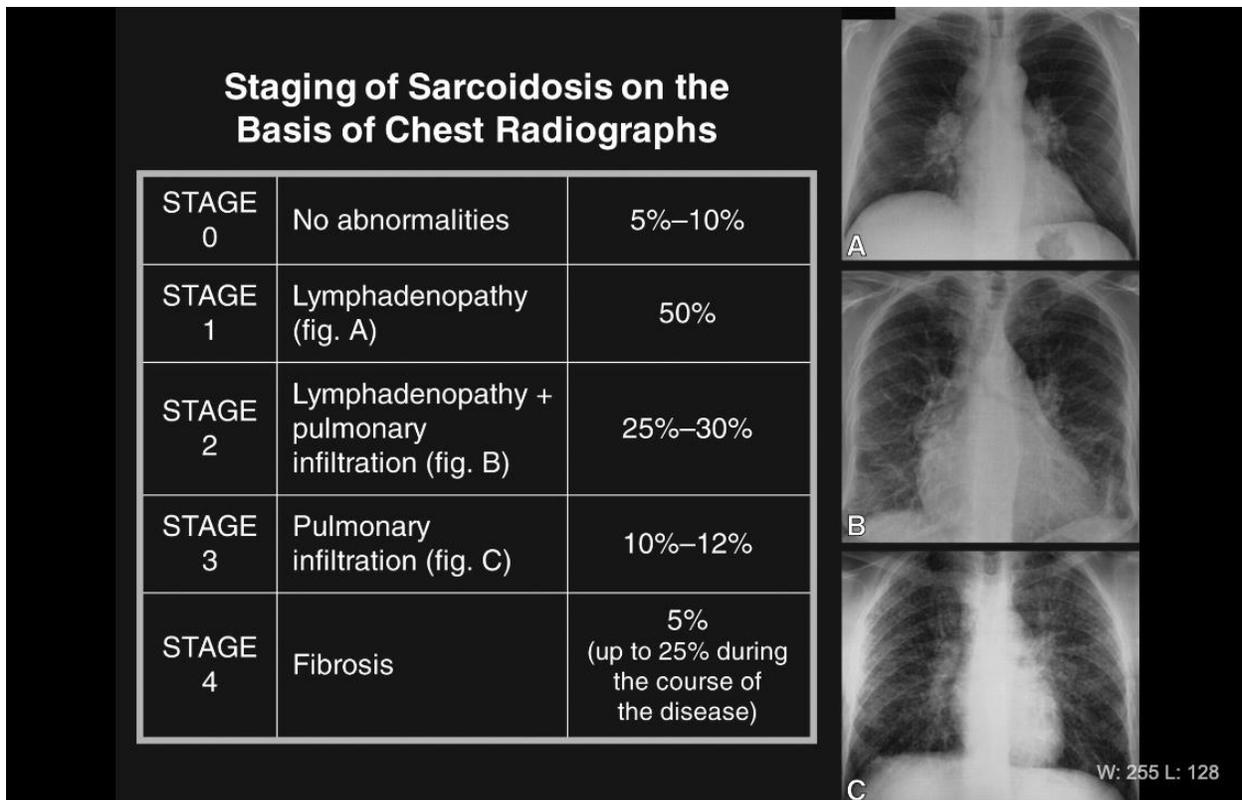


Figure 1. Chest Radiographic Staging showing pulmonary inflammation type and estimated percent of patients presenting with the inflammations.

\*Source: Criado et al., 2010

\*A more elaborate drawing has been attached in Appendix C.

#### **i. Extrapulmonary Sarcoidosis**

Extrapulmonary involvement may occur priorly, concurrently, or after the development of pulmonary sarcoidosis. With the most common types involving the skin, eyes, and the heart, cardiac sarcoidosis is the leading cause of death from sarcoidosis. In the US, cardiac sarcoidosis causes between 13-25 percent of sarcoidosis deaths, while in Japan, cardiac sarcoidosis-related deaths range from 58-85 percent of sarcoidosis deaths (Iwai et al., 1994; Rybicki et al., 1997; Silverman et al., 1978). Approximately 5 percent of sarcoidosis patients in the US show clinical symptoms of cardiac sarcoidosis while as much as 30 percent of autopsy analyses show the presence of myocardial granulomas (Silverman et al., 1978; “Statement on Sarcoidosis,” 1999).

Severe forms of cardiac involvement can cause arrhythmias, atrioventricular block, and dilated cardiomyopathy (Silverman et al., 1978).

Skin or cutaneous sarcoidosis affects 20-35 percent of all sarcoidosis patients (Haimovic et al., 2012). Cutaneous sarcoidosis may be specific or non-specific. Granulomas are found in specific cutaneous sarcoidosis, whereas they are absent in non-specific cutaneous sarcoidosis. Erythema nodosum is the most common nonspecific type (Baughman et al., 2001). The most common forms of skin lesions found in cutaneous sarcoidosis include papular, maculopapular, and plaque lesions (Rao & Dellaripa, 2013). Ocular sarcoidosis is the third most common extrapulmonary manifestation and affects 10-60 percent of sarcoidosis patients (Herbort et al., 2009). Some forms of this ocular sarcoidosis such as uveitis can be vision threatening. Other forms of extrapulmonary sarcoidosis include neurologic, musculoskeletal, gastrointestinal, and renal sarcoidosis (Rao & Dellaripa, 2013).

### **Epidemiology of sarcoidosis**

Sarcoidosis most commonly affects young and middle-aged males and females across all races and ethnicities (Arkema & Cozier, 2018). The exact incidence and prevalence rates of sarcoidosis have been difficult to estimate mainly due to undiagnosed cases, variability in ascertainment, inconsistent case definition, and disease presentation (Cozier, 2016; Erdal et al., 2012). People of African descents such as Afro-Caribbean and African American races are at a higher risk compared to other races (Rybicki et al., 1997). Such differences can be accounted for by differences in genetic susceptibility which is relatable to differences in genetic predisposition (Moller et al., 2017). However, these differences can as well be accounted for by under or over-diagnosis of cases within certain populations or geographical areas (Moller et al., 2017; Orphanet, 2019).

The highest incidence and prevalence of sarcoidosis has been observed among Nordic countries and African Americans. Several studies have provided incidence and prevalence estimates in these populations. In a population-based study that was conducted in Sweden from 2003 to 2012, the incidence of sarcoidosis was estimated to be 11.5 per 100,000 per year and prevalence was 160 per 100,000 (0.16%) (Arkema et al., 2016). In the US, Baughman et al. (2016) estimated the incidences to be 17.8, 8.1, 4.3, and 3.2 per 100,000 per year among African Americans, Whites, Hispanics, and Asians respectively. The study also estimated the prevalence rates to be 141.36, 49.8, 21.66, and 18.94 per 100,000 in those groups respectively. In the nurses' health study, Dumas et al. (2016) estimated the incidence rates to be 43 and 11 per 100,000 per year among African Americans and White women, respectively. Furthermore, this study found prevalence rates of 519 and 92 per 100,000 for African American and White women, respectively. In another study conducted in Olmsted County, Minnesota, USA, the incidence of sarcoidosis was estimated to be 10 per 100,000 per year between 1946 – 2013 (Ungprasert et al., 2017a). The study reported a slightly higher incidence among females (10.5 per 100,000) compared to males (9.4 per 100,000). A study characterizing Black women's health by Cozier et al. (2011) estimated the prevalence rate of sarcoidosis among Black women to be 1,160 per 100,000 and an incidence rate of 71 per 100,000 per year.

In recent years, other studies have described the epidemiology of sarcoidosis in other populations and regions of the world. In 2017, a Taiwanese study reported a prevalence rate of 2.7 per 100,000 (Wu et al., 2017). In France, a study conducted by Duchemann et al. (2017) estimated the incidence and prevalence in Seine-Saint-Denise County to be 4.9 per 100,000 per year and 30.2 per 100,000 respectively. This study included a diverse population which allowed the estimation of incidence rates by geography and ethnicity. Afro-Caribbean ethnic group was

reported to have the highest incidence rate of 16.9 per 100,000, North Africans followed with an incidence rate of 9.7 per 100,000, while Europeans had the lowest rate at 2.4 per 100,000 (Duchemann et al., 2017).

While most patients (70-90 percent) (“Statement on Sarcoidosis,” 1999) experience a benign clinical course of sarcoidosis that resolves spontaneously, a subset of patients (10-30 percent) experience chronic form of the disease which could be life-threatening (“Statement on Sarcoidosis,” 1999). In 2016, Jamilloux et al. (2016) reported an age-standardized mortality rate of 3.6 per 1,000,000 in a study that was conducted by the French Epidemiologic Center for Medical Course of Death. The study also reported that there was an increase in sarcoidosis-related mortality over time. Several studies have also described sarcoidosis mortality in the US, which was similar to rates reported by Jamilloux et al. (2016). Kearney et al. (2019) reported that between 1999 to 2002, the age-adjusted sarcoidosis mortality rate increased from 2.1 to 3.1 deaths per 1,000,000. The study also reported that the deaths among females were slightly higher than males and increased from 2.5 to 3.3 deaths per 1,000,000 for females compared to 1.5 to 2.6 deaths per 1,000,000 for males. In terms of race and ethnicity, the study reported the highest mortality rate among Black females at 17 deaths per 1,000,000 (Kearney et al., 2019). In another study, the reported interstitial lung disease and pulmonary sarcoidosis mortality rate increased from 27 per 1,000,000 in 1980 to 55 per 1,000,000 in 2014 using data from the National Center for Health Statistics (Dwyer-Lindgren et al., 2017). Another similar study using the same data reported a mortality rate of 2.8 per 1,000,000 between 1999 to 2010 (Mirsaeidi et al., 2015). Similar to other studies, the study reported a higher mortality rate among women (3.3) compared to men (2.3). In all the studies, African Americans had a higher mortality rate (16) compared to Caucasians (1.3) (Kearney et al., 2019; Mirsaeidi et al., 2015).

Regionally, the southern region of the US has continuously experienced the highest sarcoidosis mortality rates. According to Kearney et al. (2019), this region had an age-adjusted sarcoidosis mortality rate of 3.7 per 1,000,000 between 1996 and 2016. According to the study, the northeast region had the second-highest rate at 3.1 per 1,000,000, while the Midwest and the Western regions had an average rate of 2.8 and 1.6 per 1,000,000, respectively. Similar results have been reported by other studies (Gideon & Mannino, 1996; Mirsaeidi et al., 2015). Gideon & Mannino (1996) estimated age-adjusted sarcoidosis mortality rates in men to be 1.6 per 1,000,000 and 2.5 per 1,000,000 among women in 1991. Mirsaeidi et al. (2015) estimated the overall age-adjusted sarcoidosis mortality to be 2.8 per 1,000,000 in 2010. Among the states and regions recording some of the highest sarcoidosis mortality rates include District of Columbia, South Carolina, Maryland, and NC at 13.8, 6.6, 5.7, and 5.4 per 1,000,000, respectively (Kearney et al., 2019).

### **Risk factors for sarcoidosis**

The etiology of sarcoidosis is unknown; however, it has been associated with several risk factors including genetic, environmental, occupational, and immunologic factors. In a study conducted in Sweden among iron foundry workers, exposure to silica dust was significantly associated with an increased risk of sarcoidosis (Vihlborg et al., 2017). In similar studies, it was observed that cessation of exposure to silica resulted in regression of sarcoidosis (Drent, Wijnen, et al., 2012; Solà et al., 2009). In Iceland, the incidence rate of sarcoidosis among limestone workers was up to 4 times higher than that of the general population (Rafnsson et al., 1998). Contrary to these studies, a study conducted in Italy evaluating the probable correlation between environmental exposures and the development of sarcoidosis (Beghè et al., 2017) found that

mineral particle air pollution failed to conclusively determine any association between environmental risk and emergence of sarcoidosis.

In the US, studies have associated exposure to dust and other respirable particles to a higher incidence of sarcoidosis among responders and firefighters responding to the World Trade Center (WTC) Attacks on 11 September 2001 (henceforth referred to as 9/11) (Crowley et al., 2011; Jordan et al., 2011; Sunil et al., 2019). In a span of 12 years after 9/11, the fire department of the City of New York reported an age-adjusted incidence rate of sarcoidosis among male rescue/recovery workers of 25 per 100,000 (Webber et al., 2017). Prior to 9/11 (1985 – 1998), the average annual sarcoidosis cases stood at 12.9 per 100,000 (Prezant et al., 1999). It has been hypothesized that particulate matter, fibers, volatile organic pollutants, gases, metal dust, and other combustion byproducts from the World Trade Center fires could be possible antigens that trigger abnormal immune response or inflammation that lead to sarcoidosis as summarized in Table 1 (Liroy et al., 2002).

Table 1. Environmental/Occupational exposure studies and risk factors of sarcoidosis.

<b>Environment /Occupation</b>	<b>Risk/Agent</b>	<b>Reference</b>
Firefighters	Particulate matter, dust	(Prezant et al., 1999)
Emergency response	Inorganic dust, particulate matter	(Prezant et al., 1999)
Office workers	Toner, mold	(Newman et al., 2004)
Miners	Metals, silicates, inorganic dust	(Newman et al., 2004)
Metallurgy	Metals, particulate matter, fluid aerosols, silica	(Jonsson et al., 2019; Vihlborg et al., 2017)
Construction workers	Inorganic dust	(Newman et al., 2004)
Farmers	Pesticides, dust	(Kajdasz et al., 2001; Newman et al., 2004)

Before other hypotheses were proposed, infectious agents were hypothesized to be the cause of sarcoidosis, especially due to its clinical and etiological resemblance to tuberculosis (Saidha et al., 2012). A wide spectrum of bacteria (Gupta et al., 2007; Svendsen et al., 2008; Yamada et al., 2002), viruses (Hofland et al., 2014; Lebbé et al., 1999), and fungi (Stopinšek et al., 2016; Suchankova et al., 2015) have been evaluated in causation studies over the years. The most prominent studies have focused on *Mycobacterium tuberculosis* and *Cutibacterium acnes* (Drake & Newman, 2006; Esteves et al., 2016). However, the mechanisms by which the proposed infectious agent initiates and sustains the granulomatous inflammatory process are still elusive (Drake & Newman, 2006).

Lifestyle factors have as well been hypothesized to be associated with the risk of sarcoidosis. Newman et al. (2004) found out that having ever smoked was associated with a 35% reduction in odds of developing sarcoidosis while current smoking reduced the risk by 66 percent

(Ungprasert et al., 2016). A similar protective effect of ever smoking was observed in a Swedish study among a cohort of construction workers (Carlens et al., 2010). The understanding of this controversial association is still not clear. However, smoking has been found to induce suppression of adaptive immune response thus confer some protection against the disease (Margaritopoulos et al., 2015). Obesity is another lifestyle factor suggested to increase risk of sarcoidosis development. Cozier et al. (2015) identified an increased risk of sarcoidosis among obese individuals (Cozier et al., 2015). In 2017, Dumas et al. also identified body mass index (BMI) as a significant risk factor for sarcoidosis among women (Dumas et al., 2017). Reverse causality has also been suggested. In a study from Olmsted County, Minnesota, individuals were identified to be 2-5 times more likely to be obese around diagnosis compared to control (Ungprasert et al., 2016a). While the inflammatory pathways are poorly understood, dysfunction of adipose tissue among obese individuals is believed to influence immune regulation in the lungs (Harpsøe et al., 2014).

Socioeconomic factors have also been shown to influence sarcoidosis incidence, prevalence, and disease severity. In populations with limited or fewer resources and barriers to access to care, severe sarcoidosis cases are more prevalent (Rabin et al., 2001, 2004). Some of the highlighted socioeconomic factors include income, education, and insurance coverage. Such socioeconomic factors may further compound other known sarcoidosis risk factors such as race and gender. As Rabin et al. (2004) observed, low income was highly correlated with Black race and being female. Similarly, barriers to access to care such as lack of insurance was also correlated to race. Barriers to access to care may delay diagnosis of asymptomatic or mild sarcoidosis cases which could mean that populations where these barriers exist may only get diagnosed with severe cases (Rabin et al., 2004). Consequently, this could result in poor disease

outcomes and could play a role in indicated morbidity and mortality among these at-risk populations.

### **Treatment of Sarcoidosis**

A general principle regarding the treatment of sarcoidosis is that not all patients require immunosuppressive medications or steroids (James & Judson, 2020). Patients with nonacute or no symptoms may only require close monitoring without therapy (Hunninghake et al., 1994; Obi et al., 2021; Rahaghi et al., 2020). For these patients, the disease may resolve spontaneously. On the other hand, patients with cardiac, ocular, neurologic, or severe progressive pulmonary involvement require treatment to manage symptoms and prevent organ dysfunction.

Corticosteroids are the mainstay of therapy in sarcoidosis treatment. Corticosteroids are used for all manifestation of sarcoidosis (Paramothayan & Jones, 2002). While smaller doses usually suffice for other organs, neurologic and cardiac involvement require high doses of corticosteroid treatment. In cases where the patient cannot tolerate steroid therapy or when steroidal therapy cannot be tapered, steroid-sparing therapies such as Methotrexate, chloroquine, and hydroxychloroquine are used (Baughman & Lower, 1997, 1999; James & Baughman, 2018; Obi et al., 2021). Other therapies that are used include anti-tumor necrosis factor antibodies such as infliximab and adalimumab (Murray et al., 2011).

Patients with severe and progressive pulmonary involvement as indicated by lung function tests or radiography are generally treated with systemic corticosteroids (prednisone) at doses ranging from 0.5 to 1 mg/kg (Paramothayan & Jones, 2002; Rahaghi et al., 2020). Doses are usually tapered over the course of treatment and with improvements in pulmonary function or other clinical manifestations. Higher doses of prednisone ranging from 1 to 1.5 mg/kg may be used to treat cardiac inflammation (Dubrey & Falk, 2010). Similar to cardiac sarcoidosis,

neurologic involvement may require higher doses of corticosteroids (1 to 1.5 mg/kg) in addition to close monitoring of MRI abnormalities (Zajicek et al., 1999). Management of cutaneous sarcoidosis may be done by the use of topical or systemic corticosteroids (Haimovic et al., 2012). Ophthalmologic sarcoidosis can either be treated using topical corticosteroids or systemic corticosteroids for patients that do not respond to topical steroids. For patients with renal involvement, management includes caution against high dietary calcium, sun exposure, oxalate intake, and vitamin D supplementation which are involved in the formation of kidney stones. Additional therapies including corticosteroid therapy are used to lower serum calcium (Murray et al., 2011; Singer & Evans, 1986). Unlike in other manifestations, musculoskeletal involvement does not require corticosteroid therapy but rather requires high doses of nonsteroidal anti-inflammatory drugs (NSAIDs) unless adequate control is not achieved (Murray et al., 2011).

## **CHAPTER 3: ENVIRONMENTAL EXPOSURE TO RESPIRABLE PARTICLES AND ESTIMATED RISK OF SARCOIDOSIS - A SYSTEMATIC REVIEW AND META-ANALYSIS (1998-2019)**

### **Introduction**

Sarcoidosis is an autoimmune multisystem disease that commonly presents as noncaseating granulomas in the affected organs (Liu et al., 2016). The most common organ affected in over 90% of the cases is the lungs (ATS, 1999). Over recent years, the incidence of sarcoidosis has increased considerably in the United States and globally. Several studies have highlighted the increasing sarcoidosis related mortality over the past few years (Hanley et al., 2011; Swigris et al., 2011; Yoon et al., 2018).

The disease has no known etiology, but it has been associated with a number of risk factors including genetic, environmental and immunologic factors (Moller et al., 2017). In a study conducted in Sweden among iron foundry workers, exposure to silica dust was significantly associated with risk of sarcoidosis (Vihlborg et al., 2017). In similar studies, it was observed that cessation of exposure to silica resulted to regression of persistent sarcoidosis (Drent et al., 2012; Solà et al., 2009). In Iceland, the incidence rate of sarcoidosis among limestone workers was up to 4 times higher than that of the general population (Rafnsson et al., 1998). However, a study conducted in Italy to investigate the probable correlation between environmental exposures including mineral particle air pollution failed to conclusively determine any association between environmental risk and emergence of sarcoidosis ().

In the US, several research studies have shown an increased incidence of sarcoidosis among emergency responders and firefighters and exposure to dust and other respirable particles (Crowley, Herbert, Moline, Wallenstein, Shukla, Schechter, Skloot, Udasin, Luft, Harrison,

Shapiro, Wong, Sacks, Landrigan, et al., 2011; Jordan et al., 2011; Sunil et al., 2019). Webber and colleagues (2017) found an increased incidence (25 per 100,000) of sarcoidosis among male rescue/recovery workers 12 years after the WTC bombings on September 11, 2001. It has been hypothesized that occupational exposures to varying products and substances, such as particulate matter, fibers, volatile organic pollutants, gases, metal dusts and other combustion byproducts from the WTC fires could be considered etiological factors that trigger inflammation or an abnormal immune response in the body that lead to the development of sarcoidosis disease (Lioy Paul J et al., 2002). Although several studies provide convincing evidence of an association between exposure to respirable particles and sarcoidosis, there has not been a systematic review and meta-analysis published to date to aggregate the evidence.

Systematic reviews are considered the gold standard for evaluating the quality of the available evidence for making informed decisions. The objectives of this study were to 1) critically evaluate the literature related to environmental/occupational exposures of respirable particulate matter (PM), including dust and the association with physician diagnosed sarcoidosis, and 2) construct a meta-analysis to assess the strength of measured effects found from relevant studies. The results of this study will provide a risk estimate of the effect of environmental/occupational exposure to respirable particulate matter including dust and physician diagnosed sarcoidosis.

## **Methods**

### **Search Strategy, Inclusion/Exclusion Criteria**

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement (Page et al., 2021) structured format was used to critically appraise and synthesize the published literature. PRISMA is a 27-item checklist (Appendix D) set of evidence-based items developed as a means of being objective and improving transparency in the reporting of systematic reviews and meta-analyses (Page et al., 2021).

Scientific database search engines were used to identify relevant articles using keywords, titles, and abstracts (Table 2). The search was restricted using the following inclusion criteria published in English, observational studies (i.e., cohort, case analysis/case series, and case-control studies), and published between January 1, 1998, to October 31, 2019. Exclusion criteria were studies that were not published in English, were experimental or intervention (i.e., randomized control trials), and studies outside of the specified inclusion dates. Hand-searching the grey literature and reviewing relevant references from published articles were conducted to

identify additional studies. The following key term, phrases and words were used as part of the electronic search; “respirable particles and sarcoidosis”, “dust and sarcoidosis”, and “particulate matter and sarcoidosis”.

Table 2. Databases Searched

<b>Search Engine Database</b>	<b>Coverage</b>
1. PubMed	1998 to 2019
2. Ovid	1998 to 2019
Medline	1998 to 2019
Embase and Embase Classic	1998 to 2019
3. Scopus	1998 to 2019
4. ProQuest Central	1998 to 2019
5. Google Scholar	1998 to 2019
6. Cochrane Library	1998 to 2019

### **Data Synthesis and Meta-Analysis**

Following a comprehensive literature search and retrieval of all publications that met the inclusion criteria, a thorough review assessment was conducted by one independent reviewer (DW). Papers and reports that met the inclusion criteria and included analytical measures of effect were used for the meta-analysis.

Eligibility criteria for a paper to be included in the meta-analysis were 1) a clearly defined measure of associated risk (i.e., relative risk ratio or odds ratio; 2) ICD 10 classification (D86.0 - sarcoidosis of the lung; D86.1 - sarcoidosis of lymph nodes; D86.2 - sarcoidosis of the lung with sarcoidosis of lymph nodes; D86.3 - sarcoidosis of skin; D86.8 - sarcoidosis of other and combined sites; D86.9 - unspecified sarcoidosis) or noted as a physician-diagnosed sarcoidosis case, and 3) observational by design and included an exposure group, and/or individuals who had prior exposure to respirable dust particles. For the last criteria item, studies had to include a comparison or control group with no prior exposure to respirable dust particles. Case-control studies needed to include matched comparisons (e.g., gender, age, occupation) as applicable to eliminate potential sampling and/or selection bias. Respirable dust particles were defined as particles with an aerodynamic diameter of 10 micrometers ( $\mu\text{m}$ ) or less in size ( $\text{PM}_{10}$  or lesser).

Information and data from the search were conducted in accordance with the PRISMA Statement guidelines and included article title, authors' information, sample size, study population, follow-up time, outcome measure, and estimated risk (risk ratio or odds ratio) where applicable. This study did not meet the human subjects' criteria and was considered exempt by ECU, Institutional Review Board.

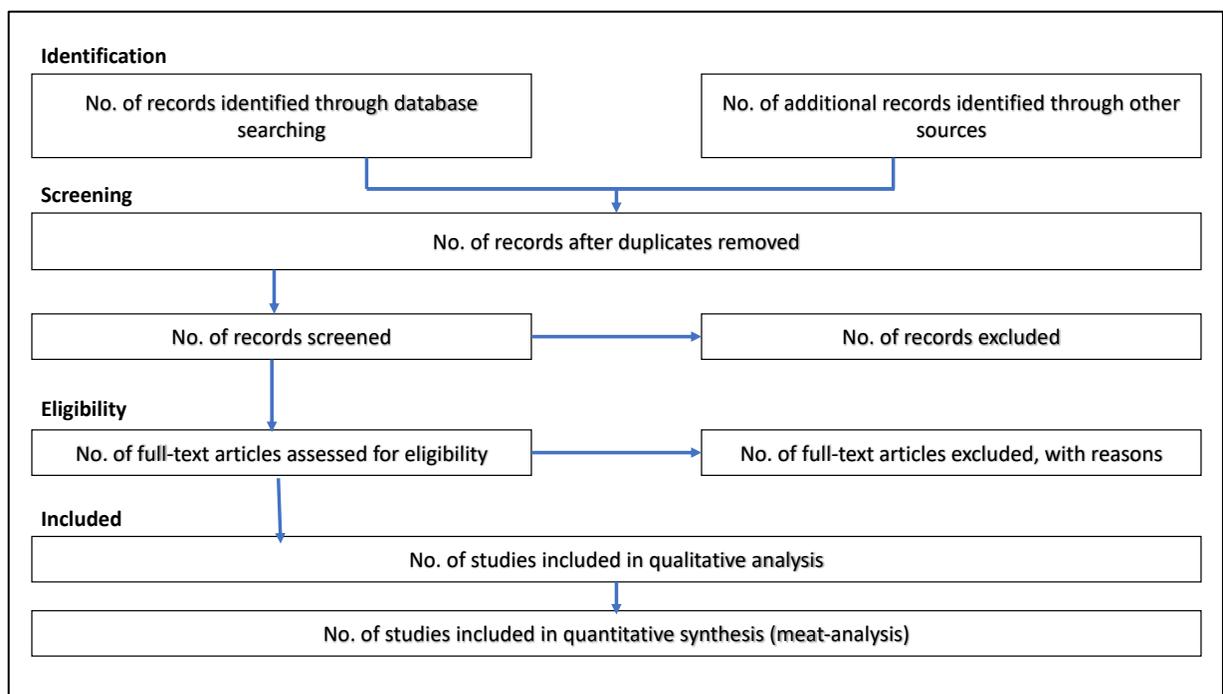


Figure 2. Systematic Review Flow Diagram

\*Adapted from Liberati et al. 2009

## Data analysis

A meta-analysis was conducted using RevMan V5.3 software from the Cochrane Collaboration (London, UK). “Meta-analysis is a quantitative, formal, epidemiological study design used to systematically assess the results of previous research to derive conclusions about that body of research” (Haidich, 2010). Systematic reviews and meta-analyses are epidemiological tools used to summarize evidence produced by other studies accurately and reliably. Commonly used to evaluate the effects of interventions from clinical trials, systematic reviews and meta-analysis can also be used to provide the best risk estimate useful for public health decision making. Systematic reviews and meta-analyses rank the highest in the hierarchy of epidemiological evidence as indicated in Figure 3 and therefore deemed appropriate for this study.

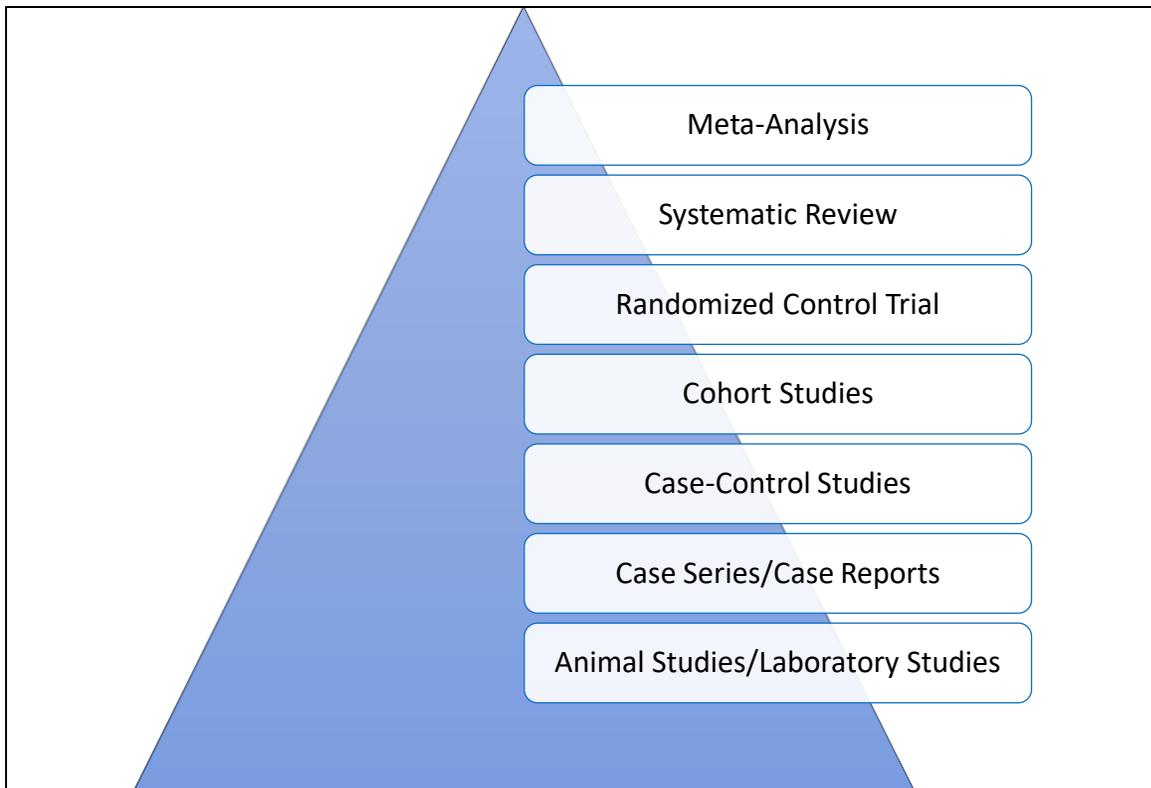


Figure 3. Hierarchy of Epidemiological Evidence  
 \*Source: (Haidich, 2010)

RevMan V5.3 was used to generate the systematic review flow diagram as well as the meta-analysis forest plot. The numbers of cases and controls provided by individual studies were entered into RevMan and pooled risk estimates were recalculated using a random effect model to generate study weights. A random-effects model was appropriate in this study to account for between-study variability. The random-effects model is described below in Equation I.

$$E = \frac{\sum_{i=1}^k W_i Y_i}{\sum_{i=1}^k W_i} \dots\dots\dots \text{Equation I}$$

Where E is the pooled risk estimate,  $W_i$  is the weight for study  $i$ ,  $Y_i$  the observed effect size of study  $i$ , and  $k$  is the number of studies included in the meta-analysis.

Weights for individual studies were used to compute a pooled risk estimate. To test the heterogeneity of the studies included, a Cochran Q test was also performed. With only few studies eligible for this systematic review and meta-analysis, reporting bias was minimal. Searching for grey literature such as government and institutional reports minimized the risk of publication bias. With only four studies included in the meta-analysis, a funnel plot (Appendix E) was less useful as a tool to assess publication bias.

### Results

As shown in Figure 4, the initial literature search yielded 105 related articles. Auxiliary searches identified from citations and references in key papers yielded an additional eight articles for a total of 113 papers. After removing duplicate articles, 74 papers remained. After screening

titles and abstracts, it was determined that 65 articles did not meet the inclusion criteria, leaving nine articles that included either or both, qualitative and/or quantitative analysis and were considered for full-text review. Among those nine articles, only four included a meta-analysis (Figure 4). A summary of studies included in the review are shown in Table 3.

The studies included in this review measured the associated risk factor for developing sarcoidosis among people exposed to different respirable particulate matter. Different studies had different follow-up periods and the particles exposures assessed were varied in terms of composition. Of the nine studies reviewed, six looked at the exposure among the 9/11 WTC responders or firefighters and their risk of sarcoidosis. Two studies were specific on the chemical composition of particulate exposure that they assessed which was silica dust (Rafnsson et al., 1998). The studies included in the review demonstrated biological plausibility of development of granulomas following exposure to respirable particles, worsening of symptoms, and increased incidence and prevalence of the disease.

Quantitative analysis of evidence in four papers that met the inclusion criteria for a meta-analysis was inconclusive on the risk of development of sarcoidosis due to environmental or occupational exposure to dust. The recalculated risk estimates were slightly different to those provided in individual studies because of the weight and estimation method used. The summarized results for the meta-analysis are shown in Figure 5. The overall odds ratio was 2.18 (95% CI, 0.79 – 5.97). This indicated that people that are exposed to respirable particles are about two times more likely to develop sarcoidosis compared to unexposed. The overall heterogeneity detected by the model was 78%, ( $I^2=78%$ ). Three of the four studies indicated higher odds of developing sarcoidosis among those exposed compared to the unexposed (Jordan et al., 2011; Rafnsson et al., 1998; Vihlborg et al., 2017). However, only one study showed statistically significant higher odds among those exposed (Rafnsson et al., 1998). Two of the studies included in the meta-analysis assessed the risk of developing sarcoidosis among those exposed to silica respirable particles (Rafnsson et al., 1998; Vihlborg et al., 2017). These findings were consistent with the findings of the individual studies included.

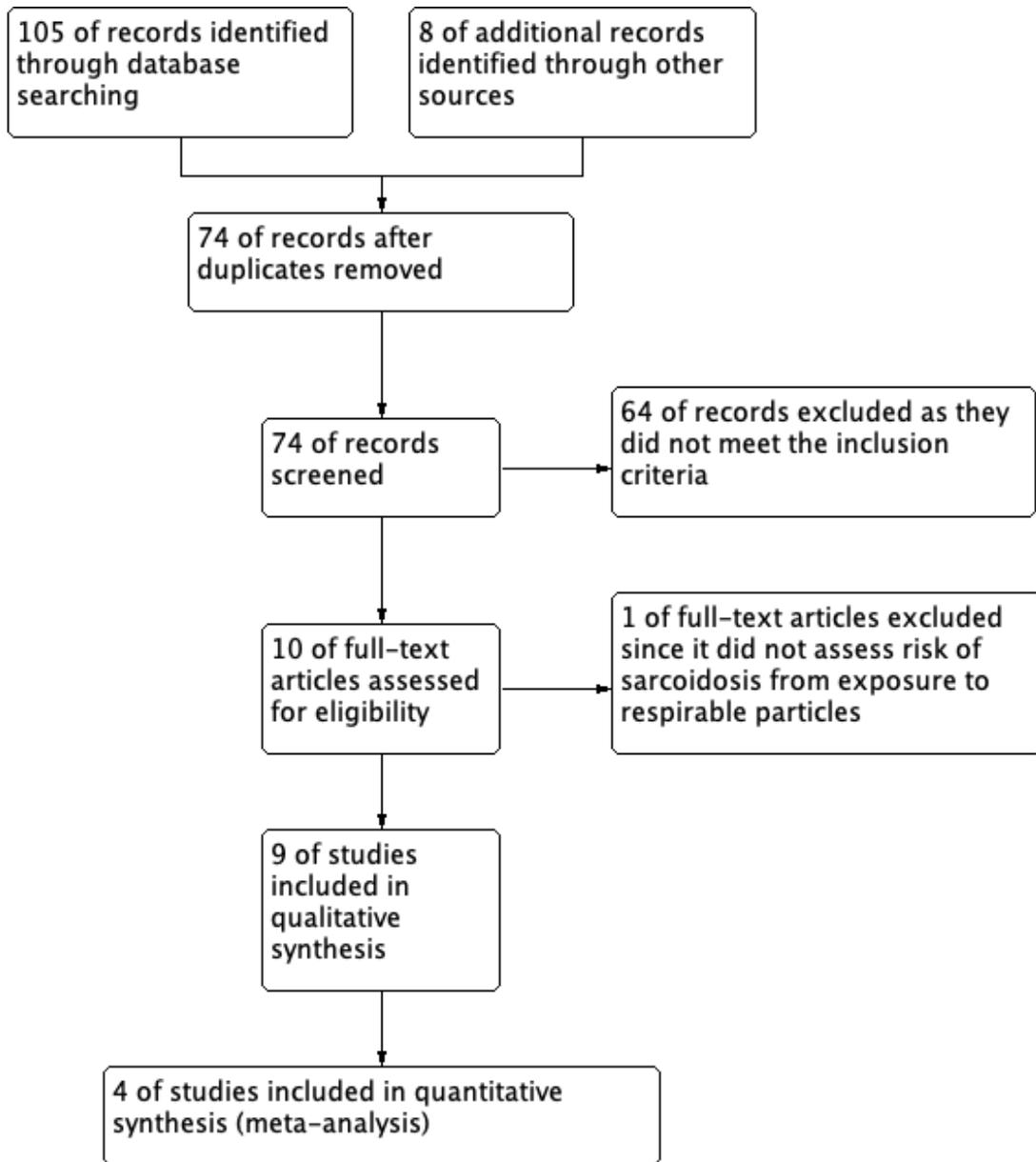


Figure 4. Study Flow Diagram

Table 3. Summary results of eligible sarcoidosis and exposure studies (1998-2019)

Study author(s)	Study design	Publication year	Case definition	Year(s) of study	Follow-up period (years)	No. of Cases	No. of Controls	Sample size	Mean age	Participant/occupation description	Country	Relative Risk (95% CI)
Vihlborg et al. 2017	Retrospective Cohort	2017	ICD-10 (D86-0-3,8); RA M05 (0-9) and M06 (0-4,8,9) 9 code 135)	2001-2013	12	7	-	n=2187	-	Iron foundry workers	SE	3.92
Hena et al. 2019	Retrospective cohort	2019	ICD-10 (D86)	2005 - 2018	13	87	5144	n=11600	41.5	WTC Bellevue hospital	USA	0.90
Sunil et al. 2019	Case evaluation	2019	ICD-10 (D86)	09/2001 - 12/2001	-	6	-	-	-	WTC cohort	USA	NP
Crowley et al. 2011	Case evaluation	2011	(ICD-9 code 135) ;(ICD-9 code 516.3	2008	-	38	-	n=19756	-	WTC responders	USA	NP
Izbicki et al. 2007	Case analysis	2007	ICD-10 (D86)	2001-2006	5	26	-	-	-	WTC responders	USA	NP
Hena et al. 2018	Retrospective cohort	2018	ICD-10 (D86)	2001 - 2015	14	59	-	-	-	WTC firefighters	USA	NP
Pirozzi et al. 2018	Cohort	2018	ICD-10 (D86)	2013 - 2015	2	16	-	-	59	University of Cincinnati Medical Center	USA	NP
Rafnsson et al. 1998	Case-Control	1998	-	1974 - 1993	19	8	70	n=4500	-	Husavik health center/hospital	Iceland	13.2
Jordan et al. 2011	Case-Control	2011	Tissue biopsy (noncaseating granulomas)	2002 - 2008	6	19994	24142	n=45942	-	WTC health registry	USA	1.0

Note: WTC – World Trade Center; NP – not provided

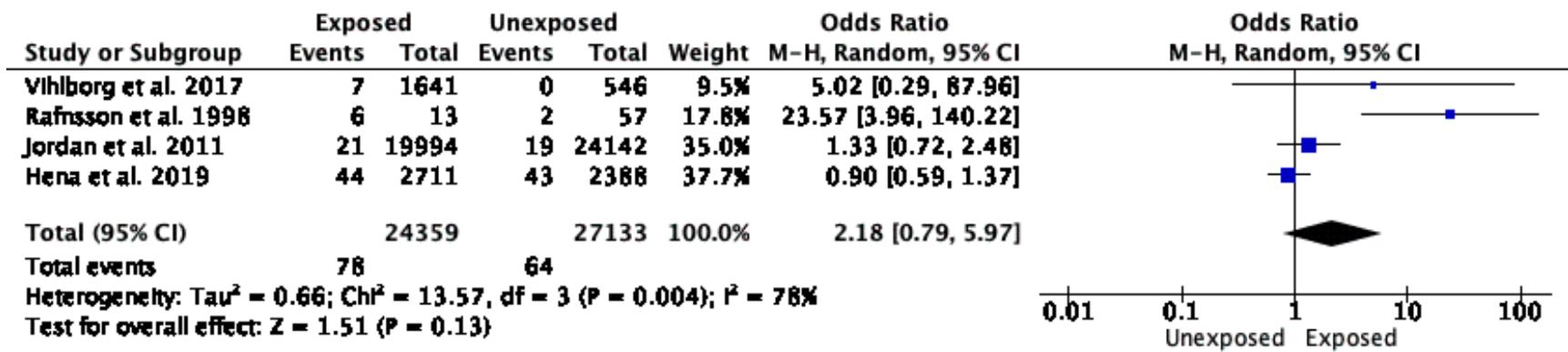


Figure 5. Meta-analysis results of eligible studies (1998-2019)

## Discussion

Exposure to respirable particulate matter is known to have adverse health effects. Particulate matter adversely affects the respiratory health of individuals. While the body has mechanisms that remove particles in inspired air, some ultrafine particles can escape these mechanisms and are deposited onto the respiratory surfaces. Their presence in the alveolar spaces can trigger immunologic responses leading to inflammation and fibrosis. Pathogenicity of respirable particles is dependent on composition, origin, size, ability to produce reactive oxygen species and solubility (Xing et al., 2016). The smallest particles cause the most damage due to their smaller diameters and large surface area. Inflammation is common when particles and fibers are inhaled. Studies among respondents of 9/11 have linked exposure to dust to the pathogenesis of various pulmonary diseases (Fubini & Hubbard, 2003; Rimal et al., 2005; Valavanidis et al., 2013). Lung and lymph node samples analyzed from patients exposed to silica particles have shown the presence of pro-inflammatory cytokines such as inducible nitric oxide synthetase (iNOS), cyclooxygenase-2 (COX-2), tumor necrosis factor (TNF), and ADP-ribosylation factor-like GTPase 11 (ARL11). iNOS is known to mediate the production of reactive nitrogen species while COX-2 is associated with eicosanoids (Laskin et al., 2011; Platko et al., 2018; Sunil et al., 2015).

This study has collected and aggregated available evidence on exposure to respirable particles to the risk of developing sarcoidosis. Although the risk estimate from the meta-analysis results was inconclusive, the study provides additional qualitative and quantitative evidence analyzing the risk of developing sarcoidosis due to environmental or occupational exposure to dust or other forms of particulate matter. The studies included were few and most studies were

conducted for a specific population. In this regard, the results obtained may not be generalizable to other populations with different exposure patterns from those included in this study.

Over the years, long lines of epidemiological, clinical, immunologic, microbiologic, and animal models evidence have suggested that some environmental and occupational exposures put individuals at risk of sarcoidosis and sarcoidosis-like illnesses (Newman, 2012). Some of these exposures occur in occupations such as agriculture, bird handling, metalworking, lifeguards, defense industries, electronic factories, allow manufacturing industries, mining, transportation, construction, and wood burning. Suspected agents from these workplaces include fungal antigens, bacterial antigens, beryllium, aluminum, barium, rare earth metals, silica, carbon nanoparticles, bird protein antigens, inorganic dust, and mold. A study that focused on health outcomes of a group of occupants of a water-damaged office building identified an association between the indoor environmental quality and development of respiratory diseases including sarcoidosis (Laney et al., 2009). In this study, exposure-response relationship between fungal concentrations and respiratory complaints from the occupants was identified. In a follow-up study involving occupants who continued to work from the building demonstrated persistent respiratory health problems including hypersensitivity pneumonitis and sarcoidosis (Iossifova et al., 2011). Fungal antigens have been suggested to play a role in the development of sarcoidosis among those who live in moldy environments. Immunological reactions have been demonstrated against fungal cell wall agents in vivo and in vitro. Additionally, statistical correlation between high fungal cell wall agents in air samples and secretion of interleukin-12 in sarcoidosis patient cell cultures (Terčelj et al., 2011).

Histologic similarities between sarcoidosis, tuberculosis and nontuberculous mycobacterial infection have resulted to speculations from researchers and clinicians about the

role of mycobacteria in the development of sarcoidosis. Consequently, several studies have extended this hypothesis and provided further credence on this association. In 2010, Oswald-Richter identified the ability of CD4+, CD8+ and bronchioalveolar T cells from sarcoidosis patients to bind to mycobacterial antigens (Oswald-Richter et al., 2010). In workplace settings, two studies have linked mycobacteria-contaminated metal-working fluids with sarcoidosis-like hypersensitivity pneumonitis (Roussel et al., 2011; Tillie-Leblond et al., 2011). In these environments an aerosol is generated from spraying of metal parts with semi-synthetic oils. In this regard, sarcoidosis patients who priorly worked in metal machining industries are more likely to have mycobacteria-targeted form of granulomatous inflammation (Newman, 2012).

While the contribution of inorganic particles in the development of sarcoidosis has not been clearly defined, it has been speculated that development of sarcoidosis occurs due to inflammation as a result of an antigen presented to the CD4+ T lymphocytes. T cells proliferate, differentiate, produce inflammatory cytokines, and attract other cells which results to granuloma formation in the presence of a persistent antigen and an adjuvant signal. Implicated inorganic dusts that could play the role of adjuvants included various silicates, mineral fibers and alkaline dust that was generated in the 2001 collapse of the World Trade Center (Newman, 2012). This systematic review has summarized the results from eligible studies that focused on exposure to respirable particles and the development of sarcoidosis. Although the pooled risk estimate in the meta-analysis was not statistically significant, available evidence suggest that individuals exposed to dust have increased disease risk compared to unexposed (Bowers et al., 2010; Crowley, Herbert, Moline, Wallenstein, Shukla, Schechter, Skloot, Udasin, Luft, Harrison, Shapiro, Wong, Sacks, Teirstein, et al., 2011; Hena et al., 2018, 2019; Jordan et al., 2011; Rafnsson et al., 1998; Vihlborg et al., 2017).

The few numbers of studies identified in this review was a limitation in this study. There were only four studies that were utilized in the meta-analysis, which limits the robustness of the pooled risk estimate computed. Also, the few numbers of identified studies did not allow assessment of publication bias risk. Majority of studies synthesized in this review utilized data from the 9/11 WTC first responder's cohort and therefore may not be generalizable across other populations. Lastly, there was only one independent reviewer and therefore judgement of inclusion or exclusion of studies was only based on the judgement of one reviewer.

### **Conclusion and Implications for Public Health Practice**

This study highlights important aspects of occupational and environmental risk factors that in congruence with other studies underscore their involvement in sarcoidosis disease outcomes. The findings of this dissertation can inform public health practice especially in instituting regulations and policies that will address some of these highlighted risk factors. Although these findings identified a small, increase in risk, the relationship remains unclear. More rigorous and robust studies are needed to generate results to determine specific causal pathways and mechanisms more accurately through which exposure to respirable particles could lead to the development of sarcoidosis.

## **CHAPTER 4: SARCOIDOSIS MORTALITY IN NORTH CAROLINA AND ASSOCIATED RISK FACTORS**

### **Introduction**

Sarcoidosis is a rare disease characterized by aberrant formation of granulomas (cellular clumps involved in immune responses and inflammation) in different organs or tissues (Flavell, 2020). International Classification Disease Codes 10 (ICD-10) for sarcoidosis is D86, unspecified sarcoidosis D86.9, sarcoidosis of lung is D86.0, sarcoidosis of lymph node is D86.1 and sarcoidosis of other sites is D86.8 (CDC, 2020). Sarcoidosis most frequently involves the lung, but up to 30 percent of patients present with extra-thoracic manifestations of sarcoidosis (Baughman et al., 2001; Judson et al., 2012). Diffuse interstitial lung disease is the classic type of lung involvement; other less common pulmonary manifestations include pleural thickening and pulmonary hypertension (Judson et al., 2012). The extra-pulmonary manifestations of sarcoidosis involve the cardiac system, skin, lymph nodes, eyes and organs of the digestive system (Judson et al., 2012).

Sarcoidosis most commonly affects young and middle-aged people, both males and females across all races and ethnicities (Arkema & Cozier, 2018; Spagnolo, 2015). The exact incidence and prevalence rates of sarcoidosis have been difficult to estimate mainly due to undiagnosed cases, variability in ascertainment, inconsistency case definition, disease presentation variability and presence of other commonly recognized granulomatous diseases such as tuberculosis (Arkema et al., 2016; Dubrey & Falk, 2010; Gribbin et al., 2006; Judson, 2014). People of African descent such as Afro-Caribbean and African American races

are more affected compared to other races while Caucasians present with asymptomatic and chronic disease (Rybicki et al., 1997). Such differences can be accounted for by differences in genetic susceptibility which is relatable to difference in genetic background. However, these differences can as well be accounted for by under or over diagnosis of cases within certain populations or geographical areas.

The highest incidence and prevalence of sarcoidosis has been observed among Nordic countries and African Americans (Arkema et al., 2016; Baughman et al., 2016b; Dumas et al., 2016). These studies have provided contemporary incidence and prevalence estimates in these populations. Studies outside of these populations estimates the prevalence to be greater than 0.05% which is an indication that the disease is rare as previously thought (Arkema & Cozier, 2018). In Sweden, a study that was conducted using population data from 2003 to 2012 estimated sarcoidosis incidence to be 11.5 per 100,000 per year while prevalence was 160 per 100,000 (0.16%) (Arkema et al., 2016). In the US, Baughman et al., (2016) estimated the incidences to be 17.8, 8.1, 4.3 and 3.2 per 100,000 per year among African Americans, White, Hispanics and Asians respectively (Baughman et al., 2016b). The study also estimated the prevalence rates to be 14, 50, 22 and 19 per 100,000 among African American, White, Hispanics and Asians respectively (Baughman et al., 2016b). In another predominantly female prospective cohort study, the Nurses' Health Study, Dumas et al., (2016) estimated the incidence rates to be 46 and 11 per 100,000 per year among African Americans and Whites respectively (Dumas et al., 2016). The study estimated the prevalence rates to be 519 and 92 per 100,000 for African Americans and White women respectively. In another study conducted among healthcare workers in Mayo Clinic (Olmsted County, Minnesota, USA), the incidence of sarcoidosis was estimated to be 11 per 100,000 per year (Ungprasert et al., 2017a). Using data from the NHSII

study conducted among a prospective female nurses' cohort followed from 1989, Dumas et. al, (2016), reported a prevalence rate of 0.10% (Dumas et al., 2016). Using the same data which had majority of White nurses and 4% Black nurses, Ungprasert et.al, (2016) reported a prevalence rate of 0.52% among Black nurses. This estimate was lower compared to that reported in the Black Women's Health Study that reported a prevalence rate of 2.0% (Cozier et al., 2011).

Only a few studies have described sarcoidosis mortality in the US. In one of the earliest published mortality studies identified, Mirsaeidi and colleagues (2015) reported that between 1999 and 2010, a mortality rate of 2.8 (per 1,000,000 persons) was estimated in the U.S. with higher mortality rates observed among women (3.3 per 1,000,000) compared to men (2.3 per 1,000,000). African Americans had a higher mortality rate (16) compared to Caucasians (16.0 versus 1.3 deaths per 1,000,000) (Mirsaeidi et al., 2015). In a separate study, Dwyer-Lindgren and colleagues, reported that the overall sarcoidosis mortality rate increased from 2.7 per 100,000 in 1980 to 5.5 per 100,000 in 2014 (Dwyer-Lindgren et al., 2017).

Among more recent studies, a comprehensive evaluation of sarcoidosis deaths in the U.S was published by Kearney and colleagues (2019). Findings identified that from 1999 to 2002, age adjusted sarcoidosis mortality rates in the U.S. increased from 2.1 to 3.1 deaths per 1,000,000. The study also reported higher death rates among females than males (2.5 to 3.3 deaths per 1,000,000 for females compared to 1.5 to 2.6 deaths per 1,000,000 for males. The highest mortality rate was observed among Black females (17 deaths per 1,000,000 (Kearney et al., 2019). Across the U.S., the highest death rates were found in the south with a mean of 3.7 deaths/1,000,000. NC ranked fourth in highest death rates per 1,000,000 in the country (5.4) after District of Columbia (13.8), South Carolina (6.6), and Maryland (5.4).

The objectives of this study were to 1) identify sarcoidosis mortality clusters or hot spots across NC (2000 – 2018); and 2) evaluate the association between sarcoidosis-related mortality and risk factors including obesity, race, occupation, and ambient PM<sub>2.5</sub> across NC. From my literature search, of available published studies, no studies on sarcoidosis mortality in NC could be identified. A study is needed to inform public health officials, clinicians, and healthcare decision makers on sarcoidosis mortality trends across NC.

## **Methods**

### **Study design and criteria**

A cross-sectional, ecological study design was adopted and the county was used as the unit of analysis (Levin, 2003). Because sarcoidosis is a rare disease, there are relatively few numbers of death and therefore statistical analysis would require aggregation. The data analyzed in this study were therefore aggregated with county being the unit for analysis.

For purposes of this evaluation, an eligible mortality case was defined as a death between the years 2000 to 2018 in NC (n=100 counties), and reported as a sarcoidosis-related death, listed as primary or underlying cause of death with an ICD-10-D86.x code (i.e., D86.0 - sarcoidosis of the lung; D86.1 - sarcoidosis of lymph nodes; D86.2 - sarcoidosis of the lung with sarcoidosis of lymph nodes; D86.3 - sarcoidosis of skin; D86.8 -sarcoidosis of other and combined sites; D86.9 - unspecified sarcoidosis).

### **Data and data sources**

Mortality data was obtained through the Centers for Disease Control and Prevention, Wide-ranging Online Data for Epidemiologic Research (CDC, WONDER), a national public use, online database (<https://wonder.cdc.gov/>). CDC WONDER derives mortality data from the National Vital Statistics System (NVSS), the U.S. official central vital statistics database

repository that maintains all death certificates reported by states, tribes, Commonwealth, and territories.

Based on the literature, considerations were made to examine possible social determinants of mortality risk factors, including race, occupation, obesity, smoking and air quality. Data, aggregated to the county-level, were downloaded from the Agency for Healthcare Research Quality (AHQR, 2021) and the Robert Wood Johnson Foundation, County Health Ranking & Roadmaps (RWJ, 2021). The independent social determinant variables selected, included (county-level) percent of African American population, percent of occupation-population working in nature, (e.g., agriculture, mining, fishing, forestry), percent of obese adult population, percent of smoking adults, percent of population below poverty level, and average annual PM<sub>2.5</sub>. Because the social determinant data was aggregated by NC County (n=100), and by year (2009-2018 and 2012 – 2018 for percent of population below poverty level), mean average values were calculated for each respective social determinant risk factor, or predictor variable grouping (i.e., race, occupation, obesity, smoking and air quality).

## **Measures**

As shown in Table 4, the social determinant measures were either continuous or categorical variables. Continuous variables included mortality rate, percent working in nature (e.g., mining, fishing, hunting, agriculture, forestry, etc.), and percent of obese adults. Categorical variables were stratified by age (0-44, 45-54, 55-64, 65 and older); race (White, Black/African American, native Indian, other) and sarcoidosis type (lungs, other sites, unspecified), annual average ambient PM<sub>2.5</sub> (per county).

Table 4. Social determinant variables and measures

<u>Continuous</u>	<u>Categorical</u>
Mortality Rate	Age: 1. 0-44 2. 45-54 3. 55-64 4. >= 65
Percent (%) of population (18-64 years) below poverty level	Race: 1. White, 2. Black/African American, 3. Indian, 4. Other
Percent (%) working in nature i.e., mining, fishing, hunting, agriculture, forestry, etc.	
Percent (%) of obese adults	Sarcoidosis type: 1. Lungs 2. Other sites 3. Unspecified
Percent (%) of smoking adults	Sex: 1. Male 2. Female
Annual average ambient PM <sub>2.5</sub>	Region: 1. Western, 2. Piedmont 3. Eastern

\*Data aggregated to county level

### Procedures

Unadjusted and age-adjusted sarcoidosis mortality rates (per 100,000 population) were calculated for each county using number of sarcoidosis deaths as the numerator and total population as the denominator, using the 2000 US Census. To assess variability of sarcoidosis mortality across NC, counties were categorized into three identifiable regions, Western, Piedmont, and Eastern (Figure 6).

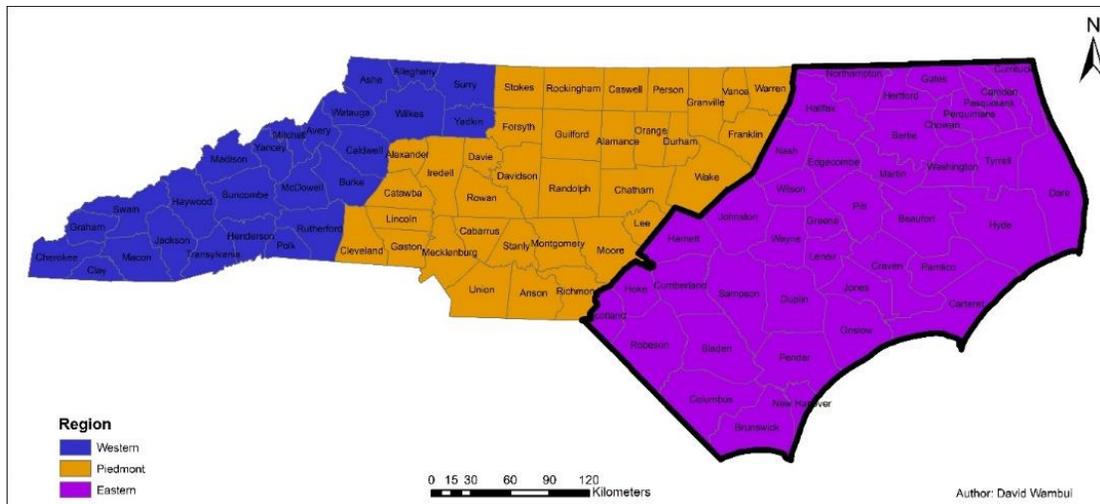


Figure 6. NC: Western, Piedmont, and Eastern regions

Mortality data was processed and analyzed using R (R Core Team, 2020). All data were checked, cleaned, and evaluated for errors, missing values, and outliers by running data queries, sorting, and filtering. Columns, rows, or cells with missing data were omitted, kept in a separate datafile, and later deleted when deemed appropriate. Cartographic boundary shapefiles were downloaded from the U.S. Census Bureau’s MAF/TIGER database. To spatially visualize mortality clustering and associated risk factors, other geospatial shapefiles were also used as appropriate for processing and carrying out spatial joins. Maps were created using ArcGIS (Environmental Systems Research Institute, ESRI, Version 10.8.1).

### Data Analysis

Descriptive analysis was used to summarize the numbers of sarcoidosis deaths by race, sex, age category, and sarcoidosis type stratified by region. Fisher’s exact test was conducted to test for statistically significant differences of sarcoidosis deaths by race. A Fisher’s exact was deemed the appropriate test since the expected number of deaths for “Indian” and “Other” race categories were less than five in Piedmont and Western regions. Pearson’s chi-squared test of independence was conducted to evaluate statistical differences between observed mortality rates

by sex, age category, and sarcoidosis type across the three regions. To explore differences in the regional distribution of identified sarcoidosis risk factors, a Kruskal-Wallis rank sum test was conducted since the variables were not normally distributed. Dunn pairwise test with false discovery rate p-value adjustment was conducted to identify regions that differed significantly in the distribution of the identified sarcoidosis risk factors.

ArcGIS was used to map mortality rates by county and assess spatial autocorrelations and clustering. A spatial join using NC County field name with NAD83-NC (projection) to create a county-level, sarcoidosis mortality shapefile. As stated above, sarcoidosis has relatively low mortality, meaning confidence level with the rates is a concern, as well as unstable estimates because of the variability in the relative standard error. Global Moran's I and Local Moran's I were used within to assess spatial autocorrelation and to detect sarcoidosis mortality clustering respectively. The results of global clustering are attached in Appendix F.

Cluster and Outlier Analysis (Anselin Local Moran's I) was carried out to identify where clustering of sarcoidosis mortality occurred. Contiguity edges and corners (Queens's contiguity) were used to define neighbors. This technique identified high-high clusters (counties with high mortality rates surrounded by counties with high mortality rates); low-low clusters (counties with low mortality rates surrounded by counties with low mortality rates) and outliers (counties with high mortality rates surrounded by counties with low mortality rates and vice-versa).

In instances where data were suppressed or unavailable because of low numbers, the K-Nearest Neighbor method and Inverse Distance Weighting were used to interpolate values between provided data values.

Because some of the county level mortality was either absent or suppressed because of confidentiality issues by the data provider, several issues, including visual gaps and poor-quality

interpolation were encountered when converting mortality rates from polygons to centroids. Therefore, counties that were missing data were disregarded and not used in the analysis. The interpolated mortality map is attached in Appendices G & H.

To evaluate the association between sarcoidosis mortality and social determinant risk factors, an ordinary least squares multivariate regression model was fit to estimate the strength of association. The modeled association is summarized by Equation II below.

$$Y_i = \beta_0 + \beta_1x_1 + \beta_2x_2 + \dots + \beta_jx_j + \epsilon \dots\dots\dots \text{Equation II,}$$

*Where  $Y_i$  is the response variable (predicted crude sarcoidosis mortality rate),  $\beta_0$  model intercept,  $\beta_1$  to  $\beta_j$  representing the estimated parameters for explanatory variables  $x_1$  to  $x_j$  (region, percent of African Americans, percent of people working in nature, percent of obese adults, percent of adults smoking, percent of population below poverty level, and annual average ambient  $PM_{2.5}$ .) and  $\epsilon$  representing the error term (Schneider et al., 2010).*

Histogram plots of raw data and regression diagnostic plots (residuals vs fitted, Q-Q, scale-location, and residuals vs leverage plots) for the model were used to examine the assumptions for linear regression model. The outcome (crude sarcoidosis mortality rate) and predictor variables met the assumptions for linear regression i.e., linearity, normality, homoskedasticity, and independence of residual error terms. These tests are attached in Appendix I.

## **Results**

As shown in table 5, between 2000 and 2018, there were a total of 1,035 sarcoidosis-related deaths across the 3 regions. Eastern NC experienced the highest number of sarcoidosis-related deaths (n=514), while Western NC recorded the least number of sarcoidosis-related deaths (n=50). In both Eastern and Piedmont regions, Black/African Americans accounted for the largest percent of total sarcoidosis-related deaths by race (81.5% and 75.3% respectively). In Western NC, Whites accounted for the largest percent (62.0%) of sarcoidosis deaths across the

three regions. Overall, females experienced more sarcoidosis deaths (63.5%, 63.8%, and 68%) compared to males in Eastern, Piedmont, and Western regions respectively. In general, sarcoidosis mortality increased with age across the three regions. While most deaths were from unspecified sarcoidosis cases, lung involvement was the most common organ specified. The observed differences in mortality rates across the three regions for race and age category were statistically significant with p-values of <0.001 and 0.003 respectively.

Table 5. Summary of sarcoidosis deaths in NC by region (2000 - 2018)

<b>Characteristic</b>	<b>Eastern <i>n=471</i></b>	<b>Piedmont <i>n=514</i></b>	<b>Western <i>n=50</i></b>	<b><i>p</i>-value</b>
<b>Race:</b>				
White	80 (17.0%)	122 (23.7%)	31 (62.0%)	<0.001
Black/AA	384 (81.5%)	387 (75.3%)	18 (36.0%)	
Indian	5 (1.06%)	4 (0.78%)	1 (2.00%)	
Other	2 (0.42%)	1 (0.19%)	0 (0.00%)	
<b>Sex:</b>				
Female	299 (63.5%)	328 (63.8%)	34 (68.0%)	0.818
Male	172 (36.5%)	186 (36.2%)	16 (32.0%)	
<b>Age category (years):</b>				
0-44	90 (19.1%)	71 (13.8%)	6 (12.0%)	0.003
45-54	104 (22.1%)	115 (22.4%)	5 (10.0%)	
55-64	154 (32.8%)	147 (28.6%)	16 (32.0%)	
>=65	122 (26.0%)	181 (35.2%)	23 (46.0%)	
<b>Underlying course of death:</b>				
Lungs	82 (17.4%)	84 (16.3%)	15 (30.0%)	0.160
Other sites	51 (10.8%)	49 (9.53%)	5 (10.0%)	
Unspecified	338 (71.8%)	381 (74.1%)	30 (60.0%)	

As shown in Figure 7, aggregated crude mortality rate between 2000-2018 was highest in Eastern NC (1.16 per 100,000) followed by the Piedmont region (0.49 per 100,000) and the lowest mortality rate was in Western NC (0.32 per 100,000). Eastern NC crude mortality was greater than the state and the national average. The age-adjusted mortality pattern was not different with Eastern NC recording the highest rate at 1.07 per 100,000 as shown in Figure 8. Figure 9 shows the overall sarcoidosis deaths trend in NC from 2000 to 2018. Overall, the

number of deaths has been shown to double from 22 deaths in 2000 to 53 deaths in 2018. The crude mortality rate was however seen to generally fluctuate between 1.7 per 100,000 in 2000 and 1.6 per 100,000 in 2018 with the highest rates being recorded in 2009 (2.7 per 100,000) and 2015 (2.5 per 100,000) (Figure 10).

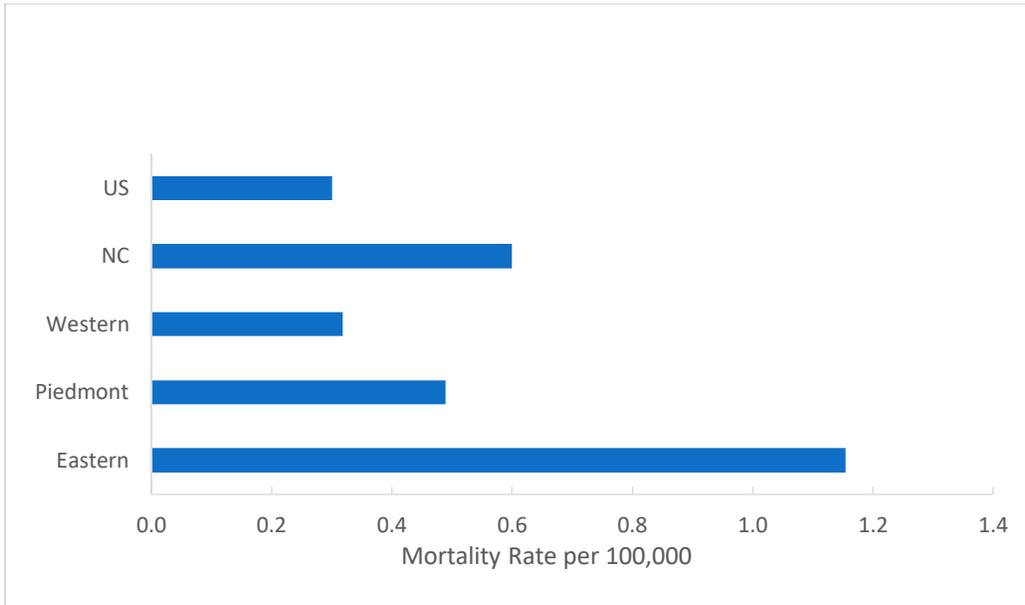


Figure 7. Average sarcoidosis crude mortality rates in NC regions compared to the national and state rates (2000 - 2018)

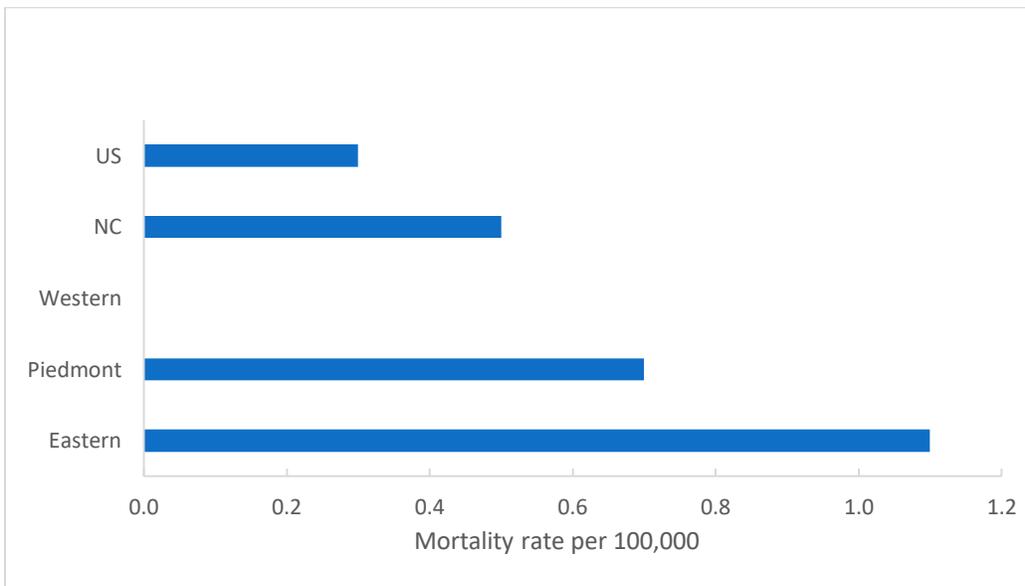


Figure 8. Average sarcoidosis age-adjusted mortality rates in NC regions compared to the national and state rates (2000-2018).

Note: Western NC data was unavailable.

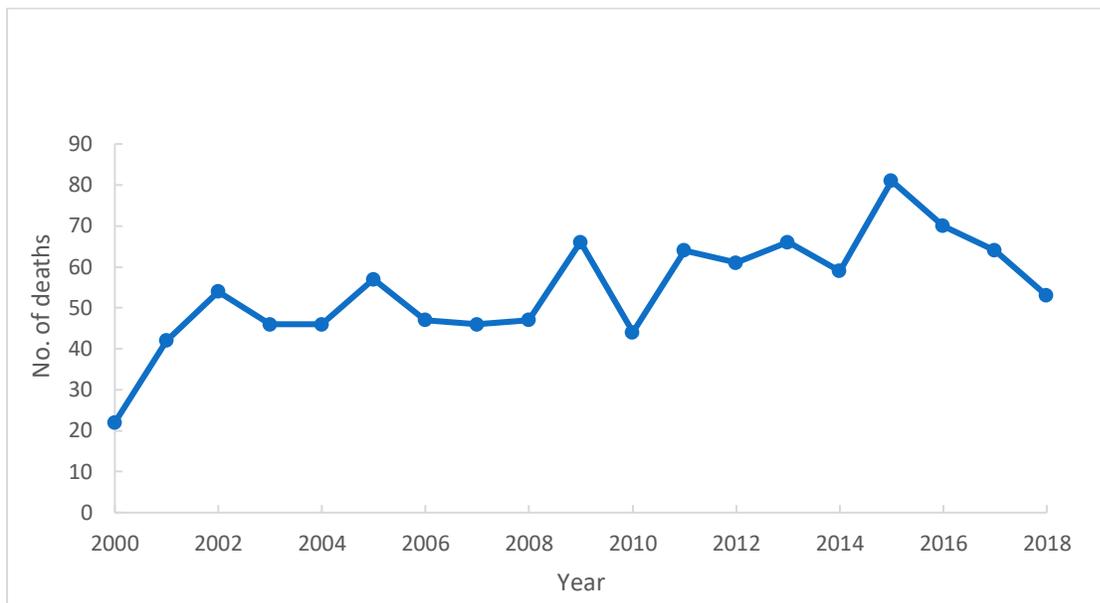


Figure 9. Number of sarcoidosis deaths in NC (2000-2018)

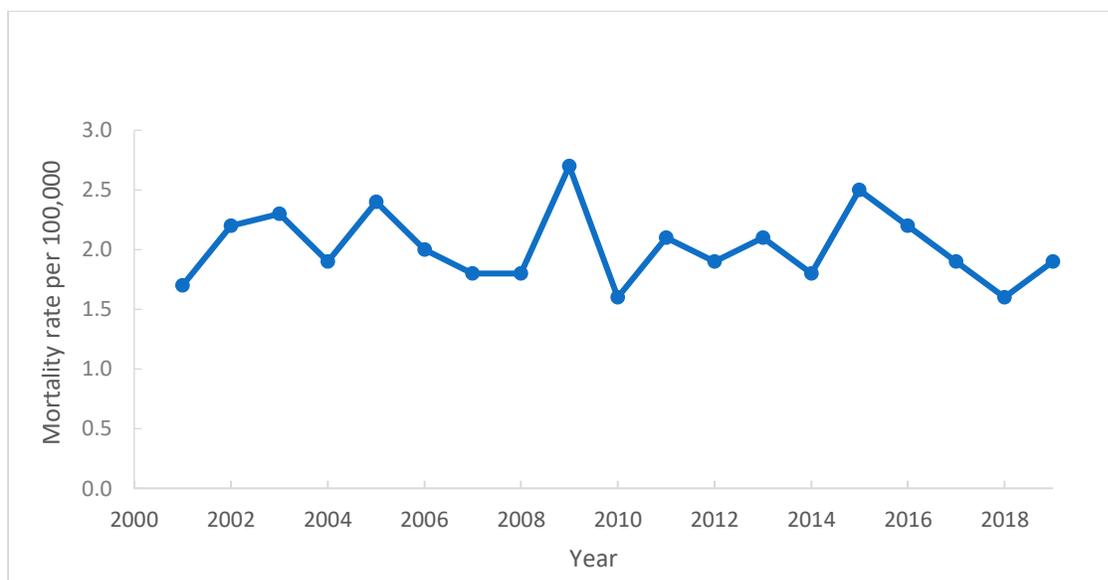


Figure 10. Sarcoidosis mortality rates in NC (2000-2018)

When stratified by race, Black or African Americans experienced the most deaths (Figure 11) and highest crude mortality rates (1.9 per 100,000) compared to Whites (0.32 per 100,000) as shown in Figure 12. Across the period, the number of deaths increased from 18 in 2000 to 37 in 2018 among Blacks/African Americans. The increasing trend was also noted for Whites. Stratification by region indicated that Eastern and central/Piedmont regions recorded more

sarcoidosis deaths compared to the Western region (Figure 13). Crude mortality rate was highest in Eastern NC followed by the Piedmont region while Western NC recorded the lowest crude mortality rates between 2000 and 2018.

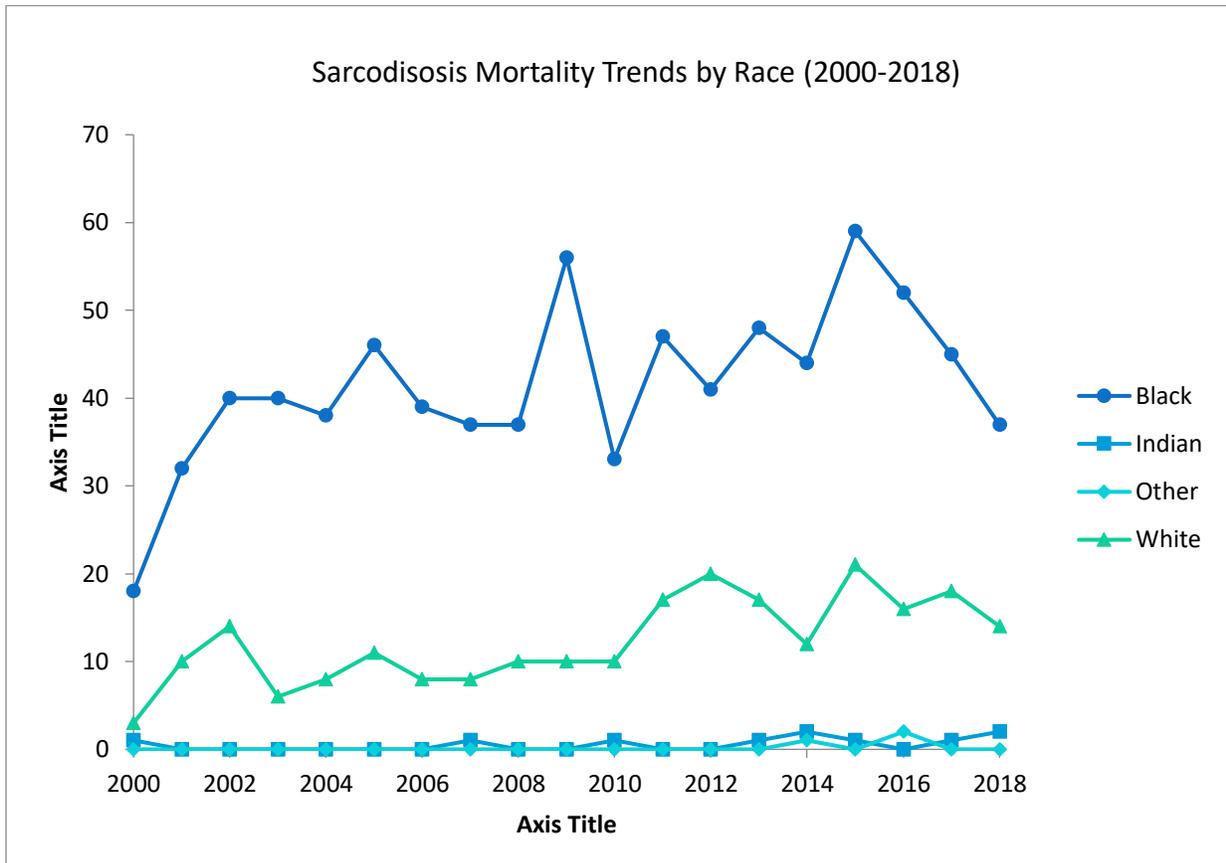


Figure 11. Sarcoidosis deaths in NC by race (2000-2018)

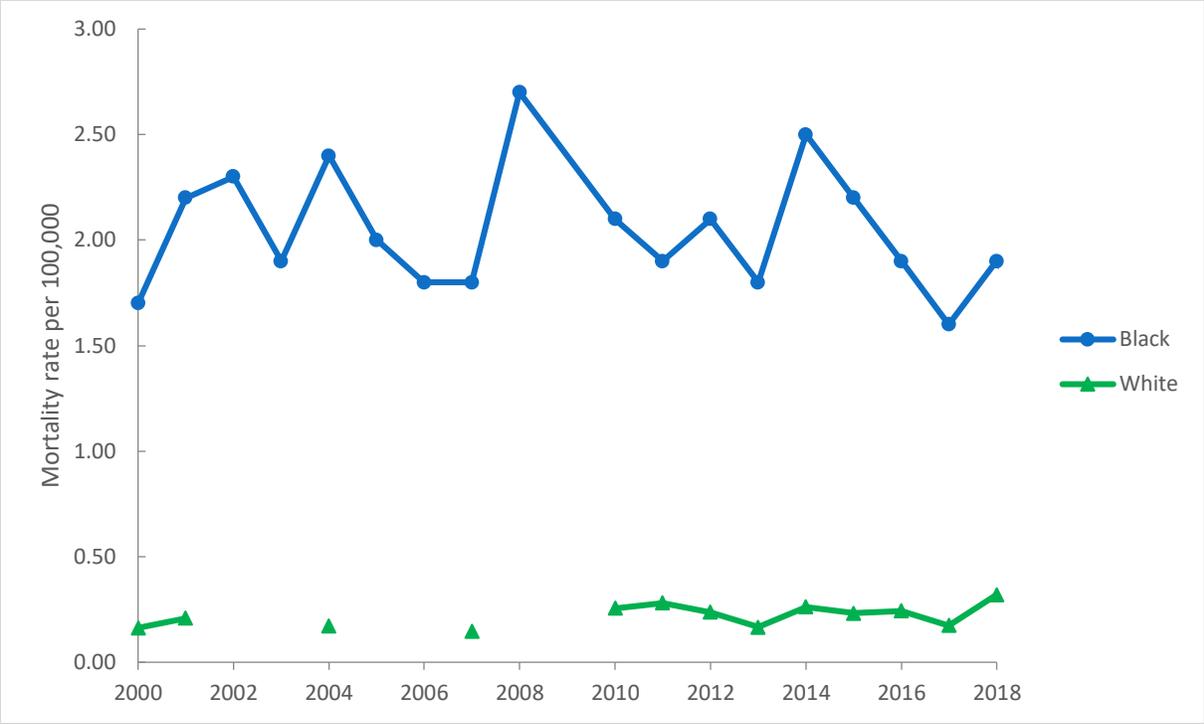


Figure 12. Crude sarcoidosis mortality rates comparing African Americans and Whites in NC (2000-2018)

\*Data was suppressed for some years for Whites

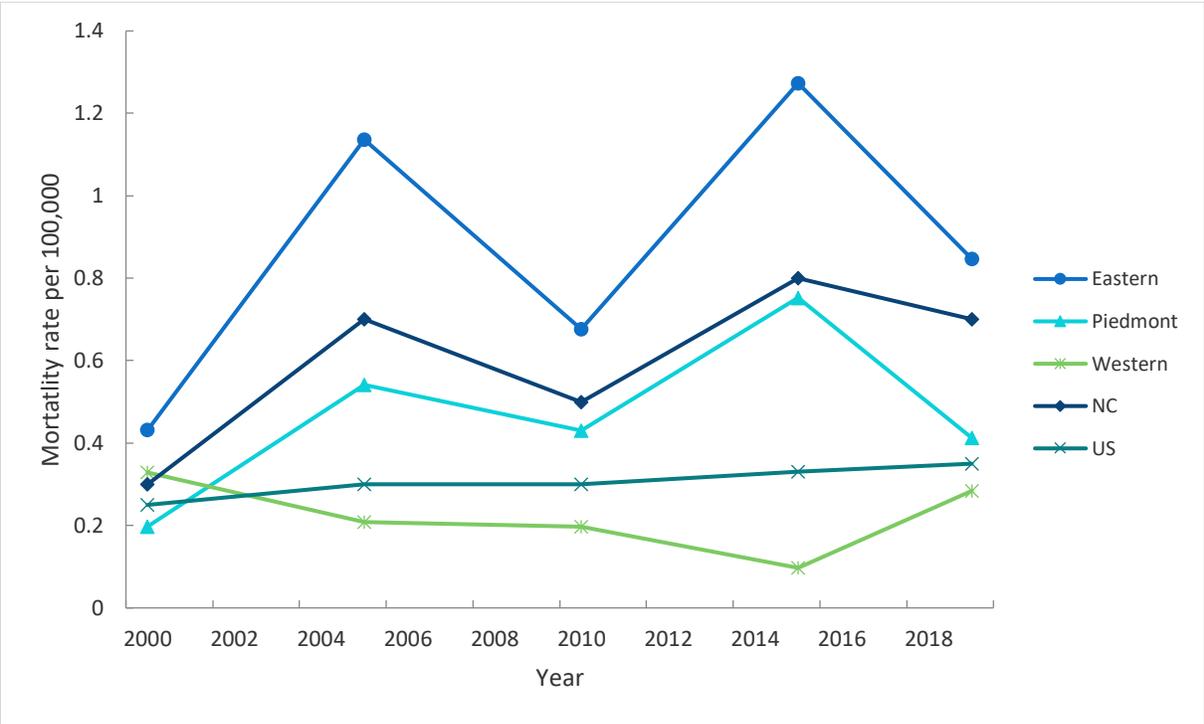


Figure 13. Crude sarcoidosis mortality rates in US, NC, and NC regions (2000-2018)

Figure 14 shows the spatial distribution of sarcoidosis mortality rates aggregated between 2000 and 2018. As the map indicates, counties in the Eastern region of the state recorded higher mortality rates compared to the central/Piedmont and Western regions. While some counties recorded the highest mortality rates (1.9 – 2.9 per 100,000) in the Eastern region of the state, counties in the Western region recorded as low as (0.1 – 0.4 per 100,000). Although most of the age-adjusted mortality data in CDC WONDER was suppressed, Figure 15 indicates that some of the highest age-adjusted sarcoidosis mortality rates were recorded in the Eastern region.

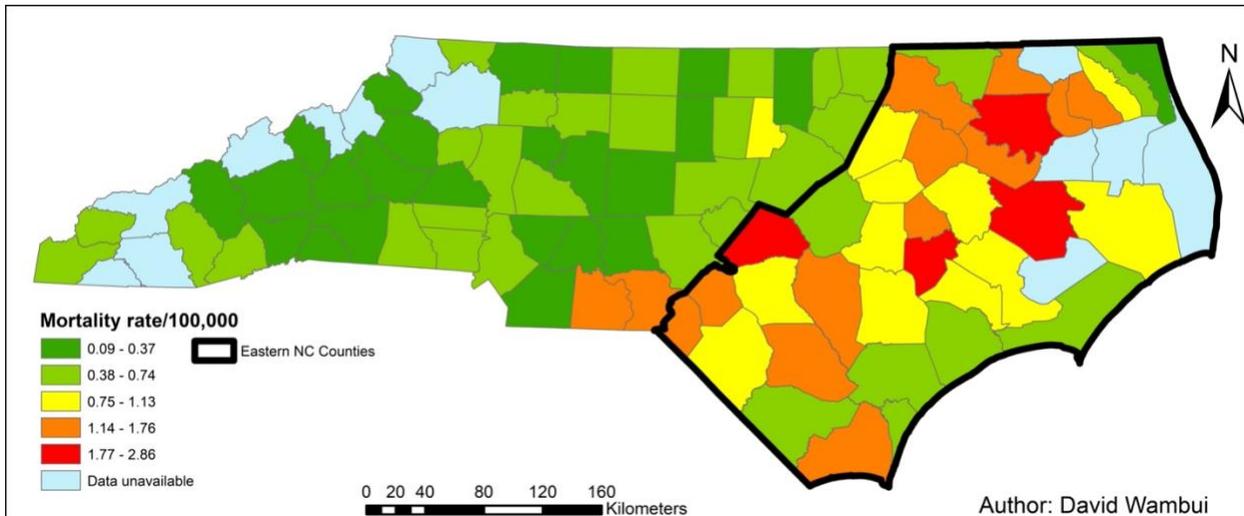


Figure 14. Crude sarcoidosis mortality in NC (2000-2018)

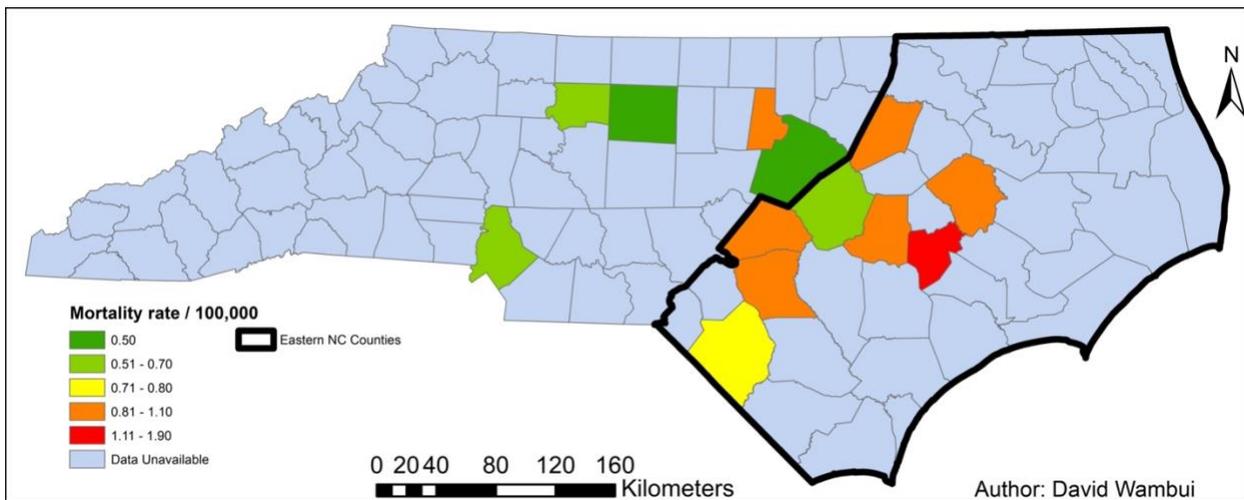


Figure 15. Age-adjusted sarcoidosis mortality rates in NC (2000-2018)

Spatial autocorrelation analysis with a Global Moran’s I indicated a statistically significant clustering pattern with a p-value of <0.001. A closer examination of the clustering pattern using Local Moran’s I indicated that there were clusters of high sarcoidosis mortality rates (high-high cluster) in the Eastern part of the state and clusters of low sarcoidosis mortality rates (low-low cluster) in the Western part of the state (Figure 16).

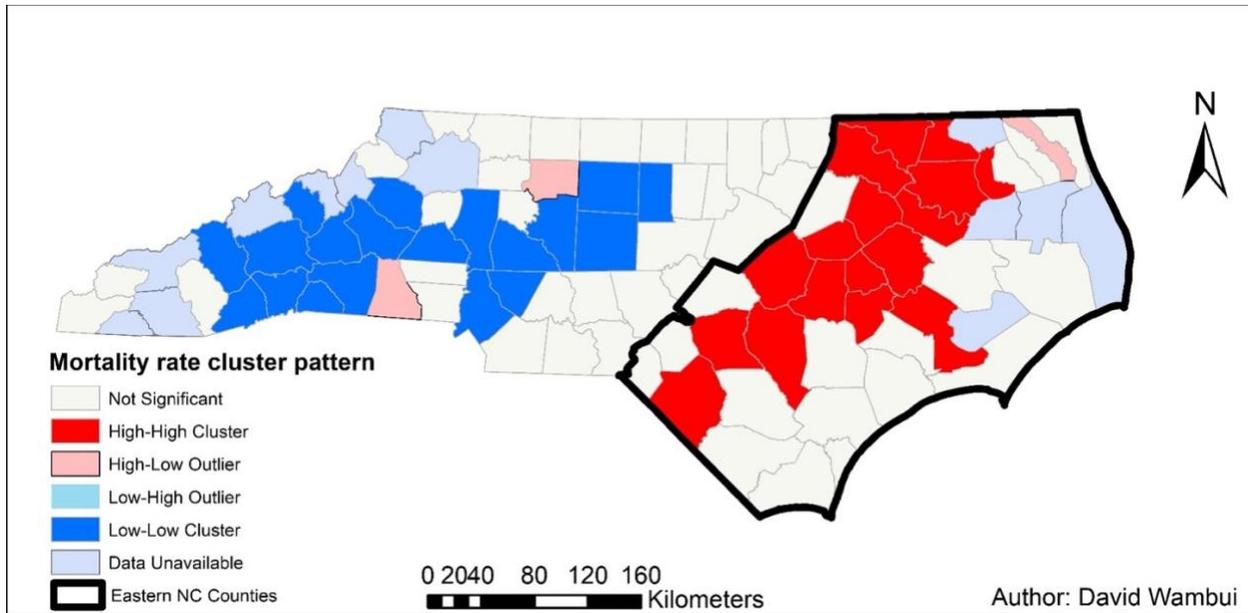


Figure 16. Crude sarcoidosis mortality rate clusters in NC (2000-2018)

Table 6 shows a summary of explored sarcoidosis mortality risk factors by region. The results indicate that Eastern NC had the highest percent of African Americans, percent of people working in nature and percent of obese adults compared to Piedmont and Western regions. Dunn pairwise test identified statistically significant differences (adjusted p-value <0.05) in the distribution of these factors. Similarly, the differences observed between Piedmont and Western regions for percent of African Americans, percent working in nature, and percent of obese adults were statistically significant as shown in Appendix J. Western region had the largest percent of smokers while Piedmont had the highest annual ambient PM2.5 although the differences were not statistically significant.

Table 6. Descriptive summary of sarcoidosis mortality risk factors stratified by region

<b>Characteristic</b>	<b>Eastern, <i>n</i> = 41</b>	<b>Piedmont, <i>n</i> = 34</b>	<b>Western, <i>n</i> = 25</b>	<b><i>p</i>- value<sup>2</sup></b>
Percent African Americans <sup>1</sup>	32 (19, 37)	18 (12, 30)	3 (1, 4)	<0.001
Percent working in Nature <sup>1</sup>	3.25 (2.02, 6.29)	1.31 (0.83, 2.04)	1.98 (1.52, 3.10)	<0.001
Percent obese Adults <sup>1</sup>	34.1 (31.7, 35.2)	30.8 (29.5, 33.2)	28.3 (27.1, 30.7)	<0.001
Percent smoking Adults <sup>1</sup>	18.4 (16.7, 20.7)	19.4 (16.7, 21.4)	20.1 (18.0, 21.3)	0.3
Percent of people below poverty level	20 (17.0, 22.9)	16.0 (14.2,18.0)	19.6 (17.6,20.5)	<0.001
Average annual PM2.5 (µg/m <sup>3</sup> ) <sup>1</sup>	8.22 (7.44, 9.04)	9.32 (3.14, 9.81)	8.66 (5.05, 9.35)	0.3

<sup>1</sup> Median (Q1, Q3 - 25<sup>th</sup>, 75<sup>th</sup> percentile)

<sup>2</sup> Kruskal-Wallis rank sum test

Choropleth maps were used to demonstrate the spatial distribution of identified risk factors. As shown in Figure 17, Eastern NC counties had among the highest percent of Black/African Americans of up to 61% of the population. The Western region had the lowest percentage of Black/African Americans (>1 – 12 %). Similarly, the Eastern region had some the highest percentage of obese adults compare to the Piedmont and Western regions (Figure 18). The Eastern region also had counties with the highest percentage of the population working in agriculture, mining, forestry, fishing, and hunting compared to the other two regions as shown in Figure 19. Piedmont region had counties with the highest annual average ambient PM<sub>2.5</sub>. However, no county had an average greater than the EPA recommended average of 12 µg/m<sup>3</sup>(Figure 20). Bertie, Herford, Halifax and Edgecombe counties were among the highest in crude mortality rates as well as percent of African Americans, percent of obese adults, and percent of people working in nature.

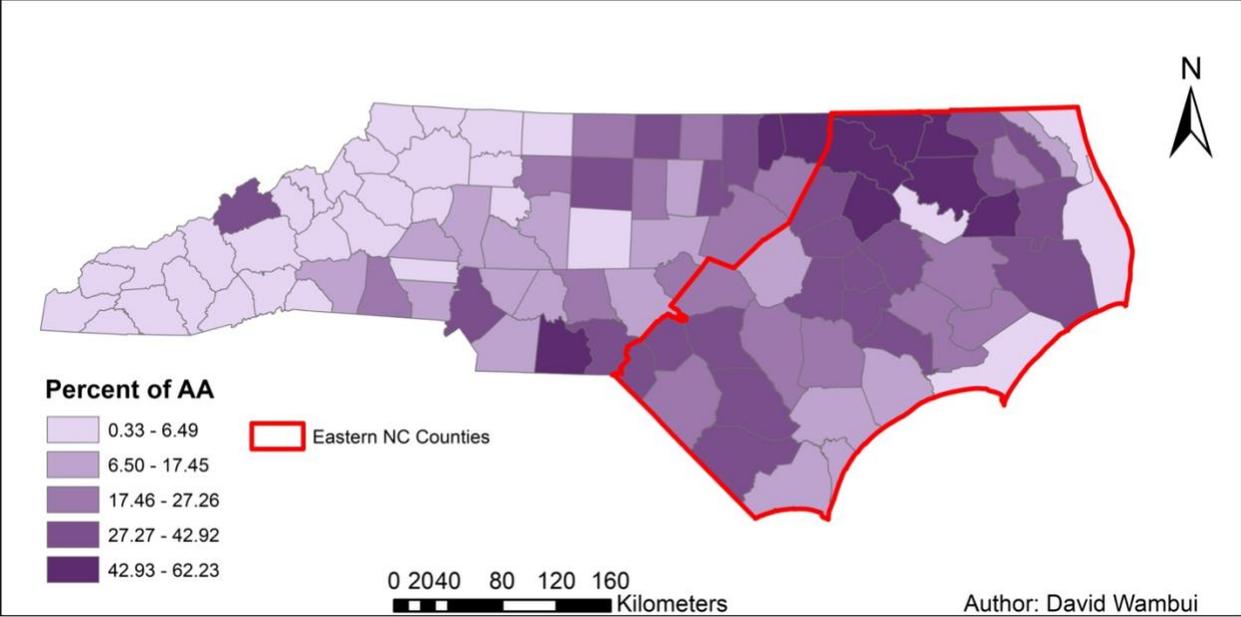


Figure 17. Percent of Black/African American population between 2009 - 2018

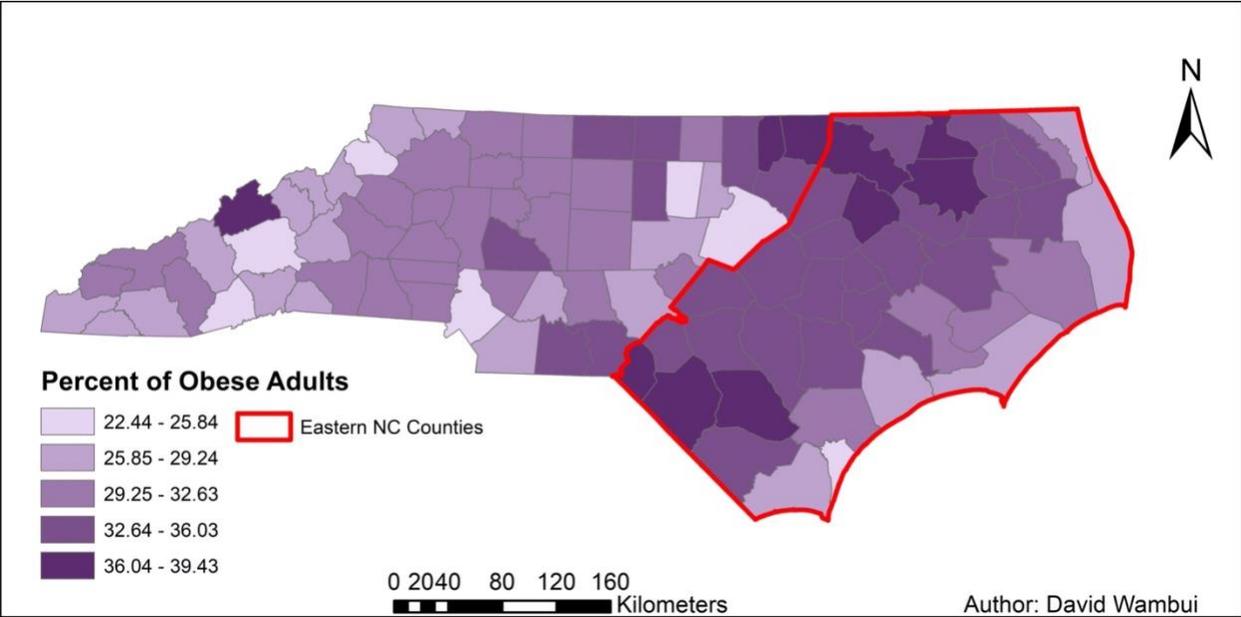


Figure 18. Percent of obese adults in NC between 2009 - 2018

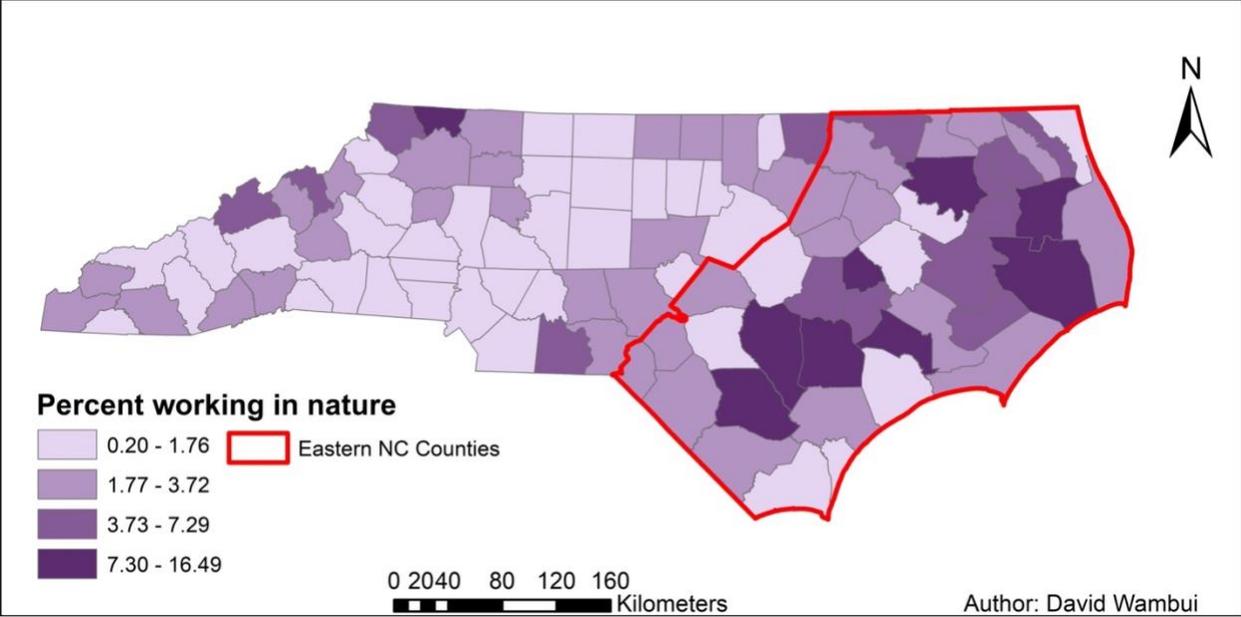


Figure 19. Percent of Workers in agriculture, mining, forestry, fishing, and hunting in NC between 2009 - 2018

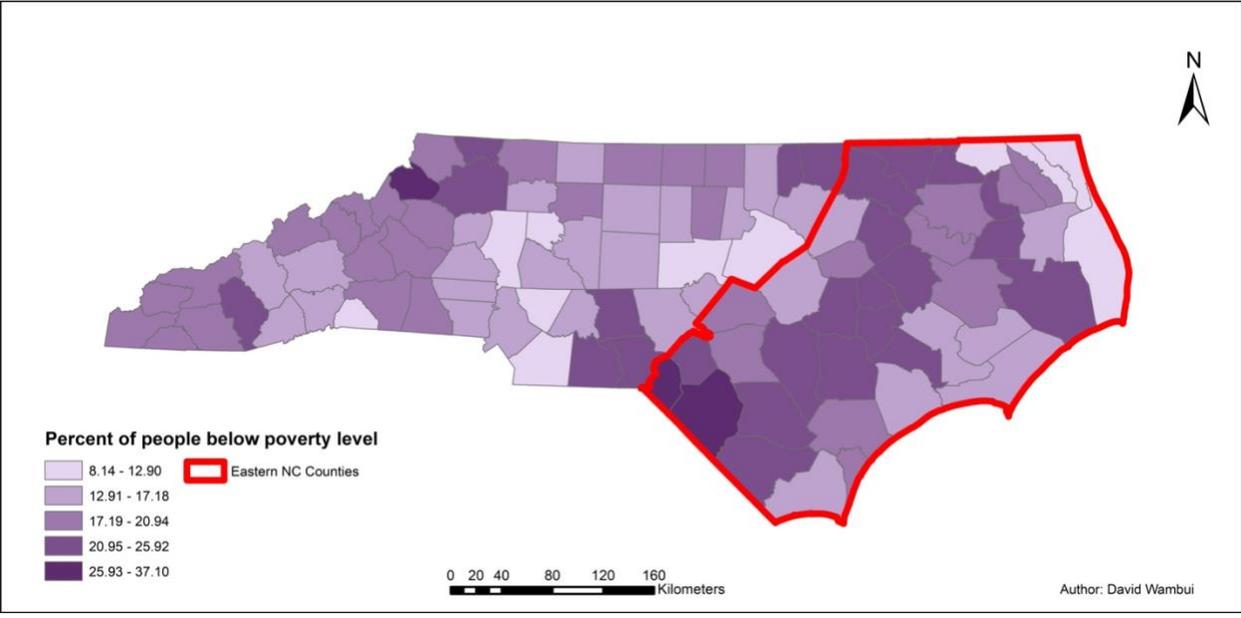


Figure 20. Percent of people (18-64 years) living below poverty level between 2012-2018

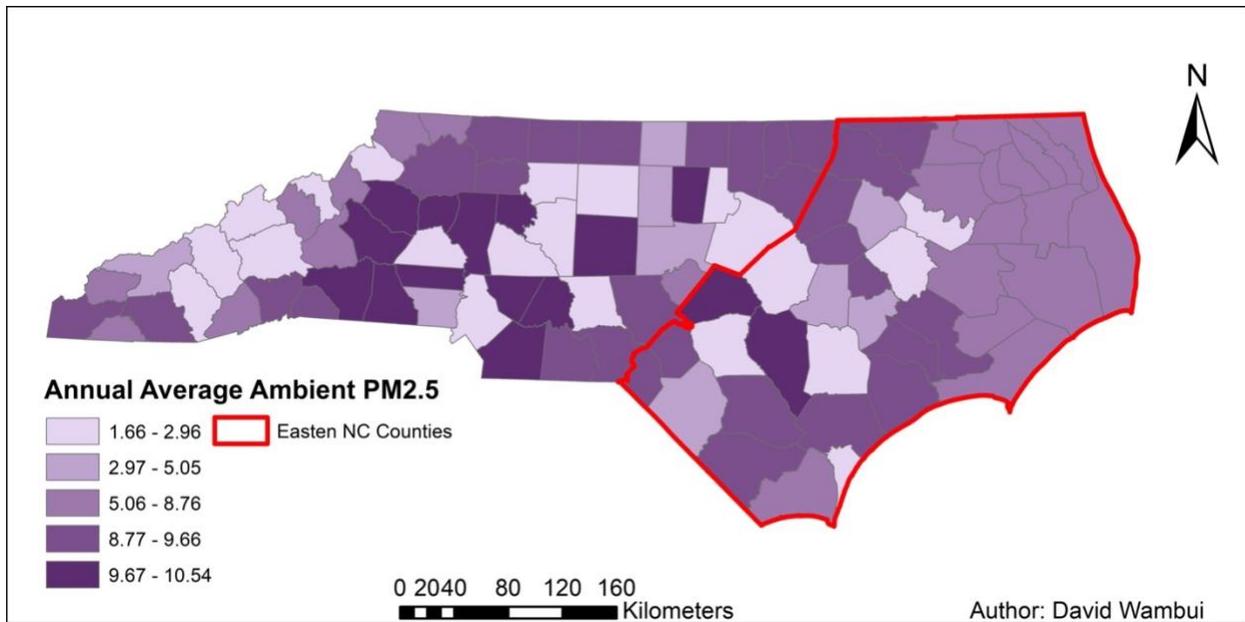


Figure 21. Annual average PM<sub>2.5</sub> in NC between 2009 - 2018

Multiple linear regression results shown in Table 7 indicates that region and percent of African Americans were statistically significant factors influencing sarcoidosis mortality rates in NC. Compared to the Eastern region, sarcoidosis mortality rates were estimated to be 45% lower in Piedmont region and 40% lower in Western region. One unit increase in percent of African Americans in a county was shown to result to 2% increase in the estimated mortality rate. Percent of population working in nature, percent of obese adults, percent of population below poverty level, percent of adults smoking, and annual average ambient PM<sub>2.5</sub> were not statistically significant. Overall, the risk factors evaluated accounted for 53% of observed variability in sarcoidosis mortality in NC as indicated by the model's adjusted R-squared of 0.53.

Table 7. Factors associated with sarcoidosis mortality in NC: Multiple linear regression using the eastern region as the intercept.

Characteristic	Estimate	SE	p-value
(Intercept)	0.63	0.44	0.16
Eastern	(ref)	-	-
Piedmont	-0.45	0.10	<0.001
Western	-0.40	0.14	0.005
Percent African American	0.02	0.00	0.001
Percent working in nature	0.02	0.02	0.21
Percent obese adults	-0.01	0.02	0.54
Percent of population below poverty level	0.01	0.01	0.41
Percent of adults smoking	0.01	0.01	0.57
Average annual PM2.5 ( $\mu\text{g}/\text{m}^3$ )	0.02	0.01	0.16
<i>Multiple R-squared = 0.57</i>			
<i>Adjusted R-squared = 0.53</i>			
<i>P-value = &lt;0.001</i>			

## Discussion

In this study, mortality rate by race were highest among African Americans followed by Whites in all the regions. The observed differences in death by race across the three regions were statistically significant. The percent of African Americans in a community was a significant predictor in the regression (Table 7). Furthermore, when analyzing county-level sarcoidosis mortality and social determinants of health, a clear positive trend is discernible between percent of African American and crude mortality rates (Figs. 14 & 17). Similar results have been reported in several studies (Iwai et al., 1994; Kearney et al., 2019; Mirsaeidi et al., 2015; Rybicki et al., 1997) where most deaths were reported among African Americans in comparison to other races and among females in comparison to males. While most deaths occurred among females, the difference between deaths among females and males across the three regions was not

statistically significant. A further assessment of the spatial distribution of sarcoidosis mortality rates indicated that the Eastern NC experiences high mortality sarcoidosis clusters compared to the Eastern/Piedmont and the Western regions.

The observed differences in sarcoidosis mortality by race suggest genetic predisposition in disease outcomes. Several studies have highlighted the role of the human leucocyte antigen (HLA) in sarcoidosis susceptibility and development (Iannuzzi, 2007; Judson et al., 2006; Rybicki et al., 1997; “Statement on Sarcoidosis,” 1999). The A\*1, B\*8, DQB1\*0602, DRB1\*1101, and DRB3\*0101 alleles have been suggested to influence susceptibility of individuals to development of sarcoidosis. The DQB1\*0201, and DRB1\*04 have been suggested to confer protection against development of sarcoidosis (Gray-McGuire et al., 2006). The differences in expression of these associated genes may account for the observed differences in disease pathophysiology and disease outcomes among different races and ethnicities. Although only few strong genetic associations have been demonstrated, it is believed that sarcoidosis is the end result of certain environmental agents inducing immune responses that are influenced by host’s genetic factors (Lazarus, 2009). The ACCESS study demonstrating familial predisposition may put individuals at a higher risk of developing sarcoidosis compared to individuals without familiar predisposition (Newman et al., 2004).

By region, most sarcoidosis deaths occurred in Eastern NC. Similarly, high mortality rates were observed in Eastern NC. Multivariate linear regression results indicated that region was significantly associated with mortality rate with Piedmont and Western regions showing significantly lower mortality estimates compared to Eastern region. Spatial analysis using a Local Moran’s I indicated the presence of high-high mortality rate clusters in Eastern NC and low-low mortality rate clusters in Western NC. These observed mortality clusters may have been

as a result of the demographic characteristics such as race and ethnicity as has been postulated by other studies (Kearney et al., 2019; Mirsaeidi et al., 2015; Swigris et al., 2011). Similar to other studies, this study showed that counties in Eastern NC have more African Americans compared to counties in Piedmont and Western NC which could explain this disproportionate distribution of sarcoidosis mortality (Stanford, 2018; Tippett, 2019). As seen in the choropleth maps, the high prevalence and overlap of percent of African Americans, people working in nature, poverty level, and obesity in counties in Eastern NC such as Bertie, Edgecombe, and Halifax could potentially drive incidence and prevalence rates of sarcoidosis. However, it's important to mention that some counties along the coast, a region referred to as Tidewater such as Currituck, Camden, Carteret, Onslow, and New Hanover had low sarcoidosis mortality rates compared to the rest of Eastern NC (Inner Coastal Plain). These counties also had lower prevalence of social determinants risk factors evaluated compared to other counties in the Eastern NC region which could explain the low sarcoidosis mortality observed. Furthermore, it was observed that crude mortality rates from sarcoidosis and the highest frequency of low-low county clusters occurred in the western portion of North Carolina. These trends in mortality align with lower observed prevalence in percent of African Americans, people working in nature, obesity, and poverty level. Collectively, the social determinants of health data were an effective tool at gauging at-risk sarcoidosis mortality, but more work is needed to further understand etiological factors behind sarcoidosis. For example, air quality was initially considered a potentially significant predictor. However, this study did not find this to be the case with an insignificant regression result (Table 7), little overlap between counties with high mortality rate and elevated PM2.5 (Figs. 14 & 21), and no statistically significant difference in PM2.5 across the three regions in NC (Appendix J).

A closer look at Eastern NC, health inequities have been noted to disadvantage and adversely affect the health of the population in the region. In addition, counties with the highest percent of obese adults were in Eastern NC. Several studies have highlighted health inequities such as poverty, lack of access to care, and poor housing that persist in the state of NC which disproportionately affect the people by race, geography, and income groups (Jones & Mansfield, 2014; Mansfield et al., 2001; Mansfield & Novick, 2012; Mirsaeidi et al., 2015). According to the Center for Health Disparities, 41 counties in Eastern NC generally experience significantly poorer health than the rest of the state (*Center for Health Disparities*, n.d.). Although there has been progress in addressing health disparities in NC, Eastern NC still lags behind (Duong et al., 2020). As a result, health issues such as obesity are more rampant in Eastern NC and present more significant problems compared to the Western and Piedmont regions. Obesity has been implicated as a risk factor for sarcoidosis (Cozier et al., 2015; Harpsøe et al., 2014; Wambui et al., 2020) which could drive prevalence and incidence rates in the region.

The relationship between sarcoidosis and obesity has been suggested to be two way (Cozier et al., 2018). Sarcoidosis patients may experience pain, fatigue, exercise intolerance, and cognitive limitations (Drent et al., 2015; Drent, Lower, et al., 2012). Severity of such symptoms may affect patient's physical activity and may result to weight gain (Cox et al., 2004). Additionally, treatment of sarcoidosis includes use of steroids which may increase redistribution of body fat and consequent weight gain, fatigue, and physical inactivity which may contribute to development of obesity. On the other hand, obesity has been associated with increased risk of developing autoimmune diseases including sarcoidosis (Belojević & Marić-Zivković, 2005;; Wambui et al., 2020). Obesity has also been shown to affect physiological respiratory factors such as lung volume, spirometry, gas exchange, and upper airway mechanical function in

absence of respiratory disease (Lin & Lin, 2012). For sarcoidosis patients, these changes may significantly influence disease development and disease outcome.

As a risk factor for sarcoidosis, recent prospective studies have provided data that assess the relationship between obesity and sarcoidosis. Adipose tissue that was once considered inert storage tissue has been shown to be highly active endocrine organ that plays an important role in inflammatory process through adipokine secretion (Cao, 2014; Denison et al., 2010).

Additionally, adipose tissue hosts immune cells that play a role in innate and adaptive immune responses (Juge-Aubry et al., 2005; Subramanian & Ferrante, 2009; Wozniak et al., 2009). In obese individuals, expansion of adipose tissue has been shown to incur changes in the population of immune cells. Such changes result to secretion of proinflammatory cytokines and loss of anti-inflammatory cytokines (Strissel et al., 2010). Similar changes in immune phenotype have been shown to occur in lungs of obese individuals which could lead to development of sarcoidosis which is believed to result from polarized immune response induced by persistent T-helper cells (Iannuzzi et al., 2007; Lugogo et al., 2012).

While access to care may determine the health outcome of an individual, environmental factors may play an important role in the development and progress of sarcoidosis (Izbicki et al., 2007; Judson, 2020; Saidha et al., 2012; Spagnolo et al., 2008). While PM 2.5 was seen to be higher in the Piedmont region, presence of other environmental factors in Eastern NC may influence incidence and mortality rates. Environmental exposures such as dust, pesticides, and animal waste having been associated with the risk of sarcoidosis, Eastern NC experiences the largest share of concentrated animal feeding operations (CAFOs) (NC Environmental Quality, 2021) which could as well play a role in the disproportionate sarcoidosis mortality in the state. A

more deterministic approach in understanding the distribution of environmental factors associated with sarcoidosis would help in addressing such concerns.

This study utilized longitudinal data obtained from CDC WONDER tool to demonstrate the sarcoidosis mortality temporal trend and spatial distribution in NC from 2000 to 2019. Also, the study looked at sarcoidosis risk factors that could be associated with sarcoidosis in the region between the study period covered. The study demonstrated the differences in sarcoidosis mortality trends by across Eastern, Piedmont and Western NC regions. The study indicated statistically significant higher sarcoidosis mortality in the Eastern region compared to the rest of the state. The spatial analysis helped to identify high mortality clusters in the Eastern region and low mortality clusters in the Western region. Additionally, the spatial distribution of sarcoidosis risk factors demonstrated health inequities are present in Eastern NC.

One limitation of the study was the suppression of age-adjusted sarcoidosis mortality by CDC WONDER due to the small number of deaths observed in some counties. This limited the ability to explore age-adjusted sarcoidosis mortality clusters in the state and thereby compelling us to use crude mortality rates to demonstrate clustering. Also, the year ranges did not match up between the two data sources used and therefore could not allow inferential statistical analysis to explore potential associations between mortality rates and risk factors. Additionally, CDC WONDER mortality data is derived from death certificates, and it is possible that these certificates may not have been correctly completed or causes and/or contributions to death may be overlooked. With sarcoidosis being a disease of exclusion due to its similarity with other diseases as well as non-specificity of clinical presentation, there is a chance that a death from sarcoidosis may not notated or a death from another cause may be listed as a sarcoidosis death in the death certificate. This would either result in underestimation or overestimation of sarcoidosis

mortality rates respectively. Also, the fact that prevalence of sarcoidosis is higher in Eastern NC compared to the other regions could influence mortality rates regardless of other risk factors included in this analysis.

Another limitation of the study was the inability to use Poisson regression to model predicted crude sarcoidosis mortality rates due to data limitations. Ideally, Poisson regression would have been a better fit for the data compared to an ordinary least squares (linear) regression model in estimating the rates. Naturally, a rate can only take 0 as the lowest estimate and cannot take negative values. A linear regression model can yield negative estimates which would not sense. However, to fit a Poisson regression model for mortality rates data, an offset of follow time would need to be added to the model. The mortality rate data from CDC WONDER does not provide the follow up time and therefore it was not possible to fit a Poisson regression.

### **Conclusion and Implications for Public Health Practice**

This study being the first to explore sarcoidosis mortality clustering in NC has provided a basis in which interventions, policies, and programs can be instituted and tailored to address the observed differences. As other studies have pointed out, addressing health inequities as well as health disparities may help in addressing these challenges. Similarly, a more focused look at some of the risk factors that could be driving the high sarcoidosis mortality in Eastern NC would be beneficial in understanding the phenomenon better. Additionally, a more focused approach may help in creating recommendations that would enable remediation of the problems.

## **CHAPTER 5: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS AMONG SARCOIDOSIS PATIENTS IN THE ECUSAR**

### **Introduction**

Sarcoidosis is an inflammatory, multi-system granulomatous disorder characterized pathologically by the presence of noncaseating granulomas (Chen & Moller, 2008). The etiology of the disease remains relatively undetermined, however a combination of genetic variants and/or the influence of environmental factors have been suggested. Environmental and occupational exposures such as exposure to pollen, rural residence, animal dust, molds, and silica have been indicated to increase incidence and prevalence of sarcoidosis (Chen & Moller, 2008). Clinical and histologic comparability between sarcoidosis and infectious granulomatous disease suggest etiologic similarities. Newer molecular techniques have allowed close examination and generation of evidence on the role of certain microbial antigens in development of sarcoidosis (Gupta et al., 2007; Hance, 1998). Genetic and family studies have identified genetic susceptibility among individuals (Gray-McGuire et al., 2006; Iannuzzi, 2007; Moller et al., 2017).

Although mortality rates have been increasing over time, the prognosis of sarcoidosis is relatively positive, and sarcoidosis rarely leads to death. For diagnosed individuals, clinical considerations for disease treatment are often based on disease progression and presentation of symptoms (Iannuzzi & Fontana, 2011; Judson et al., 2012; Murray et al., 2011). However, variations of symptomatic response and toxicity profiles between patients vary, which add to the complexity of decision making for clinicians. Among patients receiving treatment, the presence of noncaseating granulomatous inflammation can lead to organ damage resulting in co-morbidities and decreased health-related quality of life issues, such as decreased work ability

(Gerke, 2014). In most cases, a multi-disciplinary disease management approach is the prescribed and preferred treatment.

The incidence and prevalence of sarcoidosis and its clinical presentation vary greatly across geographical regions, gender, ethnicity, and age group. The exact incidence and prevalence rates of sarcoidosis have been difficult to estimate mainly due to undiagnosed cases, variability in ascertainment, inconsistency case definition, disease presentation variability and presence of other commonly recognized granulomatous diseases such as tuberculosis.

In the United States, Black or African American race has consistently been shown to have higher incidence and prevalence rates compared to Whites. Black women are affected the more compared to Black men (Hena, 2020). Incidence rate among Black people has been estimated to decrease from 35.5 per 100,000 in 1994 to 17.8 per 100,000 in 2013. Among Whites, the incidence rates have been estimated to fall from 10.9 per 100,000 in 1994 to 8.1 per 100,000 in 2013. (Baughman et al., 2016a; Rybicki et al., 1997). Similarly, the prevalence rates have been estimated to be higher among Black people compared to other races. In 2016, the prevalence rate of sarcoidosis in Black people in the US was estimated at 141.4 per 100,000 while that of White people was estimated at 49.8 per 100,000 (Baughman et al., 2016a). In the same study, women were estimated to be twice as likely to have sarcoidosis compared to men. Black women had the highest prevalence rate at 178.5 per 100,000 (Baughman et al., 2016a).

Despite the relatively high incidence and prevalence rates, sarcoidosis mortality in the US remains relatively low. In 2019, Kearney et al. estimated an overall sarcoidosis mortality rate of 2.9 per 1,000,000. The observed mortality was higher among Black people at 15.0 per 1,000,000 compared to White people at 1.4 per 1,000,000 (Kearney et al., 2019). Black women had the

highest morality rate estimated at 17.0 per 1,000,000 (Kearney et al., 2019). Regionally, the southern US had the highest mortality rate compared to the other three regions.

Available data on crude and age-adjusted estimates, geography, etc., for selected causes of death can be queried and downloaded from CDC WONDER. In recent findings by indicated in the previous chapter (Chapter IV) sarcoidosis mortality in NC was examined (2000-2018) and found that counties that were rural, poor and had a higher percent of Black or African Americans had significantly higher unadjusted and age-adjusted mortality rates in Eastern NC (2021).

In 2018, ECUSaR, longitudinal registry was created with the purpose of gathering data to learn more about the disease. The ECU Sarcoidosis clinic is recognized as a Sarcoidosis Center of Excellence by the Foundation for Sarcoidosis Research and World Association for Sarcoidosis and Other Granulomatous Disorders (WASOG). The program is highly unique because of its shared speciality faculty and the unique needs of the patient population. The ECUSaR is a registry of patients seen in the ECU sarcoidosis clinic. It includes demographic, clinical, radiographic and other patient data and information and is highly complete. The ECUSaR database contains useful information but has not been fully explored to examine basic similarities and differences in the clinical characteristics of its patient population. A study to summarize this data could provide meaningful results so that clinicians are better informed about the patients they are caring for in Eastern NC.

The overarching aims of this project were two-fold. First to examine demographics and clinical characteristics of sarcoidosis patients in the ECUSaR registry to detect common themes (symptoms and socialdemographic characteristics). Second, inform high risk populations groups (primarily, underserved African Americans in rural areas) by developing sarcoidosis information brochure to raise awareness and better inform high risk patient population of ECU Sarcoidosis

clinic medical treatment services. The deliverables of this project will be useful for enabling healthcare managers and physicians develop effective programs that will be suitable in managing sarcoidosis patients in the region.

## **Methods**

### **Study design and data source**

This was an exploratory study that sought to examine the sociodemographic characteristics of sarcoidosis patients that are currently enrolled in the ECUSaR. Data for this project was obtained from ECUSaR, a longitudinal registry of sarcoidosis patients seen at the ECU pulmonary and sarcoidosis clinic that was established in 2018. Patients currently enrolled in the registry are mostly from Eastern NC as shown in Figure 21. The purpose of the registry is to gather demographic, clinical, radiographic, and other important data points that would be used to help understand the socioeconomic determinants of disease, disease exposure risk factors, management, and treatment modalities for sarcoidosis patients in eastern NC. The study was approved by ECU IRB (UMCIRB #: 06-0312). The IRB approval and approval letter are attached in Appendix A and Appendix B respectively. Table 8 summarizes the demographic and clinical characteristics evaluated in this study.

Table 8. Summary of ECUSaR patients' characteristics evaluated

<b>Continuous</b>	<b>Nominal/Categorical</b>
Age	<ol style="list-style-type: none"> <li>1. Race:</li> <li>2. Black/African American</li> <li>3. Caucasian</li> <li>4. Other</li> </ol>
BMI	BMI Categories (Adiposity): <ol style="list-style-type: none"> <li>1. Underweight</li> <li>2. Normal</li> <li>3. Overweight</li> <li>4. Obese</li> </ol>
Age at Diagnosis	Biopsy Positive: <ol style="list-style-type: none"> <li>1. Yes</li> <li>2. No</li> </ol>
Predicted % forced expiratory volume in 1 second (FEV1)	Smoking Status: <ol style="list-style-type: none"> <li>1. Never (&lt;100 cigarettes in a lifetime)</li> <li>2. Current smoker</li> <li>3. Ex-smoker</li> <li>4. Other</li> </ol>
Absolute FEV1	Marijuana Use: <ol style="list-style-type: none"> <li>1. Never</li> <li>2. Current user</li> <li>3. Not specified/stated</li> </ol>
Predicted % forced vital capacity (FVC)	Family history of Sarcoidosis: <ol style="list-style-type: none"> <li>1. Yes</li> <li>2. No</li> <li>3. Not known/stated</li> </ol>
Absolute FVC	Connective Tissue Disease: <ol style="list-style-type: none"> <li>1. Yes</li> <li>2. No</li> <li>3. Not Known/stated</li> </ol>
Predicted % diffusion lung capacity for carbon monoxide (DLCO)	Lung Scadding stage: <ol style="list-style-type: none"> <li>1. Normal</li> <li>2. Bi hilar LAD</li> <li>3. Hilar LAD + Parenchymal</li> <li>4. Parenchymal only</li> <li>5. Fibrotic lung</li> <li>6. CXR not available</li> <li>7. Other</li> </ol>
Absolute DLCO	TLC (total lung capacity): <ol style="list-style-type: none"> <li>1. Restricted</li> <li>2. Normal</li> </ol>
Total lung capacity (TLC)	FEV1/FVC: <ol style="list-style-type: none"> <li>1. Obstructed</li> <li>2. Normal</li> </ol>
6-minute walk distance (6MWD)	Lung fibrosis present: <ol style="list-style-type: none"> <li>1. Yes</li> <li>2. No</li> </ol>
Fatigue Assessment Score (FAS)	Sex: <ol style="list-style-type: none"> <li>1. Male</li> <li>2. Female</li> </ol>

## **Data Analysis**

Descriptive data analysis was conducted in R (R Core Team, 2020) and charts were developed in Microsoft Excel. Stratified by sex, means and standard deviations (SD) were used to summarize data for normally distributed continuous variables, medians and Q1 and Q3 for non-normally distributed continuous variables while proportions were used to summarize categorical data. A matrix of scatterplots with histograms was used to visualize the distributions of continuous variables (Appendix K) and a Shapiro test was used to determine whether the variable was normally or non-normally distributed (Appendix L). Comparisons were made between males and females using an independent t-test for age, predicted diffusion lung capacity for carbon monoxide (DLCO), absolute DLCO which were normally distributed, while a Wilcoxon test was conducted for BMI, age at diagnosis, forced expiratory volume in 1 second (FEV), forced vital capacity (FVC), fatigue assessment score (FAS), and six-minute walk distance (6-MWD) which were all non-normally distributed. A chi-square test of independence was conducted for the categorical variables listed in Table 8 to assess any statistically significant differences between males and females. Evaluating these differences was particularly important as literature has postulated that sex could be a risk factor for sarcoidosis as well as clinical manifestation where women could be more affected compared to men (Birnbaum & Rifkin, 2014; De Vries et al., 1999; Ungprasert et al., 2017a).

## **Results**

As shown in Table 9, there were 167 (32.5%) male patients and 347 (67.5%) female patients. The mean age and standard deviation of male patients were 49.5 years and 13.2 while that of female patients was 55.7 years and 13.0 respectively. This difference in age distribution was statistically significant with a p-value <0.001. About 85% of patients in the registry were

Black/African American and about 14 % were Caucasian/White. The overall median body mass index (BMI) was 30.4 with Q1 and Q3 being 26.4 and 37.2 respectively. Female patients had a significantly higher median BMI (33.0, Q1 = 27.6 and Q3 =39.1) compared to that of males (29.0, Q1 = 24.6 and Q3 = 32.2). Similarly, women had a significantly higher median age at which sarcoidosis was diagnosed (40.0, Q1 = 30.2 and Q3 = 49.0) compared to men (36.0, Q1 = 29.0 and Q3 = 45.0). Twice as many men than women were reported to be current smokers (26.2%). Overall, 32.0% of patients reported having a family history of sarcoidosis. With respect to chest radiography, 33.7% and 26.5% were Scadding stages I and II respectively at diagnosis. For pulmonary function tests, the overall median of predicted forced expiratory volume in 1 second (FEV1) was normal at 80.0%. The median FEV1 for men was significantly lower (78.0, Q1 = 62.5 and Q3 = 91.0) compared to that of women (81.0, IQR = 69.0 – 94.0) with a p-value of 0.02. About 42% of the patients had restricted total lung capacity (TLC <80). FEV1/FVC ratio indicated that approximately 20% of patients had obstructed airways. Among the 81 patients that were assessed for the presence of lung fibrosis, 48.1% showed the presence of fibrosis. The overall median of the 6MWD was 381 meters (Q1 = 317 and Q3 = 434). Women had a lower 6MWD median of 375 meters (Q1 = 291 and Q3 = 427) compared to men (386 meters, Q1 = 332 and Q3 = 447).

Table 9. Demographic and clinical characteristics of ECUSaR patients

<b>Characteristics</b>	<b>[ALL] N=514</b>	<b>Male N=167</b>	<b>Female N=347</b>	<b>p-overall</b>
Age [mean, SD]	53.7 (13.3)	49.5 (13.2)	55.7 (13.0)	<0.001
Race				0.856
Black/ African American	438 (85.4%)	141 (84.9%)	297 (85.6%)	
Caucasian	73 (14.2%)	24 (14.5%)	49 (14.1%)	
Other	2 (0.39%)	1 (0.60%)	1 (0.29%)	
BMI [median, Q1; Q3]	30.4 [26.4;37.2]	29.0 [24.6;32.2]	33.0 [27.6;39.1]	0.001
BMI Categories				0.010
Underweight	6 (3.02%)	4 (5.41%)	2 (1.60%)	
Normal	25 (12.6%)	14 (18.9%)	11 (8.80%)	
Overweight	52 (26.1%)	23 (31.1%)	29 (23.2%)	
Obese	116 (58.3%)	33 (44.6%)	83 (66.4%)	
Age at diagnosis [median, Q1; Q3]	39.0 [30.0;48.0]	36.0 [29.0;45.0]	40.0 [30.2;49.0]	0.007
Biopsy done				1.000
Yes	452 (93.4%)	145 (93.5%)	307 (93.3%)	
No	32 (6.61%)	10 (6.45%)	22 (6.69%)	
Biopsy positive				0.150
Yes	337 (95.5%)	111 (98.2%)	226 (94.2%)	
No	16 (4.53%)	2 (1.77%)	14 (5.83%)	
Smoking status				<0.001
Never Smoker [< 100 cigarettes/lifetime]	261 (51.5%)	60 (36.6%)	201 (58.6%)	
Current Smoker	85 (16.8%)	43 (26.2%)	42 (12.2%)	
Ex-Smoker	154 (30.4%)	58 (35.4%)	96 (28.0%)	
Other	7 (1.38%)	3 (1.83%)	4 (1.16%)	
Marijuana use				<0.001
Never Used marijuana	213 (54.8%)	49 (38.6%)	164 (62.6%)	
Current Marijuana Use	19 (4.88%)	15 (11.8%)	4 (1.53%)	
Prior use of Marijuana	52 (13.4%)	24 (18.9%)	28 (10.7%)	
Not specified / Not Stated	105 (27.0%)	39 (30.7%)	66 (25.2%)	
Family History of Sarcoidosis				0.953
Yes	136 (32.0%)	44 (32.4%)	92 (31.8%)	
No	265 (62.4%)	85 (62.5%)	180 (62.3%)	
I don't know/Not stated	24 (5.65%)	7 (5.15%)	17 (5.88%)	
Connective Tissue Disease				0.460
Yes	49 (13.1%)	13 (10.7%)	36 (14.2%)	
No	281 (75.1%)	91 (75.2%)	190 (75.1%)	
I don't Know/Not stated	44 (11.8%)	17 (14.0%)	27 (10.7%)	

Table 9 Continued

Characteristics	[ALL] N=514	Male N=167	Female N=347	p-overall
Lung scadding stage [chest x-ray]				
0 [Normal CXR]	60 (14.6%)	15 (11.5%)	45 (16.0%)	
1 [Bil hilar LAD]	139 (33.7%)	39 (30.0%)	100 (35.5%)	
2 [Hilar LAD + Parenchymal dx]	109 (26.5%)	38 (29.2%)	71 (25.2%)	
3 [Parenchymal dx only]	61 (14.8%)	20 (15.4%)	41 (14.5%)	
4 [Fibrotic lung dx]	13 (3.16%)	6 (4.62%)	7 (2.48%)	
CXR done but results not available	28 (6.80%)	10 (7.69%)	18 (6.38%)	
Other - write into the bubble	2 (0.49%)	2 (1.54%)	0 (0.00%)	
Predicted % FEV1 [median, Q1; Q3]	80.0 [65.0;93.0]	78.0 [62.5;91.0]	81.0 [69.0;94.0]	0.023
FEV1 Absolute [median, Q1; Q3]	2.04 [1.67;2.70]	2.82 [2.25;3.30]	1.87 [1.52;2.35]	<0.001
Predicted % FVC [median, Q1; Q3]	82.0 [70.0;92.0]	82.0 [68.5;92.5]	82.0 [70.0;91.0]	0.957
FVC Absolute [median, Q1; Q3]	2.62 [2.12;3.37]	3.61 [3.01;4.26]	2.40 [1.96;2.79]	<0.001
Predicted % DLCO [median, Q1; Q3]	71.5 (24.3)	73.7 (27.7)	70.4 (22.4)	0.314
DLCO Absolute [median, Q1; Q3]	19.4 (8.52)	24.3 (8.43)	17.7 (7.93)	<0.001
TLC				0.157
restricted	125 (41.7%)	47 (48.0%)	78 (38.6%)	
normal	175 (58.3%)	51 (52.0%)	124 (61.4%)	
FEV1/FVC Category				0.011
obstructed airways	68 (20.0%)	31 (28.4%)	37 (16.0%)	
non-obstructed airways	272 (80.0%)	78 (71.6%)	194 (84.0%)	
Lung fibrosis present				1.000
Yes	40 (49.4%)	12 (50.0%)	28 (49.1%)	
No	41 (50.6%)	12 (50.0%)	29 (50.9%)	
Fatigue Assessment Score [median, Q1; Q3]	24.0 [19.0;29.2]	24.0 [18.0;29.0]	24.0 [19.0;30.0]	0.700
6-MWD [meters] [median, Q1; Q3]	381 [317;434]	386 [332;447]	375 [291;427]	0.052

As shown in Figure 22, the most common organ involvement observed among the patients was the lungs at 96% followed by the skin and extrathoracic lymph nodes involvement at 25% and 21% respectively. Muscle and bone marrow involvement was the least common organ involvement observed at 2% and 1% respectively. Those who had been followed up for

less than one year and those who had been followed up for 3 years had the highest median number of organs involved at 2, IQR = 0 – 7 as shown in Table 10.

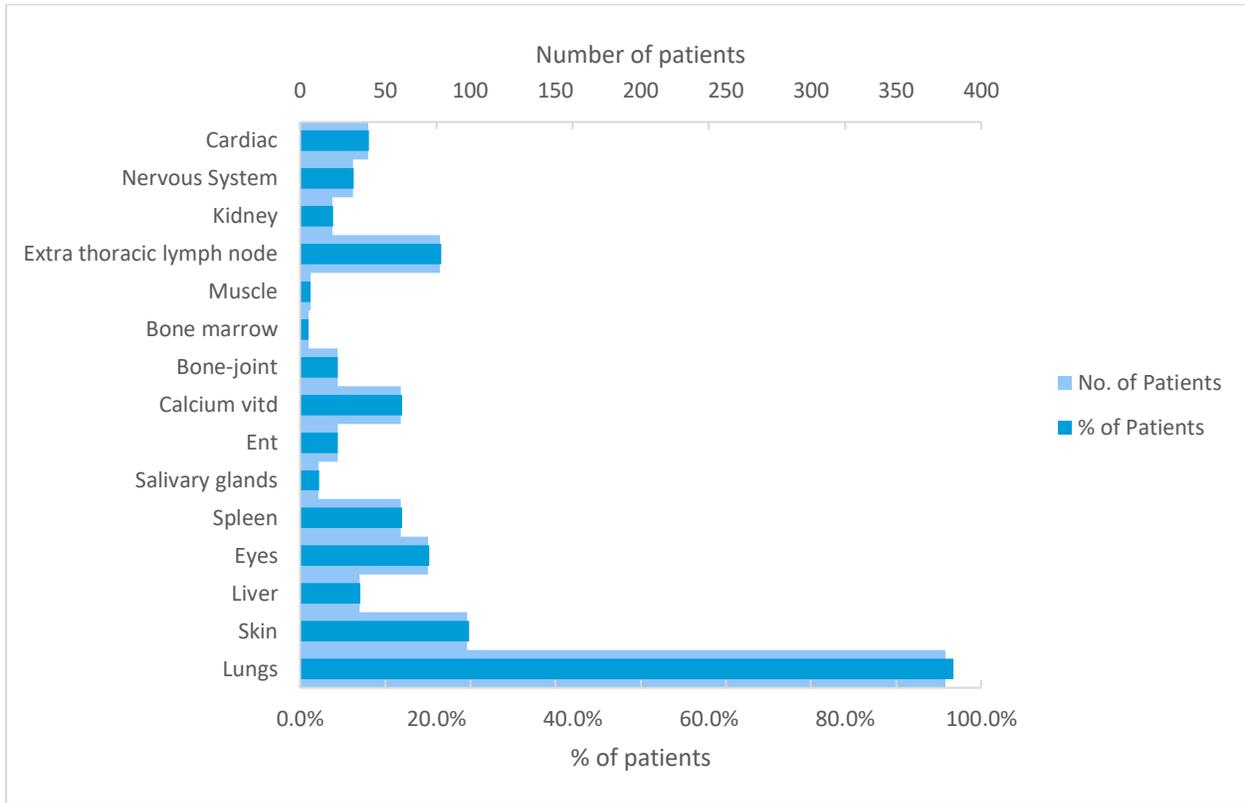


Figure 22. Organ involvement among ECUSaR Patients

While 9% of the patients did not have any comorbidity, 91% had at least 1 comorbidity. One patient had 11 comorbidities as shown in Figure 23. Regarding comorbidities, hypertension was the most common one at 57% followed by obesity and diabetes at 36% and 30% respectively. However, pulmonary hypertension was among the less common comorbidities among the patients as shown in Figure 24. Among the most reported symptoms include dyspnea, coughing, and constitutional symptoms (fever, chills, night sweats, poor appetite, weight loss) at 63%, 48%, and 32% respectively as shown in Figure 25. A closer look at whether patients were on medication indicated that 64% of patients received some medication. Prednisone was the most common treatment received at 36% as shown in Figure 26

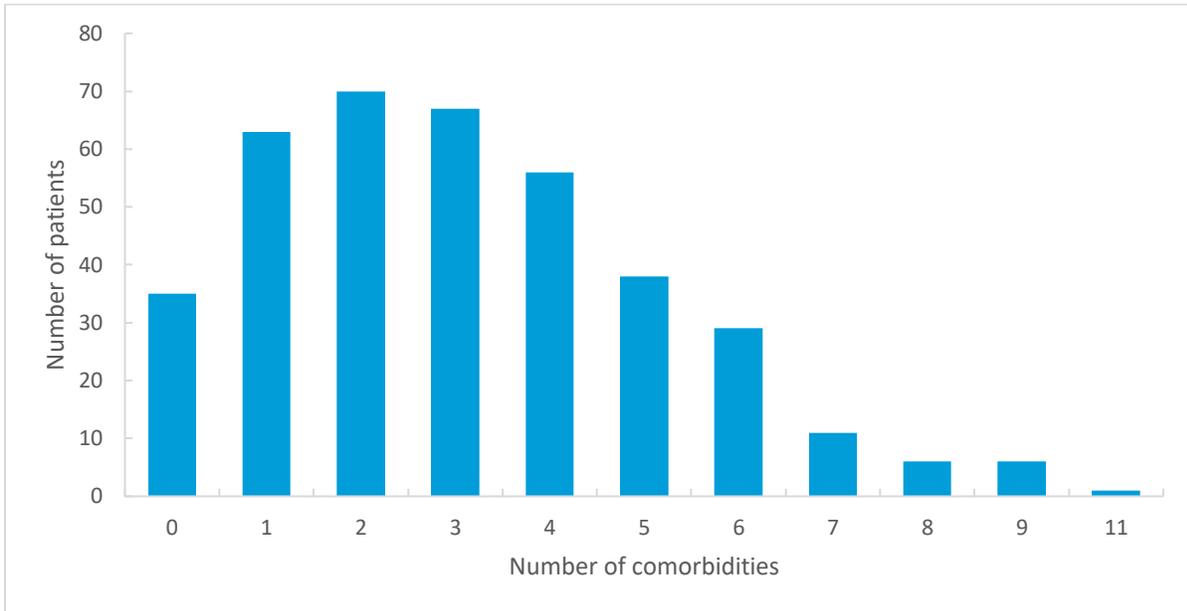


Figure 23. Number of comorbidities among ECUSaR patients

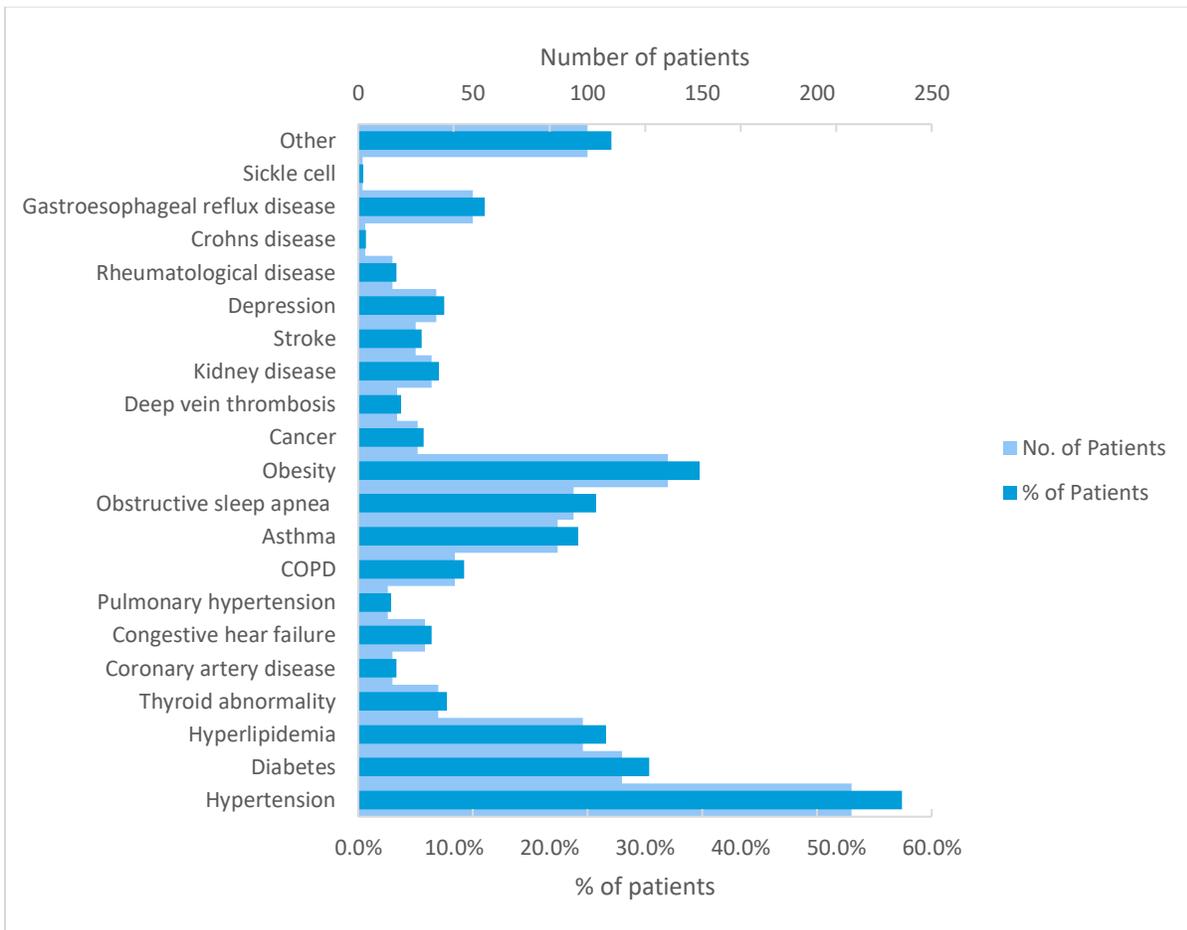


Figure 24. Comorbidities among ECUSaR patients

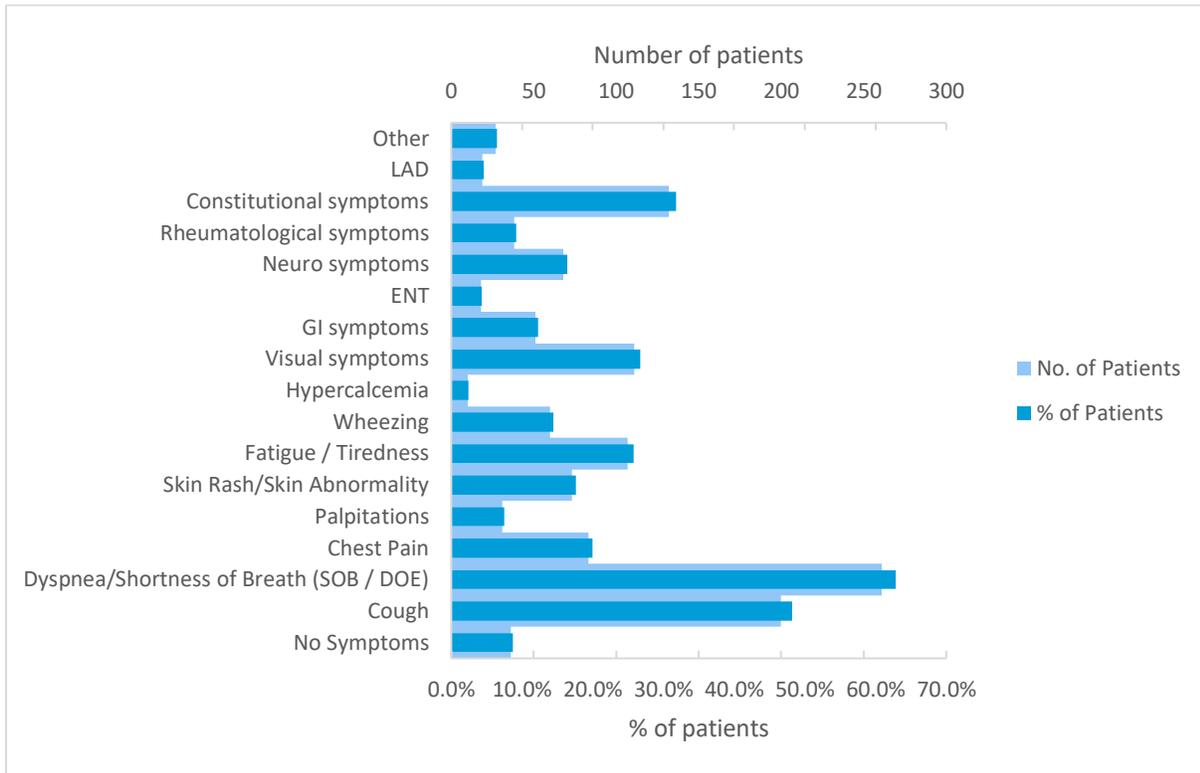


Figure 25. Common symptoms among ECUSaR patients

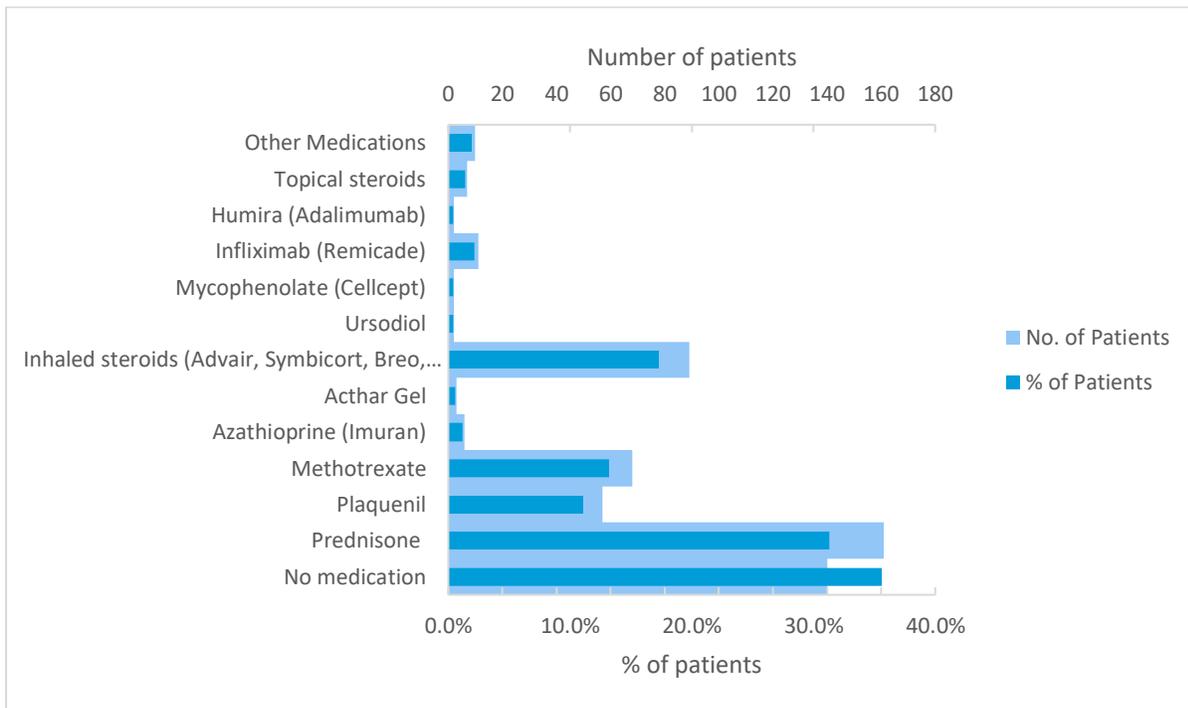


Figure 26. Medication use among ECUSaR patients

## Discussion

In this registry, the most common organ involved was the lungs. There were 326 patients (42%) who were classified as either a biopsy confirmed, highly probable, or at least possible for lung sarcoidosis. This mirrors observations that have been made in similar studies (Freemer & King, 2001; Markevitz et al., 2017; Te et al., 2020; Ungprasert et al., 2017b). While a causal relationship has not been established, the interaction between environmental factors and genetics and the role they play in the pathogenesis of sarcoidosis, differences, and the nature of exposure may contribute to the observed high incidence cases of pulmonary involvement. About 43% of patients in the registry had lung scadding stage II or III while about 3% had stage IV usually indicative of lung fibrosis and often requiring closer management by a physician. While this study did not assess mortality, pulmonary sarcoidosis has been shown to result in sarcoidosis-related morbidity and mortality (Swigris et al., 2011). Pulmonary sarcoidosis has also been associated with rising healthcare costs and hospitalizations (Gerke, 2014). Additionally, pulmonary sarcoidosis affects the quality of life through combinations of symptoms that may sometimes require treatment to improve disease progression (Judson et al., 2019).

While most patients received treatment, there were 129 (23%) patients who did not receive treatment. While some symptoms may resolve spontaneously, sarcoidosis patients need to be monitored and treated as indicated. However, this proportion was less than that observed by Judson et al. (2012) where up to 40% of sarcoidosis patients were not receiving treatment. The most common medication administered was prednisone and the dosage was relative to the level of inflammation observed in the patient. The inhaled steroid was the second most common medication administered at 16%. This is in line with the pathogenesis of sarcoidosis where most patients had pulmonary involvement

Skin, extrathoracic lymph nodes, eye, and spleen were the most common organ involvement observed in this cohort. Other studies have also indicated skin, eye, and extrathoracic lymph nodes as common extrathoracic organs involved in sarcoidosis (Judson et al., 2012). Spleen involvement has not been reported as common organ involvement in other studies. However, a study conducted in India indicated that spleen involvement could account for 10% to 50% of sarcoidosis cases (Sreelesh et al., 2014). However, differences observed in extrapulmonary involvement may be attributable to population differences, exposure scenarios, and follow-up times. Assessment of follow-up times and average organ involvement indicated that patients who had been followed up for less than one year and those that had been followed up for 3 years had a mean number of organs involved of 2.38 and 2.24 respectively. A similar study by Judson et al. (2012) indicated that the number of organs involved increased by follow-up time. This was similar to our study where the number of organs involved increased for individuals that had been followed up for at least a year. The ACCESS study also had similar observations where the study indicated that a patient developed 0.3 new organ involvement within a 2-year follow-up period (Freemer & King, 2001).

Another important finding in this study was that the mean BMI was 32.8. Women were observed to have a higher mean BMI (35.3) compared to men. In a systematic review conducted by Wambui et al. (2020), BMI was indicated as a risk factor for the development of sarcoidosis (Wambui et al., 2020). The relationship between obesity and sarcoidosis remains unclear on temporality as defined in Hill's criteria (Rothman & Greenland, 2005). Studies have also indicated that corticosteroid medication such as that used in sarcoid patients may result in weight gain and obesity (Livingstone et al., 2000; Pasquali et al., 1993).

One limitation of this study was that some patients had missing data. Missing data on some patient records or incorrect entries is a potential way of introducing bias in a study which might skew the results during data analysis. Secondly, approximately 85% of all participants were Black/African American. In this regard, the finding obtained may not be generalizable across other different populations whose racial demographics are dissimilar. Another limitation is the follow-up period. While sarcoidosis may be chronic, patients in this registry had only been followed up to a maximum of three years. This phenomenon may not be ideal in determining phenotypic characteristics of the patients such as the number of organs involved which might be influenced by follow-up time.

### **Conclusion and Implications for Public Health Practice**

The results of this project created two deliverables; 1) assisted ECUSaR healthcare professionals with insight into the ECUSaR patient population, thus providing understanding of the demographic and clinical characteristics of their sarcoidosis patient population, and 2) developed an ECUSaR informational brochure (Appendix M) to help inform, educate, and increase visibility of sarcoidosis screening and patient management to targeted populations in Eastern NC. Additionally, this analysis provides an understanding of sarcoidosis incidence and morbidity in Eastern NC. Historically, Eastern NC experiences a higher burden of disease compared to other regions in the state (Center for Health Disparities, 2021). The insights that this study provides will be instrumental to health care managers, policymakers, and physicians in understanding the distribution of sarcoidosis cases in the region. This study also created a foundation on which other studies can be built on to focus on specific attributes highlighted in the descriptive analysis. It would be important to study spatial and temporal distribution of

comorbidities that were common among the patients to help uncover possible patterns that may exist in Eastern NC.

## CHAPTER 6: CONCLUSION

Overall, this study has provided important highlights in the epidemiology of sarcoidosis in NC. The study has as well highlighted the spatial distribution of sarcoidosis-related mortality in the state with a closer look at Eastern NC. Spatial cluster analysis of sarcoidosis-related mortality identified the existence of high mortality clusters in counties in Eastern NC compared to the rest of the state. The structure of this dissertation was designed to synthesize literature across the world on risk of sarcoidosis following exposure to respirable particles in chapter 3. This review and meta-analysis were to set precedence for chapter 4 which sought to assess sarcoidosis mortality in NC as well as associated risk factors identified in literature review chapter as well as chapter 3. After describing spatial distribution of sarcoidosis mortality burden in NC, chapter 5 was set to zoom into eastern NC region and was focused on analyzing and understanding the sociodemographic and clinical characteristics of sarcoidosis patients in the regions.

Systematic review of literature and meta-analysis consolidated evidence regarding exposure to respirable particles and the risk of developing sarcoidosis. With NC being among the highest states (fourth) in the country in terms of sarcoidosis burden, looking at the possible risk factors may highlight important considerations for public health including identifying communities and populations at risk and mortality and/or morbidity driving forces which may then be helpful in formulating possible solutions to address the challenges. It is concerning that exposure to respirable particles especially with occupational exposures may put individuals at risk of developing sarcoidosis or other respiratory diseases. Focusing on Eastern NC, prevalence of sarcoidosis risk factors including percent of African Americans, percent of people working in Agriculture, percent of obese adults were prevalent in comparison to the Piedmont and Western

regions. These factors were seen to be associated with mortality the high mortality rates. Eastern NC as a region has the largest share of health inequities According to the NC Department of Environmental Quality, most swine farm permits have been issued in Eastern NC (Appendix N). Hog farms have been identified as considerable sources of environmental pollution that could affect the health of those around the hog firms. Data from Environmental Protection Agency also shows that there is considerable amount of toxic substances released in the region (Appendix O). While this study could not answer the questions on whether these circumstances could be contribution to observed sarcoidosis mortality burden, they do raise pertinent issues around toxic substances regulation, environmental justice, waste management, agricultural practices, build environment and occupational health and safety.

As has been discussed earlier in the study, certain exposures to toxic chemicals and respirable particles could put individuals at increased risk of developing sarcoidosis. Managing releases of both toxic and non-toxic pollutants from industrial and/or agricultural facilities is important to mitigate uncontrolled releases of dangerous substances into the environment, without which could result in unintentional exposures among communities adjacent to these facilities and those that live downstream and/or downwind. Agricultural activities including use of chemical fertilizers and pesticides could also result to release of these chemicals into ambient air and thereby resulting to exposures among those living within the farms or near the farms. Enforcement of regulations such as those provided by The Clean Air Act is paramount to the success of environmental preservation and conservation efforts to safeguard environmental health, thereby protecting public health in communities surrounding land uses that generate and release these pollutants.

Occupational health and safety outlines and highlight the importance of occupational protection of workers against workplace exposures. With Eastern NC hosting most of animal feeding operations in the state, it is pertinent that workers in these facilities are protected against hazardous exposures including dust from feeding lots and animal housing units during work. The Occupational Safety and Health Administration (OSHA) has provided regulations that help protect workers against exposures at work and a more dedicated enforcement of the provisions provided would help mitigate workplace exposures. Additionally, consideration of enforcing the regulation for workplaces that are currently exempt such as those with 10 or less employees and those that do not provide temporary housing for employees would help tighten the loopholes (OSHA, 1998) .

The North Carolina Department of Environmental Quality oversees issuance of animal operation permits and conducts yearly inspection in these facilities to ensure adherence to set standards. The department must ensure they assess laid out procedures on potential exposures to workers and those living around the facilities and plans to mitigate or minimize the risk of exposures. Such plans should include appropriate disposal of waste, good agricultural practices including prevention of erosion especially in areas with silicious soils, and emergency reporting in cases of unseen circumstances that would put workers or those living nearby at risk of hazardous exposures.

### **Future Steps and Recommendations**

This study being the first to explore sarcoidosis mortality clustering in NC has provided a basis in which policies and programs can be instituted to help address the observed differences. As other studies have pointed out, addressing health inequities as well as health disparities may help in addressing these challenges. The analysis and results of this dissertation will be useful as

a basis at which sarcoidosis burden in the state can be addressed. In East Carolina University pulmonary and sarcoidosis clinic, the information brochure will be utilized to recruit sarcoidosis patients to the ECUSaR. Results from Chapter 4 found that percent of African American was a strong predictor of sarcoidosis mortality. Furthermore, spatial analysis yielded information suggesting that obesity, people working in nature, and poverty level could potentially be important etiological factors. Therefore, products from Chapter 4 (e.g., Figs. 14 – 21) are useful data that could be utilized to initiate recruitment for ECUSaR moving forward. More specifically, spatial analyses could be modified to identify the top 10 counties in Eastern NC with the highest percent of African American populations, obesity, people working in nature, and living in poverty. These counties could then be analyzed at a finer geospatial scale (e.g., neighborhood, census block, zip code, etc.) to identify healthcare clinics, pharmacies, hospitals, emergency care centers, schools, and other informational hubs to share sarcoidosis recruitment materials. Therefore, results from this dissertation have strong potential to positively influence ECUSaR recruitment, which could enable detect more sarcoidosis cases earlier and enroll the patients into care and management and overall improve their health outcomes.

In addition to improving healthcare outcomes pertaining to sarcoidosis, this dissertation will disseminate research findings in manuscripts and presentations. Results from Chapters 3, 4, and 5 will be submitted for publication in the North Carolina Medical Journal (NCMED) and PLOS1. Furthermore, these results will also be presented at regional, state, national, and/or international conferences. Disseminating this information to the larger scientific and medical community is vital to further the understanding of sarcoidosis epidemiology in the North Carolina and nationally.

Additional more focused research on exposure scenarios that could be driving the high sarcoidosis mortality in Eastern NC would be beneficial in understanding the phenomenon better. A case-control study focusing on occupational exposure may help establish association between the risk of developing sarcoidosis among different occupations and exposures. Using cases already identified in the ECUSaR, matched controls from Eastern NC region with similar exposure scenario as the cases may be selected for such a study. Both the cases and the controls would then be followed retrospectively to establish their exposures based on occupations which would help establish and assess their risks of developing sarcoidosis. Understanding the associated risk may then help enforce regulations to mitigate exposures or develop strategies to reduce or remove the risk factors identified.

As required by the Council for Education on Public Health (CEPH), this dissertation addressed three foundation and two concentration public health competencies as indicated in Appendix P.

## REFERENCES

- Arkema, E. V., & Cozier, Y. C. (2018). Epidemiology of sarcoidosis: Current findings and future directions. *Therapeutic Advances in Chronic Disease*, 9(11), 227–240. <https://doi.org/10.1177/2040622318790197>
- Arkema, E. V., Grunewald, J., Kullberg, S., Eklund, A., & Askling, J. (2016). Sarcoidosis incidence and prevalence: A nationwide register-based assessment in Sweden. *The European Respiratory Journal*, 48(6), 1690–1699. <https://doi.org/10.1183/13993003.00477-2016>
- ATS. (1999). Statement on Sarcoidosis. *American Journal of Respiratory and Critical Care Medicine*, 160(2), 736–755. <https://doi.org/10.1164/ajrccm.160.2.ats4-99>
- Baughman, Field, S., Costabel, U., Crystal, R. G., Culver, D. A., Drent, M., Judson, M. A., & Wolff, G. (2016a). Sarcoidosis in America. Analysis Based on Health Care Use. *Annals of the American Thoracic Society*, 13(8), 1244–1252. <https://doi.org/10.1513/AnnalsATS.201511-7600C>
- Baughman, R. P., Culver, D. A., & Judson, M. A. (2011). A Concise Review of Pulmonary Sarcoidosis. *American Journal of Respiratory and Critical Care Medicine*, 183(5), 573–581. <https://doi.org/10.1164/rccm.201006-0865CI>
- Baughman, R. P., Field, S., Costabel, U., Crystal, R. G., Culver, D. A., Drent, M., Judson, M. A., & Wolff, G. (2016b). Sarcoidosis in America. Analysis Based on Health Care Use. *Annals of the American Thoracic Society*, 13(8), 1244–1252. <https://doi.org/10.1513/AnnalsATS.201511-7600C>
- Baughman, R. P., & Lower, E. E. (1997). Steroid-sparing alternative treatments for sarcoidosis. *Clinics in Chest Medicine*, 18(4), 853–864. [https://doi.org/10.1016/s0272-5231\(05\)70423-8](https://doi.org/10.1016/s0272-5231(05)70423-8)
- Baughman, R. P., & Lower, E. E. (1999). A clinical approach to the use of methotrexate for sarcoidosis. *Thorax*, 54(8), 742–746. <https://doi.org/10.1136/thx.54.8.742>
- Baughman, R. P., Teirstein, A. S., Judson, M. A., Rossman, M. D., Yeager, H., Bresnitz, E. A., DePALO, L., Hunninghake, G., Iannuzzi, M. C., Johns, C. J., McLENNAN, G., Moller, D. R., Newman, L. S., Rabin, D. L., Rose, C., Rybicki, B., Weinberger, S. E., Terrin, M. L., Knatterud, G. L., ... Group, A. C. C. E. S. of S. (access) R. (2001). Clinical Characteristics of Patients in a Case Control Study of Sarcoidosis. *American Journal of Respiratory and Critical Care Medicine*, 164(10), 1885–1889. <https://doi.org/10.1164/ajrccm.164.10.2104046>
- Beghè, D., Dall'Asta, L., Garavelli, C., Pastorelli, A. A., Muscarella, M., Sacconi, G., Aiello, M., Crisafulli, E., Corradi, M., Stacchini, P., Chetta, A., & Bertorelli, G. (2017). Sarcoidosis

- in an Italian province. Prevalence and environmental risk factors. *PLOS ONE*, 12(5), e0176859. <https://doi.org/10.1371/journal.pone.0176859>
- Belojević, G., & Marić-Zivković, J. (2005). [Sarcoidosis and obesity]. *Medicinski prehled*, 58 Suppl 1, 44–45
- Birnbaum, A. D., & Rifkin, L. M. (2014). Sarcoidosis: Sex-Dependent Variations in Presentation and Management. *Journal of Ophthalmology*, 2014, e236905. <https://doi.org/10.1155/2014/236905>
- Bonham, C. A., Streck, M. E., & Patterson, K. C. (2016). From granuloma to fibrosis: Sarcoidosis associated pulmonary fibrosis. *Current Opinion in Pulmonary Medicine*, 22(5), 484–491. <https://doi.org/10.1097/MCP.0000000000000301>
- Bowers, B., Hasni, S., & Gruber, B. L. (2010). Sarcoidosis in World Trade Center rescue workers presenting with rheumatologic manifestations. *Journal of Clinical Rheumatology: Practical Reports on Rheumatic & Musculoskeletal Diseases*, 16(1), 26–27. <https://doi.org/10.1097/RHU.0b013e3181c78856>
- Cao, H. (2014). Adipocytokines in obesity and metabolic disease. *The Journal of Endocrinology*, 220(2), T47-59. <https://doi.org/10.1530/JOE-13-0339>
- Carlens, C., Hergens, M.-P., Grunewald, J., Ekblom, A., Eklund, A., Höglund, C. O., & Askling, J. (2010). Smoking, use of moist snuff, and risk of chronic inflammatory diseases. *American Journal of Respiratory and Critical Care Medicine*, 181(11), 1217–1222. <https://doi.org/10.1164/rccm.200909-1338OC>
- CDC. (2020). *ICD-10-CM*. <https://icd10cmtool.cdc.gov/?fy=FY2021&q=sarcoidosis> Center for Health Disparities. (n.d.). Center for Health Disparities. Retrieved March 1, 2021, from <https://healthdisparities.ecu.edu/>
- Center for Health Disparities. (2021). *Center for Health Disparities*. Center for Health Disparities. <https://healthdisparities.ecu.edu/>
- Chen, E. S., & Moller, D. R. (2008). Etiology of sarcoidosis. *Clinics in Chest Medicine*, 29(3), 365–377, vii. <https://doi.org/10.1016/j.ccm.2008.03.011>
- Costabel, U. (1997). CD4/CD8 ratios in bronchoalveolar lavage fluid: Of value for diagnosing sarcoidosis? *The European Respiratory Journal*, 10(12), 2699–2700. <https://doi.org/10.1183/09031936.97.10122699>
- Costabel, U., & Hunninghake, G. W. (1999). ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. *European Respiratory Journal*, 14(4), 735–737

- Cox, C. E., Donohue, J. F., Brown, C. D., Kataria, Y. P., & Judson, M. A. (2004). Health-related quality of life of persons with sarcoidosis. *Chest*, *125*(3), 997–1004. <https://doi.org/10.1378/chest.125.3.997>
- Cozier, Y. C. (2016). Assessing the worldwide epidemiology of sarcoidosis: Challenges and future directions. *European Respiratory Journal*, *48*(6), 1545–1548. <https://doi.org/10.1183/13993003.01819-2016>
- Cozier, Y. C., Berman, J. S., Palmer, J. R., Boggs, D. A., Serlin, D. M., & Rosenberg, L. (2011). Sarcoidosis in black women in the United States: Data from the Black Women’s Health Study. *Chest*, *139*(1), 144–150. <https://doi.org/10.1378/chest.10-0413>
- Cozier, Y. C., Coogan, P. F., Govender, P., Berman, J. S., Palmer, J. R., & Rosenberg, L. (2015). Obesity and weight gain in relation to incidence of sarcoidosis in US black women: Data from the Black Women’s Health Study. *Chest*, *147*(4), 1086–1093. <https://doi.org/10.1378/chest.14-1099>
- Cozier, Y. C., Govender, P., & Berman, J. S. (2018). Obesity and sarcoidosis: Consequence or contributor? *Current Opinion in Pulmonary Medicine*, *24*(5), 487–494. <https://doi.org/10.1097/MCP.0000000000000503>
- Criado, E., Sánchez, M., Ramírez, J., Arguis, P., de Caralt, T. M., Perea, R. J., & Xaubet, A. (2010). Pulmonary Sarcoidosis: Typical and Atypical Manifestations at High-Resolution CT with Pathologic Correlation. *RadioGraphics*, *30*(6), 1567–1586. <https://doi.org/10.1148/rg.306105512>
- Crouser, E. D., Maier, L. A., Wilson, K. C., Bonham, C. A., Morgenthau, A. S., Patterson, K. C., Abston, E., Bernstein, R. C., Blankstein, R., Chen, E. S., Culver, D. A., Drake, W., Drent, M., Gerke, A. K., Ghobrial, M., Govender, P., Hamzeh, N., James, W. E., Judson, M. A., ... Westney, G. E. (2020). Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. *American Journal of Respiratory and Critical Care Medicine*, *201*(8), e26–e51. [https://doi.org/10.1164/rccm.202002-0251<sup>ST</sup>](https://doi.org/10.1164/rccm.202002-0251ST)
- Crowley, L. E., Herbert, R., Moline, J. M., Wallenstein, S., Shukla, G., Schechter, C., Skloot, G. S., Udasin, I., Luft, B. J., Harrison, D., Shapiro, M., Wong, K., Sacks, H. S., Landrigan, P. J., & Teirstein, A. S. (2011). “Sarcoid like” granulomatous pulmonary disease in World Trade Center disaster responders. *American Journal of Industrial Medicine*, *54*(3), 175–184. <https://doi.org/10.1002/ajim.20924>
- Crowley, L. E., Herbert, R., Moline, J. M., Wallenstein, S., Shukla, G., Schechter, C., Skloot, G. S., Udasin, I., Luft, B. J., Harrison, D., Shapiro, M., Wong, K., Sacks, H. S., Teirstein, A. S., & Landrigan, P. J. (2011). Response to Dr. Reich’s letter: “‘Sarcoid-like’ granulomatous pulmonary disease in world trade center disaster responders: influence of incidence computation methodology in inferring airborne dust causation”: “Sarcoid-like” granulomatous pulmonary disease in World Trade Center disaster responders.

- American Journal of Industrial Medicine*, 54(11), 894–895.  
<https://doi.org/10.1002/ajim.20995>
- de Prost, N., Kerrou, K., Sibony, M., Talbot, J.-N., Wislez, M., & Cadranel, J. (2010). Fluorine-18 fluorodeoxyglucose with positron emission tomography revealed bone marrow involvement in sarcoidosis patients with anaemia. *Respiration; International Review of Thoracic Diseases*, 79(1), 25–31. <https://doi.org/10.1159/000204901>
- De Vries, J., Van Heck, G. L., & Drent, M. (1999). Gender differences in sarcoidosis: Symptoms, quality of life, and medical consumption. *Women & Health*, 30(2), 99–114. [https://doi.org/10.1300/j013v30n02\\_07](https://doi.org/10.1300/j013v30n02_07)
- Denison, F. C., Roberts, K. A., Barr, S. M., & Norman, J. E. (2010). Obesity, pregnancy, inflammation, and vascular function. *Reproduction (Cambridge, England)*, 140(3), 373–385. <https://doi.org/10.1530/REP-10-0074>
- Descombes, E., Gardiol, D., & Leuenberger, P. (1997). Transbronchial lung biopsy: An analysis of 530 cases with reference to the number of samples. *Monaldi Archives for Chest Disease = Archivio Monaldi Per Le Malattie Del Torace*, 52(4), 324–329
- Drake, W. P., & Newman, L. S. (2006). Mycobacterial antigens may be important in sarcoidosis pathogenesis. *Current Opinion in Pulmonary Medicine*, 12(5), 359–363. <https://doi.org/10.1097/01.mcp.0000239554.01068.94>
- Drent, M., Lower, E. E., & Vries, J. D. (2012). Sarcoidosis-associated fatigue. *European Respiratory Journal*, 40(1), 255–263. <https://doi.org/10.1183/09031936.00002512>
- Drent, M., Strookappe, B., Hoitsma, E., & De Vries, J. (2015). Consequences of Sarcoidosis. *Clinics in Chest Medicine*, 36(4), 727–737. <https://doi.org/10.1016/j.ccm.2015.08.013>
- Drent, M., Wijnen, P. A., Boots, A. W., & Bast, A. (2012). Cat litter is a possible trigger for sarcoidosis. *European Respiratory Journal*, 39(1), 221–222. <https://doi.org/10.1183/09031936.00074411>
- Dubrey, S. W., & Falk, R. H. (2010). Diagnosis and management of cardiac sarcoidosis. *Progress in Cardiovascular Diseases*, 52(4), 336–346. <https://doi.org/10.1016/j.pcad.2009.11.010>
- Duchemann, B., Annesi-Maesano, I., Jacobe de Naurois, C., Sanyal, S., Brillet, P.-Y., Brauner, M., Kambouchner, M., Huynh, S., Naccache, J. M., Borie, R., Piquet, J., Mekinian, A., Virally, J., Uzunhan, Y., Cadranel, J., Crestani, B., Fain, O., Lhote, F., Dhote, R., ... Nunes, H. (2017). Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. *The European Respiratory Journal*, 50(2). <https://doi.org/10.1183/13993003.02419-2016>

- Dumas, O., Abramovitz, L., Wiley, A. S., Cozier, Y. C., & Camargo, C. A. (2016). Epidemiology of Sarcoidosis in a Prospective Cohort Study of U.S. Women. *Annals of the American Thoracic Society*, 13(1), 67–71. <https://doi.org/10.1513/AnnalsATS.201508-568BC>
- Dumas, O., Boggs, K., Cozier, Y., Stampfer, M., & Camargo, C. (2017). *Prospective study of body mass index and risk of sarcoidosis in US women*. <https://www.hal.inserm.fr/inserm-01764141>
- Duong, Y., February 7, N. C. H. N., & 2020. (2020, February 7). *Access to care inequality in NC persists, study shows—NC Health News*. North Carolina Health News. <https://www.northcarolinahealthnews.org/2020/02/07/north-carolina-lags-in-shrinking-disparities-in-access-to-care/>
- Dwyer-Lindgren, L., Bertozzi-Villa, A., Stubbs, R. W., Morozoff, C., Shirude, S., Naghavi, M., Mokdad, A. H., & Murray, C. J. L. (2017). Trends and Patterns of Differences in Chronic Respiratory Disease Mortality Among US Counties, 1980-2014. *JAMA*, 318(12), 1136–1149. <https://doi.org/10.1001/jama.2017.11747>
- Ehlers, S., & Schaible, U. E. (2013). The Granuloma in Tuberculosis: Dynamics of a Host-Pathogen Collusion. *Frontiers in Immunology*, 3. <https://doi.org/10.3389/fimmu.2012.00411>
- Erdal, B. S., Clymer, B. D., Yildiz, V. O., Julian, M. W., & Crouser, E. D. (2012). Unexpectedly high prevalence of sarcoidosis in a representative U.S. Metropolitan population. *Respiratory Medicine*, 106(6), 893–899. <https://doi.org/10.1016/j.rmed.2012.02.007>
- Esteves, T., Aparicio, G., & Garcia-Patos, V. (2016). Is there any association between Sarcoidosis and infectious agents? A systematic review and meta-analysis. *BMC Pulmonary Medicine*, 16(1), 165. <https://doi.org/10.1186/s12890-016-0332-z>
- Flavell, L. (2020). *Types of Sarcoidosis—Sarcoidosis News*. <https://sarcoidosisnews.com/types-of-sarcoidosis/>
- Freemer, M., & King, T. E. (2001). The ACCESS Study. *American Journal of Respiratory and Critical Care Medicine*, 164(10), 1754–1755. <https://doi.org/10.1164/ajrccm.164.10.2109111b>
- Fubini, B., & Hubbard, A. (2003). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation by silica in inflammation and fibrosis. *Free Radical Biology and Medicine*, 34(12), 1507–1516. [https://doi.org/10.1016/S0891-5849\(03\)00149-7](https://doi.org/10.1016/S0891-5849(03)00149-7)
- Gerke, A. K. (2014). Morbidity and Mortality in Sarcoidosis. *Current Opinion in Pulmonary Medicine*, 20(5), 472–478. <https://doi.org/10.1097/MCP.0000000000000080>

- Gideon, N. M., & Mannino, D. M. (1996). Sarcoidosis mortality in the United States 1979-1991: An analysis of multiple-cause mortality data. *The American Journal of Medicine*, *100*(4), 423–427. [https://doi.org/10.1016/S0002-9343\(97\)89518-6](https://doi.org/10.1016/S0002-9343(97)89518-6)
- Gray-McGuire, C., Sinha, R., Iyengar, S., Millard, C., Rybicki, B. A., Elston, R. C., Iannuzzi, M. C., & SAGA Study Consortium. (2006). Genetic characterization and fine mapping of susceptibility loci for sarcoidosis in African Americans on chromosome 5. *Human Genetics*, *120*(3), 420–430. <https://doi.org/10.1007/s00439-006-0201-6>
- Gribbin, J., Hubbard, R. B., Le Jeune, I., Smith, C. J. P., West, J., & Tata, L. J. (2006). Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. *Thorax*, *61*(11), 980–985. <https://doi.org/10.1136/thx.2006.062836>
- Gupta, D., Agarwal, R., Aggarwal, A. N., & Jindal, S. K. (2007). Molecular evidence for the role of mycobacteria in sarcoidosis: A meta-analysis. *European Respiratory Journal*, *30*(3), 508–516. <https://doi.org/10.1183/09031936.00002607>
- Haidich, A. B. (2010). Meta-analysis in medical research. *Hippokratia*, *14*(Suppl 1), 29–37
- Haimovic, A., Sanchez, M., Judson, M. A., & Prystowsky, S. (2012). Sarcoidosis: A comprehensive review and update for the dermatologist: part I. Cutaneous disease. *Journal of the American Academy of Dermatology*, *66*(5), 699.e1-18; quiz 717–718. <https://doi.org/10.1016/j.jaad.2011.11.965>
- Hance, A. J. (1998). The role of mycobacteria in the pathogenesis of sarcoidosis. *Seminars in Respiratory Infections*, *13*(3), 197–205
- Hanley, A., Hubbard, R. B., & Navaratnam, V. (2011). Mortality trends in Asbestosis, Extrinsic Allergic Alveolitis and Sarcoidosis in England and Wales. *Respiratory Medicine*, *105*(9), 1373–1379. <https://doi.org/10.1016/j.rmed.2011.05.008>
- Harpsøe, M. C., Basit, S., Andersson, M., Nielsen, N. M., Frisch, M., Wohlfahrt, J., Nohr, E. A., Linneberg, A., & Jess, T. (2014). Body mass index and risk of autoimmune diseases: A study within the Danish National Birth Cohort. *International Journal of Epidemiology*, *43*(3), 843–855. <https://doi.org/10.1093/ije/dyu045>
- Hem, E. (1999). [Multiple benign sarcoid of the skin—100 years since Caesar Boeck's pioneering article]. *Tidsskrift for Den Norske Laegeforening: Tidsskrift for Praktisk Medicin, Ny Raekke*, *119*(30), 4567–4569
- Hena, K. M. (2020). Sarcoidosis Epidemiology: Race Matters. *Frontiers in Immunology*, *11*. <https://doi.org/10.3389/fimmu.2020.537382>
- Hena, K. M., Murphy, S., Zhang, Y., Shao, Y., Kazeros, A., & Reibman, J. (2019). Clinical Evaluation of Sarcoidosis in Community Members with World Trade Center Dust

- Exposure. *International Journal of Environmental Research and Public Health*, 16(7).  
<https://doi.org/10.3390/ijerph16071291>
- Hena, K. M., Yip, J., Jaber, N., Goldfarb, D., Fullam, K., Cleven, K., Moir, W., Zeig-Owens, R., Webber, M. P., Spevack, D. M., Judson, M. A., Maier, L., Krumerman, A., Aizer, A., Spivack, S. D., Berman, J., Aldrich, T. K., & Prezant, D. J. (2018). Clinical Course of Sarcoidosis in World Trade Center-Exposed Firefighters. *Chest*, 153(1), 114–123.  
<https://doi.org/10.1016/j.chest.2017.10.014>
- Herbort, C. P., Rao, N. A., Mochizuki, M., & members of Scientific Committee of First International Workshop on Ocular Sarcoidosis. (2009). International criteria for the diagnosis of ocular sarcoidosis: Results of the first International Workshop on Ocular Sarcoidosis (IWOS). *Ocular Immunology and Inflammation*, 17(3), 160–169.  
<https://doi.org/10.1080/09273940902818861>
- Hofland, R. W., Thijsen, S. F., Bouwman, J., van der Wel, M., & Bossink, A. W. J. (2014). Sarcoidosis and Purified Protein Derivative reactivity. *Sarcoidosis, Vasculitis, and Diffuse Lung Diseases: Official Journal of WASOG*, 31(2), 142–148
- Hunninghake, G. W., Gilbert, S., Pueringer, R., Dayton, C., Floerchinger, C., Helmers, R., Merchant, R., Wilson, J., Galvin, J., & Schwartz, D. (1994). Outcome of the treatment for sarcoidosis. *American Journal of Respiratory and Critical Care Medicine*, 149(4 Pt 1), 893–898. <https://doi.org/10.1164/ajrccm.149.4.8143052>
- Iannuzzi, M. C. (2007). Genetics of Sarcoidosis. *Seminars in Respiratory and Critical Care Medicine*, 28(1), 15–21. <https://doi.org/10.1055/s-2007-970330>
- Iannuzzi, M. C., & Fontana, J. R. (2011). Sarcoidosis: Clinical Presentation, Immunopathogenesis, and Therapeutics. *JAMA*, 305(4), 391–399.  
<https://doi.org/10.1001/jama.2011.10>
- Iannuzzi, M. C., Rybicki, B. A., & Teirstein, A. S. (2007). Sarcoidosis. *The New England Journal of Medicine*, 357(21), 2153–2165. <https://doi.org/10.1056/NEJMra071714>
- Iossifova, Y. Y., Cox-Ganser, J. M., Park, J.-H., White, S. K., & Kreiss, K. (2011). Lack of respiratory improvement following remediation of a water-damaged office building. *American Journal of Industrial Medicine*, 54(4), 269–277.  
<https://doi.org/10.1002/ajim.20910>
- Iwai, K., Sekiguti, M., Hosoda, Y., DeRemee, R. A., Tazelaar, H. D., Sharma, O. P., Maheshwari, A., & Noguchi, T. I. (1994). Racial difference in cardiac sarcoidosis incidence observed at autopsy. *Sarcoidosis*, 11(1), 26–31
- Izbicki, G., Chavko, R., Banauch, G. I., Weiden, M. D., Berger, K. I., Aldrich, T. K., Hall, C., Kelly, K. J., & Prezant, D. J. (2007). World Trade Center “sarcoid-like” granulomatous

- pulmonary disease in New York City Fire Department rescue workers. *Chest*, 131(5), 1414–1423. <https://doi.org/10.1378/chest.06-2114>
- James, W. E., & Baughman, R. (2018). Treatment of sarcoidosis: Grading the evidence. *Expert Review of Clinical Pharmacology*, 11(7), 677–687. <https://doi.org/10.1080/17512433.2018.1486706>
- James, W. E., & Judson, M. A. (2020). Therapeutic strategies for pulmonary sarcoidosis. *Expert Review of Respiratory Medicine*, 14(4), 391–403. <https://doi.org/10.1080/17476348.2020.1721284>
- Jones, K., & Mansfield, C. (2014). Premature Mortality in North Carolina: Progress, Regress, and Disparities by County and Race, 2000–2010. *North Carolina Medical Journal*, 75, 159–168. <https://doi.org/10.18043/ncm.75.3.159>
- Jonsson, E., Järholm, B., & Andersson, M. (2019). Silica dust and sarcoidosis in Swedish construction workers. *Occupational Medicine (Oxford, England)*, 69(7), 482–486. <https://doi.org/10.1093/occmed/kqz118>
- Jordan, H. T., Stellman, S. D., Prezant, D., Teirstein, A., Osahan, S. S., & Cone, J. E. (2011). Sarcoidosis diagnosed after september 11, 2001, among adults exposed to the world trade center disaster. *Journal of Occupational and Environmental Medicine*, 53(9), 966–974. Scopus. <https://doi.org/10.1097/JOM.0b013e31822a3596>
- Judson, M. A. (2008). The diagnosis of sarcoidosis. *Clinics in Chest Medicine*, 29(3), 415–427, viii. <https://doi.org/10.1016/j.ccm.2008.03.009>
- Judson, M. A. (2014). Advances in the diagnosis and treatment of sarcoidosis. *F1000Prime Reports*, 6. <https://doi.org/10.12703/P6-89>
- Judson, M. A. (2015). The Clinical Features of Sarcoidosis: A Comprehensive Review. *Clinical Reviews in Allergy & Immunology*, 49(1), 63–78. <https://doi.org/10.1007/s12016-014-8450-y>
- Judson, M. A. (2020). Environmental Risk Factors for Sarcoidosis. *Frontiers in Immunology*, 11. <https://doi.org/10.3389/fimmu.2020.01340>
- Judson, M. A., Boan, A. D., & Lackland, D. T. (2012). The clinical course of sarcoidosis: Presentation, diagnosis, and treatment in a large white and black cohort in the United States. *Sarcoidosis, Vasculitis, and Diffuse Lung Diseases: Official Journal of WASOG*, 29(2), 119–127
- Judson, M. A., Hirst, K., Iyengar, S. K., Rybicki, B. A., El Ghormli, L., Baughman, R. P., Donohue, J. F., Elston, R. C., Kavuru, M. S., Moller, D. R., Newman, L. S., Rabin, D. L., Rossman, M. D., Teirstein, A. S., & Iannuzzi, M. C. (2006). Comparison of Sarcoidosis Phenotypes

- Among Affected African American Siblings. *Chest*, 130(3), 855–862.  
<https://doi.org/10.1378/chest.130.3.855>
- Judson, M. A., Preston, S., Hu, K., Zhang, R., Jou, S., Modi, A., Sukhu, I., Ilyas, F., Rosoklija, G., & Yucel, R. (2019). Quantifying the relationship between symptoms at presentation and the prognosis of sarcoidosis. *Respiratory Medicine*, 152, 14–19.  
<https://doi.org/10.1016/j.rmed.2019.03.012>
- Juge-Aubry, C. E., Henrichot, E., & Meier, C. A. (2005). Adipose tissue: A regulator of inflammation. *Best Practice & Research. Clinical Endocrinology & Metabolism*, 19(4), 547–566. <https://doi.org/10.1016/j.beem.2005.07.009>
- Kajdasz, D. K., Lackland, D. T., Mohr, L. C., & Judson, M. A. (2001). A current assessment of rurally linked exposures as potential risk factors for sarcoidosis. *Annals of Epidemiology*, 11(2), 111–117. [https://doi.org/10.1016/s1047-2797\(00\)00179-4](https://doi.org/10.1016/s1047-2797(00)00179-4)
- Kearney, G. D., Obi, O. N., Maddipati, V., Mohan, A., Malur, A., Carter, J. C., & Thomassen, M. J. (2019). Sarcoidosis deaths in the United States: 1999-2016. *Respiratory Medicine*, 149, 30–35. <https://doi.org/10.1016/j.rmed.2018.11.010>
- Krieger, N. (1994). Epidemiology and the web of causation: Has anyone seen the spider? *Social Science & Medicine* (1982), 39(7), 887–903. [https://doi.org/10.1016/0277-9536\(94\)90202-x](https://doi.org/10.1016/0277-9536(94)90202-x)
- Krieger, N. (2001). Theories for social epidemiology in the 21st century: An ecosocial perspective. *International Journal of Epidemiology*, 30(4), 668–677.  
<https://doi.org/10.1093/ije/30.4.668>
- Laney, A. S., Cragin, L. A., Blevins, L. Z., Sumner, A. D., Cox-Ganser, J. M., Kreiss, K., Moffatt, S. G., & Lohff, C. J. (2009). Sarcoidosis, asthma, and asthma-like symptoms among occupants of a historically water-damaged office building. *Indoor Air*, 19(1), 83–90.  
<https://doi.org/10.1111/j.1600-0668.2008.00564.x>
- Laskin, D. L., Sunil, V. R., Gardner, C. R., & Laskin, J. D. (2011). Macrophages and tissue injury: Agents of defense or destruction? *Annual Review of Pharmacology and Toxicology*, 51, 267–288.  
<https://doi.org/10.1146/annurev.pharmtox.010909.105812>
- Lazarus, A. (2009). Sarcoidosis: Epidemiology, Etiology, Pathogenesis, and Genetics. *Disease-a-Month*, 55(11), 649–660.  
<https://doi.org/10.1016/j.disamonth.2009.04.008>
- Lebbé, C., Agbalika, F., Flageul, B., Pellet, C., Rybojad, M., Cordoliani, F., Farge, D., Vignon-Pennamen, M. D., Sheldon, J., Morel, P., Calvo, F., & Schulz, T. F. (1999). No evidence for a role of human herpesvirus type 8 in sarcoidosis: Molecular and serological

analysis. *The British Journal of Dermatology*, 141(3), 492–496.  
<https://doi.org/10.1046/j.1365-2133.1999.03043.x>

Levin, K. A. (2003). *Study Design VI - Ecological Studies*. 1

Lin, C.-K., & Lin, C.-C. (2012). Work of breathing and respiratory drive in obesity. *Respirology (Carlton, Vic.)*, 17(3), 402–411. <https://doi.org/10.1111/j.1440-1843.2011.02124.x>

Lioy Paul J, Weisel Clifford P, Millette James R, Eisenreich Steven, Vallero Daniel, Offenbergl John, Buckley Brian, Turpin Barbara, Zhong Mianhua, Cohen Mitchell D, Prophete Colette, Yang Ill, Stiles Robert, Chee Glen, Johnson Willie, Porcja Robert, Alimokhtari Shahnaz, Hale Robert C, Weschler Charles, & Chen Lung Chi. (2002). Characterization of the dust/smoke aerosol that settled east of the World Trade Center (WTC) in lower Manhattan after the collapse of the WTC 11 September 2001. *Environmental Health Perspectives*, 110(7), 703–714.  
<https://doi.org/10.1289/ehp.02110703>

Liu, H., Patel, D., Welch, A. M., Wilson, C., Mroz, M. M., Li, L., Rose, C. S., Van Dyke, M., Swigris, J. J., Hamzeh, N., & Maier, L. A. (2016). Association Between Occupational Exposures and Sarcoidosis. *Chest*, 150(2), 289–298.  
<https://doi.org/10.1016/j.chest.2016.01.020>

Livingstone, D. E. W., Jones, G. C., Smith, K., Jamieson, P. M., Andrew, R., Kenyon, C. J., & Walker, B. R. (2000). Understanding the Role of Glucocorticoids in Obesity: Tissue-Specific Alterations of Corticosterone Metabolism in Obese Zucker Rats1. *Endocrinology*, 141(2), 560–563. <https://doi.org/10.1210/endo.141.2.7297>

Lugogo, N. L., Hollingsworth, J. W., Howell, D. L., Que, L. G., Francisco, D., Church, T. D., Potts-Kant, E. N., Ingram, J. L., Wang, Y., Jung, S.-H., & Kraft, M. (2012). Alveolar macrophages from overweight/obese subjects with asthma demonstrate a proinflammatory phenotype. *American Journal of Respiratory and Critical Care Medicine*, 186(5), 404–411. <https://doi.org/10.1164/rccm.201109-16710C>

Lynch, J. P. (2003). Computed tomographic scanning in sarcoidosis. *Seminars in Respiratory and Critical Care Medicine*, 24(4), 393–418. <https://doi.org/10.1055/s-2003-42375>

Mansfield, C., Kirk, D., Curry, M., & Bobbitt-Cooke, M. (2001). The challenge of eliminating health disparities in North Carolina. *North Carolina Medical Journal*, 62, 19–25

Mansfield, C., & Novick, L. (2012). Poverty and Health: Focus on North Carolina. *North Carolina Medical Journal*, 73, 366–373. <https://doi.org/10.18043/ncm.73.5.366>

Margaritopoulos, G. A., Vasarmidi, E., Jacob, J., Wells, A. U., & Antoniou, K. M. (2015). Smoking and interstitial lung diseases. *European Respiratory Review*, 24(137), 428–435. <https://doi.org/10.1183/16000617.0050-2015>

- Markevitz, N., Epstein Shochet, G., Levi, Y., Israeli-Shani, L., & Shitrit, D. (2017). Sarcoidosis in Israel: Clinical Outcome Status, Organ Involvement, and Long-Term Follow-Up. *Lung*, *195*(4), 419–424. <https://doi.org/10.1007/s00408-017-0015-4>
- Mirsaeidi, M., Machado, R. F., Schraufnagel, D., Sweiss, N. J., & Baughman, R. P. (2015). Racial difference in sarcoidosis mortality in the United States. *Chest*, *147*(2), 438–449. <https://doi.org/10.1378/chest.14-1120>
- Moller, D. R., Rybicki, B. A., Hamzeh, N. Y., Montgomery, C. G., Chen, E. S., Drake, W., & Fontenot, A. P. (2017). Genetic, Immunologic, and Environmental Basis of Sarcoidosis. *Annals of the American Thoracic Society*, *14*(Supplement\_6), S429–S436. <https://doi.org/10.1513/AnnalsATS.201707-5650T>
- Murray, P. I., Bodaghi, B., & Sharma, O. P. (2011). Systemic treatment of sarcoidosis. *Ocular Immunology and Inflammation*, *19*(2), 145–150. <https://doi.org/10.3109/09273948.2010.542870>
- NCDHHS. (2018). *North Carolina Health Equity Report 2018*. [https://schs.dph.ncdhhs.gov/SCHS/pdf/MinorityHealthReport\\_Web\\_2018.pdf](https://schs.dph.ncdhhs.gov/SCHS/pdf/MinorityHealthReport_Web_2018.pdf)
- NCIOM. (2020). *Healthy North Carolina 2030*. <https://nciom.org/wp-content/uploads/2020/01/HNC-REPORT-FINAL-Spread2.pdf>
- Newman, K. L., & Newman, L. S. (2012). Occupational Causes of Sarcoidosis. *Current Opinion in Allergy and Clinical Immunology*, *12*(2), 145–150. <https://doi.org/10.1097/ACI.0b013e3283515173>
- Newman, L. S., Rose, C. S., Bresnitz, E. A., Rossman, M. D., Barnard, J., Frederick, M., Terrin, M. L., Weinberger, S. E., Moller, D. R., McLennan, G., Hunninghake, G., DePalo, L., Baughman, R. P., Iannuzzi, M. C., Judson, M. A., Knatterud, G. L., Thompson, B. W., Teirstein, A. S., Yeager, H., ... ACCESS Research Group. (2004). A case control etiologic study of sarcoidosis: Environmental and occupational risk factors. *American Journal of Respiratory and Critical Care Medicine*, *170*(12), 1324–1330. <https://doi.org/10.1164/rccm.200402-2490C>
- Newman, L. S., Rose, C. S., Bresnitz, E. A., Rossman, M. D., Barnard, J., Frederick, M., Terrin, M. L., Weinberger, S. E., Moller, D. R., McLennan, G., Hunninghake, G., DePalo, L., Baughman, R. P., Iannuzzi, M. C., Judson, M. A., Knatterud, G. L., Thompson, B. W., Teirstein, A. S., Yeager, H., ... Cherniack, R. (2004). A Case Control Etiologic Study of Sarcoidosis. *American Journal of Respiratory and Critical Care Medicine*, *170*(12), 1324–1330. <https://doi.org/10.1164/rccm.200402-2490C>
- Newman, L. S., Rose, C. S., & Maier, L. A. (1997). Sarcoidosis. *New England Journal of Medicine*, *336*(17), 1224–1234. <https://doi.org/10.1056/NEJM199704243361706>

- Nishiyama, Y., Yamamoto, Y., Fukunaga, K., Takinami, H., Iwado, Y., Satoh, K., & Ohkawa, M. (2006). Comparative Evaluation of 18F-FDG PET and 67Ga Scintigraphy in Patients with Sarcoidosis. *Journal of Nuclear Medicine*, 47(10), 1571–1576
- Noor, A., & Knox, K. S. (2007). Immunopathogenesis of sarcoidosis. *Clinics in Dermatology*, 25(3), 250–258. <https://doi.org/10.1016/j.clindermatol.2007.03.002>
- North Carolina Environmental Quality. (2021). *DWR Animal Operation Permits*. <https://ncdenr.maps.arcgis.com/apps/webappviewer/index.html?id=85ae6392d0e94010a305eedf06e3f288>
- Obi, O. N., Lower, E. E., & Baughman, R. P. (2021). Biologic and advanced immunomodulating therapeutic options for sarcoidosis: A clinical update. *Expert Review of Clinical Pharmacology*, 14(2), 179–210. <https://doi.org/10.1080/17512433.2021.1878024>
- Orphanet. (2019). *Prevalence and incidence of rare diseases: Bibliographic data*. [https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence\\_of\\_rare\\_diseases\\_by\\_alphabetical\\_list.pdf](https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf)
- OSHA. (1998). *Enforcement Exemptions and Limitations under the Appropriations Act. | Occupational Safety and Health Administration*. <https://www.osha.gov/enforcement/directives/cpl-02-00-051>
- Oswald-Richter, K. A., Beachboard, D. C., Zhan, X., Gaskill, C. F., Abraham, S., Jenkins, C., Culver, D. A., & Drake, W. (2010). Multiple mycobacterial antigens are targets of the adaptive immune response in pulmonary sarcoidosis. *Respiratory Research*, 11, 161. <https://doi.org/10.1186/1465-9921-11-161>
- Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., ... Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, 372, n71. <https://doi.org/10.1136/bmj.n71>
- Paramothayan, S., & Jones, P. W. (2002). Corticosteroid therapy in pulmonary sarcoidosis: A systematic review. *JAMA*, 287(10), 1301–1307. <https://doi.org/10.1001/jama.287.10.1301>
- Pasquali, R., Cantobelli, S., Casimirri, F., Capelli, M., Bortoluzzi, L., Flamia, R., Labate, A. M., & Barbara, L. (1993). The hypothalamic-pituitary-adrenal axis in obese women with different patterns of body fat distribution. *The Journal of Clinical Endocrinology and Metabolism*, 77(2), 341–346. <https://doi.org/10.1210/jcem.77.2.8393881>

- Pietinalho, A., Hiraga, Y., Hosoda, Y., Löfroos, A. B., Yamaguchi, M., & Selroos, O. (1995). The frequency of sarcoidosis in Finland and Hokkaido, Japan. A comparative epidemiological study. *Sarcoidosis*, *12*(1), 61–67
- Platko, K., Lebeau, P., & Austin, R. C. (2018). MAPping the kinase landscape of macrophage activation. *The Journal of Biological Chemistry*, *293*(25), 9910–9911. <https://doi.org/10.1074/jbc.H118.003380>
- Prezant, D. J., Dhala, A., Goldstein, A., Janus, D., Ortiz, F., Aldrich, T. K., & Kelly, K. J. (1999). The Incidence, Prevalence, and Severity of Sarcoidosis in New York City Firefighters. *CHEST*, *116*(5), 1183–1193. <https://doi.org/10.1378/chest.116.5.1183>
- Prisoners of the Proximate: Loosening the Constraints on Epidemiology in an Age of Change. (2017). *American Journal of Epidemiology*, *185*(11), 1206–1216. <https://doi.org/10.1093/aje/kwx111>
- R Core Team. (2020). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing. <https://www.R-project.org/>
- Rabin, D. L., Richardson, M. S., Stein, S. R., & Yeager, H. (2001). Sarcoidosis severity and socioeconomic status. *The European Respiratory Journal*, *18*(3), 499–506. <https://doi.org/10.1183/09031936.01.00056201>
- Rabin, D. L., Thompson, B., Brown, K. M., Judson, M. A., Huang, X., Lackland, D. T., Knatterud, G. L., Yeager, H., Rose, C., & Steimel, J. (2004). Sarcoidosis: Social predictors of severity at presentation. *The European Respiratory Journal*, *24*(4), 601–608. <https://doi.org/10.1183/09031936.04.00070503>
- Rafnsson, V., Ingimarsson, O., Hjalmarsson, I., & Gunnarsdottir, H. (1998). Association between exposure to crystalline silica and risk of sarcoidosis. *Occupational and Environmental Medicine*, *55*(10), 657–660
- Rahaghi, F. F., Baughman, R. P., Saketkoo, L. A., Sweiss, N. J., Barney, J. B., Biring, S. S., Costabel, U., Crouser, E. D., Drent, M., Gerke, A. K., Grutters, J. C., Hamzeh, N. Y., Huizar, I., James, W. E., Kalra, S., Kullberg, S., Li, H., Lower, E. E., Maier, L. A., ... Scholand, M. B. (2020). Delphi consensus recommendations for a treatment algorithm in pulmonary sarcoidosis. *European Respiratory Review*, *29*(155). <https://doi.org/10.1183/16000617.0146-2019>
- Rao, D. A., & Dellaripa, P. F. (2013). Extrapulmonary Manifestations of Sarcoidosis. *Rheumatic Diseases Clinics of North America*, *39*(2), 277–297. <https://doi.org/10.1016/j.rdc.2013.02.007>
- Rimal, B., Greenberg, A. K., & Rom, W. N. (2005). Basic pathogenetic mechanisms in silicosis: Current understanding. *Current Opinion in Pulmonary Medicine*, *11*(2), 169–173. <https://doi.org/10.1097/01.mcp.0000152998.11335.24>

- Rothman, K. J., & Greenland, S. (2005). Hill's Criteria for Causality. In P. Armitage & T. Colton (Eds.), *Encyclopedia of Biostatistics* (p. b2a03072). John Wiley & Sons, Ltd. <https://doi.org/10.1002/0470011815.b2a03072>
- Roussel, S., Rognon, B., Barrera, C., Reboux, G., Salamin, K., Grenouillet, F., Thaon, I., Dalphin, J.-C., Tillie-Leblond, I., Quadroni, M., Monod, M., & Millon, L. (2011). Immuno-reactive proteins from Mycobacterium immunogenum useful for serodiagnosis of metalworking fluid hypersensitivity pneumonitis. *International Journal of Medical Microbiology: IJMM*, 301(2), 150–156. <https://doi.org/10.1016/j.ijmm.2010.07.002>
- Rybicki, B. A., Major, M., Popovich, J., Maliarik, M. J., & Iannuzzi, M. C. (1997). Racial differences in sarcoidosis incidence: A 5-year study in a health maintenance organization. *American Journal of Epidemiology*, 145(3), 234–241. <https://doi.org/10.1093/oxfordjournals.aje.a009096>
- Saidha, S., Sotirchos, E. S., & Eckstein, C. (2012). Etiology of Sarcoidosis: Does Infection Play a Role? *The Yale Journal of Biology and Medicine*, 85(1), 133–141
- Schneider, A., Hommel, G., & Blettner, M. (2010). Linear Regression Analysis. *Deutsches Ärzteblatt International*, 107(44), 776–782. <https://doi.org/10.3238/arztebl.2010.0776>
- Shaikh, F., Abtin, F. G., Lau, R., Saggar, R., Belperio, J. A., & Lynch, J. P. (2020). Radiographic and Histopathologic Features in Sarcoidosis: A Pictorial Display. *Seminars in Respiratory and Critical Care Medicine*, 41(5), 758–784. <https://doi.org/10.1055/s-0040-1712534>
- Sharma, O. P. (2005). Definition and history of sarcoidosis. In M. Drent & U. Costabel (Eds.), *Sarcoidosis* (pp. 1–12). European Respiratory Society. <https://doi.org/10.1183/1025448x.00032001>
- Silverman, K. J., Hutchins, G. M., & Bulkley, B. H. (1978). Cardiac sarcoid: A clinicopathologic study of 84 unselected patients with systemic sarcoidosis. *Circulation*, 58(6), 1204–1211. <https://doi.org/10.1161/01.cir.58.6.1204>
- Singer, D. R., & Evans, D. J. (1986). Renal impairment in sarcoidosis: Granulomatous nephritis as an isolated cause (two case reports and review of the literature). *Clinical Nephrology*, 26(5), 250–256
- Solà, R., Boj, M., Hernandez-Flix, S., & Camprubí, M. (2009). Silica in oral drugs as a possible sarcoidosis-inducing antigen. *The Lancet*, 373(9679), 1943–1944. [https://doi.org/10.1016/S0140-6736\(09\)61057-6](https://doi.org/10.1016/S0140-6736(09)61057-6)
- Spagnolo, P. (2015). Sarcoidosis: A Critical Review of History and Milestones. *Clinical Reviews in Allergy & Immunology*, 49(1), 1–5. <http://dx.doi.org/10.1007/s12016-015-8480-0>

- Spagnolo, P., Cullinan, P., & duBois, R. (2011). *Sarcoidosis. In: Interstitial Lung Disease* (Schwarz MI, King TE Jr (Eds), Vol. 5). People's Medical Publishing House
- Spagnolo, P., & Grunewald, J. (2013). Recent advances in the genetics of sarcoidosis. *Journal of Medical Genetics*, 50(5), 290–297. <https://doi.org/10.1136/jmedgenet-2013-101532>
- Spagnolo, P., Richeldi, L., & du Bois, R. M. (2008). Environmental triggers and susceptibility factors in idiopathic granulomatous diseases. *Seminars in Respiratory and Critical Care Medicine*, 29(6), 610–619. <https://doi.org/10.1055/s-0028-1101271>
- Sreelesh, K. P., Kumar, M. L. A., & Anoop, T. M. (2014). Primary splenic sarcoidosis. *Proceedings (Baylor University. Medical Center)*, 27(4), 344–345
- Stanford, J. (2018, February 8). *NC in Focus: Black Population in North Carolina, 2016*. Carolina Demography. <https://www.ncdemography.org/2018/02/08/nc-in-focus-black-population-in-north-carolina-2016/>
- Statement on Sarcoidosis. (1999). *American Journal of Respiratory and Critical Care Medicine*, 160(2), 736–755. <https://doi.org/10.1164/ajrccm.160.2.ats4-99>
- Stopinšek, S., Ihan, A., Salobir, B., Terčelj, M., & Simčič, S. (2016). Fungal cell wall agents and bacterial lipopolysaccharide in organic dust as possible risk factors for pulmonary sarcoidosis. *Journal of Occupational Medicine and Toxicology*, 11(1), 46. <https://doi.org/10.1186/s12995-016-0135-4>
- Strissel, K. J., DeFuria, J., Shaul, M. E., Bennett, G., Greenberg, A. S., & Obin, M. S. (2010). T-cell recruitment and Th1 polarization in adipose tissue during diet-induced obesity in C57BL/6 mice. *Obesity (Silver Spring, Md.)*, 18(10), 1918–1925. <https://doi.org/10.1038/oby.2010.1>
- Subramanian, V., & Ferrante, A. W. (2009). Obesity, inflammation, and macrophages. *Nestle Nutrition Workshop Series. Paediatric Programme*, 63, 151–159; discussion 159-162, 259–268. <https://doi.org/10.1159/000209979>
- Suchankova, M., Paulovicova, E., Paulovicova, L., Majer, I., Tedlova, E., Novosadova, H., Tibenska, E., Tedla, M., & Bucova, M. (2015). Increased antifungal antibodies in bronchoalveolar lavage fluid and serum in pulmonary sarcoidosis. *Scandinavian Journal of Immunology*, 81(4), 259–264. <https://doi.org/10.1111/sji.12273>
- Sunil, V. R., Francis, M., Vayas, K. N., Cervelli, J. A., Choi, H., Laskin, J. D., & Laskin, D. L. (2015). Regulation of ozone-induced lung inflammation and injury by the  $\beta$ -galactoside-binding lectin galectin-3. *Toxicology and Applied Pharmacology*, 284(2), 236–245. <https://doi.org/10.1016/j.taap.2015.02.002>

- Sunil, V. R., Radbel, J., Hussain, S., Vayas, K. N., Cervelli, J., Deen, M., Kipen, H., Udasin, I., Laumbach, R., Sunderram, J., Laskin, J. D., & Laskin, D. L. (2019). Sarcoid-Like Granulomatous Disease: Pathologic Case Series in World Trade Center Dust Exposed Rescue and Recovery Workers. *International Journal of Environmental Research and Public Health*, *16*(5). <https://doi.org/10.3390/ijerph16050815>
- Susser, M., & Susser, E. (1996). Choosing a future for epidemiology: II. From black box to Chinese boxes and eco-epidemiology. *American Journal of Public Health*, *86*(5), 674–677. <https://doi.org/10.2105/ajph.86.5.674>
- Svendsen, C. B., Milman, N., Høier-Madsen, M., Dziegiel, M. H., & Krogfelt, K. A. (2008). Determination of rickettsial and antinuclear antibodies in Danish patients with sarcoidosis. *The clinical respiratory journal*, *2*(4), 202–207
- Swigris, J. J., Olson, A. L., Huie, T. J., Fernandez-Perez, E. R., Solomon, J., Sprunger, D., & Brown, K. K. (2011). Sarcoidosis-related Mortality in the United States from 1988 to 2007. *American Journal of Respiratory and Critical Care Medicine*, *183*(11), 1524–1530. <https://doi.org/10.1164/rccm.201010-1679OC>
- Te, H. S., Perlman, D. M., Shenoy, C., Steinberger, D. J., Cogswell, R. J., Roukoz, H., Peterson, E. J., Zhang, L., Allen, T. L., & Bhargava, M. (2020). Clinical characteristics and organ system involvement in sarcoidosis: Comparison of the University of Minnesota Cohort with other cohorts. *BMC Pulmonary Medicine*, *20*. <https://doi.org/10.1186/s12890-020-01191-x>
- Terčelj, M., Stopinšek, S., Ihan, A., Salobir, B., Simčič, S., Wraber, B., & Rylander, R. (2011). In vitro and in vivo reactivity to fungal cell wall agents in sarcoidosis. *Clinical and Experimental Immunology*, *166*(1), 87–93. <https://doi.org/10.1111/j.1365-2249.2011.04456.x>
- Tillie-Leblond, I., Grenouillet, F., Reboux, G., Roussel, S., Chouraki, B., Lorthois, C., Dalphin, J.-C., Wallaert, B., & Millon, L. (2011). Hypersensitivity pneumonitis and metalworking fluids contaminated by mycobacteria. *The European Respiratory Journal*, *37*(3), 640–647. <https://doi.org/10.1183/09031936.00195009>
- Tippett, R. (2019, December 5). *2018 County Population Estimates: Race & Ethnicity*. Carolina Demography. <https://www.ncdemography.org/2019/12/05/2018-county-population-estimates-race-ethnicity/>
- Ungprasert, P., Crowson, C. S., & Matteson, E. L. (2016a). Smoking, obesity and risk of sarcoidosis: A population-based nested case-control study. *Respiratory Medicine*, *120*, 87–90. <https://doi.org/10.1016/j.rmed.2016.10.003>
- Ungprasert, P., Crowson, C. S., & Matteson, E. L. (2016b). Smoking, obesity and risk of sarcoidosis: A population-based nested case-control study. *Respiratory Medicine*, *120*, 87–90. <https://doi.org/10.1016/j.rmed.2016.10.003>

- Ungprasert, P., Crowson, C. S., & Matteson, E. L. (2017a). Influence of Gender on Epidemiology and Clinical Manifestations of Sarcoidosis: A Population-Based Retrospective Cohort Study 1976-2013. *Lung*, *195*(1), 87–91. <https://doi.org/10.1007/s00408-016-9952-6>
- Ungprasert, P., Crowson, C. S., & Matteson, E. L. (2017b). Epidemiology and clinical characteristics of sarcoidosis: An update from a population-based cohort study from Olmsted County, Minnesota. *Reumatismo*, *69*(1), 16–22. <https://doi.org/10.4081/reumatismo.2017.965>
- Valavanidis, A., Vlachogianni, T., Fiotakis, K., & Loridas, S. (2013). Pulmonary oxidative stress, inflammation and cancer: Respirable particulate matter, fibrous dusts and ozone as major causes of lung carcinogenesis through reactive oxygen species mechanisms. *International Journal of Environmental Research and Public Health*, *10*(9), 3886–3907. <https://doi.org/10.3390/ijerph10093886>
- Vihlborg, P., Bryngelsson, I.-L., Andersson, L., & Graff, P. (2017). Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure in Swedish iron foundries: A retrospective cohort study. *BMJ Open*, *7*(7), e016839. <https://doi.org/10.1136/bmjopen-2017-016839>
- von Bartheld, M. B., Dekkers, O. M., Szlubowski, A., Eberhardt, R., Herth, F. J., in 't Veen, J. C. C. M., de Jong, Y. P., van der Heijden, E. H. F. M., Tournoy, K. G., Claussen, M., van den Blink, B., Shah, P. L., Zoumot, Z., Clementsen, P., Porsbjerg, C., Mauad, T., Bernardi, F. D., van Zwet, E. W., Rabe, K. F., & Annema, J. T. (2013). Endosonography vs Conventional Bronchoscopy for the Diagnosis of Sarcoidosis: The GRANULOMA Randomized Clinical Trial. *JAMA*, *309*(23), 2457. <https://doi.org/10.1001/jama.2013.5823>
- Wambui, D. W., Obi, O. N., & Kearney, G. D. (2020). Association Between Obesity and Sarcoidosis: A Systematic Review and Meta-analysis. *American Journal of Internal Medicine*, *8*(5), 237. <https://doi.org/10.11648/j.ajim.20200805.18>
- Webber, M. P., Yip, J., Zeig-Owens, R., Moir, W., Ungprasert, P., Crowson, C. S., Hall, C. B., Jaber, N., Weiden, M. D., Matteson, E. L., & Prezant, D. J. (2017). Post-9/11 Sarcoidosis in WTC-Exposed Firefighters and Emergency Medical Service Workers. *Respiratory Medicine*, *132*, 232–237. <https://doi.org/10.1016/j.rmed.2017.06.004>
- Wozniak, S. E., Gee, L. L., Wachtel, M. S., & Frezza, E. E. (2009). Adipose tissue: The new endocrine organ? A review article. *Digestive Diseases and Sciences*, *54*(9), 1847–1856. <https://doi.org/10.1007/s10620-008-0585-3>
- Wu, C.-H., Chung, P.-I., Wu, C.-Y., Chen, Y.-T., Chiu, Y.-W., Chang, Y.-T., & Liu, H.-N. (2017). Comorbid autoimmune diseases in patients with sarcoidosis: A nationwide case-control study in Taiwan. *The Journal of Dermatology*, *44*(4), 423–430. <https://doi.org/10.1111/1346-8138.13654>

- Xing, Y.-F., Xu, Y.-H., Shi, M.-H., & Lian, Y.-X. (2016). The impact of PM2.5 on the human respiratory system. *Journal of Thoracic Disease*, 8(1), E69–E74. <https://doi.org/10.3978/j.issn.2072-1439.2016.01.19>
- Yamada, T., Eishi, Y., Ikeda, S., Ishige, I., Suzuki, T., Takemura, T., Takizawa, T., & Koike, M. (2002). In situ localization of *Propionibacterium acnes* DNA in lymph nodes from sarcoidosis patients by signal amplification with catalysed reporter deposition. *The Journal of Pathology*, 198(4), 541–547. <https://doi.org/10.1002/path.1243>
- Yoon, H.-Y., Kim, H. M., Kim, Y.-J., & Song, J. W. (2018). Prevalence and incidence of sarcoidosis in Korea: A nationwide population-based study. *Respiratory Research*, 19. <https://doi.org/10.1186/s12931-018-0871-3>
- Zajicek, J. P., Scolding, N. J., Foster, O., Rovaris, M., Evanson, J., Moseley, I. F., Scadding, J. W., Thompson, E. J., Chamoun, V., Miller, D. H., McDonald, W. I., & Mitchell, D. (1999). Central nervous system sarcoidosis—Diagnosis and management. *QJM: Monthly Journal of the Association of Physicians*, 92(2), 103–117. <https://doi.org/10.1093/qjmed/92.2.103>
- Zissel, G. (2014). Cellular activation in the immune response of sarcoidosis. *Seminars in Respiratory and Critical Care Medicine*, 35(3), 307–315. <https://doi.org/10.1055/s-0034-1376861>
- Zumla, A., & James, D. G. (1996). Granulomatous Infections: Etiology and Classification. *Clinical Infectious Diseases*, 23(1), 146–158. <https://doi.org/10.1093/clinids/23.1.146>

# Appendix A: IRB Approval

8/18/2021

Activity Details

East Carolina University

Hello, Gregory Kearney ▾

Dashboard

Home

IRB  
Studies

Issues

IRB Studies > Sarcoidosis Patient Registry

<< Return to Workspace

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Next >

## Activity Details (Edited Approval Letter)

**Author:** Suzanne Sparrow (UMCIRB Office)  
**Logged For (Study):** Sarcoidosis Patient Registry  
**Activity Date:** 8/18/2021 8:13 AM

Activity Form

Property Changes

Documents

Notifications

### Instructions:

- This form allows you to create the Approval letter (it does not send it to anyone)
- A default Approval letter is shown below with information merged in from this application. Edit the text of the letter as necessary
- Click the OK button to save the letter



**EAST CAROLINA UNIVERSITY**  
University & Medical Center Institutional Review Board  
4N-64 Brody Medical Sciences Building - Mail Stop 682  
600 Moye Boulevard - Greenville, NC 27834  
Office 252-744-2914 • Fax 252-744-2284 • [reds.ecu.edu/umcirb/](https://reds.ecu.edu/umcirb/)

### Notification of Amendment Approval

**From:** Biomedical IRB  
**To:** Ogugua Obi  
**CC:** Anagha Malur  
**Date:** 8/18/2021  
**Re:** Ame16\_UMCIRB 06-0312  
UMCIRB 06-0312  
Sarcoidosis Patient Registry

Your Amendment has been reviewed and approved using expedited review for the period of 8/18/2021 to 9/1/2021. It was the determination of the UMCIRB Chairperson (or designee) that this revision does not impact the overall risk/benefit ratio of the study and is appropriate for the population and procedures proposed.

Please note that any further changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. A continuing or final review must be submitted to the UMCIRB prior to the date of study expiration. The investigator must adhere to all reporting requirements for this study.

Approved consent documents with the IRB approval date stamped on the document should be used to consent participants (consent documents with the IRB approval date stamp are found under the Documents tab in the study workspace).

The approval includes the following items:

Document	Description
HIPAA-Authorization-6-17-21(0.08)	HIPAA Documentation
Sarcoidosis Patient Registry Consent (0.10)	Consent Forms

## Appendix B: Approval Letter

DocuSign Envelope ID: C0C90316-7B72-4B11-93CB-E04B7ACB1121

David Wambui  
115 Heart Drive, Department of Public Health  
Greenville, NC 27834

November 1, 2021

Ogugua Obi, MD  
Brody School of Medicine  
Addressee's City, State, Zip Code

Dear Dr. Obi:

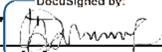
This letter will confirm our recent work together on the ECU, Sarcoidosis Patient Registry project. I am completing a doctoral dissertation at East Carolina University entitled "An Epidemiologic Analysis of Sarcoidosis in North Carolina." I would like your permission to reprint in my dissertation excerpts from the following:

East Carolina University Sarcoidosis Registry (ECUSaR): An ongoing longitudinal registry and database of all patients seen in the East Carolina University (ECU) pulmonary clinic with pulmonary and extra pulmonary sarcoidosis {Data set} <https://internal-medicine.ecu.edu/pulmonary/sarcoidosis-center>

The excerpts to be reproduced are: attached brochure.

The requested permission extends to any future revisions and editions of my dissertation, including non-exclusive world rights in all languages, and to the prospective publication of my dissertation by UMI. These rights will in no way restrict republication of the material in any other form by you or by others authorized by you. Your signing of this letter will also confirm that you own [or ECU] the copyright to the above-described material.

If these arrangements meet with your approval, please sign this letter where indicated below and return it to me in the enclosed return envelope. Thank you very much.

Sincerely,  
DocuSigned by:  
  
\_\_\_\_\_  
David Wambui 06111055AAU348

PERMISSION GRANTED FOR THE USE REQUESTED ABOVE:

Ogugua Obi, MD

10/30/2021 | 8:21 AM EDT

Date

## Appendix C: Scadding Stages for Pulmonary Sarcoidosis

### The Stages of Pulmonary Sarcoidosis

The stages of sarcoidosis can be confusing, especially for newly diagnosed patients. The use of numbered stages implies that these categories indicate the severity or progression of the disease, however they are simply for categorization. They help describe the location and nature of the disease, not severity.

#### Stage 0

##### NO SARCOIDOSIS

The patient presents with a normal x-ray. There is no sign of granulomas.



#### Stage I

##### LYMPHADENOPATHY

Granulomas are only present in the lymph nodes.



#### Stage II

##### LYMPHADENOPATHY AND PULMONARY INFILTRATES

Sarcoidosis is present in the lymph nodes and lung tissue.



#### Stage III

##### PULMONARY INFILTRATES

Granulomas are only present in the lung tissue.



#### Stage IV

##### PULMONARY FIBROSIS

There is scarring in the tissues of the lungs, indicating irreversible damage.



For more info on sarcoidosis, visit  
[www.stopsarcoidosis.org](http://www.stopsarcoidosis.org)



FOUNDATION FOR  
SARCOIDOSIS RESEARCH

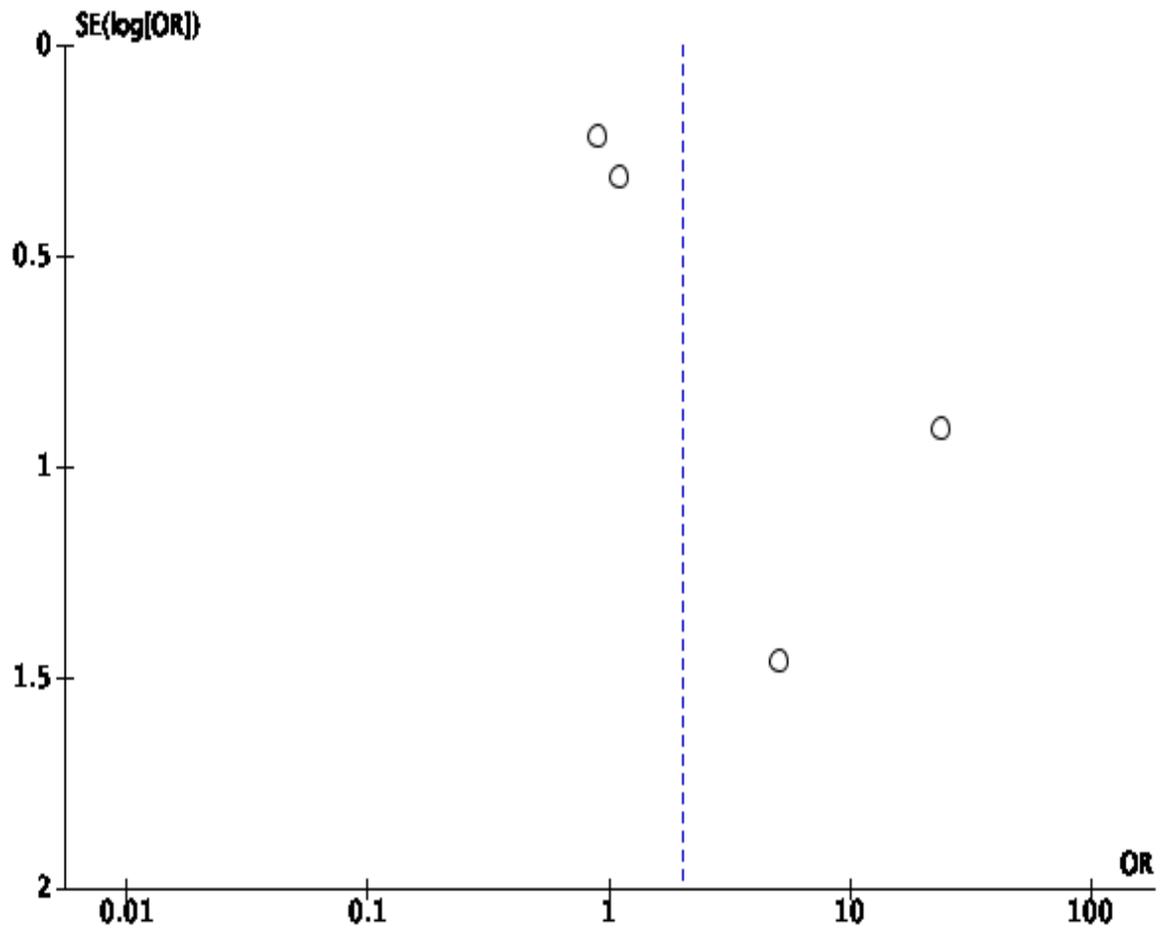
## Appendix D: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
<b>METHODS</b>			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	

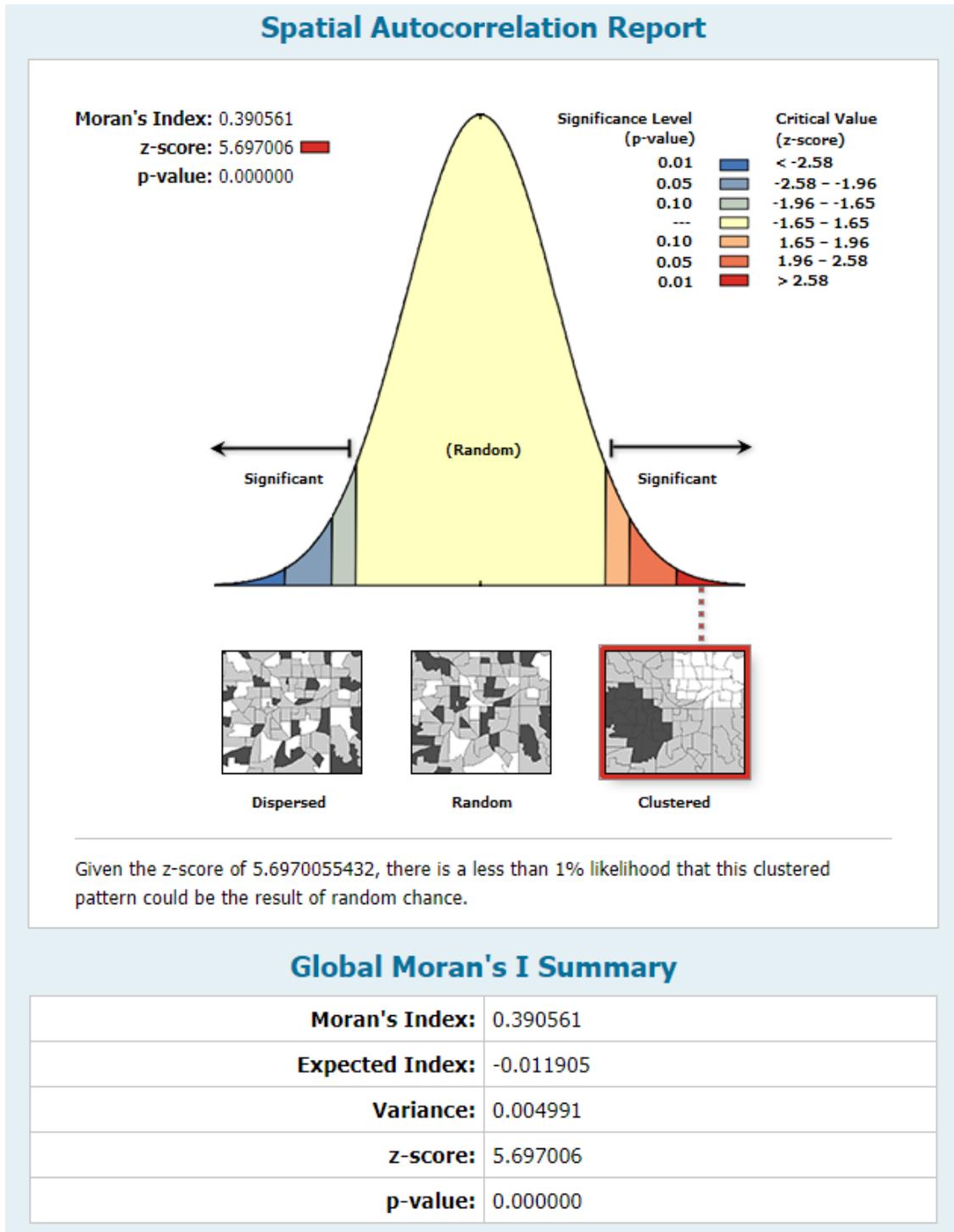
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
<b>RESULTS</b>			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	

	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
<b>DISCUSSION</b>			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
<b>OTHER INFORMATION</b>			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

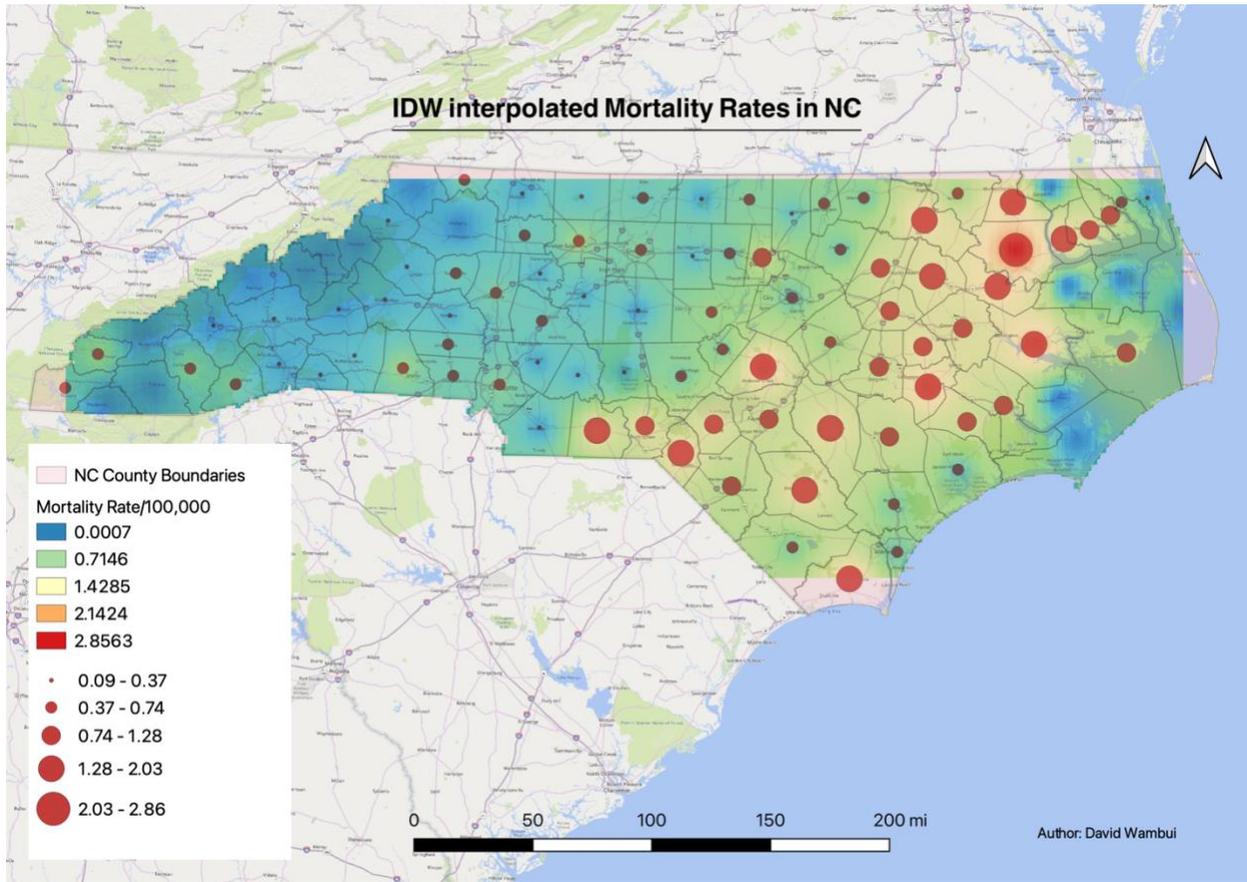
**Appendix E: Funnel Plot for Meta-Analysis Showing Test for Publication Bias.**



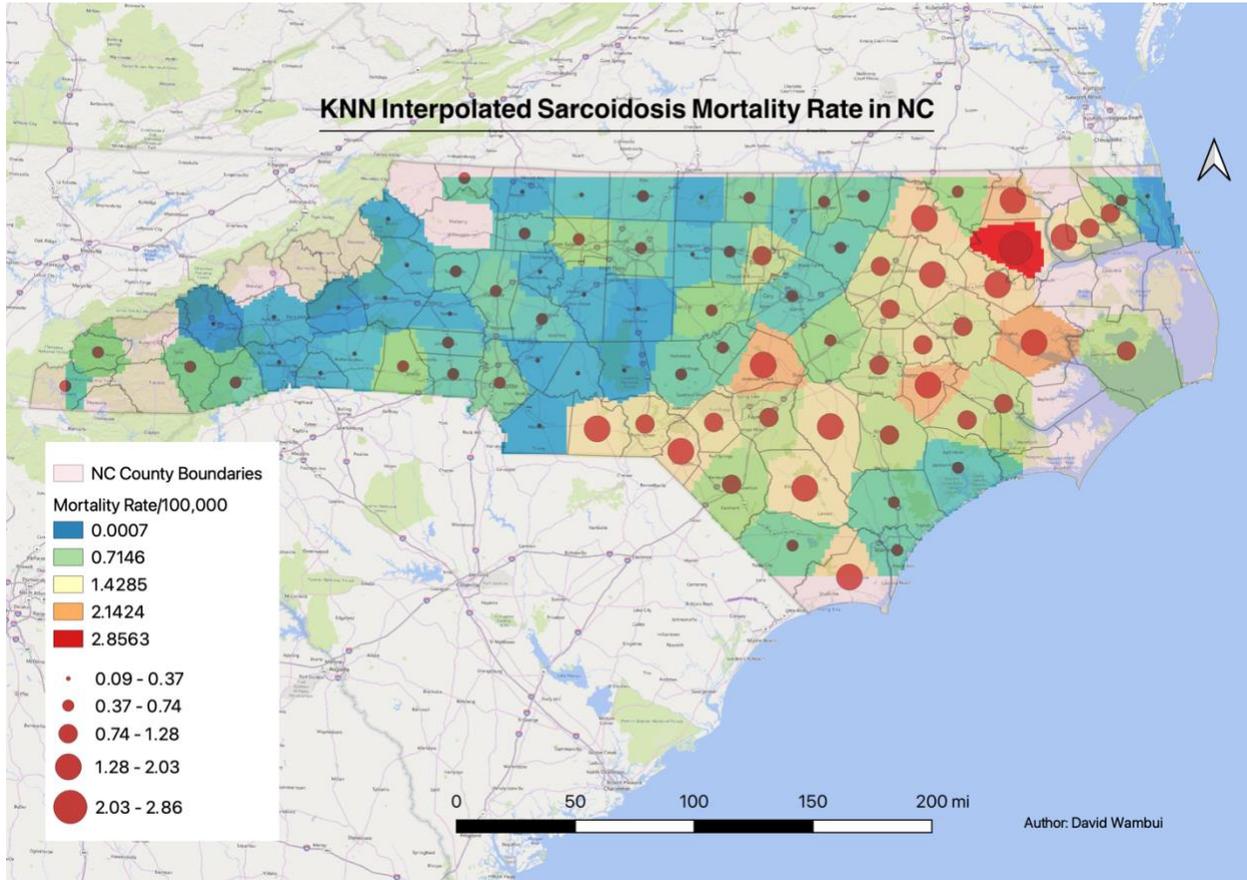
## Appendix F: Spatial Autocorrelation Analysis with Global Moran's I



# Appendix G: Inverse Distance Weight Interpolated Sarcoidosis Mortality Rates in NC

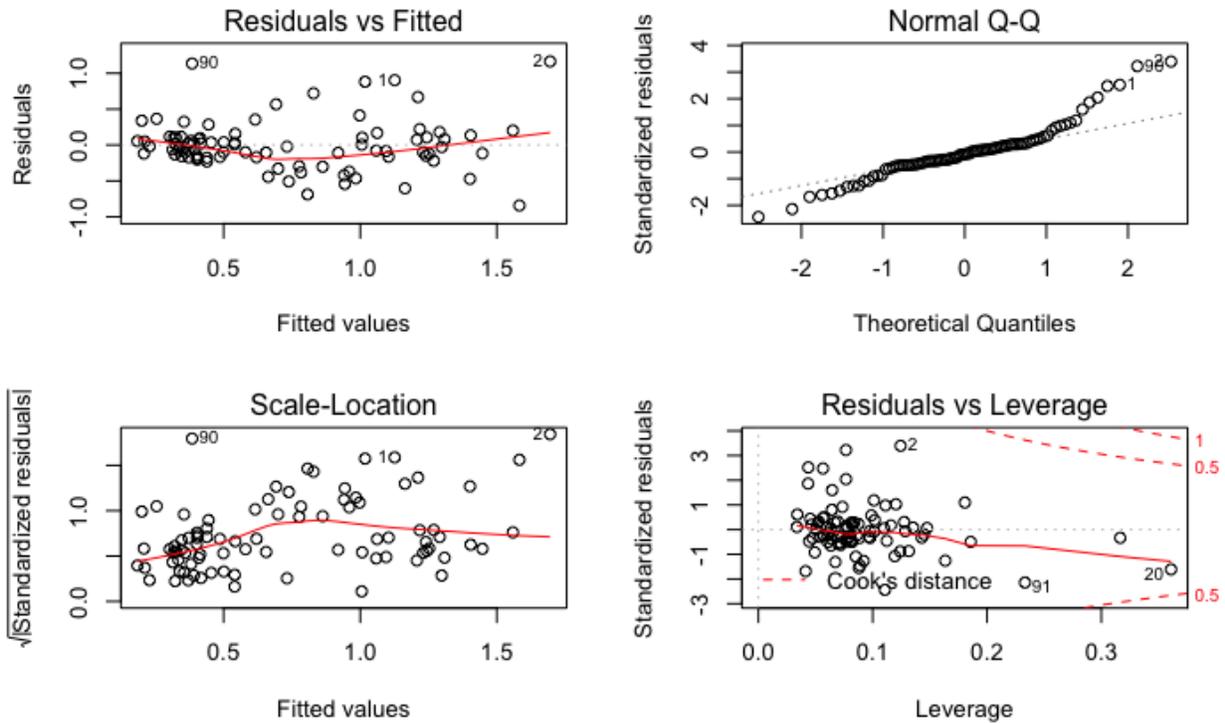


# Appendix H: K Nearest Neighbor Interpolated Sarcoidosis Mortality Rates in NC



## Appendix I: Linear Regression Assumption Tests

### Overall model tests



### Test for residuals autocorrelation

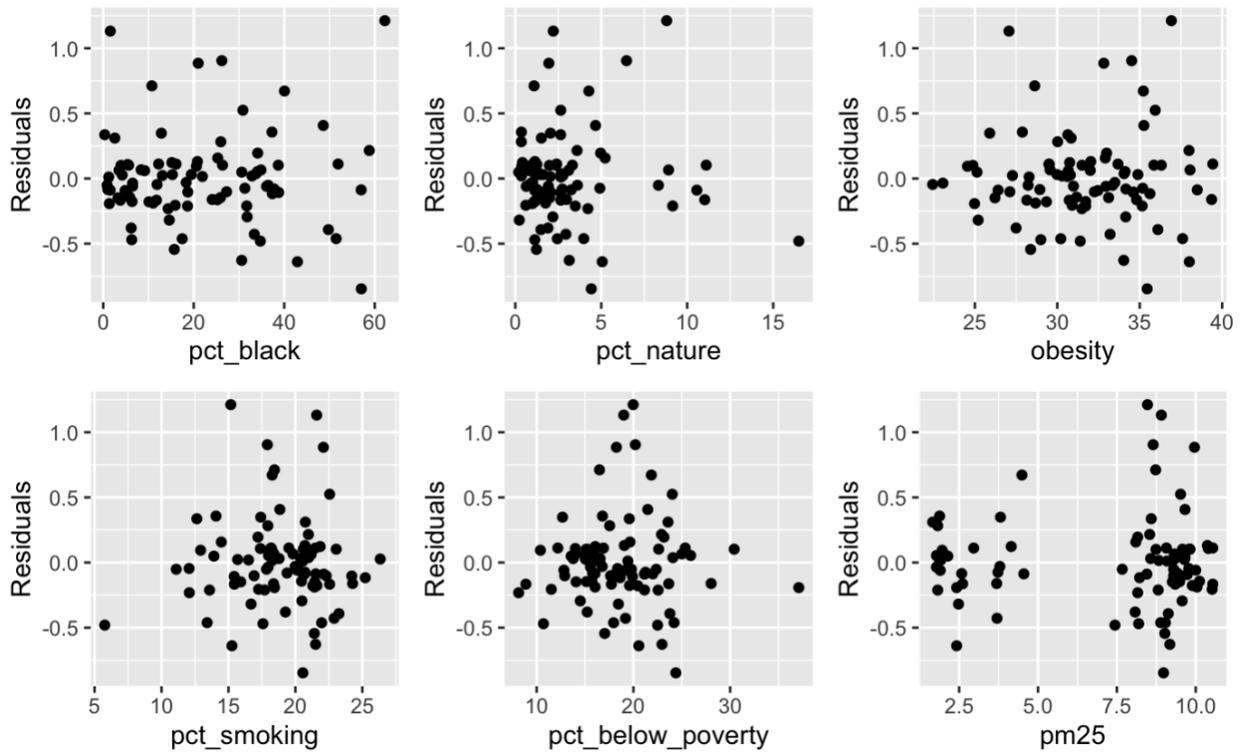
Durbin-Watson test

data: Model

DW = 1.6978, p-value = 0.07166

alternative hypothesis: true autocorrelation is greater than 0

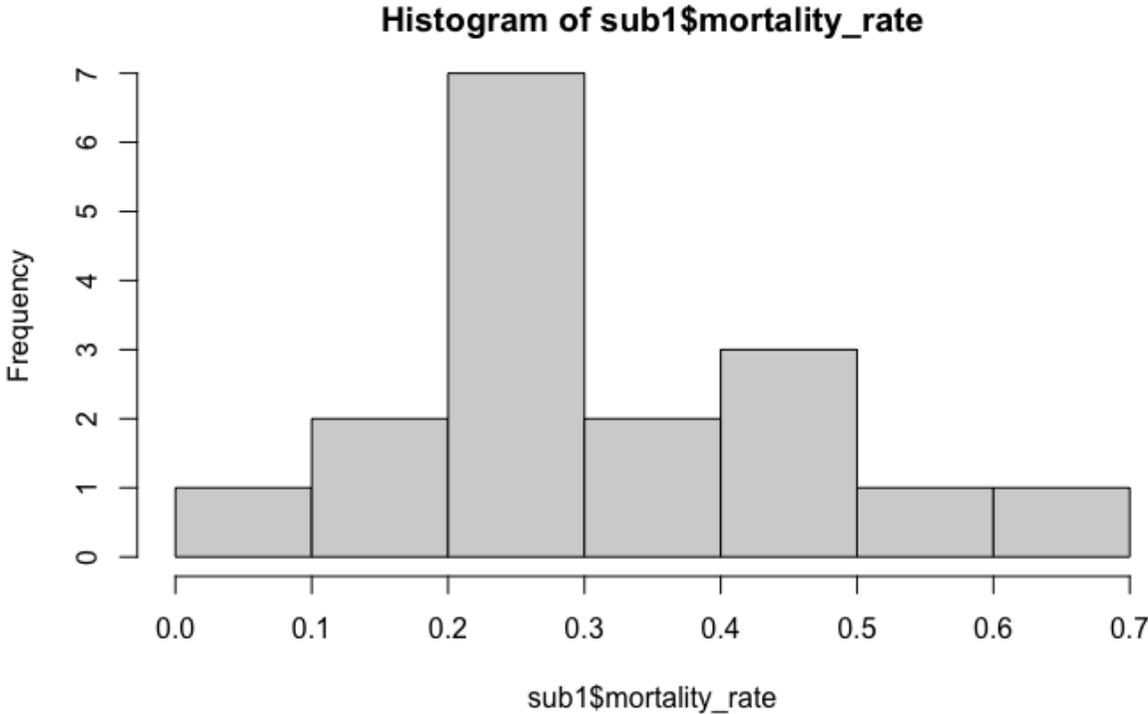
### Residuals vs predictors



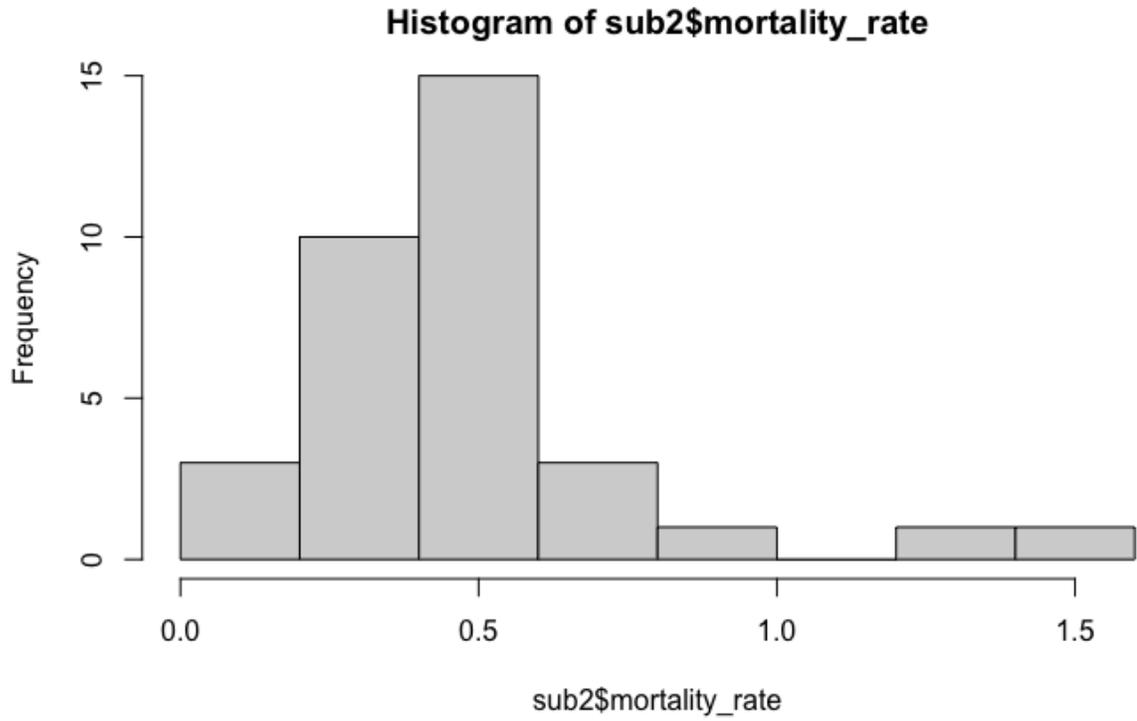
### Model variable inflation factor

Region- Piedmont	Region - Western	% Black	% Nature	% Obese	% Smoking	PM2.5
1.592122	1.876736	2.869441	1.737858	3.116537	1.660929	1.081647

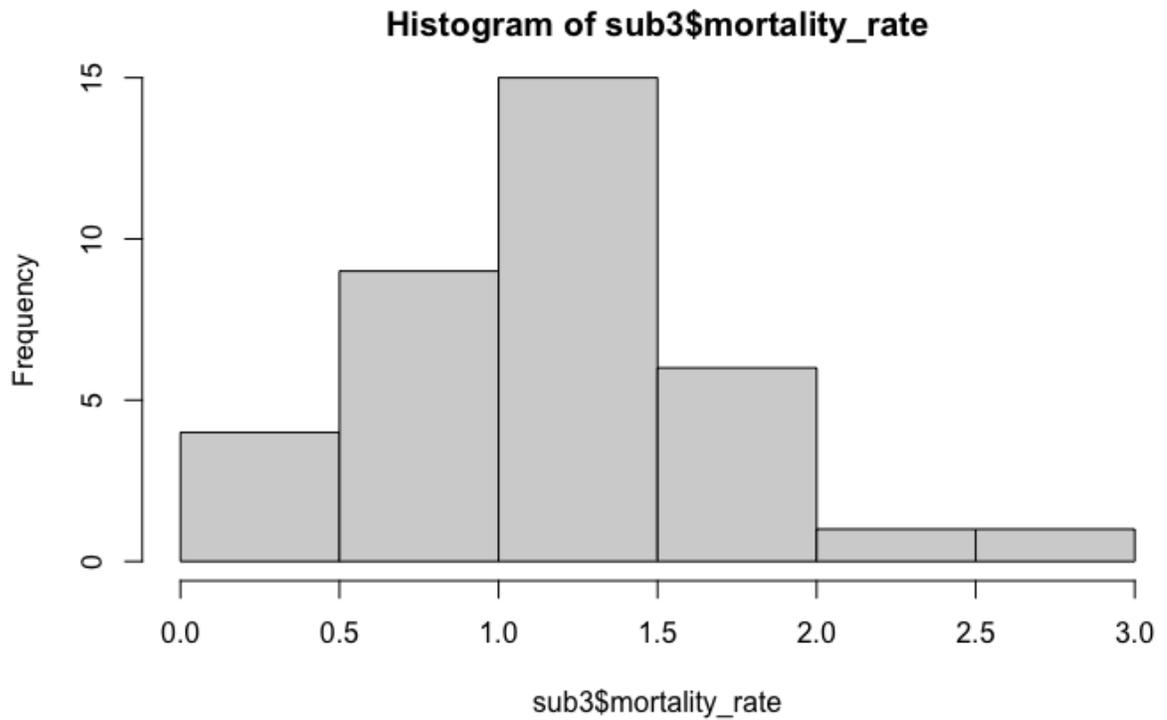
**Raw data test for normality subset by region**



Subset 1. Excluding counties in the Western region

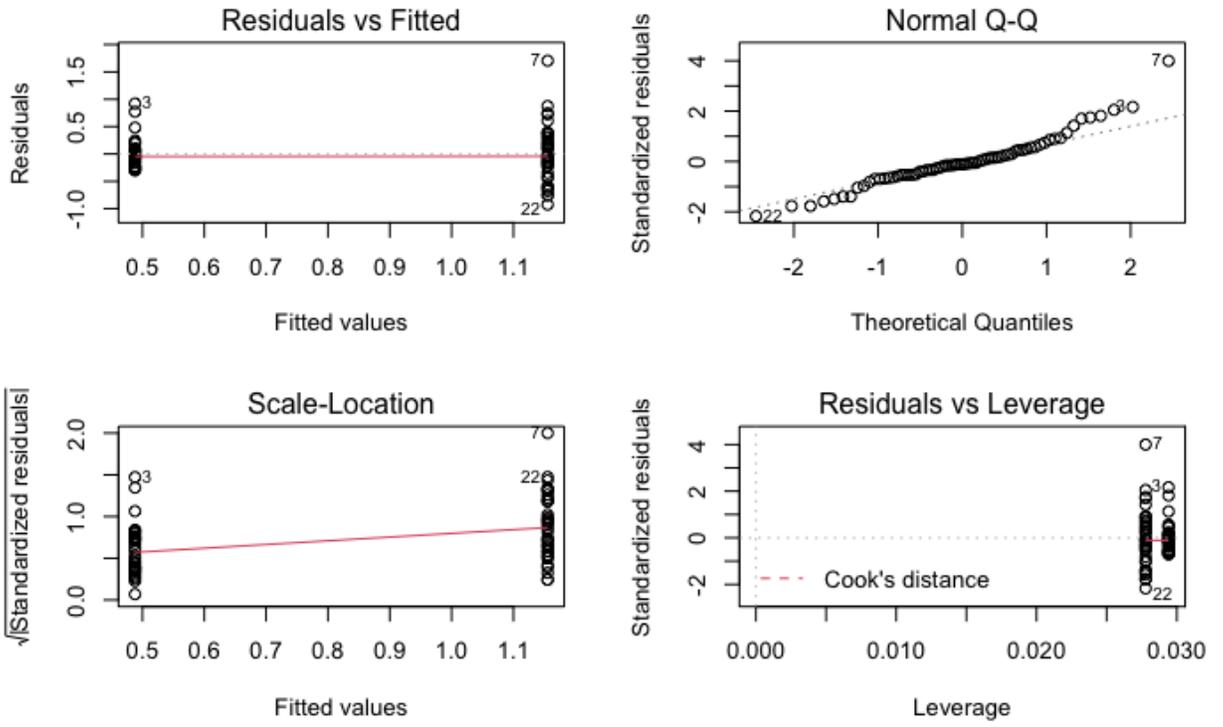


Subset 2. Excluding counties in the Piedmont region

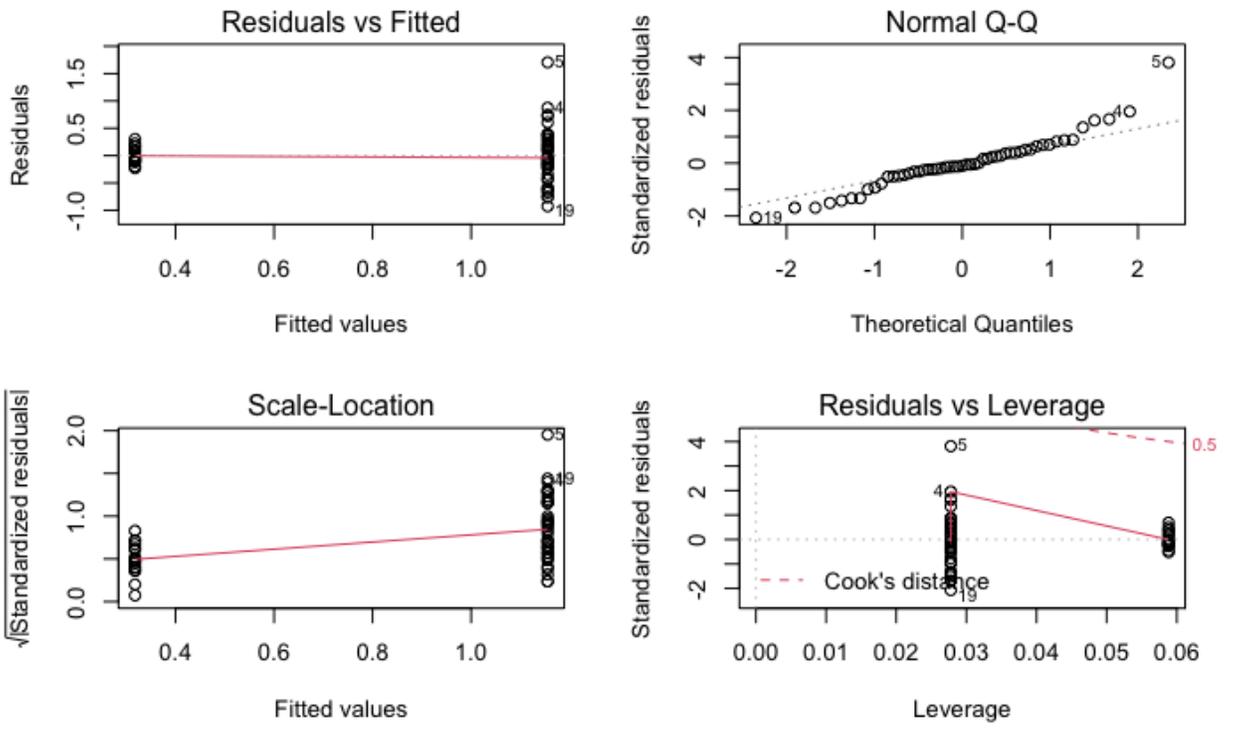


Subset 3. Excluding counties in the Eastern region

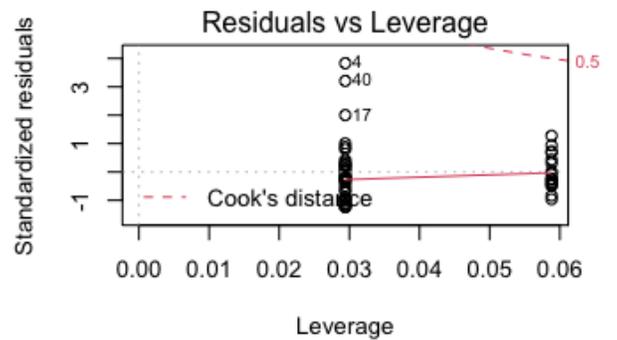
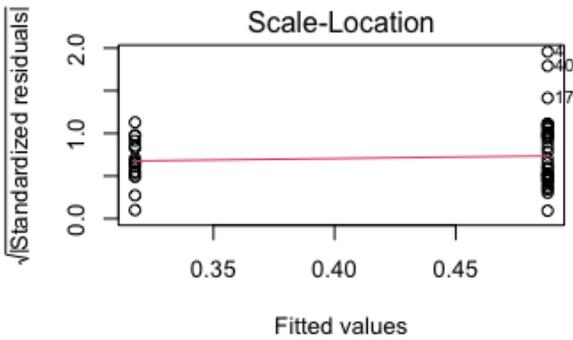
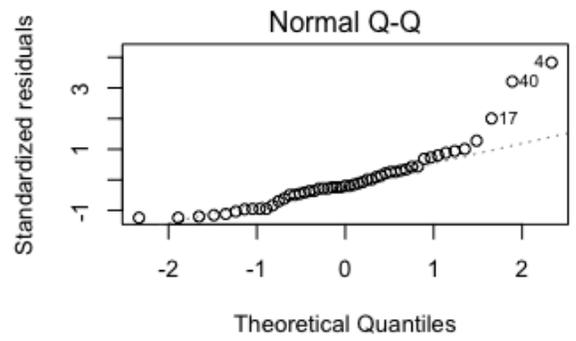
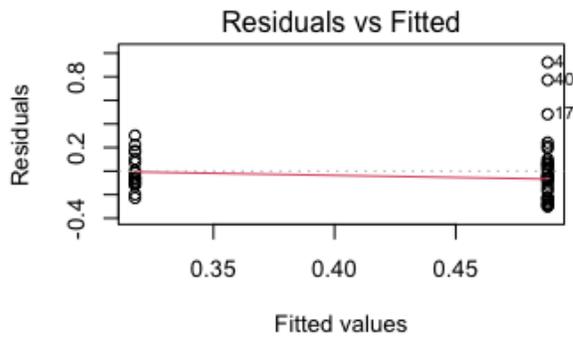
### Linearity test for categorical variable in the model



Model excluding counties in the Western region



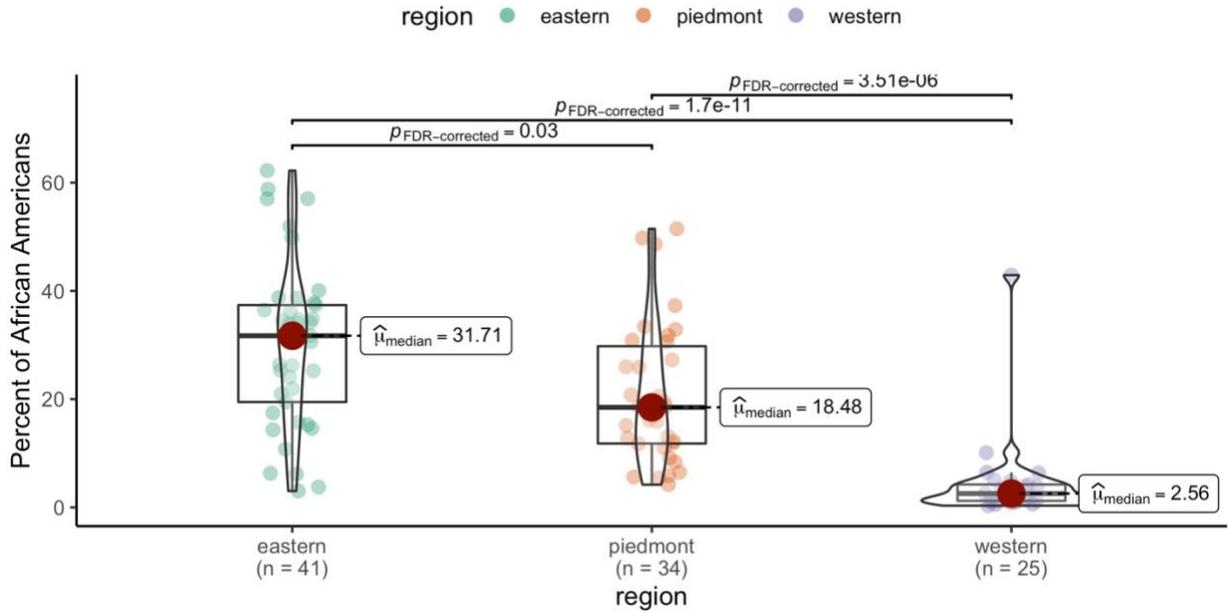
Model excluding counties in the Piedmont region



Model excluding counties in the Eastern region

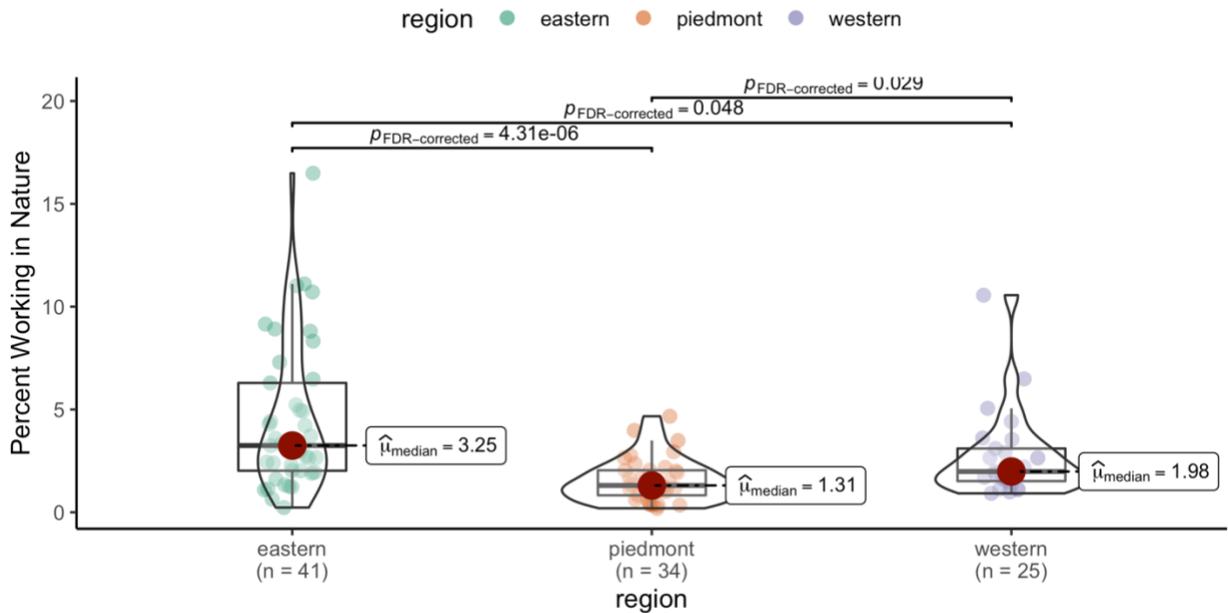
## Appendix J. Dunn test (Kruskal-Wallis Post-hoc Test)

$$\chi^2_{\text{Kruskal-Wallis}}(2) = 48.00, p = 3.77\text{e-}11, \hat{\epsilon}^2_{\text{ordinal}} = 0.48, \text{CI}_{95\%} [0.36, 1.00], n_{\text{obs}} = 100$$



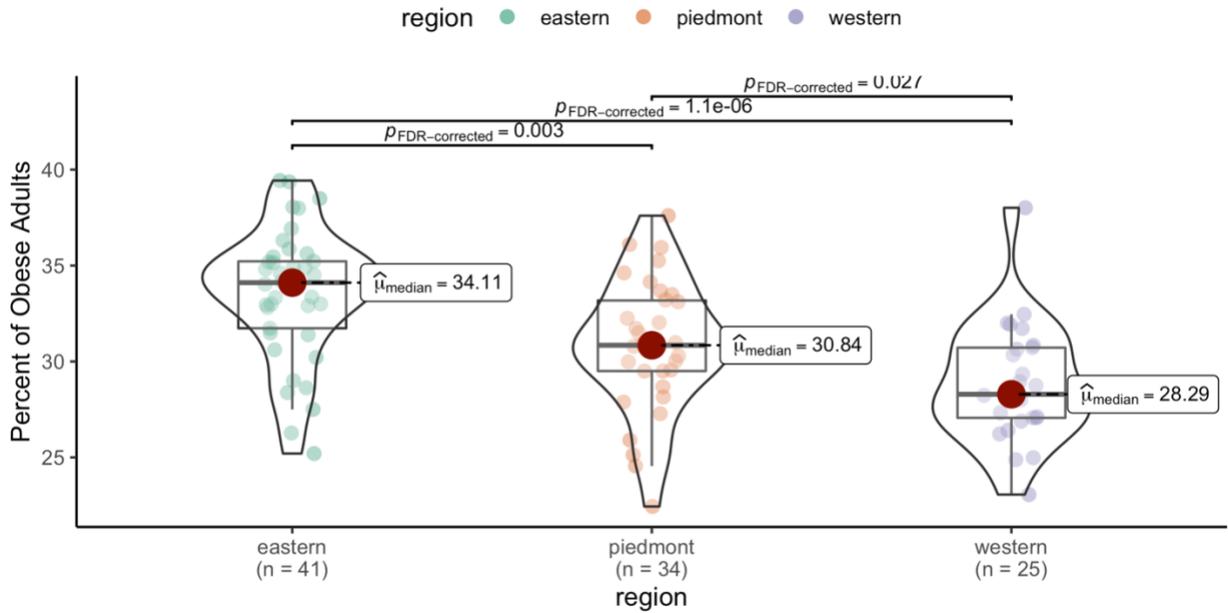
Pairwise test: **Dunn test**; Comparisons shown: **only significant**

$$\chi^2_{\text{Kruskal-Wallis}}(2) = 23.23, p = 9.02\text{e-}06, \hat{\epsilon}^2_{\text{ordinal}} = 0.23, \text{CI}_{95\%} [0.12, 1.00], n_{\text{obs}} = 100$$

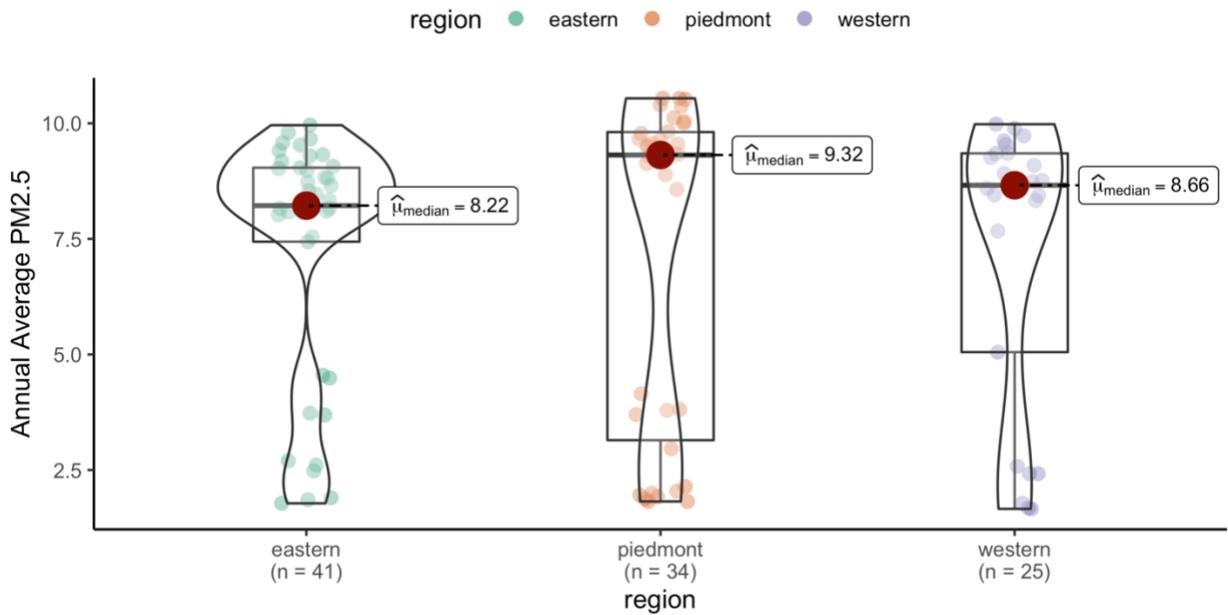


Pairwise test: **Dunn test**; Comparisons shown: **only significant**

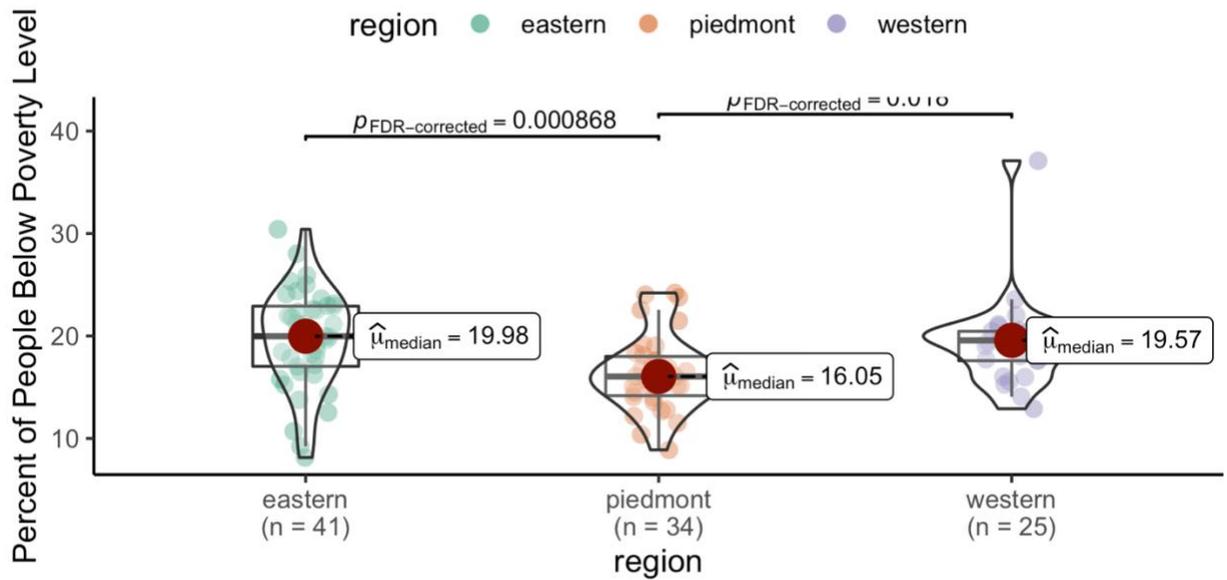
$\chi^2_{\text{Kruskal-Wallis}}(2) = 26.95, p = 1.41\text{e-}06, \hat{\epsilon}^2_{\text{ordinal}} = 0.27, \text{CI}_{95\%} [0.16, 1.00], n_{\text{obs}} = 100$



$\chi^2_{\text{Kruskal-Wallis}}(2) = 2.76, p = 0.252, \hat{\epsilon}^2_{\text{ordinal}} = 0.03, \text{CI}_{95\%} [5.66\text{e-}03, 1.00], n_{\text{obs}} = 100$

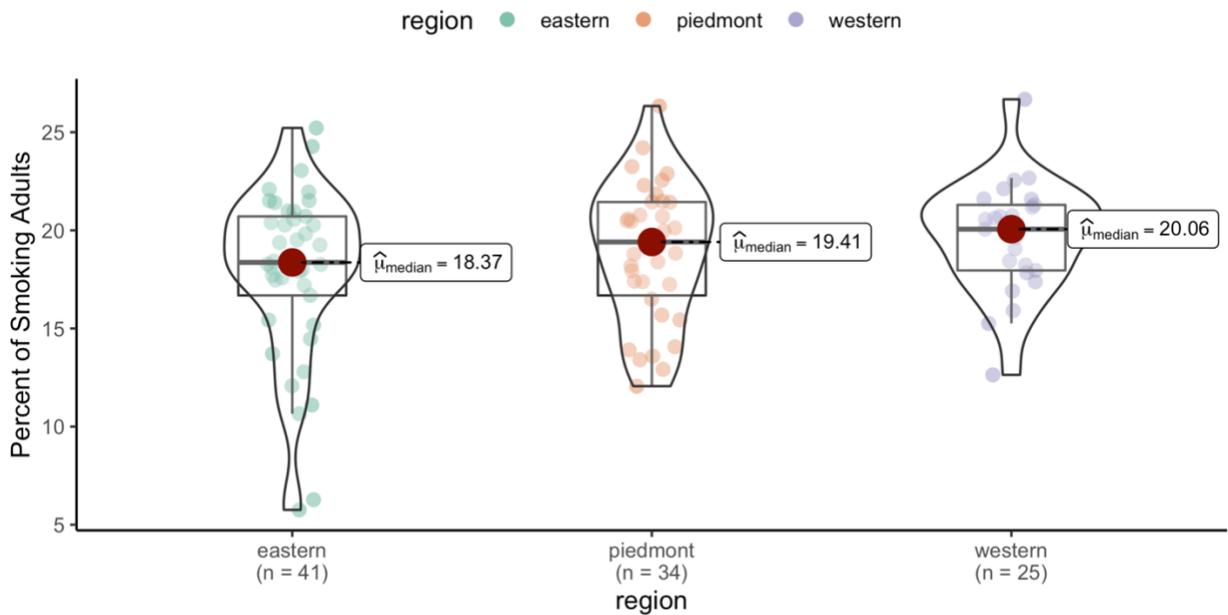


$\chi^2_{\text{Kruskal-Wallis}}(2) = 13.90, p = 9.59e-04, \hat{\epsilon}^2_{\text{ordinal}} = 0.14, CI_{95\%} [0.07, 1.00], n_{\text{obs}} = 100$



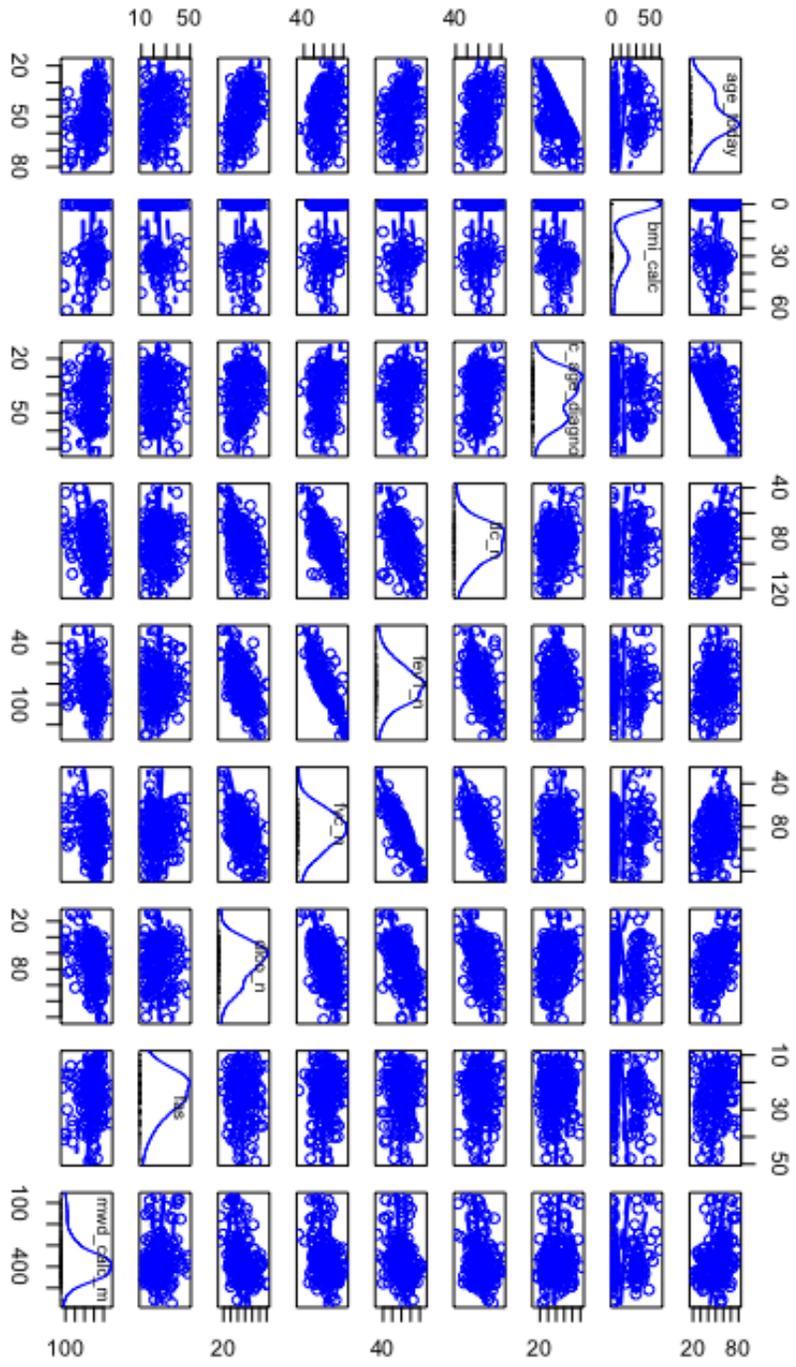
Pairwise test: **Dunn test**; Comparisons shown: **only significant**

$\chi^2_{\text{Kruskal-Wallis}}(2) = 2.36, p = 0.307, \hat{\epsilon}^2_{\text{ordinal}} = 0.02, CI_{95\%} [7.63e-03, 1.00], n_{\text{obs}} = 100$



Pairwise test: **Dunn test**; Comparisons shown: **only significant**

# Appendix K: Variable Distribution Visualization



## Appendix L: Test for Normality

### Shapiro test

<b>Variable</b>	<b>Shapiro-test statistic</b>	<b>p-value</b>
Age	0.9947945	7.952063e-02
BMI	0.7307741	5.759245e-28
Age at diagnosis	0.9837989	1.989981e-05
Predicted DLCO	0.9953609	5.304970e-01
FAS	0.9779659	5.273304e-04
Predicted FEV1	0.9823125	3.110565e-04
Predicted FVC	0.9883360	7.382948e-03
6-MWD	0.9350029	3.288364e-08

# Appendix M: ECUSaR Brochure

## East Carolina University Sarcoidosis Patient Registry (ECUSaR)

### Understanding Sarcoidosis

Sarcoidosis is an inflammatory disease that most often affects the lungs and lymph nodes but can involve the eyes, skin, heart and other organs.

Presently, the cause of sarcoidosis is unknown. Current research suggests that there is likely both a familial and environmental factor required.

There is no cure for the disease. Steroids are the common therapy but are not ideal and have many side effects. Many patients do not require therapy and in some, symptoms disappear within 2 to 3 years of the initial diagnosis.

### Statistics

- 90% of the cases of sarcoidosis are found in the lungs, 20 to 30% of these patients are left with permanent lung damage.
- African-Americans are diagnosed with sarcoidosis up to 10 times more often than Caucasians.
- 10% of the people with sarcoidosis in the U.S. have a relative who also has the disease.

## Sarcoidosis in North Carolina

Sarcoidosis Crude Mortality Rates by Race in NC (2001-2018)

### What is East Carolina University Sarcoidosis Patient Registry (ECUSaR)?

The East Carolina University Sarcoidosis Patient Registry (ECUSaR) is a research study that enrolls patients with sarcoidosis into a database. The information will then be evaluated for quality of life, common familial and environmental factors that may be linked to the disease, so that better therapies may be developed for treating or even

### The purposes of the study are:

- To understand if what patients come in contact with at home or at work causes sarcoidosis.
- To help identify and recruit sarcoidosis patients for future research studies.
- To better understand how patients with sarcoidosis function on a day-to-day basis in order to develop better therapies for the treatment of sarcoidosis.

### Who can Join ECUSaR?

People who:

- Have been diagnosed with sarcoidosis
- Wish to participate

### May I participate if:

- I am not a ECU patient or I live outside of NC? **YES**
- I was diagnosed with sarcoidosis but never developed symptoms? **YES**
- I no longer have any symptoms; the disease has gone into remission? **YES**
- I am under 18 years of age and my parents give their permission? **YES**
- I am not currently under a doctor's care? **YES**

### How do I Participate?

*For more information on the study or if you would like to take part*

**Contact:**  
Anagha Malur, Ph.D  
Pulmonary Lab Manager  
(252) 744-2542

**OR**

*You may fill out the back of this slip and leave it with the receptionist or in the box provided.*

*The coordinator will call you for registration.*

## YES, I WANT TO PARTICIPATE IN THE EAST CAROLINA UNIVERSITY SARCOIDOSIS PATIENT REGISTRY!

**PLEASE CONTACT ME FOR ENROLLMENT:**

(PLEASE PRINT) LAST NAME: .....

(PLEASE PRINT) FIRST NAME: .....

(AREA CODE) HOME PHONE: .....

(DAY-TIME) PHONE: .....

STREET ADDRESS: .....

CITY: .....

STATE: .....

ZIP CODE: .....

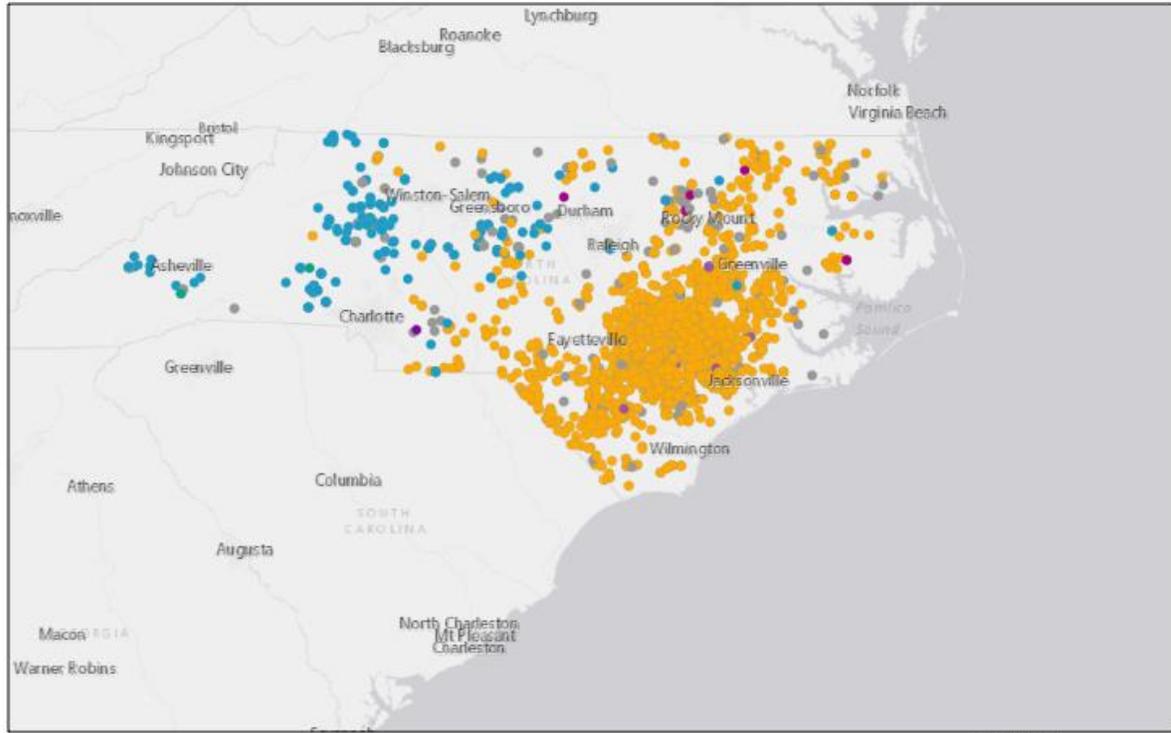
Place tear off this portion and leave it with the-

### Study Site

**ECU Physicians  
Pulmonary Clinic**  
521 Moye Boulevard  
East Carolina University  
Greenville, NC 27834

# Appendix N: Animal Feeding Operation Permits in NC in 2021

## Animal Operation Permits in NC

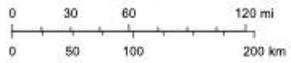


11/21/2021, 12:04:08 PM

Animal Feed Operation Permits (View)

- Swine State COC
- Cattle State COC
- Cattle NPDES COC
- Swine NPDES COC
- Wet Poultry State COC
- Wet Poultry NPDES COC
- Animal Individual State

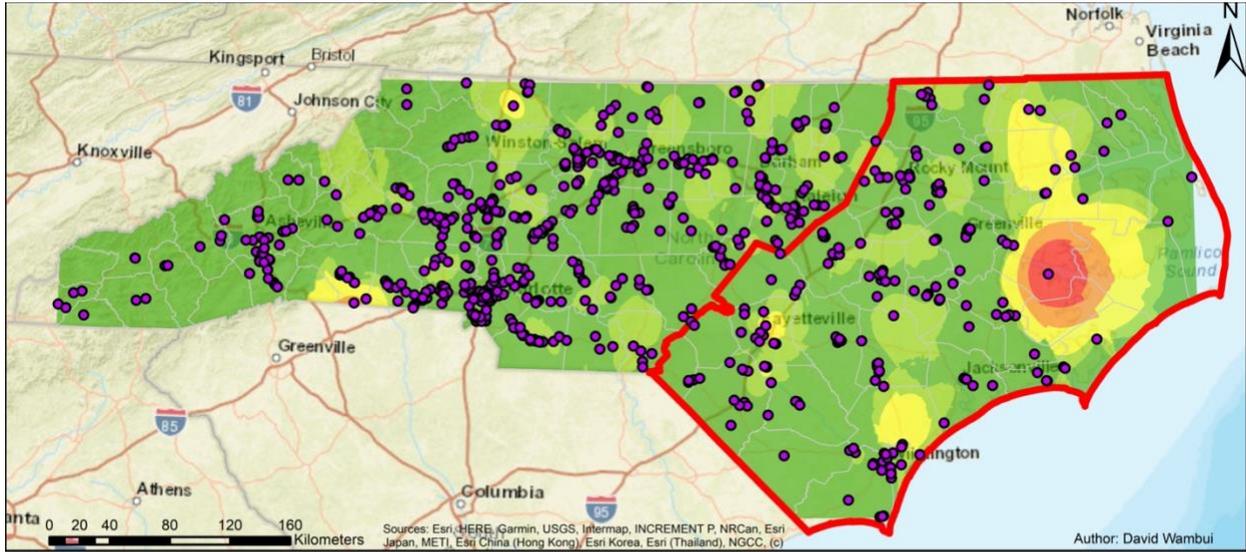
1:4,622,324



Esri, HERE, NPS, Esri, HERE, Garmin, USGS, EPA, NPS

DENR DWR  
Esri, HERE, Garmin, USGS, EPA, NPS | NCDENR - Division of Water Resources | Esri, HERE, NPS |

# Appendix O: USEPA Toxic Release Inventory NC in 2018



## Total toxic substances released (lbs)



## **Appendix P: DrPH Competencies Addressed**

This dissertation addressed both foundational and concentration competencies as outlined in the ECU DrPH Handbook. The three foundational competencies addressed are 1) Explain qualitative and quantitative research to address public health issues. All three studies involved data gathering, analyzing, and interpreting qualitative and quantitative data to identify and address health issues at multiple levels. 2) Design a qualitative and quantitative project to address public health issue and, 3) Integrate knowledge, approaches, and methods from multiple professionals in addressing public health problems. The second studies sought to incorporate epidemiological and geographical methods and techniques to assess sarcoidosis burden in NC with particular emphasis on the disproportionate higher mortality in Eastern NC compared to the rest of the state. Consequently, the outcomes were utilized to develop communication material to help inform the public in Eastern NC about the nature of sarcoidosis in the region. Additionally, the results of these studies have allowed the making of policy and program recommendations that would help in addressing the problem.

The two environmental and occupational concentration competencies this study addressed were: 1) Interpreting results of data analysis for public health research. This competency was addressed in all three studies and, 2) Synthesize and evaluate research on an environmental or occupational public health topic conducted by others. This competency was addressed in the first paper through a systematic review and meta-analysis.

