South Boston Scleroderma and Lupus Health Study

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I. Introduction

In 1998, residents of South Boston and then State Senator Stephen Lynch contacted Suzanne K. Condon, Associate Commissioner of the Massachusetts Department of Public Health (MDPH) and Director of the Bureau of Environmental Health (BEH), regarding concerns about a suspected cluster of scleroderma and other autoimmune diseases in that area of the City of Boston. The primary concerns focused on a perceived "cluster" of women who grew up in South Boston diagnosed with either scleroderma or lupus and any potential relationship to historical opportunities for environmental exposures in that area of the city of Boston, MA. Residents expressed concern about a number of historical sources of environmental pollution in the area including the Coastal Oil site, a former power plant, other hazardous waste sites and the proximity of the neighborhood to Logan International Airport.

There were several challenges associated with investigating both the prevalence of these diseases and their possible association with environmental factors. Scleroderma and lupus are both relatively rare and chronic autoimmune diseases for which the causes remain largely unknown. Further, although the American College of Rheumatology developed criteria for diagnosing systemic scleroderma (SSc) and systemic lupus erythematosus (SLE), both diseases display diverse and often overlapping clinical manifestations (Simard and Costenbader 2007). Therefore, the chance for misdiagnosis among patients is increased given their clinical similarities and the fact that both SSc and SLE have many shared symptoms with other autoimmune and connective tissue diseases. At the time that residents of South Boston reported their concerns to the MDPH, Massachusetts did not

have a registry or other coordinated reporting system for the surveillance or identification of individuals diagnosed with autoimmune diseases such as SSc or SLE. (Note: At present, MDPH is attempting to conduct statewide surveillance of SLE in response to a legislative directive). Therefore, in order to evaluate whether a cluster of SSc or SLE might exist, it was necessary to first identify individuals from South Boston diagnosed with these diseases, confirm their diagnoses, and evaluate whether the prevalence and/or incidence of SSc and SLE in South Boston was above expected rates.

The MDPH contacted the South Boston Community Health Center (SBCHC) as well as area rheumatologists to obtain an estimate of the number of individuals from that area of the city that were currently being treated for a diagnosis of SSc or SLE. The MDPH also established a community advisory committee (CAC), a group composed of approximately 20 individuals including current and former residents of South Boston, health care providers, legislative representatives and others. MDPH, in partnership with the CAC, conducted community outreach encouraging current and former South Boston residents to contact the MDPH if they had a diagnosis of SSc, SLE or mixed connective tissue disease (MCTD) or if they knew someone who was a current/former resident of South Boston who had any of these diagnoses. Mixed connective tissue disease is considered an "overlap" of three diseases: systemic lupus erythematosus, scleroderma, and polymyositis (a disease that causes inflammation of the muscles). People with MCTD may experience a variety of signs and symptoms associated with these diseases. The outreach was intended to capture reports of both current and former South Boston residents who not only had been diagnosed with SSc and SLE but also those individuals who may have clinical manifestations of these diseases but whose symptoms had not met

ACR criteria for a definitive diagnosis of SSc or SLE. In this way, the MDPH could evaluate disease prevalence across the broader spectrum of disease (i.e., mild to severe disease).

Based on the preliminary case finding effort, 12 individuals from South Boston self-reported to the MDPH that they had a diagnosis of SSc and 23 individuals reported a diagnosis of SLE. A number of former South Boston residents also reported either a diagnosis of SSc, SLE or some other connective tissue disease. For a population the size of South Boston (estimated as 30,000 by the 1990 U.S. Census), the number of cases expected would range between 1 and 9 for SSc and between 7 and 12 for SLE. These figures are based on the prevalence estimates reported in various population-based studies published for SSc and SLE at the time that the study was launched (Michet et al. 1985; Maricq et al. 1989; Johnson et al. 1995; Mayes 1996; Silman and Hochberg 1996; Jacobsen et al. 1997; Gourley et al. 1997). The data based on preliminary case finding suggested that the crude prevalence of both SSc and SLE was higher than expected among current South Boston residents (possibly 33%-1100% higher for SSc and 92%-229% for SLE based on the published prevalence estimates). Although the preliminary data suggested an increased prevalence of SSc and SLE in South Boston, these estimates represented only preliminary findings that were based on self-reported and unconfirmed cases of SSc and SLE. Further, it was unknown whether environmental or other common factors might be related to the development of SSc and SLE among residents in South Boston.

II. Background

A. Demographics

South Boston is a peninsula located in the eastern portion of the City of Boston. The South Boston neighborhood is approximately 3.1 square miles in area with a population of approximately 30,000 residents. According to 2004 zoning maps, this area of the city is a mix of residential and industrial properties. The residences are primarily multi-family dwellings with some single family homes that are surrounded by major shipping and industrial properties located along Boston Harbor (Figure 1).

According to U.S. Census data, the population of South Boston declined from approximately 55,000 residents in 1950 to approximately 30,000 in 2000 (Figure 2). During that time, the age distribution of the population remained steady with the majority of the South Boston population under age 35 (Figure 3). While the racial and ethnic distribution has changed somewhat more recently, the large majority of residents are Caucasian. The percentage of white residents has changed from nearly 100% in 1950 to 87% in 2000 (Figure 4). At present, approximately 2-3% of South Boston residents are African American and approximately 7-8% of South Boston residents are Hispanic. In 1950, foreign-born South Boston residents included those of Irish, Lithuanian, Canadian, or Italian descent. Currently, approximately 50% of South Boston residents report being of Irish heritage. Since 1960, the median household income of South Boston has consistently fallen below that of the state median income (Figure 5).

B. South Boston Industrial History

Unlike the rest of Boston, the area known today as South Boston was developed according to a predetermined grid, which was planned to meet the needs of the city's industrial growth (Town Online 2000). At the turn of the 19th century, South Boston was a 600-acre peninsula known as Dorchester Neck, which stretched into Boston Harbor from the town of Dorchester. Dorchester Neck was originally a very small agricultural community, until real estate developers recognized the land's industrial and residential potential (City of Boston Environment Department 1997). For the next several decades South Boston was characterized by industrialization and rapid population growth. The landscape was constantly changing as companies, particularly the Boston Wharf Company, began to fill in areas of the harbor to create more wharf and storage facilities (City of Boston Environment Department 1997). Broadway Street became an axis for commercial and residential uses while industrial activities began to focus around the Fort Point Channel.

In 1861, the first petroleum refinery in the city was built in South Boston, followed by the advance of oil works industries (B.R.A. 1999). Additionally, the completion of the Commonwealth Pier in South Boston in 1914 provided greater access to Boston Harbor activity and soon made the pier one of international importance. The Massachusetts Port Authority (Massport) was established in 1956 specifically to revitalize ports in the area. The organization built the Castle Island Container Terminal to keep up with the advances in international trade and shipping. In 1980, Massport built the Paul W. Conley

Terminal, a larger and more up-to-date facility, located on the Reserve Channel. The 101-acre terminal currently serves as Boston's center for large cargo handling (B.R.A. 1999).

The layout of South Boston has not changed substantially since 1962, when the city drafted the first zoning map of the area. Land was clearly divided into residential, business, and industrial districts, with much of the heavy manufacturing surrounding the Fort Point Channel, the Reserve Channel and along established rail-lines (Figure 1). Most of the coastal land was designated for industrial purposes, except for the southern side of the South Boston peninsula, which was primarily used for beaches and recreation. The residential neighborhoods that spread south from East 1st Street lie next to some of South Boston's most industrialized parcels of land. The Conley Terminal (formally known as the Castle Island Terminal), the Coastal Oil Company, the Boston Edison and MBTA Power Plants, the King Terminal area, and other industrial and manufacturing companies were lined up between the southern edge of the Reserve Channel and the northern side of East 1st Street. Retail stores, office buildings and light manufacturing companies created a narrow buffer zone between the heavier industrial areas and residential properties, although some residential areas, including a public playground and park, lie immediately next to industrial properties.

C. Review of SSc and SLE Literature

Systemic scleroderma (SSc) is a relatively rare autoimmune disease. It is a multisystem disorder of connective tissue that is characterized by over-production of collagen and other constituents of the skin and targeted internal organs. The term "scleroderma" literally means hardening of the skin. SSc occurs among females during reproductive and

early menopausal years with a peak incidence at ages 45 to 54. It rarely occurs in children or men under age 35 (Valentini and Black 2002). The ratio of female to male cases ranges from 3:1 to 8:1. Racial differences in disease progression and manifestation, such as an earlier age at onset and increased disease severity in African Americans, have been observed (Laing et al. 1997). Recent literature has suggested that the prevalence and incidence of scleroderma may be higher in black women compared to white women (Laing et al. 1997; Mayes 2003).

Recent estimates of the prevalence of SSc in the United States have been relatively consistent and indicate that the prevalence (i.e. the number of all individuals alive with a diagnosis of SSc) is 276 cases per million among adults and up to 371 cases per million among white females (Mayes 2003). Review of a number of population-based studies has shown that the incidence of SSc in the United States increased during the period 1947 to 1973 and remained relatively stable from 1973 to 2002 (Mayes 2003). Two of the largest studies to date have observed similar SSc incidence rates (i.e. the number of new cases) of 9.6 to 19.3 new cases per million population per year and between 13 and 27 new cases per million population per year for white females in particular (Steen et al. 1997; Laing et al. 1997; Mayes 2003). Rates of scleroderma vary throughout the world with the United States and Australia having higher incidence rates and prevalence estimates than observed in European countries and Japan.

SSc has a wide variability among patients in its clinical presentation, disease progression and prognosis. In 1980, the American College of Rheumatology established criteria for the diagnosis and classification of SSc (Valentini and Black 2002). The criteria were

derived from an analysis of patients from various medical centers in the United States. The features of these patients were compared with those of patients with other connective tissue diseases (such as systemic lupus erythematosus, polymyosititis dermatomyosititis and Raynaud's phenomenon). Three main subsets of the disease have been proposed and include diffuse cutaneous disease, limited cutaneous disease and scleroderma with overlap of other connective tissue disease (LeRoy et al. 1988).

The epidemiology of scleroderma has been difficult to examine both because of the rarity of the disease and because of the overlap in symptoms which has led to misdiagnoses with other connective tissue diseases including systemic lupus erythematosus (SLE). Although the etiology of SSc is unknown, the current hypothesis is that both genetic and environmental risk factors are associated with SSc development. Studies to date indicate that a genetic predisposition coupled with one or more environmental factors influence disease development. Since SSc occurs predominantly among females, it is hypothesized that hormonal or reproductive factors might be related. Some studies have suggested that the number of pregnancies may influence disease expression but studies examining reproductive history have produced conflicting results (Mayes 1999; Pisa et al. 2002; Lambe et al. 2004)

Strong evidence for genetic risk factors for SSc is found in studies of the Choctaw Native Americans where the disease prevalence is at least 20 times greater than in the general population (Arnett et al. 1996). Studies of SSc among twins are limited; however, a recent study of twins suggests that though monozygotic (identical) twins have a concordance rate similar to that observed in dizygotic (fraternal) twins (4.2% and 5.6%,

respectively), monozygotic twins had a significantly higher concordance rate for autoantibodies (90% vs. 40%) (Feghali-Bostwick et al. 2003). This finding suggests that factors other than inheritance play a role in the development of SSc and likely involve environmental agents or acquired genetic alterations.

Detection of a greater number of genetic polymorphisms has also been observed among SSc patients. However, both strong and weak associations have been detected in regards to the distinct HLA halotypes identified (Medsger 1994; Valentini and Black 2002). Although unusual, SSc has been observed to cluster in families (Maddison et al. 1986; Mayes 2003). Multiple cases of SSc occurring in families is infrequent, however the risk of developing SSc is increased 10 to 15 fold among first degree relatives with the disease (Mayes 2003). In addition, some studies have shown that family members of individuals with SSc, including spouses, are more likely to have an increased prevalence of antinuclear antibody (ANA) positivity than are healthy controls, thus providing support that exposure to shared environmental factors appears to play a role in the development of SSc (Maddison et al. 1986). However, this trend has not universally been found and more recent studies report the percentage of spouses who are positive for ANAs closer to 5% as is seen in the general healthy population (Barnett and McNeilage 1993).

A number of environmental agents are suggested as factors which may act to trigger SSc. A variety of organic solvents and other environmental toxicants have been implicated in the etiology of SSc and scleroderma-like syndromes mainly from occupational studies (Silman and Jones 1992; Erasmus 1957; Nietert et al. 1998; Lacey et al. 1999). In some instances, clusters or outbreaks of cases related to exposures have implicated particular

environmental agents including vinyl chloride monomer, toxic oil syndrome (adulterated rapeseed oil), and eosinophilia myalgia syndrome (L-tryptophan contaminant) (Tabuenca 1981; Belongia et al. 1990; Veltman et al. 1975). Occupational studies suggest that exposure to silica dust and organic solvents may also be related to SSc development (Haustein and Ziegler 1985; Bovenzi et al. 1995; Steenland and Brown 1995; Silman and Hochberg 1996; Nietert et al. 1998; Mayes 1999; Parks et al. 2002; Garabrandt and Dumas 2000; Bovenzi et al. 2001; Diot et al. 2002; Garabrandt et al. 2003; Bovenzi et al. 2004). Though smaller case studies have had mixed results, larger registry-based studies of silica exposure and risk of SSc have shown a strong association (Parks et al. 1999).

In addition, geographic clusters of SSc have also been reported including increased disease prevalence around airport locations in London and geographic clustering in southern Australia (Silman et al. 1990; Chandran et al. 1995; Roberts-Thomson et al. 2001; Roberts-Thomson et al. 2006). A cluster of five SSc patients and 11 individuals with scleroderma-like disease was also observed in a rural area near Rome, Italy (Valesini et al. 1993). Although no specific environmental exposures were identified in relation to these clusters, the observation of SSc clustering suggests that the disease may occur in a non-random fashion.

Systemic lupus erythematosus (SLE) is also a relatively rare autoimmune disease with clinical and epidemiologic patterns similar to SSc. SLE is a chronic multisystem inflammatory disorder with a variety of clinical manifestations (Hopkinson 1991). Although the precise cause of SLE is unknown, like SSc it is believed to be multifactorial in nature with genetic, hormonal and environmental factors influencing disease

development. Also similar to scleroderma, SLE is heterogeneous in its clinical expression and is characterized by an increased production of autoantibodies (Simard and Costenbader 2007).

SLE is most commonly diagnosed in women of reproductive and early menopausal age but can occur among males and females of all ages. The usual disease onset is between ages 15 and 40 with a female to male ratio of 9 to 1. The prevalence and incidence of this disease vary throughout the world. The overall prevalence estimates for SLE range from 14.6 to 149.5 cases per 100,000, of which 90% are women (Hochberg 1990; Ward 2004; Danchenko et al. 2006; Chakravarty et al. 2007). However, a large, recent study based on nationally-representative NHANES III data found SLE prevalence to be 53.6 per 100,000 for the general population and 100 per 100,000 for females (Ward 2004). The lowest incidence rates are observed among Caucasian Americans, Canadians and Spaniards with an estimated incidence in the United States of 1.4 cases per 100,000 (Simard and Costenbader 2007). Incidence rates for females, specifically, have been estimated at anywhere between 2.5 and 9.4 per 100,000 (Uramoto et al. 1999; Danchenko et al. 2006). There are marked racial differences in the prevalence and incidence of SLE with greater rates consistently found among African-Americans. Studies have reported a three to four fold age-adjusted increase in the incidence of SLE in blacks versus whites (Hochberg 1990). Higher incidence rates and prevalence have been observed among individuals of sub-Saharan African descent living in the United States, Europe, and the Caribbean. It has been hypothesized that this difference is related to a mix of genetic and environmental factors (Hochberg 1990; Hopkinson 1991; Cooper et al. 1999; Maddison 1999; Simard and Costenbader 2007)

SLE also appears to have identifiable genetic risk factors as suggested by population, family and twin studies. Studies in twins show a monozygotic concordance rate of between 24% and 60%, whereas the concordance rate observed among dizygotic twins is 2% to 5% (Winchester and Lahita 1987, Simard and Costenbader 2007). However, the true concordance rate may be at the lower end of this range, as described in a large 1992 twin study (Deapen et al 1992). In this study, over 100 pairs of twins yielded a 24% concordance rate for monozygotic twins and 2% for dizygotic twins. DNA fingerprinting was used to validate reported zygosity in a sub-sample of the twins and SLE diagnoses confirmed by medical record review. Since recruitment bias in twin studies is likely to result in overestimation of disease concordance, the true concordance rate may be even lower. While the fact that monozygotic twins did experience higher disease concordance than dizygotic twins indicates a genetic susceptibility, the overall low concordance rates in this study point to other contributing environmental factors.

Rare cases of twins separated at birth and raised in different environments but both developing SLE within a short time of each other have also been documented (Hopkinson 1991). The genetic factors influencing SLE development are complex and over 100 different genes could potentially contribute to SLE susceptibility (Tsao 2004; Simard and Costenbader 2007).

Hormonal factors are also believed to play a role in the development of SLE. Estrogen can influence regulation of the immune system and have either pro or anti-inflammatory actions. Age at menarche (first menstruation) may be a marker for a women's duration of estrogen exposure and has therefore been studied as a possible risk factor in SLE. White

women with an early age at menarche (i.e., less than age 10) had a 4.6 fold odds of developing SLE when compared to women with average age at menarche of 13 years (Simard and Costenbader 2007). Investigations of oral contraceptive use have yielded mixed results; though some case-control studies have not found a statistically significant association with SLE development, larger studies like the Nurses Health Study observed an increased risk of SLE among women who ever used oral contraceptives versus women who reported never using oral contraceptives (Strom et al. 1994; Sanchez-Guerrero et al. 1997; Mayes 1999). Additionally, women who currently used oral contraceptives and those who used oral contraceptives containing higher levels of ethinyl estradiol were at significantly increased risk of SLE (Bernier et al. 2009). Early age at menopause and use of hormone replacement therapy post menopause have also been suggested as associated with an increased risk of the disease (Sanchez-Guerrero et al. 1995; Meier et al. 1998; Mayes 1999)

As with SSc, environmental agents are suspected of acting in concert with genetic factors to promote the development of SLE. Some have suggested that geographic areas of high prevalence of SLE may be associated with exposure to environmental contaminants (Walsh and Fenster 1997). Occupational exposure to silica dust is thought to be associated with the development of SLE as higher than expected prevalence estimates have been observed in uranium workers (D'Cruz 2000). It has also been reported that non-occupationally-related, intentional exposure to scouring powder, which contains up to 95% silica, can lead to MCTD (Vincent et al. 1996). Experimental mouse models which mimic SLE disease development have shown that silica exposure can alter immunoglobulin and cytokine levels as well as a number of B- and T-cell types involved

in immune activity (Brown et al. 2004). Other proposed silica-associated mechanisms involve silica-mediated interference with cell apoptosis (Cooper et al. 2008). Exacerbated disease pathology and increased immune activity in lupus-like mouse models coupled with occupational data provide compelling evidence for further epidemiologic investigation of even low-dose silica exposure (Parks et al. 1999).

Heavy metals such as mercury have also been observed to induce renal autoimmunity in animal models (Hultman et al. 1994). A study in Gainesville, Georgia reported an incidence of SLE among African-Americans in that area that was nine times greater than the highest prevalence estimates reported in other studies. The authors suggested that long-standing exposure to industrial emissions may be related to lupus risk in this community (Kardestuncer and Frumkin 1997). A study of residents in Nogales, Arizona also showed an increased prevalence of SLE. The researchers documented past exposure to chlorinated pesticides among both cases and controls in the study but did not observe a statistical association with increased risk of SLE (Balluz et al. 2001). Also, the results from a case-control study investigating the relationship between undifferentiated connective tissue disease (UCTD) and occupational solvent exposures suggested that there was an increased risk in UCTD development among persons with exposure to solvents and/or compounds that are petroleum-based (i.e., petroleum distillates) (Lacey et al. 1999).

Though autoimmune diseases represent a diverse group of diseases with varying clinical manifestations, they are all characterized by damage to tissues and organs that arises from a response to self-antigens. A large, multi-center SLE cohort study found familial

aggregation not only of SLE, but also of rheumatoid arthritis and autoimmune diseases in general (Alarcon-Segovia et al. 2005). Despite epidemiologically-based familial clustering of disease, ANA levels alone do not explain the relationship and instead point to more complex immuno-genetic interactions.

Overall, evidence from epidemiologic studies and case reports suggest that both SSc and SLE are autoimmune rheumatic diseases that occur when a genetically predisposed individual is exposed to one or more environmental triggers. Both diseases share common clinical and epidemiologic traits in that they occur predominantly in women of reproductive and early post-menopausal age and may be caused by a combination of genetic, hormonal and environmental factors.

Because of the apparent elevation in SSc and SLE prevalence estimated from the preliminary case finding efforts and the potential association between environmental factors (particularly petroleum-related exposures) as possible causative agents for both SSc and SLE, the MDPH designed an exploratory epidemiologic study to assess the role of possible risk factors (both environmental and non-environmental) in the development of these diseases among South Boston residents. The MDPH collaborated with rheumatologists and a clinical epidemiologist at Boston Medical Center (BMC) and rheumatologists at Tufts Medical Center (formerly New England Medical Center) to conduct a retrospective case-control study of SSc and SLE in the South Boston community.

III. Methods

A. Study Hypothesis

Epidemiologic studies involve statistical hypothesis testing which typically focus on the null hypothesis (H_o). The null hypothesis assumes no association between the factors under investigation. This hypothesis states that the results observed in a study are no different from results that might have been observed as a result of chance alone (Last 1988). By conducting statistical analyses and comparisons, researchers can determine whether the data collected in a study provide evidence counter to the null hypothesis. If so, then the null hypothesis can be rejected in favor of the research or study hypothesis (H_a). Given that causative factors for SSc and SLE are not well established and remain primarily unknown, the South Boston Scleroderma and Lupus Study was an exploratory study intended to evaluate relationships between risk factors and risk of developing SSc or SLE. The primary study aims were:

- To medically confirm the diagnosis of self-identified cases of SSc and SLE in South Boston;
- To identify additional cases of these autoimmune diseases through community outreach and by contacting area rheumatologists and hospitals and searching death certificate registries in order to calculate more accurate prevalence/incidence rates for South Boston; and

- To identify possible contributing factors (environmental and non-environmental) among individuals with SSc and SLE and a randomly selected comparison group from South Boston.

B. Study Design

The South Boston Scleroderma and Lupus Study is a retrospective study using a case-control approach where risk factor information and exposure histories of current and former South Boston residents diagnosed with systemic scleroderma (SSc) and systemic lupus erythematosus (SLE) were compared to the exposure histories of current South Boston residents without the disease(s) of interest. Due to the rarity of the diseases under investigation as well as the exploratory nature of the study, a population based case-control study design was used. A case-control study design is often the preferred method for exploratory studies when investigating risk factors for the purpose of generating etiologic hypotheses and for studying diseases of low incidence (dos Santos Silva 1999; Schlesselman 1982). Cases were individually matched based on age and gender to controls randomly selected from the South Boston population.

C. Case Definition

A case was defined as any individual who lived in South Boston between January 1, 1950 and December 31, 2000 and had a medically confirmed diagnosis of SSc or SLE. All cases were required to be at least 21 years of age at the time of study and to have lived in South Boston for at least one year prior to the onset of disease. The year of the first non-Raynaud's symptom that was referable to the disease was used as the incidence year for

both SSc and SLE[1]. While we recognize some ambiguity regarding initial symptoms versus the time at which a patient meets ACR classification criteria, given that SSc and SLE cases were combined for analysis, the first non-Raynaud's symptom was used as the incidence date for all cases in large part for consistency. Both living and deceased individuals meeting the above criteria were included in the study. SSc and SLE occur less frequently in pediatric populations, and given the demographics of the cases initially reported to the MDPH, very little enrollment was anticipated among individuals under age 21.

D. Case Identification and Ascertainment

Initial case identification was completed through contact with area rheumatologists and hospitals as well as through a search of death certificates at the MDPH, Registry of Vital Statistics. Applicable ICD codes used to identify potential cases by area rheumatologists and death certificates are listed in Table 1. Letters sent to area hospitals and rheumatologists asked that they contact all patients with a diagnosis specified by the provided ICD codes. Physician letters to patients requested that all individuals who lived in South Boston for at least one year during the period 1950 to 2000 with a diagnosis of SSc or SLE contact the MDPH. Detailed information about the study was then provided to interested patients and contact information was obtained for follow-up diagnostic confirmation. Death certificate searches were limited to searching the immediate and underlying cause(s) of death or other contributing conditions at the time of death for

[1] Raynaud's phenomenon is a vascular disorder that causes discoloration of the extremities. As upwards of 90% individuals diagnosed with SSc and SLE also suffer from Raynaud's, it is not considered a specific disease indicator (Korn and Merkel 2005).

individuals who died while residing in South Boston during the years 1969-2000. The year 1969 is the first year that death certificate data is available in electronic format for searching. The MDPH sent requests for patient identification to approximately 26 rheumatology practices and 5 major academic hospitals in Boston and the surrounding area. Of these practices and institutions, four reported they had no patients that met the established case criteria; four responded by contacting relevant patients; and the remainder did not respond.

Given the low response from hospital and physician contacts, additional case identification was completed through outreach to the South Boston community. Collaboration with the CAC led to the development of an outreach flyer that explained the nature of the investigation and asked individuals diagnosed with either SSc, SLE or mixed connective tissue disease to contact the MDPH via a pre-established toll free line. The flyer was translated into different languages (i.e., Polish, Lithuanian and Spanish) and distributed to a host of community organizations and centers, churches, schools, local business establishments, media outlets and city sponsored events and web sites. The flyer and an accompanying news story were printed several times in the South Boston Tribune (a community newspaper distributed to all current residents and a large number of former South Boston residents) as well as being posted on the community websites (southboston.com and southbostononline.com). As an additional outreach effort, the MDPH and the CAC organized a community drop in which study informational flyers were distributed door to door to every household in South Boston. A date between Thanksgiving and Christmas was chosen to maximize participation and awareness of the study as many former South Boston residents return to the area during the holiday season.

Individuals who contacted the MDPH about their diagnosis or on behalf of a deceased family member were then asked to answer a screening questionnaire to determine eligibility for the study.

As a result of the case ascertainment efforts, the MDPH received reports of 147 individuals with SSc, SLE or some other connective tissue or autoimmune disease. Of the 147 individuals initially reported to the MDPH, the majority (n=127) were self-identified to the MDPH. Of the 147 individuals reported to MDPH, 34 were excluded based on their diagnosis or residence (29 reported a diagnosis that was not relevant to the study and five individuals reported a residence other than South Boston). The remaining individuals (n=113) were contacted for enrollment in the study and additional case confirmation. Eighty-one individuals underwent additional diagnostic review (either physical exam, medical records review or both). Twelve individuals did not respond to requests for study participation (10.6 %), seven individuals refused study participation (6%), and thirteen individuals were unable to be contacted (11.5%). Results of the case identification and case ascertainment process are presented in Figure 6.

E. Case Confirmation

Upon determining study eligibility, the diagnosis of potential cases was then confirmed by physical examination and/or medical records review. Identified cases were evaluated by a board certified rheumatologist at the BMC, General Clinical Research Center who served as the diagnosing physician for the study. Medical histories and physical examinations were performed to verify a diagnosis of SSc, SLE or overlap diagnosis and identify disease sub-group and patterns of systemic organ involvement using a

standardized diagnostic exam. Blood samples were collected to determine patterns of autoantibodies for diagnostic purposes. Available medical records were collected for each case from all prior treating physicians including rheumatologists, dermatologists, physicians in general practice/internal medicine, and nephrologists.

When both data from medical records and data collected by the diagnosing rheumatologist at physical examination were available, a diagnosis of SSc or SLE was confirmed based on the American College of Rheumatology (ACR) classification criteria (Subcommittee for SSC 1980, Tan 1982). When patient medical records were insufficient to verify an individual's diagnosis using the ACR classification criteria and when there was agreement on the diagnosis based on physical examination between the study rheumatologists and the diagnosing physician, the diagnosis of SSc or SLE was considered confirmed. When medical records were insufficient to verify an individual's diagnosis and there was not agreement on the diagnosis based on physical exam between the study rheumatologists and the diagnosing physician, an adjudication committee consisting of three of the four board-certified study rheumatologists reviewed each case to determine the final diagnosis. The incident year or date of disease onset for cases was confirmed using the process outlined above and was defined as the year when the first non-Raynaud's symptom referable to the disease occurred. This date was extracted retrospectively from medical records for each patient. Of the 81 individuals who were reviewed for diagnostic confirmation, 45 individuals met the ACR classification criteria for a diagnosis of SSc or SLE and lived in South Boston at the date of their first non-Raynaud's symptom. Of these 45 individuals, four were either unable to participate or were lost to follow-up. Results of the case confirmation process are provided in Figure 7.

F. Control Identification and Recruitment

Living and deceased cases with a confirmed diagnosis of SSc or SLE were matched based on gender and age (+/- three years) to four controls. Controls were randomly selected from the South Boston residents list for 2001, an annual census compiled by the Registry Division of the City of Boston. The South Boston "list" of residents was used for control selection and recruitment because it was the best available data source that comprehensively represented the population of South Boston. The "list" was available in an electronic format and provided gender and date of birth for matching purposes as well as current address information for contacting and tracking potential controls.

Given the retrospective nature of the study and because the case group was a mix of both current and former South Boston residents, controls were also required to have lived in South Boston for at least one year prior to the incidence year for the corresponding case. For each control, the incidence year for the corresponding case was referred to as the index date for the control. This restriction was established to assure that controls selected from the current resident list would be able to be compared to cases with respect to exposure periods (residence time in South Boston). That is, because the sampling source for controls was the current list of residents and the case group reflected both current and former residents of South Boston, controls were restricted to matching individuals who resided in South Boston at least one year prior to the incidence date of the corresponding case (i.e., the date of the first non-Raynaud's symptom).

Eight potential controls were initially selected for each case to allow for successful recruitment of four controls per case as well as control replacement in the event that

individuals did not match eligibility by residing in South Boston prior to the incidence date or refused participation. When the initial control sample was exhausted and a complete match ratio of four controls per case had not been met, refusals and controls who did not respond were replaced through additional sampling of controls from the list of residents by selecting twice the amount of necessary controls to complete the intended match ratio. A total of 830 controls were sampled and identified as potential matches based on age and gender.

Potential controls that were successfully matched to a case were contacted by mail to request their participation in the study. The MDPH Human Research Review Committee (HRRC) required that the study maintain a passive recruitment process for controls where all potential controls selected from the residents list were contacted by mail requesting participation in the study. Individual controls who did not respond to the first recruitment letter were sent a second letter two weeks after the initial contact. Potential controls who did not respond to the second recruitment letter were then sent a third and final letter requesting study participation. As required by the HRRC, if there was no response from the potential control after three mailings, contact with that individual was terminated and additional controls were then selected as potential matches to the corresponding case and contacted for study participation. The first series of control recruitment letters were mailed on March 22, 2002. Additional mailings were conducted between 2002 and 2004.

Of the 830 potential controls contacted for study participation, 433 did not respond to outreach efforts (52%), 175 refused to participate (21%), 3 were lost to follow-up (<1%) and 65 agreed to participate but could not be matched with respect to index date (8%),

leaving 154 (19%) potential controls to be successfully matched. As mentioned, the study was designed with an intended match ratio of four controls per case. However, recruitment efforts were unable to achieve complete matched control sets for each of the enrolled cases. Although the majority of cases have a complete 1:4 control match or greater (73%), match ratios for the study sample are mixed. The distribution of cases and their corresponding matched controls is summarized in Table 2.

G. Community Outreach

The MDPH engaged in a variety of community outreach efforts to increase study awareness among the South Boston community and encourage study participation among both potential cases and controls. The MDPH worked with several current/former South Boston residents diagnosed with SSc and community advocates to organize the community advisory committee. The CAC consisted of South Boston residents as well as representatives from the South Boston Community Health Center, recognized community leaders, local medical professionals, Congressman Stephen Lynch (who helped launch the study while he was still with the Massachusetts State Senate) and State Senator Jack Hart as well as representatives from the MDPH/BEH. The CAC facilitated a working partnership between the community and the MDPH. In addition, the CAC provided a means for community members to provide input and actively participate in the investigation. The CAC met regularly at the South Boston Community Health Center during the past 9 years so that meetings were accessible to all community members.

During this time, written progress reports were also prepared by MDPH in an effort to keep the CAC apprised, particularly during the analytic and report preparation period. As

mentioned, with input from the CAC, the MDPH developed the outreach flyer aimed at recruitment of study participants.

Given the passive recruitment process, potential controls were provided the opportunity to refuse study participation by simply not responding to contact letters and thus terminating future attempts by MDPH at study recruitment. Therefore, the MDPH conducted a variety of community outreach efforts in order to increase study awareness and successfully recruit study participants. The CAC took an active role in determining outreach efforts to bring awareness of the study to the community. The committee developed a list of community organizations and centers, churches, schools, local business establishments and media outlets to target outreach efforts. The CAC then established subcommittees to canvas each of these groups with flyers. The MDPH and CAC members also participated in several community fundraisers and events to increase study awareness, including local charity walks and road races.

Outreach efforts in South Boston began during the summer of 2001. A flyer blitz was coordinated in January 2002. The bulk of the outreach activities were conducted during the spring of 2002 and included a media spot on cable news and neighborhood flyer drop campaign in March, a table at South Boston Environmental Health Night, a BEH website press release in April, and a resident letter from local legislators in June 2002.

Further, the MDPH's Associate Commissioner and Director of the Bureau of Environmental Health participated in a community talk show for cable television with local state legislators and Liz Lombard, a CAC member who initially asked that MDPH conduct the study, to explain the investigation and encourage participation from South

Boston residents. The study was featured in several media stories by local and national news organizations including features on ABC Nightline and was highlighted in a Self Magazine article in June 2001.

H. Study Participation/ Response Rate

Physical examinations and medical record review identified 45 individuals who had a confirmed diagnosis of SSc or SLE and were either current or former residents of South Boston during the period 1950 to 2000. Of the 45 individuals with a confirmed diagnosis of SSc or SLE, 41 agreed to participate in the study and were enrolled as cases (91%). Of the 830 individuals selected as potential controls, 219 agreed to participate in the study (26%). Of these, 154 met study eligibility criteria and were matched to cases. The total study sample therefore consists of 195 individuals. The study sample included 41 confirmed cases of SSc and SLE and 154 matched controls. The overall response rate for the study was 22% (195 study participants/875 eligible population).

I. Data Collection

1. Questionnaire

Once the study participation form was received, study participants were contacted by telephone to schedule a personal interview or a proxy interview in the case of deceased study participants with MDPH/BEH research staff. MDPH staff trained in standardized non-directive interviewing techniques administered structured questionnaires via personal interview. A rigorous, standardized method was used for all cases and controls in obtaining information by self-report, including personal and family medical history.

Signed consent to participate in research was obtained at interview. Interviews were approximately 60 minutes in length and interviewers were blinded to the study hypothesis and to the disease status of the participants. Interviews were conducted at various locations within the South Boston Community (i.e., the South Boston Community Health Center, the Neighborhood House and the South Boston Action Center). Study participants had the opportunity to schedule an interview during the weekdays, weeknights and weekends.

The questionnaire elicited information from study participants about demographics, residential history, occupational history, family history, medical history, reproductive history and questions regarding hobbies and recreational activities in South Boston. Approximately one week prior to the interview appointment, study participants were mailed a reminder and confirmation notice of the interview. A response log and contact sheet was used to record the outcome of each contact attempt. If a study participant failed to keep their scheduled interview appointment, a follow-up letter and telephone calls were made to reschedule the interview. If there was no response after several attempts to contact a study participant by telephone, a follow-up letter was sent by certified mail to the individual requesting that they contact MDPH to reschedule the interview. After no response to certified mail, the participant was considered as a refusal and unenrolled.

2. Data Management

Each study participant was assigned a unique numerical identifier to protect the confidentiality of study participants. At the completion of data collection through study

participant interviews, all questionnaires were reviewed for data coding. MDPH/BEH research staff reviewed the individual questionnaires to check the completeness of the responses and accuracy of the collected data. If information was missing, ambiguous or erroneous, study participants were contacted by telephone for follow up and the correct information noted and initialed on the questionnaire. After completed questionnaires were reviewed for quality and completeness, the data was entered into a Microsoft Access database and then exported to a SAS dataset for statistical analysis. All confidential data was password protected and kept in locked files.

J. Data Analysis

1. General Approach

The statistical analysis for the South Boston Scleroderma and Lupus Study consisted of calculation of descriptive statistics as well as both univariate and multivariate analyses to evaluate any potential relationships between known or suspected risk factors (both environmental and non-environmental factors) and the development of SSc and SLE in South Boston. Given the small sample size for each disease type (either SSc or SLE), the study had limited power to detect risk factors that were modestly associated with SSc/SLE risk. Separate analyses for SSc and SLE would only have the power to detect a minimum odds ratio of 4.2. Thus, the analyses initially evaluated associations related to environmental exposures for the diseases of interest combined as a group. Where possible and with sufficient sample size, separate subset analyses were conducted for 1) SSc cases and their matched controls and 2) SLE cases and their matched controls. Since the South Boston Scleroderma and Lupus Study was limited by the number of

confirmed cases of SSc and SLE and was unable to achieve recruitment of complete control match ratios for all cases, the analyses were conducted using primarily an unmatched approach (i.e., comparison of all cases as a group to all controls as a group) in addition to a matched analytic design. For SSc and SLE incidence calculations, the midpoint population of South Boston for the period 1970-2000 was interpolated from available U.S. Census data.

Typically, the primary reason for matching in the study design is to control for the effects of confounding factors or to eliminate bias arising from the causal pathway between exposure and disease (Feinstein 1987). In a matched case-control study, the matching is intended to select controls identical to the index case with respect to correlates of exposure. The matching enhances the study efficiency to control for confounding. That is, a fixed number of matched controls chosen for each case will improve the efficiency in a statistical analysis by reducing the number of strata in which the ratio of controls to cases varies substantially. Matching therefore reduces the loss of data from inefficient or uninformative strata. Typically, in this type of analysis, odds ratios are computed only on the complete matched pairs. Therefore, if exposure data is missing from any of the matched case-control pairs, those pairs would not be included in the analysis. Given the relatively small sample size and the mixed case-control match ratios in the South Boston Study, this would be a limitation to using a matched analytic approach.

If the matching variables can produce important bias or confounding then it would be beneficial to maintain the matched analytic design in the analysis. However, the matching in the South Boston Scleroderma and Lupus Study was aimed at assembling a

demographically comparable control group and not specifically to match cases and controls with respect to exposure or risk factors. Further, a matched-pair design that includes multiple pairs within the same matching criteria, as is the case with the current study, essentially results in producing random pairing within strata. Thus, the subsequent statistical analysis of the study data could be conducted using either a matched or an unmatched analytic approach (Rothman 1986; Feinstein 1987).

2. Univariate Analyses

The majority of data were collected in a closed-ended and dichotomous format. Therefore, categorical analysis was the method of choice for the statistical analysis of the study data. Analyses were conducted using a two-way frequency table for the computation of odds ratios (OR) and 95% confidence intervals (95% CI) using SAS statistical software (SAS 2006). This procedure utilizes the 2 x 2 contingency table with the rows being the exposure level and the columns being the presence or absence of the outcome of interest. The standard 0.05 probability level was used to determine statistical significance for all statistical tests and 95% confidence intervals. While most study questions were designed for a dichotomous response, thus employing categorical contingency table analysis as the preferred method of analysis, some questions involved continuous assessments of exposure. For these types of variables, distributions were examined for outliers and logistic regression was employed as the analytic method to determine odds ratios and 95% confidence intervals.

3. Multivariate Analyses

Conditional logistic regression was also used in the statistical analysis of study data. This is a method specifically adapted for a matched design which allowed for the evaluation of the effect of a given factor on disease risk while controlling for the effects of numerous other factors. This method also allows for testing and fitting the data to different models. The model is a mathematical expression that describes the relationship between the independent variables (suspect causes) and the dependent variables (risk of SSc or SLE). Multivariate techniques are useful in the study of diseases such as SSc or SLE for which there are potentially many causal agents. This is because they can take into account all variables that are associated with a given disease and measure the contribution that each may contribute to disease risk. The logistic model is a variation of the linear regression model in that the hypothesis being tested is whether the log odds of disease increases as the exposure of interest increases. Conditional logistic regression was used for both univariate and multivariate analyses using SAS statistical software and the PHREG procedure (SAS 2006). The Cox proportional hazards model was used to fit the conditional logistic regression to a matched case-control design and for determination of odds ratios and 95% confidence intervals.

4. Assessment and Control for Confounding

When a factor is associated with both the disease outcome and the exposure of interest, it can distort the true relationship between exposure and disease, resulting in an alternative explanation for the observed association. This type of factor is called a confounder because it mixes the effect of the exposure and disease. Such factors must first be

assessed and then held constant, or controlled for, during analysis. Some factors that can be independently associated with disease and exposure are demographic and behavioral characteristics and medical history information.

Confounding can lead to either over or underestimation of an effect between exposure and disease and must be controlled for either at the study design or during the data analysis. Age and gender were controlled for in the South Boston Scleroderma and Lupus Study by the incorporation of individual matching in the study design. The current etiologic hypothesis for SSc/SLE development is that a genetic predisposition and exposure to one or more environmental factors can influence disease risk. Therefore, in evaluating a possible relationship between SSc/SLE risk and environmental factors, it is important to account for a family history of autoimmune disease.

Confounding factors can be controlled for in analysis through two methods, stratification and multivariate analysis. Stratification occurs when separate analyses are conducted on homogenous categories (or strata) of the confounding variable. The association between the exposure and the outcome for each stratum can then be compared to see if they differ appreciably with each other and with the crude estimate without stratification. If the results for each stratum are similar and these values are similar to the crude estimate, then the factor is not confounding the true association. However, if the results are similar to each other but differ from the crude estimate, confounding has likely occurred and results from the stratified analysis can be used to estimate the association. While this is the preferred method of controlling for confounding with categorical data, it is difficult to simultaneously control for numerous factors through stratification. Therefore, multiple

logistic regression was used to control for several variables at once. Using this multivariate analysis technique, the effect of each variable included in the logistic regression model can be estimated, while controlling for the effects of the other covariates.

K. Exposure Assessment

Throughout the questionnaire, information related to potential exposure opportunities to environmental agents that previous research has hypothesized as playing a role in the development of autoimmune and/or connective tissue diseases was collected.

Because the list of suggested potential exposures is large, the analysis focused on those risk factors with strong disease associations and relied on the premise that some environmental risk factors for the constellation of autoimmune and connective tissue diseases are similar. Although few risk factors have been conclusively identified as being related to SSc/SLE risk, a number of potential environmental exposures have been suggested as being related to these diseases. Two primary environmental exposures were targeted for analysis in this study and included silica and solvent exposure (including chlorinated solvents and petroleum related compounds).

Information regarding a study participant's (and to a lesser extent their spouse's) occupational, hobby and home improvement history was collected for the purpose of evaluating exposure to certain compounds suggested to increase the risk of SSc/SLE. Participants were first asked if they had ever worked in a particular occupation,

participated in a certain hobby or performed a particular home improvement project. Pending their response they were then asked about the use of specific compounds during these activities (e.g., Have you ever used gasoline, trichloroethylene (TCE), adhesive glues, paint, etc.?). Questions inquiring about each of the compounds of interest were also asked separately in the event that a participant had used a compound but not within the context of the occupational, hobby or home improvement topics specifically asked.

Although the study questionnaire elicited information about each compound individually, because of the generally low frequency of responses for individual compound use among the study participants, the analyses were conducted on broader categories or groups of compounds. As previously described, the analyses focused on two primary exposures: silica and solvents. Within the silica and solvent categories, separate variables were created to reflect the different types of exposures that may have occurred within that category (i.e., whether the compound use was related to an occupational exposure or a hobby-related exposure). A distinction was also made between whether exposure to an agent was specific or possible. For example, a person who reported having worked at a dry cleaners was categorized as having possible occupational solvent exposure if they did not specifically indicate having used or been exposed to tetrachloroethylene. Alternatively, a person was categorized as having a specific occupational solvent exposure if they indicated having worked in dry cleaning and having used tetrachloroethylene or having worked with tetrachloroethylene but not within the context of any of the occupational, hobby or home improvement questions previously asked. The analysis categories of exposure compounds related to occupations and hobbies or activities are displayed in Figure 8.

1. GIS Spatial and Temporal Analysis

A spatial and temporal analysis of the residential history information collected during interviews was conducted using a Geographic Information System (GIS) (Environmental Systems Research Institute 2005). With over 50 years of residential address data collected during interviews with study participants, spatial analysis and statistical techniques were used to identify possible clustering of scleroderma or lupus diagnoses within smaller geographic areas or time periods within South Boston. Individual addresses contained in the residential history were geocoded for each case and control to assign geographic coordinates to each residential location reported within South Boston. Using the statistical software SaTScan™, a spatial-scan analysis was then conducted to determine if any potential historical clusters in space, time or in both space and time existed (Kulldorff 2006). As the South Boston Study has no specific a priori hypothesis regarding environmental exposures, narrowing the variables of space and time assisted in the identification of probable historical clusters (if any) and served as a screening technique for targeting the environmental exposure analysis. Mapping the residential history of each study participant allowed for proximity estimation to potential environmental exposure sources within South Boston.

For the South Boston spatial analysis, the SaTScan analysis method employed two different statistical models: the Bernoulli model and the Poisson model. The two models closely approximate each other when working with small datasets. However, the Poisson analysis takes into consideration the population density of the underlying South Boston population whereas the Bernoulli model considers the distribution of the cases and

controls. For the Poisson model, the midpoint population estimate between the 1970 and 2000 Census for South Boston, MA (persons age 20+) was used. This population estimate was chosen based upon the dates of diagnosis of the cases.

Potential historical clusters identified by SaTScan were then examined more closely. The spatial point pattern of cases in any potential cluster was examined along with information on date of diagnosis, residential history, age at diagnosis, and the population density of the area. The qualitative analysis of residential history information was particularly important. Thousands of simulations to identify potential clusters were run by SaTScan, using residential history information to plot every residence of each case and control in South Boston over time. Of particular importance was the location of longest residence in South Boston for a case or control, given that it may represent the best measure of any potential environmental exposures.

2. Hazardous Waste Sites

As previously described, South Boston is a densely populated residential area surrounded on its perimeter by a variety of industrial properties. A number of these properties have been reported to the Massachusetts Department of Environmental Protection (MDEP) as locations where a release of oil or hazardous materials (OHM) has occurred. The MDEP is responsible for the monitoring and assessment of releases of OHM to the environment and maintains an electronic database of sites where releases of OHM have been reported (MDEP 2007a; MDEP 2007b). Because one of the environmental exposures of interest in this study was possible exposure to petroleum related compounds, the MDPH used residential history information from study participants and information on the location of

waste sites to explore whether potential exposure to petroleum compounds at hazardous waste sites in South Boston could be associated with SSc or SLE risk.

The MDPH downloaded information from the MDEP website on hazardous waste sites located in South Boston (MDEP 2007a; MDEP 2007b). Information was extracted for sites within South Boston and having a reported release of OHM that occurred during the study period (i.e., prior to January 2001). The address of each hazardous waste site was geocoded to a location in South Boston and categorized as having a release of petroleum compounds or other hazardous compounds. There were 150 unique properties located in South Boston with a reported release of oil or hazardous materials during this time period prior to January 2001. Of these sites, 106 had a petroleum release and 44 had a release listed as some other hazardous material (see Figures 9 and 10).

Potential exposure to these hazardous waste sites was evaluated based on study participants' residential proximity to the reported sites determined by using residential history information. Because the latency period for SSc and SLE are unknown, two separate analyses were conducted in an attempt to evaluate a potential short-term exposure period and a long-term or more historical exposure period. The first analysis, intended to represent short-term exposure, included the South Boston residence at incident date for cases and at the index date for all corresponding controls. Therefore, this analysis included only current South Boston residences. The second analysis, intended to represent a long-term exposure, included the South Boston residence of longest duration for each study participant and included both current and former residents.

Two geographic boundaries were established in order to determine an exposure score. The first exposure zone was defined by whether a study participant lived within 30 feet of any hazardous waste site that reported a release of oil and/or petroleum-related compounds or other hazardous waste. This exposure was based on the radius established by the MDEP for assessing the potential for migration of vapor from a release of oil and hazardous materials into indoor spaces in nearby buildings/structures (MDEP 1997). The second zone was defined as a 500 foot area around each residence. The 500 foot zone was based on the geographic boundary established by MDEP in their assessment and regulation of hazardous waste sites (MDEP 1997). Using the geographic locations of both the hazardous waste sites and residences (residence at incident/index date and longest South Boston residence) of study participants, the number of hazardous waste sites located within the 30 foot zone and the 500 foot zone was determined. The number of sites with petroleum related releases and the number of sites with releases of other hazardous materials within each exposure zone (i.e., within a 30 foot radius of the residence or within a 500 foot radius of the residence) was determined for each study participant included in the analysis. These scores created continuous variables representing the count of sites with petroleum related releases within zone 1 (30 feet) and zone 2 (500 feet) and the count of sites with other hazardous materials releases within zone 1 (30 feet) and zone 2 (500 feet) which were then used in the conditional logistic regression analysis to compute any associated risk with SSc and SLE.

3. Boston Edison Company (BECo) Power Plant

The Boston Edison Company (BECo), now owned and operated by NSTAR, has been a private electric generator in South Boston since the late 1880s. The main generating facility is located on a 25-acre plot of land at 776 Summer Street. Coal was the primary fuel during the late 1800s and early 1900s until the plant began conversion to No. 6 fuel oil in 1938. Between 1939 and 1943, BECo transitioned from coal to No. 6 fuel oil which was utilized until the mid-1980s when a mixture of No.6 and No. 2 fuel was burned (RAM 1996). During the late 1980s, BECo began discussions with the MDEP regarding soot fallout from the BECo smokestacks and the deterioration of the stacks' interiors. In 1989, BECo, working with the MDEP, proposed plans to consolidate the four existing 250-foot smokestacks into a single 415-foot stack, along with other system modifications. These modifications were proposed to reduce soot emissions and minimize downwash due to air currents around the building and existing stacks. Due to the Federal Aviation Association's refusal of the 415 foot stack (the BECo facility is in close proximity to Logan International Airport), a new proposal for two 315 foot stacks was approved. Facility modifications were completed in the early 1990s at which time the plant converted to natural gas (MDEP 1991).

In response to a request from the MDPH/BEH in August 2007, the MDEP performed air dispersion modeling of historical annual SO_2 emissions from the BECo Power Plant to determine where (if at all) the maximum emissions impact area(s) was geographically located within the South Boston community. The annual concentrations of SO_2 were used as surrogates for other pollutants, which would be expected to distribute similarly

and would likely impact the same identified locations. Emissions from 1980 were modeled because there is limited historical data available to determine the concentrations or measurements of petroleum or other air pollutants in the South Boston environment. The 1980 data was most representative of both the study time period (1950-2000) as well as a time when the plant was burning fuel oil, therefore representing a possible historical exposure.

The geographic areas with the greatest opportunities for exposure to the emissions from the facility were identified through air dispersion modeling provided by the MDEP. The air modeling was performed using the EPA-approved computer dispersion model, AERMOD (Version 07026), stack data from the BECo plant, and meteorological data in order to estimate SO_2 impacts in the areas downwind from the BECo Power Plant (USEPA 2007). The air dispersion model takes into consideration the stack characteristics (e.g., stack height and diameter), emissions characteristics (e.g., rates, exit temperature and exit velocity), and meteorological data (e.g., wind speed and direction) in order to estimate a location at which ground-level concentrations would be the highest. Annual average air concentrations were estimated using stack and emissions data from 1980 when the BECo power plant was burning No. 6 fuel oil. Five years (45,000 hours) of meteorological data were used to include a comprehensive set of weather conditions in order to yield annual averages that would be representative of long-term exposure (Commonwealth of MA 1982; ENSR 1990). Surface meteorological data collected from 2001 to 2005 were obtained from the National Weather Service station (NWS station number 14739) at Logan International Airport in Boston. Upper air meteorological data

were obtained from the National Weather Service in Grey, Maine (NWS station number 54762).

To better illustrate how the facility's emissions were distributed throughout the surrounding area, MDEP also created plots of the estimated facility-related ambient air concentrations of SO_2. These plots were further enhanced using GIS by interpolating the discrete data points into a graded surface to illustrate the distribution of facility emissions throughout the South Boston community. It is important to note that actual ambient air concentrations of SO_2 would be higher than what are depicted on these maps since there are other stationary and mobile sources, located both in-state and out-of-state, that are also contributing to air pollution in the South Boston area. This would partially explain any discrepancies that might exist between the modeled ambient air concentrations and the actual ambient air measurements for any particular location.

Similar to the analysis for hazardous waste sites, potential exposure to historical power plant emissions was based on residential information obtained from residential histories of study participants during the interviews. Two analyses were conducted (residence at incident/index date and longest residence). The distribution of modeled concentrations of annual SO_2 were divided by the midpoint of the distribution to create two exposure areas representing the upper 50% range of modeled concentrations (16+ $\mu g/m^3$) and the lower 50% of range of modeled concentrations (<16 $\mu g/m^3$). Residence at incident/index date and longest South Boston residence were mapped in relation to the modeled impact areas to create a dichotomous exposure variable representing high and low. These variables

were used in conditional logistic regression and were entered into the model with other variables.

IV. Results

A. Study Population Description

Of the 195 study participants, 93% are female (n=182) and 7% are male (n=14). The average study age for the cohort was 53 years, ranging between 31 and 81 years. Females had a slightly wider age range than males (28 to 81 years versus 34 to 71 years). The study population is predominantly white (97%). The overwhelming majority of study participants (96%, n=186) and their parents (mothers 81%, fathers 75%) were born in the United States (Tables 3 & 4). Study participants also reported that the majority of their grandparents (57%, n=442) were foreign born (Table 5). Forty-four percent of study participants (n=86) reported having an Irish ancestry (Table 6). Of the study participants who reported having an Irish ancestry, 22% (n=19) had a parent who was born in Ireland and all (n=86) had a grandparent born in Ireland (Table 6).

The majority of the study population reported a household income of less than $60,000 a year (56%, n=109) and only a quarter of participants (24%, n=46) reported a household income that was less than $30,000. No statistically significant difference was observed between cases and controls with respect to household income levels (Chi-Square (χ^2) p=0.51) (Table 7). Forty percent of the study population were high school graduates (n=78) and 18% reported being a college graduate (n=36) (Table 7).

The average length of residence in South Boston among all study participants was 37.5 years with a range of 1 to 81 years. Among cases, the average length of residence was 32 years and for controls average length of residence in South Boston was nearly 39 years. The mean residence time in South Boston prior to the incident/index date was 25.8 years for cases and 26.8 years for controls.

B. Case Group Description

Of the 41 confirmed cases, 21 had a diagnosis of SSc and 20 had a diagnosis of SLE. Three of the cases were male and 38 were female. Two of the cases were biologically related (mother and daughter). Of the 21 individuals diagnosed with SSc, seven had a diagnosis of diffuse disease (33%), 13 were diagnosed with limited SSc (62%), and one individual had SSc with overlap. Among both individuals with diffuse SSc as well as those with limited SSc, approximately half were current residents and half were former residents at disease onset. Among individuals with SLE, approximately 30% were current residents and 70% were former residents at disease onset. The age at disease onset among all of the cases ranged from 10 to 76 years. The mean age at disease onset for SSc cases was 48.4 years and for SLE case was 39 years. Although the study period spans the years 1950-2000, the incident year (or year of the first non-Raynaud's symptom) for the 41 cases ranged from 1960-2000. Relatively few cases developed disease during the earlier two decades of the study period with the incident year for the majority of cases occurring after 1980 (76%). The distribution of cases by year of incidence is provided in Table 8.

Twenty-five cases were current residents of South Boston at the time of disease onset (61%) and 16 were former residents of South Boston at the time of disease onset. That is, 39% of the case group did not live in South Boston at the time of their first non-Raynaud's symptom. The mean length of residence in South Boston for cases who were current residents at their incident date was 31 years with a range of 2 to 74 years. Among former residents of South Boston the average length of South Boston residence was 17.5 years with a range of 1 to 31 years. Among cases who were former South Boston residents, the time away from South Boston prior to diagnosis onset ranged from 2 to 35 years with a mean of 16 years.

C. SSc/SLE Prevalence and Incidence

Prevalence is the estimate of the number of new individuals diagnosed in addition to all other individuals alive and diagnosed previously with the disease within a defined population at a certain point or time period (Last 1988). Incidence is the number of newly diagnosed cases of disease that occurred within a population during a specified period of time (Last 1988). Incidence rates were calculated for the time period 1970-2000 in an attempt to mitigate any effects of earlier periods of under-diagnosis and periods known to be especially challenging for case ascertainment efforts. The prevalence and incidence estimates reported here are based on all medically confirmed cases (n=45; *note:* 4 participants were lost to follow-up and did not complete the study questionnaire) of SSc or SLE and include only those individuals that were residents of South Boston at the time of their disease onset. Twenty-seven individuals had a confirmed diagnosis of SSc or SLE and were residents of South Boston at the time of disease onset between 1970 and

2000. Of these individuals, 12 were diagnosed with SSc and 15 were diagnosed with SLE. While the incidence rate covers the 31-year period of 1970-2000, the prevalence estimate was defined as a point prevalence reflecting the number of individuals with either SSc or SLE and who were current South Boston residents as of December 31, 2000. Two study participants were excluded from prevalence estimates because they were deceased as of the point prevalence date.

The point prevalence of SSc in South Boston on December 31, 2000 was 33.4 per 100,000 (95% CI= 18.3-61.4/100,000). This prevalence estimate was calculated based on the 10 individuals with a confirmed diagnosis of SSc and a current residence in South Boston as of December 31, 2000. The prevalence in South Boston appears to be higher than the prevalence of approximately 27.6 cases per 100,000 that has been observed in the general population elsewhere in the United States (Mayes 2003). Furthermore, when this estimate is refined to white females, the point prevalence of SSc in South Boston results in 72.8 cases per 100,000 (95% CI= 40.0-133.8/100,000) which is significantly higher than the approximately 37 cases per 100,000 found in the literature (Mayes 2003).

The incidence of SSc in South Boston for the period 1970-2000 was 1.13 per 100,000 per year (12 cases of SSc, 1970-2000; 95% CI= 0.58-1.98/100,000/year). This incidence rate is consistent with the 0.96-1.93 cases per 100,000 per year reported in the medical literature. A more refined estimate for white females yielded an annual incidence rate of 2.27 cases per 100,000 (95% CI= 1.18-3.98) which is also consistent with the incidence rate of 1.28 to 2.7 cases per 100,000 reported in the literature (Laing et al. 1997, Mayes 2003).

The point prevalence of SLE in South Boston on December 31, 2000 was 26.7 per 100,000 (95% CI= 13.7-52.6/100,000). This estimate was based on 8 individuals with a confirmed diagnosis of SLE who were current residents of South Boston. Localized studies of the general U.S. population have estimated the prevalence of SLE to range between 14.6 and 149.5 cases per 100,000 (Hochberg 1990; Danchenko et al. 2006, Chakravarty et al. 2007). However, more recent estimates based on national population data have found approximately 53.6/100,000 cases in the general population and 100/100,000 cases in females (Hochberg 1990; Ward 2004). The overall prevalence in South Boston is consistent with previous studies and the point prevalence for white females in South Boston, which was 50.9 cases per 100,000 (95% CI= 25.1-104.9/100,000), also appears to be consistent with the literature and possibly lower.

The incidence of SLE in South Boston for the period 1970-2000 was 1.41 per 100,000 per year (15 cases of SLE, 1970-2000; 95% CI=0.79-2.33/100,000/year), an estimate that is slightly lower than the 1.51-5.56 cases per 100,000 annually as reported in the literature (Uramoto et al. 1999). SLE incidence for white females in South Boston was 2.65 cases per 100,000 annually (95% CI= 1.45-4.46 per 100,000/year). Previous studies have reported SLE incidence for white females as being between 1.1 and 3.9 cases per 100,000 per year (Danchenko et al 2006).

D. Risk Factor Analyses

1. Family History of Autoimmune/Rheumatic Disease Diagnoses

Study participants were asked to report a history of specific autoimmune/rheumatic disease diagnosed among biological family members (i.e., parents and siblings). The specific diagnoses included rheumatoid arthritis (RA), Raynaud's disease, systemic lupus erythematosus (SLE), scleroderma (SSc), undifferentiated or mixed connective tissue disease (MCTD) and thyroid disease. Due to the low reported frequency of many of these diseases, the analyses were first conducted for all the autoimmune/rheumatic diseases of interest as one outcome and family members were combined to create general categories including "any family member," "parents," or "siblings." If positive associations were found among any general category of family members, subset analyses were then conducted to try to determine what disease and or family member may be influencing the observed association.

Forty-six percent of study participants (n=90) reported having a biological family member (i.e., mother, father, sister or brother) who was diagnosed with any of the six autoimmune/rheumatic diseases of interest (Table 9). This percentage dropped to 33% for reports of a previous autoimmune/disease among only parents (n=65). Twenty-nine percent of study participants (n=57) reported a diagnosis of an autoimmune/rheumatic disease only among mothers and 8% reported a diagnosis only among fathers (n=16). Fifty-two participants (27%) reported a sibling who had been diagnosed with one of the diseases (Table 9). A statistically significant increase in SSc/SLE risk was observed among study participants where 61% of cases versus 42% of controls reported having any

biological family member diagnosed with any of the six autoimmune/rheumatic diseases (OR=2.1, 95% CI=1.1-4.3). A similar increase in SSc/SLE risk was observed among 46% of cases who reported a parent diagnosed with any of the six autoimmune/rheumatic diseases compared to 30% of controls but this difference was of borderline statistical significance (OR=2.0, 95%CI=1.0-4.1) (Table 9). No associations were observed between SSc/SLE risk and a history of autoimmune/rheumatic disease reported among more specific categories of biological family members such as a sibling, or mother or father when evaluated separately (Table 9).

Subset analyses for different disease groupings were conducted for the biologic parent category (i.e., mother and father combined) to try to determine if any one disease or combination of diseases may be influencing the nearly significant association observed in the previous analysis of autoimmune/rheumatic disease among biologic parents. The majority of reported diagnoses among parents were either rheumatoid arthritis (12%, n=46) or thyroid disease (7%, n=28), however no statistically significant association was observed with increased risk of SSc/SLE when considering parents diagnosed with either rheumatoid arthritis or thyroid disease combined (OR=1.8: 95% CI = 0.9-3.6) (Tables 10 & 11). A parental diagnosis of only rheumatoid arthritis also did not appear to increase disease risk among cases and controls (OR=1.2) (Table 11).

The largest frequency of any reported of autoimmune/rheumatic disease among a family member was for a parental diagnosis of rheumatoid arthritis. Since the data was based on self-report of a family history of rheumatoid arthritis, the potential for bias exists due to possible misclassification by study participants of rheumatoid arthritis versus arthritis in

general. Therefore, rheumatoid arthritis was removed from the analysis to evaluate whether reports of a parental diagnosis of rheumatoid arthritis were influencing the previously observed association. A two-fold increase in SSc/SLE risk was observed when a parental diagnosis of rheumatoid arthritis was removed from the analysis (OR = 2.4: 95% CI = 1.1-5.3). This result suggests that a study participant who reported having a parent with a diagnosis of any of the autoimmune/rheumatic diseases of interest except rheumatoid arthritis had twice the risk of developing SSc or SLE (Table 11). In addition, a parental diagnosis of thyroid disease or either scleroderma, systemic lupus erythematosus or mixed connective tissue disease as a group yielded consistent positive odds ratios of 2.1 and 3.0, respectively. However, due to decreased statistical power (evident from the wider confidence intervals), these observations did not achieve statistical significance (Table 11).

2. Medical History

For exposures central to this study, a structured, standardized questionnaire was used to determine if study participants had ever been diagnosed with a variety of diseases and or medical conditions including: cancer, Parkinson's disease, tuberculosis, heart arrhythmia, rheumatoid arthritis, epilepsy and hypertension. Of these diseases, cancer was the most common diagnosis with 20% (n=39) of study respondents reporting a cancer diagnosis followed by hypertension at 15% (n=30), heart arrhythmia at 15% (n=29) and rheumatoid arthritis at 11% (n=21) (Table 12). Diagnoses of Parkinson's disease (n=1), tuberculosis (n=3) and epilepsy (n=2) were only reported by 0.5%, 1.5% and 1.0% of the study population, respectively (Table 12).

Analyses to determine if there were any differences between cases and controls that had or had not reported a previous diagnosis of any of the seven specific autoimmune/rheumatic diseases or conditions previously detailed were conducted. No statistically significant differences were observed between cases and controls that reported having a previous diagnosis of cancer, tuberculosis, heart arrhythmia, epilepsy or hypertension. Analyses were not conducted for Parkinson's disease as one of the exposure cells was zero (Table 12). The findings did, however, indicate that a four-fold increase in SSc/SLE risk existed in cases (24%) versus controls (7%) who reported having been diagnosed with rheumatoid arthritis. The increase in SSc/SLE risk was statistically significant (OR=4.2, 95% CI: 1.6-10.7) (Table 12); however, this result should be interpreted with caution since RA diagnosis was self-reported and could have been misdiagnosed as both SSc and SLE can be associated with joint swelling.

Information regarding prescription medications used in the treatment of the seven diagnoses described above as well as the use of other medication was also collected. Of the 195 study participants, 63% (n=122) reported that they had taken prescription medication to treat mild or moderate pain and 15% (n=29) reported that they had taken prescription medication to treat a psychotic disorder (Table 13). While the use of pain medication was not associated with an increased risk of SSc/SLE, a nearly statistically significant association was found between cases (24%) and controls (12%) for use of medication in the treatment of a psychotic disorder (Table 13). Separate analyses were attempted to determine the influence of chlorpromazine used in the treatment of some psychotic disorders and penicillamine used for treatment of rheumatoid arthritis. However, the frequency of use within the study population for both these medications

was low (chlorpromazine (n=2) and penicillamine (n=2)) and was therefore not sufficient to conduct analyses. Thus, the potential for these medications to be influencing the observed association is minimal and unlikely (Table 13).

No statistically significant associations were found between SSc/SLE risk and herbal remedies, specifically the use of L-Tryptophan or appetite suppressants, and analyses for alfalfa products were not conducted due to insufficient cell size (Table 14).

Study participants were also asked to recall if they had ever had various medical devices surgically implanted in their body (Table 15). None of the medically implanted devices were found to be associated with increased risk of SSc/SLE and several devices including pacemakers, intraocular lenses, and medication pumps were unable to be analyzed due to the low frequency of response (Table 15).

3. Reproductive History

Among female study participants (n=1820), 79% reported ever being pregnant (Table 16). Pregnancy was defined as all pregnancies including pregnancies resulting in live births, still births, miscarriages and abortions. No significant difference in SSc/SLE risk was found when comparing women who were ever versus never pregnant (Tables 17). Women who had ever been pregnant (n=143) had an average of 3.5 pregnancies with a range of between one and 15 pregnancies (Table 18). Cases had a slightly higher average number of pregnancies than controls (3.8 versus 3.5 pregnancies). However, no statistically significant difference in the number of pregnancies was observed between

cases and controls when considering only study participants who had ever been pregnant (Wilcoxon p=0.50) (Table 18).

The average age at first pregnancy for all study participants was 24 years with controls having a wider age range (16 to 42 years) when compared to cases (15 to 33 years) (Table 18). The difference in age at first pregnancy for cases and controls was not statistically significant (Wilcoxon p=0.11). Twenty-three percent of females who had ever been pregnant (n=143) reported that their age at first pregnancy was 20 years or younger (n=34) (Table 17). No statistically significant association was observed between females whose first pregnancy occurred at 20 years of age or younger and the development of SSc/SLE (Table 17).

The average age of menarche among all female study participants was 13 years with a range from 9 to 18 years. No statistical difference was observed in the average age of menarche between cases and controls (Wilcoxon p=0.99) (Table 19). At the time of the study, 46% of females (n=84) reported having had a natural menopause (i.e., menopause occurred in a female who had never had a hysterectomy or if a female did have a hysterectomy, her age at the time of menopause was younger than her age when the hysterectomy occurred) (Table 20). Forty-two females reported having had a hysterectomy (23%) and of those, 12 were excluded from the analysis as their date of hysterectomy either preceded or corresponded with their date of menopause (Tables 17 & 20). The average age at onset of natural menopause was 45 years ranging between 26 and 55 years and was slightly younger in cases than controls (44 versus 46 years) (Table 19). The difference in age at onset of menopause between cases and controls was not

found to be statistically significant (Wilcoxon p=0.21). No statistically significant association was found between cases and controls for ever versus never had a hysterectomy (Table 17).

Use of oral contraceptives prior to incidence date for cases or index date for controls was reported by 47% of the female study population (n=86). The average length of oral contraceptive use was 5.4 years for all female study participants and was not statistically different between cases and controls (4.8 versus 5.6 years) (Wilcoxon p=0.57) (Table 21). Only 11% of females (n=21) reported using estrogen prior to the incidence or index date with an average of 3.9 years of use (range = 1 to 17 years) (Tables 17 & 21). No statistically significant difference was found between the length of estrogen use among cases and controls prior to the incidence date for cases or index date for controls (3.0 years versus 3.9 years) (Wilcoxon p=0.57) (Table 21). Neither the use of oral contraceptives or estrogen for hormone replacement therapy prior to the incidence or index date was found to be associated with disease development (Table 17).

4. Behavioral Factors

(a) Smoking

At the time of the study, the majority of participants reported having smoked on a regular basis for six months or longer (62%, n=120); however, no significant difference was observed between cases and controls with regard to having smoked on a regular basis (Table 22). Only 30% of participants (n=58) were considered current smokers at their incidence or index date with the remaining participants being either former smokers

(30%, n=57) or non-smokers (40%, n=79) (Table 22). A former smoker was defined as a person who had quit smoking at least one year prior to the incidence/index date. No statistically significant difference was found between cases and controls for smoking status at the incidence/index date when considering current, former and non-smokers (χ^2 p-value=0.20).

The risk of developing SSc/SLE was two times greater among current smokers than former smokers (OR=2.3) but the result was not statistically significant (95% CI: 0.9-6.0) (Table 22). The average age study cases starting smoking was 16 vs. controls who began slightly older at 17 years (Table 23). The observed difference between cases and controls with respect to the age one started smoking was statistically significant (Wilcoxon p=0.04). Current and former smokers reported smoking an average of 17 years prior to the incidence/index date, with cases reporting a slightly longer smoking history of 19 years versus controls at 17 years. However, the difference in duration of years that one smoked was not statistically significant between cases and controls (Wilcoxon p=0.86) (Table 23). No increased risk of SSc/SLE was observed between cases and controls when frequency and duration of smoking history were evaluated.

(b) Alcohol

Eighty-nine percent of study participants reported that they drank alcohol (n=174). Drinking was defined as ever having consumed at least 12 alcoholic beverages in one year with an average starting age of 20 years (Tables 24 & 25). Seventy-three percent of study participants (n=143) were current drinkers at their incidence/index date, the remaining participants reported being either former drinkers (8%, n=15) or non-drinkers

(19%, n=36) (Table 24). A former drinker was defined as someone who had stopped drinking at least one year prior to the incidence/index date. No association was found for drinking status at the incidence/index date when considering current, former and non-drinkers (χ^2 p-value=0.95) nor when comparing participants who were current versus former drinkers at the incidence/index date (OR=1.1) (Table 24). On average study participants who drank alcohol reported drinking for 19 years prior to the incidence/index date (Table 25). Cases reported a shorter length of drinking prior to the incidence/index date than controls (17 years versus 19.5 years); however, the observed difference was not statistically significant (Wilcoxon p=0.25) (Table 25). The average number of alcoholic beverages consumed per week was characterized into three drinking groups: light (< 4 drinks per week), moderate (4 to 10 drinks per week) and heavy drinkers (>10 drinks per week). Sixty-three percent of respondents reported being a light drinker, 24% a moderate drinker and 13% a heavy drinker. No statistically significant difference was observed between cases and controls who reported being either a light, moderate or heavy drinker (χ^2 p=0.23) (Table 24).

(c) Other Behavioral Factors

Among female study participants (n=181), 41% (n=75) had acrylic nails applied in a salon; however no significant association was detected between cases and controls who had ever had acrylic nails versus those who had not (Table 26). Only two females reported ever having breast implants and only one ever having collagen shots for cosmetic or reconstructive purposes. Therefore, the frequency of these procedures reported among the study population was not sufficient to conduct meaningful analyses

(Table 26). Use of permanent and semi-permanent hair dye (i.e., hair coloring that washes out over time) prior to the incidence/index date was reported by 41% (n=80) and 21% (n=41) of the study population, respectively (Table 26). No increased risk in SSc/SLE was observed when cases and controls who ever used either permanent or semi-permanent hair dye was compared.

E. Exposure Analyses

1. Silica

Silica exposure among study participants was evaluated with respect to occupation, hobbies/home improvement projects, spousal occupational exposure and use of scouring powders. Twenty-four percent of respondents (n=46) reported having some type of occupational silica exposure; of these 9% (n=4) were reported as specific exposures to silica and the remaining 91% (n=42) reported an occupation where silica exposure may have been possible (Table 27). No statistically significant differences were observed between cases and controls that had any occupational silica exposure (either specific or possible) or a possible occupational silica exposure when evaluated separately. None of the cases reported specific occupational exposure to silica (Table 27).

Of the 96 participants (49%) with a hobby/home improvement related silica exposure, 90% were possible exposures meaning the respondent had participated in either ceramics/pottery or stone sculpting, as a hobby, or removal/installation of drywall as a home improvement project, but did not specify use of or contact with silica specific materials such as sand, flint filters, flux or granite (Table 27). A two-fold increase in risk

of SSc/SLE of borderline statistical significance was observed for participants with any hobby-related silica exposure where 63% of cases reported exposure compared to 46% of controls (OR=2.1, 95% CI: 1.0-4.2). Within all hobby exposures, a statistically significant two-fold increase in SSC/SLE risk was observed for participants reporting a possible hobby-related silica exposure where 61% of cases reported exposure compared to 40% of controls (OR=2.4, 95% CI: 1.2-4.8) (Table 27). Only 10 study participants (including only one case) reported a specific hobby-related silica exposure. Ceramics was included as a hobby that may have possible silica exposure (Table 27).

When the hobby-related silica exposures were evaluated individually, 23% (n=44) of respondents reported having participated in pottery/ceramics, 18% (n=35) indicated having either removed or installed dry wall, and no study participants reported involvement in stone sculpting as a hobby (Table 28). None of these possible hobby-related silica exposures were associated with an increased risk of SSc/SLE (Table 28).

Ten percent of study respondents (n=19) acknowledged use of scouring powders for cleaning purposes (5 cases, 14 controls). No statistically significant association was observed between an increased risk of SSc/SLE and ever having used scouring powders (Table 27). Likewise, no significant association was found when considering participants who reported having lived with a spouse who worked in an occupation with a silica exposure (Table 27).

The total number of silica exposures was also evaluated for each study participant. A variable representing a non-weighted count of the number of categories (i.e., occupational, spousal, hobby/home improvement and scouring powders) in which a

participant was classified as exposed was created and analyzed in an attempt to assess any possible magnitude of exposure. Sixty-seven percent of study participants (n=130) were classified as having one or more silica exposures (i.e., all exposed individuals) while the remaining 33% (n=65) were categorized as non-exposed (Table 27). When comparing cases and controls that had at least one of any type of silica exposure (i.e., occupational, hobby, spouse, etc.) to those with no exposure, no statistically significant difference was observed (Table 27). Frequency counts of reported silica exposure types indicate that the majority of reported exposures were hobby-related exposures (50%), followed by occupational exposure (24%), spousal exposure (17%) and finally exposure via use of scouring powders (9%) (Table 29).

2. Solvents

Solvent exposure among study participants was also evaluated with respect to occupational and hobby/home improvement activity exposures. As the solvent category is quite broad, secondary analyses were conducted for petroleum-related compounds and chlorinated solvent compounds separately. Additionally, the use of a portable kerosene or natural gas heater within the home was included when assessing both the total number of solvent exposures and the total number of petroleum-related exposures for each participant.

Forty-one percent of study participants (n=79) reported having an occupational solvent exposure. Of these, 52% (n=41) were described as specific exposures, and 48% (n=38) were possible exposures (Table 30). No statistically significant differences were

observed between cases and controls and having had any type of occupational solvent exposure (i.e., specific and possible both individually and together) (Table 30).

Frequency counts indicated that all respondents had at least one solvent exposure that was hobby-related (i.e., a respondent participated in a hobby/home improvement project and/or had used a solvent-based compound in a hobby-related activity) (Table 30). As all participants were classified as exposed, analysis of the broad hobby-related category was not practical and all hobby-related solvent exposures were evaluated individually (Table 31). Of the hobby-related activities inquired about in the interview questionnaire, painting as a home improvement project (81%, n=157), painting with oil or acrylic paints (34%, n=66), refinishing furniture (29%, n=56) and removal and/or installation of walls as a home improvement project (18%, n=35) were the most commonly reported activities among study participants (Table 31). With regard to solvent-based compound use in the study population, epoxy-based products (15%, n=29), silicone glues and sealants (15%, n=29) and paint thinners (10%, n=19) were reported with the greatest frequency (Table 32). Results of analysis of these solvent exposure categories indicated that there was no statistically significant association between cases and controls for any of the hobby-related activities and compounds of interest with the exception of the use of silicone-based glues and/or sealants (Tables 31 & 32). Use of silicone-based glues and/or sealants was found to have a decreased risk of SSc/SLE (OR=0.1, 95% CI: <0.1-0.9), a finding that was statistically significant. However, only one case reported a silicone-based glue and or/sealant exposure and thus this association is likely a reflection of the difference in the reported activity between cases and controls rather than an association with disease development (Table 32).

Forty-six percent of cases reported ever having ever painted with acrylic or oil paints as a hobby compared to 31% of controls and the difference in SSc/SLE risk was nearly statistically significant (OR=2.0, 95% CI: 1.0-4.0) (Table 31). This observation, while based upon sufficient cell size, should be interpreted with caution as all other hobby-related exposures, as reported in Tables 31 and 32, did not approach statistical significance.

Both petroleum-related and chlorinated solvent exposures were evaluated separately as subsets of the broader solvent exposure category. These two subcategories were created because it was difficult to obtain sufficient data on the use of specific types of compounds, as the information collected was both self-reported and historical in nature.

Twenty-two percent of study participants (n=43) reported having an occupational petroleum-related exposure. Of these 35% (n=15) were reported as specific petroleum-related exposures and the remaining 65% (n=28) were possible petroleum-related exposures (Table 33). No statistically significant difference was observed in SSc/SLE risk between cases and controls when considering occupational petroleum-related exposure (Table 33). Of the 170 respondents (87%) that recalled a hobby-related petroleum exposure, 73% (n=124) were classified as a specific exposure and the other 27% (n=46) as possible exposures (Table 33). However, no increased risk in SSc/SLE was found when comparing cases and controls that had a hobby-related exposure to petroleum compounds versus those with no hobby-related petroleum exposure (Table 33). Frequency counts of the reported exposure type indicated that the majority of the reported petroleum exposures were hobby related (69%) (Table 34).

For each address provided as part of the residential history in South Boston, study participants were asked to recall whether or not a portable kerosene or natural gas heater was used to heat the home and if the residence was located on the basement-level of the building. In total, only 22 participants (11%) indicated ever having lived in a basement-level residence (Table 35). No increased risk of SSc/SLE was observed between cases and controls who ever versus never had lived in a basement-level residence (Table 35). Seventeen percent of participants (n=34) reported use of a portable kerosene or natural gas heater to heat the home. However, no significant difference in risk of SSc/SLE was observed between cases and controls when considering use of a portable heater in heating a residence (Table 35).

Twenty-eight percent of study participants (n=55) were considered exposed to chlorinated solvents in an occupational setting (Table 36). Among these individuals, 11% (n=6) reported having an occupation with a specific chlorinated solvent exposure; the remaining 89% (n=49) reported an occupation that could be classified as an occupation where exposure to chlorinated solvents may have occurred (Table 36). No statistically significant differences were observed between cases and controls and a previous history of any type of occupational exposure involving chlorinated solvents (i.e., specific exposures and possible exposures both individually and combined) (Table 36).

F. Environmental Exposures in South Boston

1. Residential History and Spatial Clustering

For the South Boston analyses, thousands of simulations of both the Bernoulli and Poison models were conducted. From those, two areas of potential spatial clustering within South Boston were identified that required closer examination. Neither model identified any potential clustering in time.

Close examination of these spatial clusters was conducted by evaluating the point pattern of cases on a map along with information on date of diagnosis, residential history, age at diagnosis, and the population density of the area. It was concluded that the potential clusters identified reflected cases that had multiple residences over time within a neighborhood of South Boston, as opposed to a clustering of an unusual number of unique cases. The distribution of cases followed the population density patterns in South Boston.

2. Hazardous Waste Sites

Two separate analyses were conducted to evaluate the potential exposure to petroleum-related compounds as a result of living in proximity to hazardous waste sites. The first analysis evaluated residential proximity based on the residence at the time of incidence of SSC/SLE or corresponding index date for controls. This analysis included only cases and their corresponding controls who were residents of South Boston at disease onset/index date (N=112). Therefore, cases who were former residents of South Boston were excluded from the analysis. The results showed that there was no increased risk of

SSc/SLE when comparing cases versus controls who lived within either 30 feet of a hazardous waste site with a petroleum release (OR=1.3, 95% CI=0.2-8.5) or 500 feet of a hazardous waste site with a petroleum release (OR=0.4, 95% CI=0.2-1.0). These results are summarized in Tables 37 and 38.

The second analysis was intended to evaluate potential historical exposures that may have occurred as a result of living in proximity to a hazardous waste site in South Boston. The South Boston residence that each study participant resided in for the longest duration was selected for this analysis in order to evaluate potential exposures for cases that were both current and former South Boston residents and their corresponding controls. The results were similar to the previous analysis. There was no increased risk of SSc/SLE when comparing case and control residences of the longest duration that were within either 30 feet or 500 feet of a hazardous waste site with a reported petroleum release (Tables 39 & 40).

3. Boston Edison Company Power Plant

Modeling of historical air emissions at the former Boston Edison Company (BECo) Power Plant showed that the maximum impact area was in the eastern portion of South Boston in closer proximity to the coastline (Figure 11). Modeled air emissions decreased from east to west with the residential areas of South Boston showing generally lower concentrations of modeled air pollutants. Similar to the analyses for evaluation of potential exposure to hazardous waste sites in South Boston, residential history data for study participants was used to determine potential exposure to modeled impact areas based on the residence at incidence/index date and the longest South Boston residence for

study participants. The impact areas were divided into two zones representing an area of higher concentrations of modeled air pollutants and an area of lower concentrations of modeled air pollutants. Modeled concentrations across South Boston ranged from 4.0 $\mu g/m^3$ (micrograms per cubic meter) to 36.0 $\mu g/m^3$ (see Figure 11). Areas of higher and lower impact were determined by dividing the distribution of concentrations according to the midpoint value. Therefore, the area representing higher air emissions was based on modeled concentrations of 18 $\mu g/m^3$ or above and the area of lower air emissions was based on modeled concentrations of less then 18 $\mu g/m^3$.

Analysis of residence at the incidence/index date showed no increased risk of SSc/SLE when comparing cases and controls who lived in the higher impact area versus the lower impact area (OR=1.2 95%CI=0.4-3.8). Similar results were observed when the analysis included the longest residence of study participants. There was no increased risk of SSc/SLE in cases versus controls whose longest residence in South Boston was in the higher versus the lower impact area of historical air emissions from the BECo plant (OR=1.9, 95% CI=0.7-5.3). The results are provided in Table 41.

4. Swimming and Recreational Parks

Study participants were also asked a variety of questions about their activities in South Boston. Questions were asked about swimming in different areas around South Boston that may have brought residents in contact with industrial pollution as a result industrial releases to local water sources. Anecdotal information from community residents suggested individuals swam at local beaches in South Boston where an oily film was present. A map of beaches and recreational areas in South Boston is shown in Figure 12.

These areas included Pleasure Bay, Castle Island, L Street Beach, Carson Beach and the Reserve Channel. Sixty-seven percent of participants (n=131) reported having ever swam at Pleasure Bay, 37% at Castle Island (n=72), 72% at L Street Beach, 58% at Carson Beach and 6% in the Reserve Channel (Table 42). No increased risk of SSc/SLE was observed when comparing cases and controls that ever swam at Pleasure Bay, Castle Island, L Street Beach or the Reserve Channel (Table 42). A three-fold increase in SSc/SLE was observed for study participants who had reported ever swimming at Carson Beach (OR=3.5, 95% CI: 1.5-8.0) (Table 42). However, these results should be interpreted with caution. The analyses are limited by exposure misclassification due to the close proximity of the South Boston beaches to one another (i.e., L Street Beach and Carson Beach are one continuous beach and Pleasure Bay and Castle Island are often considered the same area). Therefore, it is likely that the statistically significant finding related to swimming at Carson Beach is a function of misclassification and recall bias by study participants. No map was provided to delineate beach areas as mutually exclusive and all information collected was based on self-report by study participants. A reference map of beaches in South Boston may have reduced misclassification of exposure by study participants but would not have affected recall bias (Figure 12). Furthermore, in the interview questionnaire, participants were first asked about the L Street Beach and then Carson Beach, increasing the likelihood that a participant may have recalled the area as L Street Beach as opposed to Carson Beach. This is further supported by the higher frequencies observed for having swam at L Street Beach versus Carson Beach (Table 42). Indeed, when considering having ever swam at either L Street Beach or Carson Beach as one area, the risk previously associated with swimming at Carson Beach decreases and is

no longer statistically significant (OR=1.2, 95% CI: 0.6-2.5) (Table 42). When analyzing Pleasure Bay and Castle Island Beach as one area, the risk of disease development associated with having swam in these areas of South Boston together as opposed to separately increases; however, the finding again is not statistically significant (OR=1.9, 95% CI: 0.9-3.9) (Table 42).

Study participants were also asked to recall if they ever participated in recreational activities at the M Street Park, Marine Park or Columbia Park. No statistically significant associations were observed between cases and controls and ever having participated in recreational activities at any of the three parks in South Boston (Table 43).

G. Multivariate Analyses

The multivariate analyses were conducted to evaluate the potential relationship between possible risk factors and the risk of SSc/SLE. Standard logistic regression was employed using an unmatched approach. This procedure allowed for the evaluation of effects of many variables while adjusting for effects of all variables in the model including potential confounding from a family history of autoimmune disease. Factors that indicated a statistically significant relationship to SSc/SLE risk were included in the regression model. Backward stepwise regression was used because it makes no assumptions about the relationship between the variables entered in the model and its goal is to discover any potential relationship between SSc/SLE and the exploratory variables.

The results of the multivariate analyses were similar to results observed previously in the univariate analysis where a previous diagnosis of rheumatoid arthritis as well as possible hobby-related silica exposures showed increased odds ratios that remained statistically significant in the presence of other factors. In the complete model containing all possible exploratory variables, a previous diagnosis of rheumatoid arthritis had an observed odds ratio of 3.4 (95% CI: 1.3-9.3) and possible exposure to silica through hobby-related activities was associated with a two-fold increase in risk of SSc/SLE (OR=2.3 95% CI: 1.1-4.4) (Table 44). These two factors were the only factors that remained in the overall model (i.e., final model) using stepwise backward regression. In the final regression model, both a previous diagnosis of rheumatoid arthritis and possible silica exposure through hobby-related activities remained statistically significant with odds ratios that were greater than the complete model (ORs = 4.4 and 2.4 respectively). These results are shown in Table 45.

Multivariate analyses were also conducted using a matched analytic approach. These analyses were conducted using conditional logistic regression fit to a matched case-control design for 1: *m* matched sets. As previously discussed, the analysis of the data for the South Boston Scleroderma and Lupus Study could have been conducted using either an unmatched or matched approach as the matching of controls in the study design was primarily intended for establishing a demographically similar comparison group. The matched analyses were therefore conducted to account for any differences or bias in the results from the unmatched analysis. The matched analysis takes into account the clustered nature of the data whereas the unmatched analysis ignores the clustering of matched sets and treats all observations as independent. Using the unmatched approach

has the potential to introduce a bias that can underestimate the standard error but potentially overestimate the observed associations between exploratory variables and disease risk (Allison 1999).

Results of the matched multivariate analyses were consistent with those observed using the unmatched analytic approach. Again, a previous diagnosis of rheumatoid arthritis and possible silica exposures through hobbies were suggestive of an increased risk of SSc/SLE. In the complete model, a previous self-reported diagnosis of rheumatoid arthritis and possible exposure to silica through hobby-related activities demonstrated odds ratios that were statistically significant at 3.5 (95% CI: 1.3-9.8) and 2.5 (95% CI: 1.1-5.6) respectively (Table 46). Similar to the unmatched approach, these two factors were the only variables that remained in the final model using stepwise backwards regression. Both a previous diagnosis of rheumatoid arthritis and possible silica exposure remained statistically significant in the final model with odds ratios that were greater than the complete model (Table 47). As previously discussed, although the odds ratios indicated an increased risk of SSc/SLE, these results should be interpreted with caution given the potential for bias due to misclassification and recall based on self-report

Additional matched multivariate analyses were conducted to evaluate the potential effect exposure to petroleum-related compounds as a result of living in proximity to hazardous waste sites and historical air emission from BECo may have had on disease risk when considering other possible risk factors for SSc/SLE (i.e., family history of autoimmune disease etc.). When considering exposure to petroleum-related compounds as a result of living in proximity to hazardous waste sites at their residence of longest duration in South

Boston in the multivariate analysis, the results did not indicate an increased risk of SSc or SLE for study participants (Table 48). Likewise, when historical air emissions from BECo were considered in the multivariate analysis, again the results did not indicate an increased risk of SSc or SLE for study participants who lived in the higher impact area at the time of disease onset or when considering their residence of longest duration in South Boston (Table 49).

V. Discussion

The results of this study indicate that the prevalence of SSc in South Boston is higher than expected. The annual incidence of SSc is consistent with estimates in the medical literature and both the prevalence and incidence of SLE in the South Boston area are consistent with estimates observed in populations of a similar demographic background. Given that the South Boston Scleroderma and Lupus Study population is almost entirely comprised of white females, it is important to compare the study findings to estimates for similar populations.

The South Boston point-prevalence estimate of SSc appears higher than that reported for the general population (33.4 per 100,000 vs. 27.6 per 100,000) and especially when considering white females (72.8 per 100,000 vs. 37.1 per 100,000) (Mayes 2003) (Table 50a). The prevalence of 26.7 cases of SLE per 100,000, on the other hand, was consistent with the literature. Previous, localized studies have estimated SLE prevalence to be anywhere from 14.6-149.5, however, a recent study based on nationally representative data has estimated 53.6 per 100,000 for the general population and 100 per 100,000 for females (Hochberg 1990; Chakravarty et al. 2007; Ward 2004). Although our prevalence

estimate for white females in South Boston is lower than prevalence estimates reported in the literature, the 95% confidence interval is wide and the true prevalence of SLE in South Boston might be as high as 105 cases per 100,000 annually (Table 50b).

Incidence rates for SSc and SLE vary widely between populations of different racial and ethnic backgrounds. Additionally, SSc and SLE rates have increased over the last several decades, likely due, at least in part, to improved diagnosis and standardization of case criteria (Michet et al. 1985; Steen et al. 1997; Laing et al. 1997; Mayes 2003). In this study, the overall annual incidence of 1.13 cases of SSc per 100,000 and the 2.27 cases per 100,000 white females was consistent with the 0.96-1.93 per 100,000 and the 1.28-2.7 cases per 100,000 as reported in the medical literature for the general population and white females, respectively (Steen et al. 1997, Mayes 2003, Laing et al. 1997) (Table 50a).

Annual SLE incidence, which we report as 1.41 per 100,000 for South Boston, was slightly lower than ranges published in the literature of 1.51-5.56 cases per 100,000 annually though the wide 95% confidence interval indicates that the true rate may be consistent with the literature (Table 50b). A more refined SLE incidence estimate for white females shows agreement with rates published in recent literature (2.65/100,000 annually vs. 1.1-3.9/100,000 annually) (Danchenko et al. 2006). Furthermore, the SLE incidence rate in white females in South Boston between 1970-2000 is about as expected based on previous literature estimates of approximately 2.5 for primarily white female populations in earlier decades and is slightly lower than the 3.5-9.4 per 100,000 reported

for later decades (Simard and Costenbader 2007; Uramoto et al. 1999; Danchenko et al. 2006).

Caution should be used, however, in drawing conclusions regarding the incidence of SSc and SLE in South Boston due to the small sample size and the imprecision of the estimates. Incidence rates for the South Boston Scleroderma and Lupus Health Study are based on relatively few cases as only 27 of the 45 individuals with SSc or SLE were residents of South Boston at the time of their disease onset or first non-Raynaud's symptom (12 diagnosed with SSc and 15 diagnosed with SLE). Both the SSc and the SLE incidence estimates in South Boston have wide confidence intervals and the true incidence rates may, in fact, be under-estimated. In addition, the South Boston Scleroderma and Lupus Health study calculated incidence rates for the relatively long time period of 1970-2000 and likely includes periods of historical under-diagnosis. Notably, there is a discrepancy between the high prevalence and low annual incidence of SSc in South Boston. This result may be due to under-estimation of the incidence rate because of the long time period, historical under-diagnosis of SSc within the 1970-2000 time frame, and small study numbers.

Among cases that were current residents of South Boston, the diagnoses of SSc and SLE primarily occurred during the years 1970 to 2000. Although the demographic characteristics of South Boston have shifted to a slightly younger population within the last 10 to 15 years, the population of South Boston has remained fairly stable throughout this time period (Figures 2 and 3). The frequency of SSc/SLE diagnoses nearly doubled from the 1970 to 1979 time period as compared to 1990 to 2000. However, it cannot be

concluded that the pattern of diagnoses during the study period represents an increasing trend in the diagnoses of SSc/SLE in South Boston. Given the length of the study period, the difference in the number of cases during the latter portion of the study period as compared to the earlier decades is most likely the result of better case ascertainment of more recent SSc/SLE cases.

One could argue that the observed prevalence estimates of SSc and SLE in South Boston were influenced by ascertainment bias. That is, given that the South Boston Scleroderma and Lupus Study was initiated based on a report of a suspected cluster of autoimmune disease, the observation of higher prevalence resulted from an increased level of scrutiny and targeted efforts at case ascertainment within the South Boston community compared to prevalence that may have been observed using traditional methods for case identification. However, the observed prevalence of SSc and SLE in South Boston may actually represent an underestimate of the true disease prevalence for this population. The case definition for the South Boston study required that cases of SSc and SLE meet established ACR criteria to confirm the diagnosis of SSc or SLE. Although the ACR criteria have a high percentage of sensitivity and specificity with respect to the diagnosis of connective tissue disease, they were intended to distinguish SSc and SLE from other connective tissue diseases (Valentini and Black 2002). It is estimated that the use of ACR criteria could exclude approximately 10% of patients with the limited cutaneous subset of scleroderma. As a result of the case definition for the study, the cases identified represent the more advanced cases in terms of disease expression. Individuals who may have limited scleroderma or are in the earlier stages of disease progression for SSc or SLE would not necessarily meet established criteria for a diagnosis of these diseases.

Furthermore, death certificate searches may have failed to capture all SSc and SLE cases. Though ICD codes were selected to be as complete as possible, reporting may not have been as complete in earlier years, especially regarding underlying conditions. Recruitment efforts, though comprehensive in scope (hospitals, rheumatologists' offices, and community outreach), were not exhaustive or registry-based and may not have identified all potential cases. Thus, the observed prevalence estimates for South Boston may therefore underestimate disease diffusion within this population.

The results of this study indicate that a family history of autoimmune or rheumatic disease may increase the risk of developing SSc or SLE. A two-fold increase in SSc/SLE risk that was statistically significant was observed if any family member had a previous diagnosis of autoimmune/rheumatic disease. Although not statistically significant, consistent odds ratios were observed for a parental diagnosis of autoimmune disease (OR=2.0) and a diagnosis of autoimmune disease among mothers (OR=2.5). These results are consistent with findings of other studies of autoimmune disease that have reported genetic predisposition as a risk factor for the development of these diseases. When a family history of autoimmune disease was evaluated in the presence of other possible risk factors in the multivariable analyses, the observed association was not statistically significant. A family history of autoimmune disease in this study was defined as a biological parent or sibling with a previous diagnosis of SSc, SLE, mixed or undifferentiated connective tissue disease, rheumatoid arthritis, or thyroid disease. The greatest frequency of response was a reported family history of rheumatoid arthritis followed by reports of a family history of thyroid disease. A family history of rheumatoid arthritis was therefore removed from the analysis given the potential for

misclassification of this diagnosis by study participants. However, even with the removal of rheumatoid arthritis, an increased risk of SSc/SLE was observed for cases compared to controls that had a family history of autoimmune disease. In addition, for a family member diagnosed with SSc, SLE or mixed connective tissue specifically, the odds ratio was 3.0 (95% CI: 0.6-13.8). It is possible that only one or a combination of several of these diseases may be influencing the observed association, however due to the small study size and thus small number of exposed persons, the study lacks sufficient statistical power to ascertain a more specific relationship. The South Boston sample size only achieved approximately 55% power to detect an association between family history of autoimmune disease and risk of SSc/SLE. Furthermore, it is important to keep in mind that self-reported family history was not verified and, therefore, may be susceptible to bias, particularly given that cases may have a higher level of awareness of these diseases. Even though the results did not achieve statistical significance, the observation of consistent odds ratios indicating a two-fold increase in SSc/SLE risk among individuals with a family history of autoimmune disease, specifically a parental diagnosis of autoimmune disease, is consistent with previous reports of familial clustering and suggestive that a genetic factor may have influenced the incidence of SSc/SLE among the study population.

A four-fold increase in the risk of SSc/SLE was also observed among study participants who reported a previous diagnosis of rheumatoid arthritis (OR=4.2). Again, this observation was confirmed in both the unmatched and matched analysis and the association remained statistically significant in multivariate analysis including a family history of autoimmune disease as well as other exploratory factors. Although statistically

significant, this result should be interpreted with caution as inflammatory arthritis is one of the 11 criteria established by the ACR in determining a diagnosis of SLE and is a possible pre-cursor misdiagnosis for SSc patients with less severe disease or SSc patients earlier in their disease progression. The South Boston sample size did support at least 80% statistical power to detect the association.

There were 21 individuals who reported a previous diagnosis of rheumatoid arthritis. Ten of these individuals were confirmed cases of SSc or SLE. A frequency analysis showed that of the nine cases reporting a diagnosis of rheumatoid arthritis, five were SLE cases, four were SSc cases and one was an overlap case. The remaining 11 individuals who reported a diagnosis of rheumatoid arthritis were controls. The prevalence of rheumatoid arthritis within the general adult population is estimated to be between 0.5 and 1.0% (Hochberg and Specter 1990; Mayes 2003). Therefore, within the general population of South Boston one would expect to find between 150 and 300 individuals diagnosed with rheumatoid arthritis and, within the South Boston Scleroderma and Lupus Study population, one to two cases would be expected. It is likely that the observed association in this study was due to misreporting of osteoarthritis, a far more common form of arthritis. Several large U.S.-based cohort studies have estimated the accuracy of self-reported rheumatoid arthritis to be between 7% and 15% (Cerhan 2003, Costenbader 2006, Walitt 2008). Therefore, the seemingly high prevalence of rheumatoid arthritis in controls is likely due to over-reporting of rheumatoid arthritis and is not a true reflection of higher prevalence of the disease in the South Boston population.

Silica and solvents are the two primary exposures that have been implicated as possible risk factors for developing SSc and SLE. The strongest evidence has been observed in epidemiologic studies of occupational factors and case reports of scleroderma-like disease resulting from exposure events (Finch et al. 1980; Haustein and Ziegler 1985; Cowie 1987; Czirjac and Szegedi 1987; Kahn et al. 1989; Brasington and Thorpe-Swenson 1991; Pelmear et al. 1992; Czirjac et al. 1993; Bovenzi et al. 1995; Haustein et al. 1994; Garcia-Zamalloa et al. 1994; Bovenzi et al. 2001). However, the South Boston Scleroderma and Lupus Study did not observe any increased risk in SSc or SLE associated with silica or solvent exposures related to either occupation or hobbies and other activities. Although a statistically significant association was noted regarding hobby-related silica exposures, this observation was related to exposures that were categorized as "possible" based upon the nature of the hobby or activity reported by study participants. Upon closer review, this exposure category was predominantly due to the frequency of study participants who reported ceramics or pottery as a hobby. In addition, the exposure was based on study participants reporting ever versus never participating in ceramics or pottery as a hobby and did not include information on frequency or duration in order to better quantity potential exposure. Furthermore, analysis of more specific measures of exposure due to silica-related hobbies yielded no association. Therefore, the observed association between broad categories of possible silica-related hobbies may be a chance association and not reflective of an actual increased risk due to silica exposure, although the study sample was limited and only achieved approximately 50% statistical power to detect any silica associations.

The one risk factor that demonstrated consistency with respect to an increased risk of SSc or SLE was a family history of autoimmune/rheumatic disease. It appears that genetic factors may have a stronger influence on disease development in this study population than potential chemical or environmental exposures. This is not meant to suggest that environmental factors may not have played a role in the development of SSc and SLE, but rather the environmental factors evaluated could be influenced by insufficient power to observe specific relationships based on small numbers of exposed individuals.

While the prevalence of SSc is indeed higher in South Boston compared to estimates published in the literature, the MDPH did not observe evidence of clustering of SSc/SLE cases within neighborhoods or smaller geographic areas of South Boston based on spatial and temporal analysis of the collected residential history information. Even though the spatial analysis indicated two areas where spatial clustering of case residences may not be random, close examination of the results from the spatial analysis showed that they were influenced by cases having multiple residences within particular neighborhoods. Further, no temporal (that is, time) clusters were identified during the study period of 1950 to 2000.

The study unfortunately suffered from a low response rate (22%), which may have influenced the overall results. Despite the targeted outreach efforts, the low response was likely in large part due to the passive recruitment process among the potential control population that was required by the HRRC as part of the study protocol. The actual refusal rates remained low and fairly consistent over time while the percentage of non-responders increased as the study recruitment progressed. Even though the overall

response rate was low, the larger concern with respect to any influence the low response may have had on the study is whether the control population is representative of the South Boston population that gave rise to the case group. A further evaluation of the control population by response category was conducted to assess the potential for confounding or bias with respect to age, geographic distribution, and other demographic factors that may exist between selected controls who agreed to participate in the study versus those who did not. The mean age of selected controls who agreed to participate was approximately five years younger than the selected controls who did not agree to participate (56.6 years versus 61.6 years). In addition, the difference in mean age of individuals who refused study participation versus those who did not respond to recruitment efforts was approximately 10 years (69.9 years for refusals versus 59.5 years for non-response). This evaluation indicates a possible selection bias in the control recruitment population in that the participating controls were slightly younger than non-participating controls. There was also an observed geographic difference in controls who participated in the study versus those who did not, where the yes respondents were typically from areas of South Boston that, based on census data, had a higher education level, higher median income and lower population density.

Although this assessment of the control population identified differences in the yes versus no respondents, it was likely not a factor that greatly influenced the study results. All controls in the South Boston Scleroderma and Lupus Study were randomly selected from the South Boston population and were individually matched to cases based on age and gender. In addition, most of the difference in the control population was related to control recruitment efforts for six cases that were over age 76. A total of 222 controls or

23% of the control recruitment sample needed to be contacted to attain a successful match ratio for these six cases. Therefore, over sampling of the population greater than age 75 was necessary to fulfill case-control requirements for the study. This over sampling lowered the overall study response rate.

The South Boston Scleroderma and Lupus Study was an exploratory study intended to assess the potential that risk factors (both environmental and non-environmental) may influence SSc and SLE risk in this community. As an exploratory study, it had no specific a priori hypothesis and therefore any results indicating a relationship between a certain factor or exposure and SSc/SLE risk can not be interpreted as a causal association but rather as suggestive evidence for additional research.

Further, the South Boston Scleroderma and Lupus Study had a number of limitations. The suspected cluster initially reported to the MDPH consisted of a mix of both current and former South Boston residents diagnosed with SSc or SLE. The average time that former residents had lived away from South Boston prior to their disease onset was 16 years with a range of 2 to 35 years. Given the retrospective nature of the initial cluster concerns, the study period (1950-2000) was lengthy. SSc and SLE have few well-established risk factors. Although these diseases are thought to develop from exposure to one or more environmental triggers, there is no established latency period (i.e., period of time from initial exposure to disease development) for either SSc or SLE. A few studies have suggested a possible latency period ranging from 5 to 10 years for development of SSc and SLE (Freni-Titulaer et al. 1989; Kardenstuncer and Frumkin 1997; Dahlgren et al. 2007). However, these estimates are based on observations from other studies and

provide little evidence to support a specific latency period. Given the average length of time away from South Boston prior to disease onset for former residents, if an environmental exposure related to South Boston were a factor in the development of SSc and SLE diagnoses among former residents of South Boston, this exposure would had to have occurred during childhood or early adulthood.

The study did not observe an increased risk of SSc or SLE when evaluating exposures to historical industrial/environmental sources within South Boston. However, the exposure assessment was limited due to the retrospective nature of this study. There was no available environmental data with which to measure the presence and concentrations of contaminants suspected as risk factors for SSc and SLE in South Boston in the past. Therefore, it was necessary for the study to rely on self-reported exposure opportunities collected through interviews with study participants to assess exposure potential among the study population. Consequently, the exposure assessment has the potential for misclassification and recall bias. In general, however, our results did not show evidence of over- or biased reporting of exposures such as hobbies, etc. by cases as many of the exposures of interest were reported with equal frequency by cases and controls. Further, evaluation of potential historical exposures to industrial point sources within South Boston, such as hazardous waste sites and historical emissions from the Boston Edison Power Plant, were based on residential proximity of study participants based on residential history information in relation to modeled emissions based upon more recent meteorological data. Evaluation of potential exposure that could result from a shorter latency period for SSc and SLE necessitated exclusion of all former residents from the residential based analyses. Therefore, analyses of residence at incidence or index date

were somewhat limited in power to detect a relationship between these exposures and SSc/SLE risk.

VI. Conclusions

The observed prevalence of SSc in South Boston appears to be higher than expected. However, the prevalence of SLE in South Boston appears to be consistent with prevalence estimates observed elsewhere and reported in published scientific literature. Incidence rates for both diseases are within ranges reported in the literature, however, the estimates are imprecise and based on a small number of cases over a long time period. The risk factor that demonstrated the most consistency with respect to an increased risk of SSc or SLE was a family history of autoimmune/rheumatic disease. This finding was consistent with the etiologic hypothesis in the epidemiological literature for SSc and SLE that a genetic predisposition may influence the development of these diseases. Based on the results observed in this study, it appears that genetic factors may play a role in disease development in the study population. The ability to detect an association between SSc/SLE risk and environmental exposures in the South Boston area was extremely limited due to low statistical power. However, the lack of an association with environmental exposures is not meant to suggest that environmental factors may not have played a role in the development of SSc and SLE. At this time, research currently underway involving clinical registries may better evaluate the nature of gene-environment interactions and characterize the role of environmental factors.

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Figures

Figure 1
South Boston Scleroderma and Lupus Study
Distribution of Residential and Industrial Zoning in South Boston

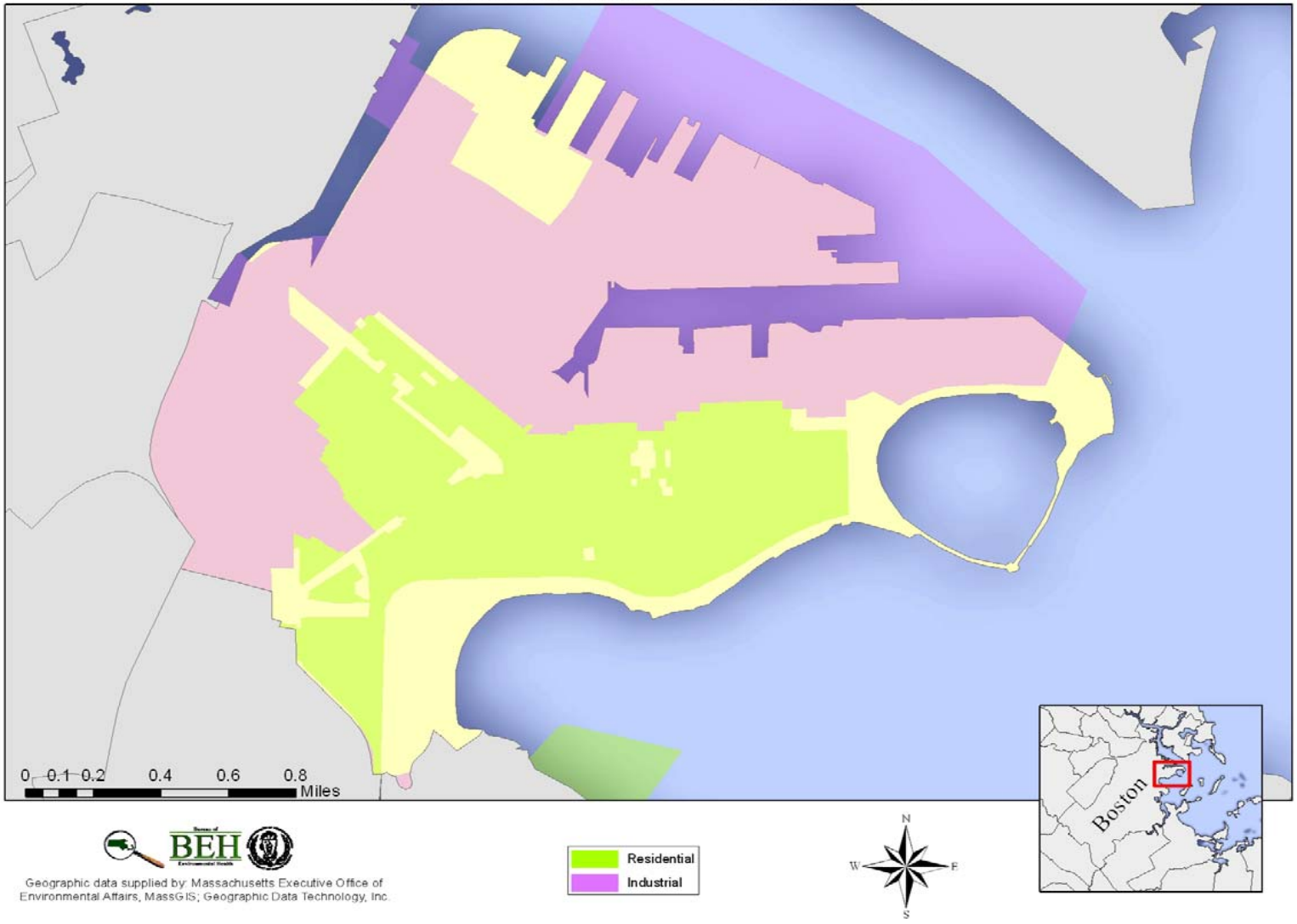


Figure 2
South Boston Scleroderma and Lupus Health Study
South Boston Population by Decade 1950-2000

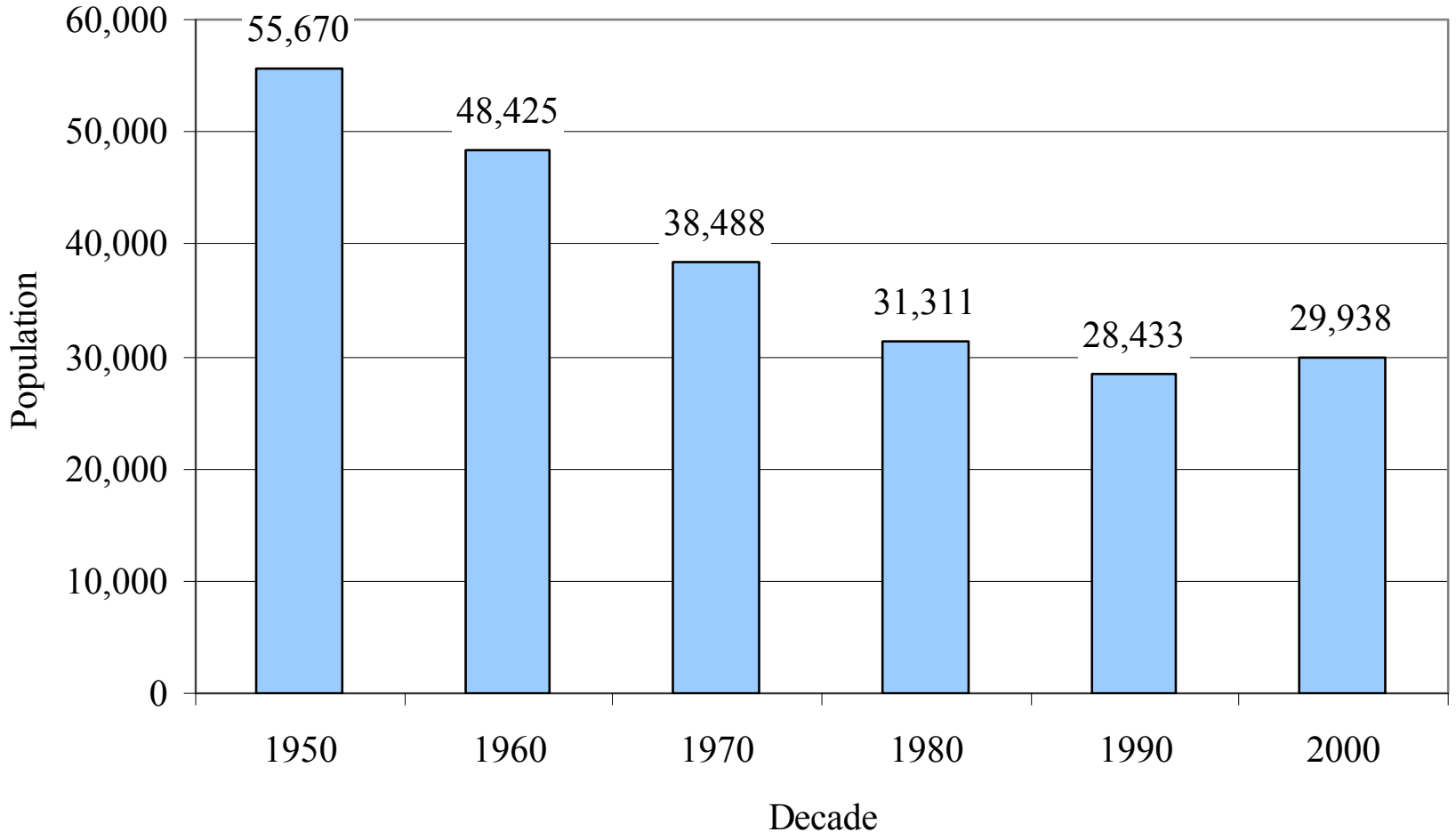


Figure 3
South Boston Scleroderma and Lupus Health Study
South Boston Population by Age and Decade

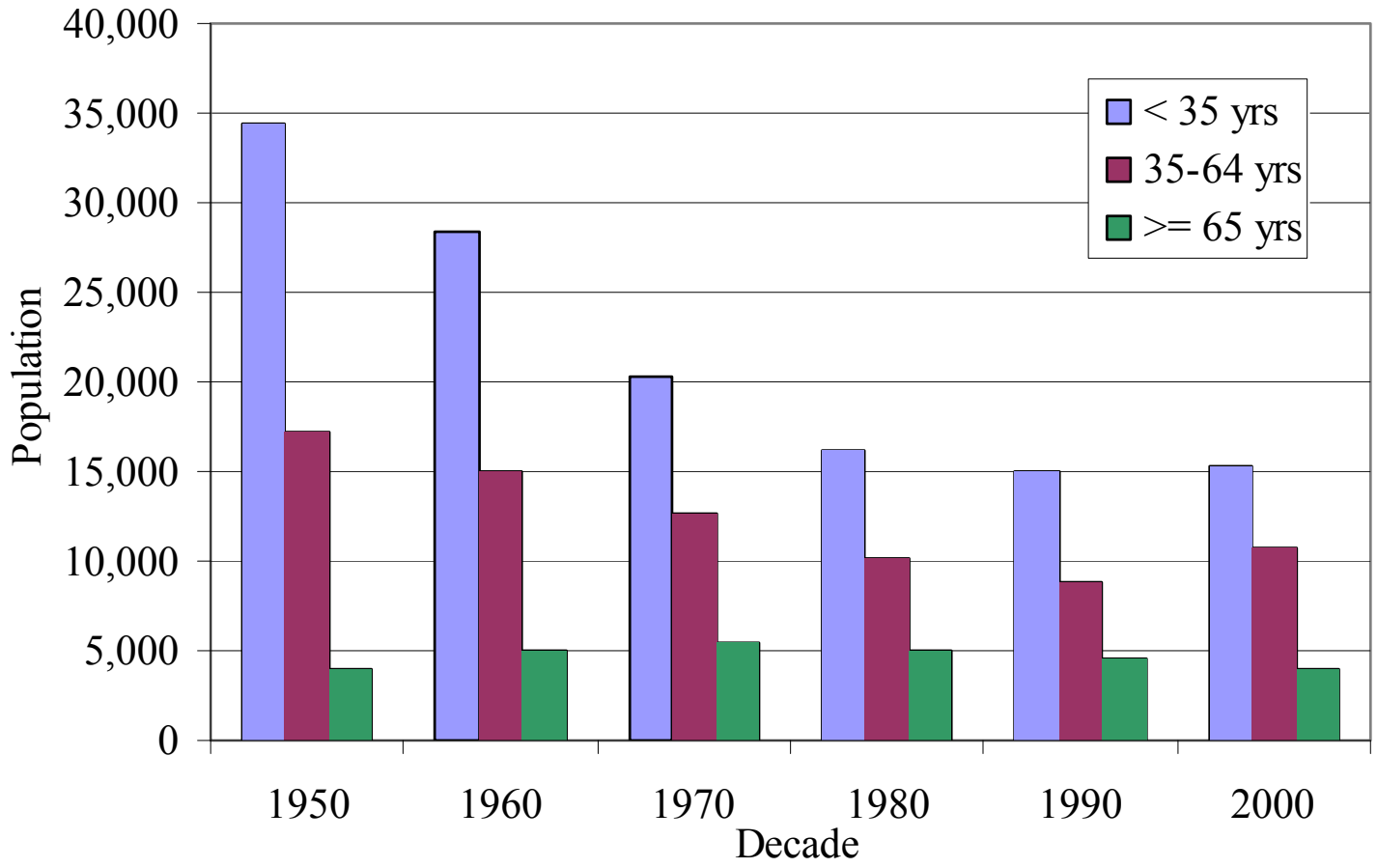
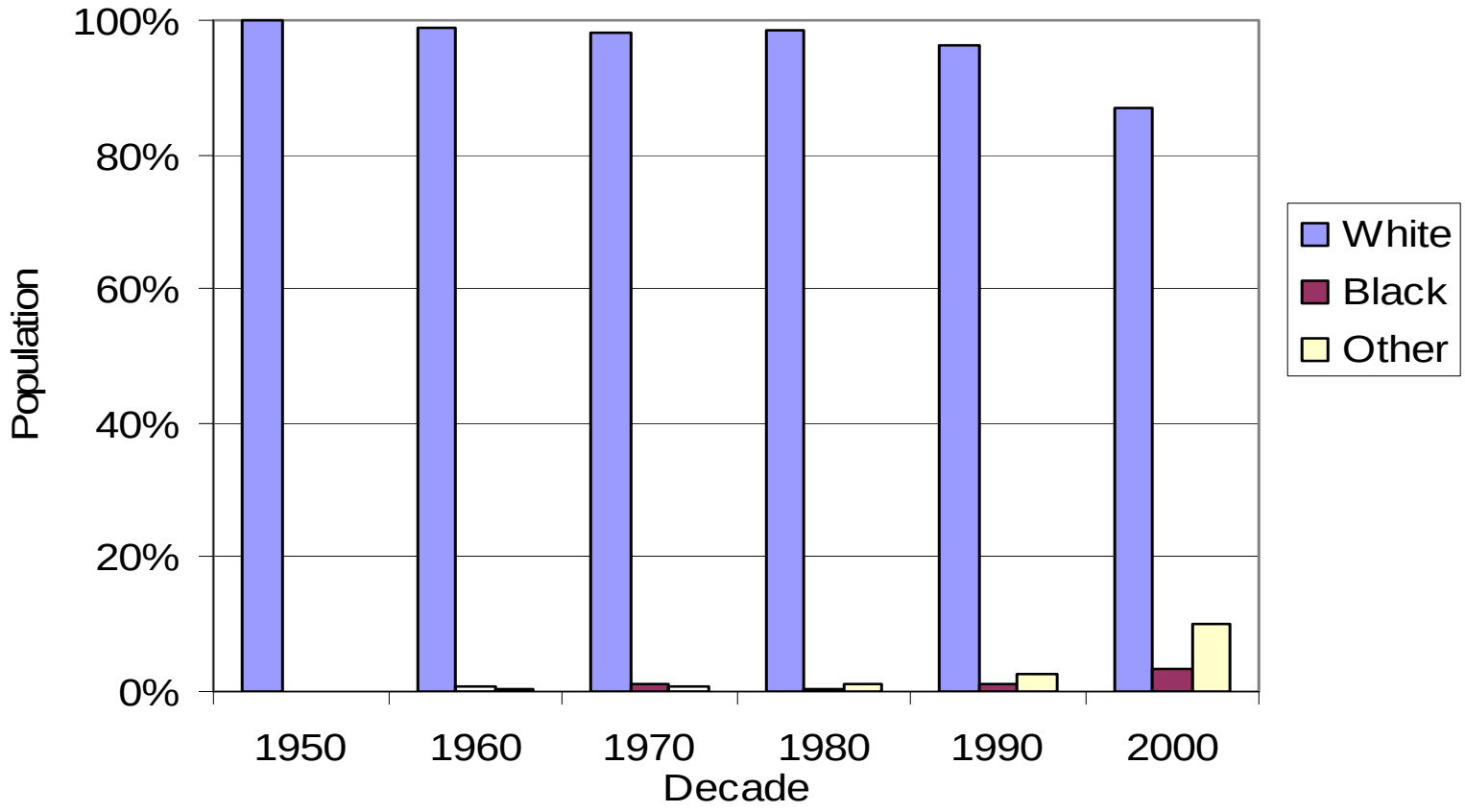
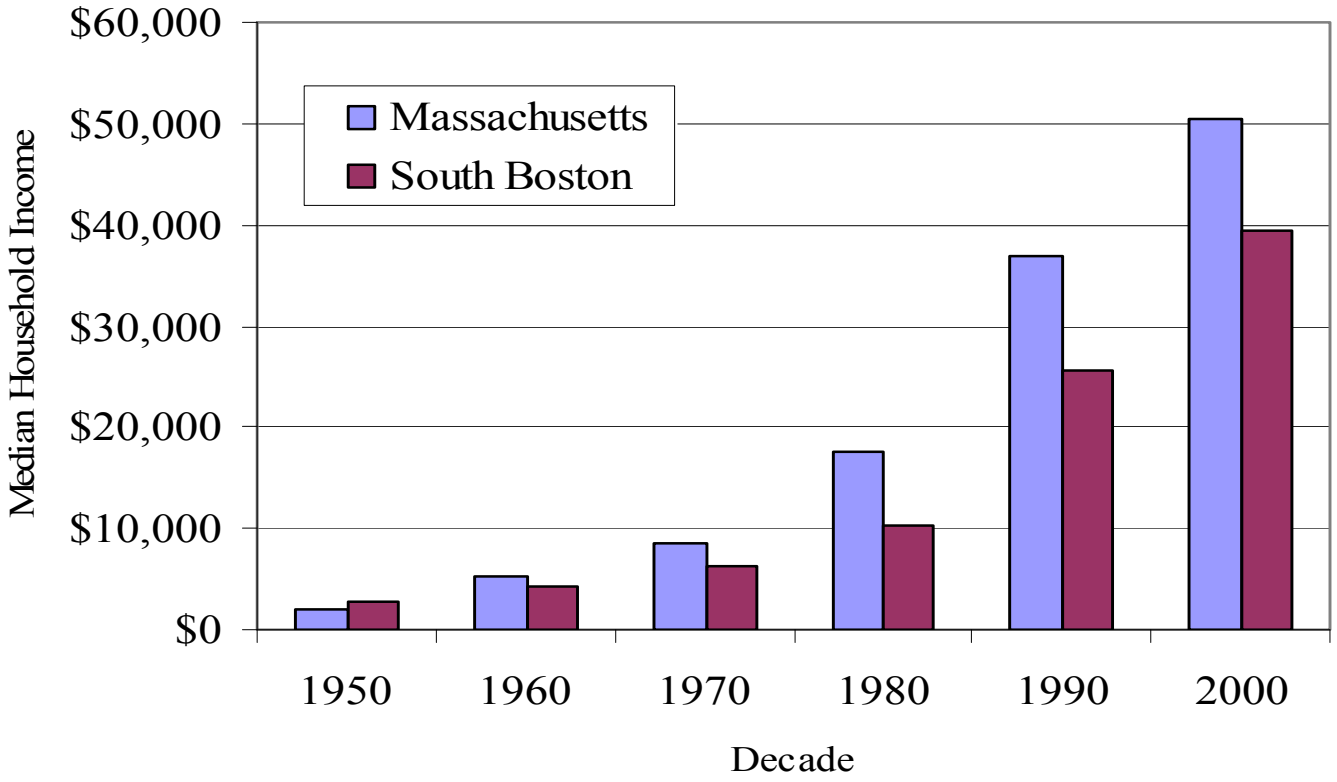


Figure 4
South Boston Scleroderma and Lupus Health Study
South Boston Population by Race and Decade, 1950-2000



Source: U.S. Census Bureau, Population Characteristics Survey, Race in the United States: 1950, 1960, 1970, 1980, 1990, and 2000.

Figure 5
South Boston Scleroderma and Lupus Health Study
South Boston Population Median Household Income by Decade, 1950-2000



Source: U.S. Census Bureau, Population Characteristics, Age in the United States: 1950, 1960, 1970, 1980, 1990, 2000.
Median household income for South Boston weighted by census tract population.

Figure 6
South Boston Scleroderma and Lupus Study
Case Ascertainment Flow-Chart

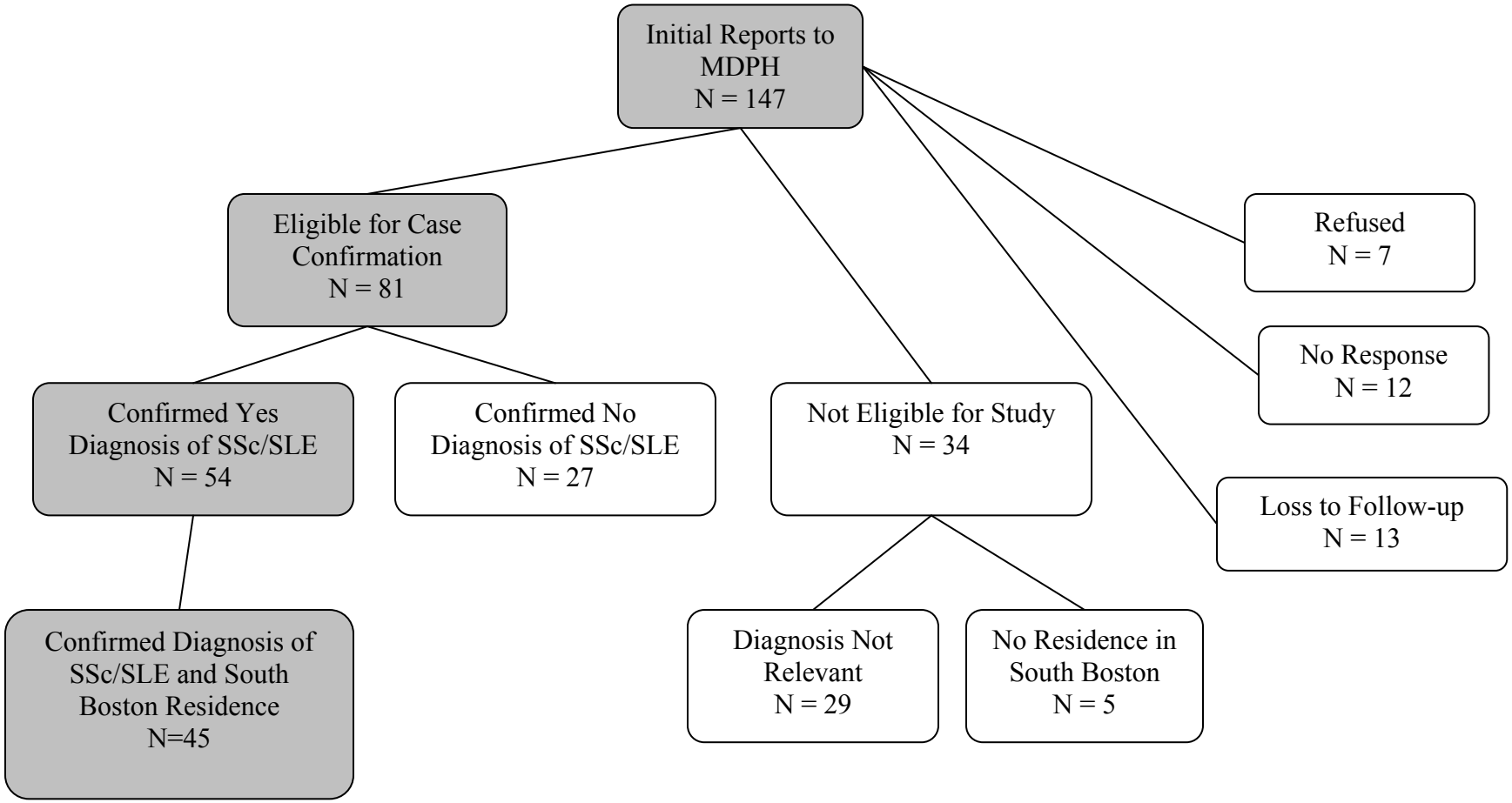


Figure 7
South Boston Scleroderma and Lupus Study
Case Confirmation Flow-Chart

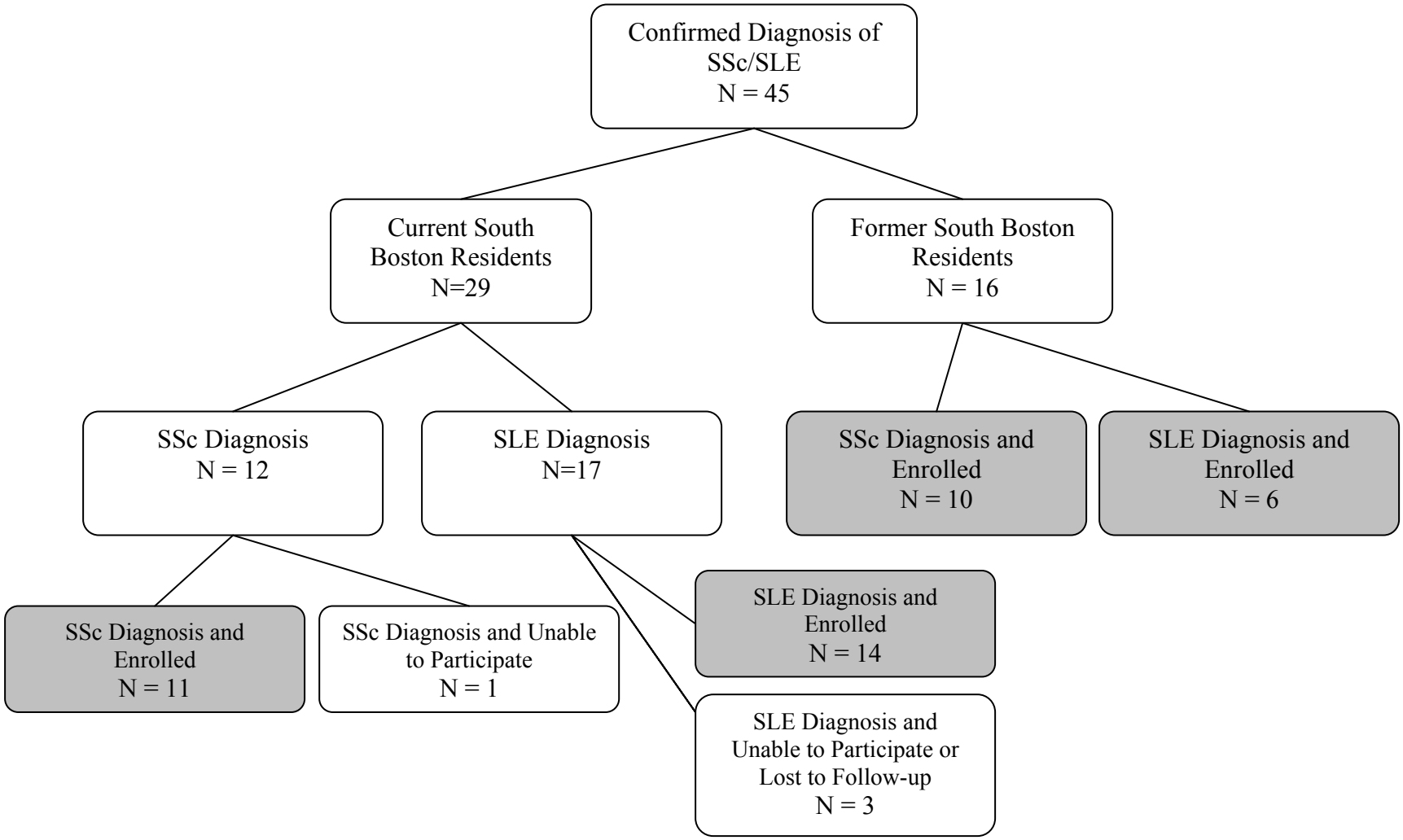
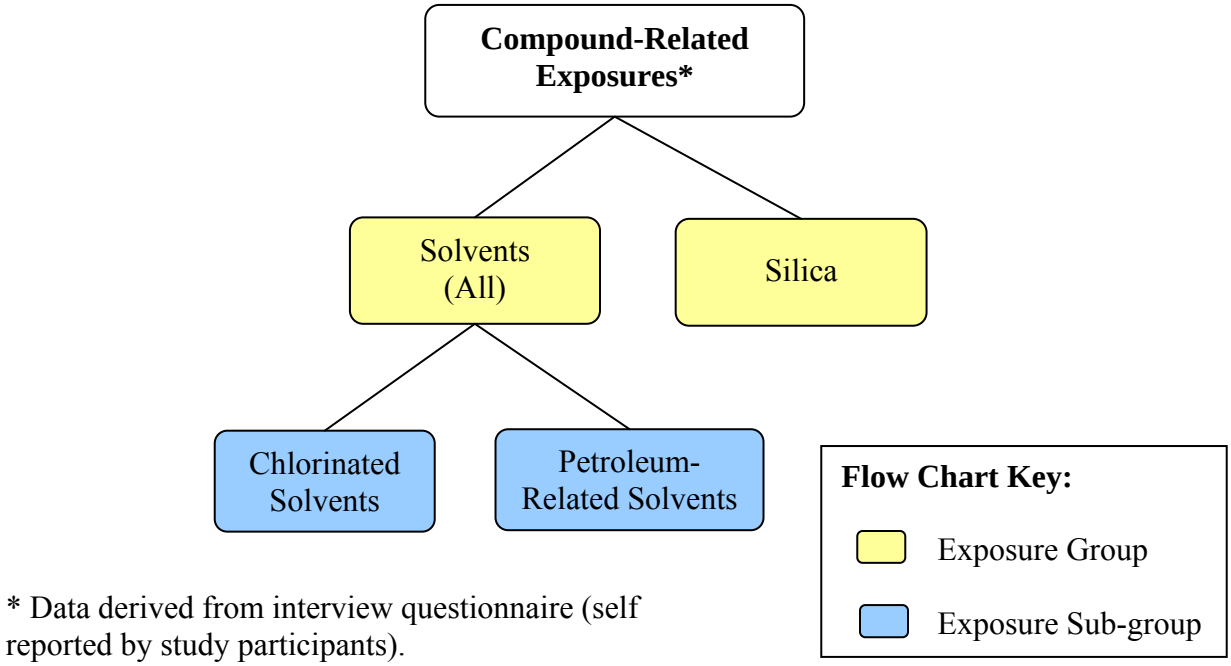


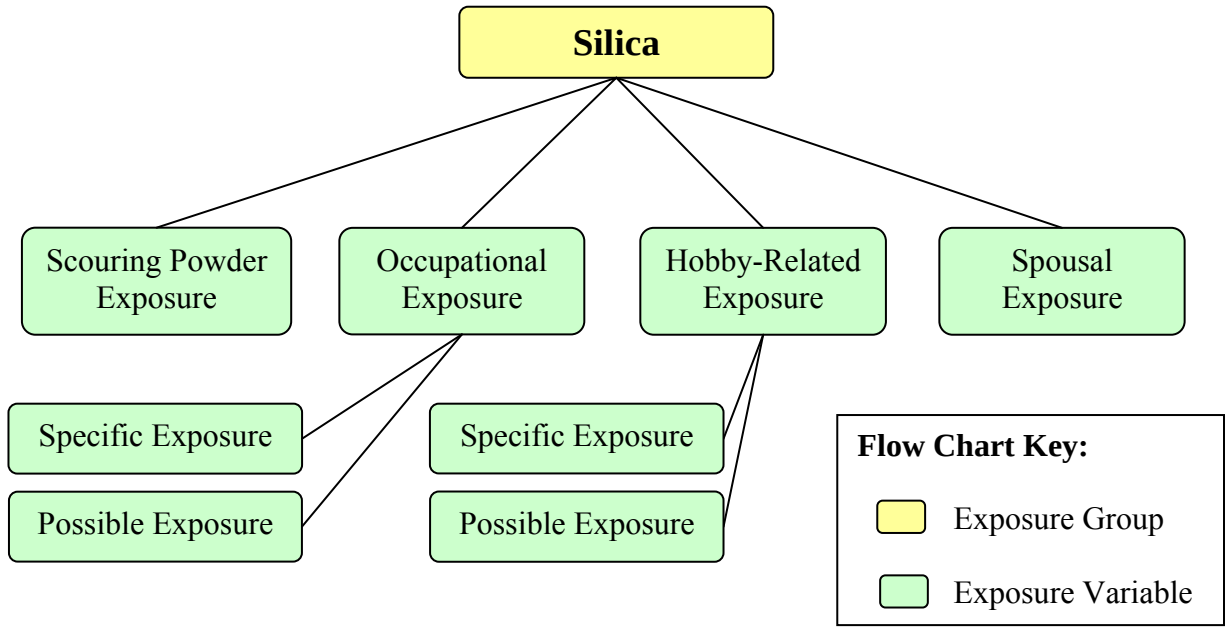
Figure 8
South Boston Scleroderma and Lupus Health Study

Exposure Group Flow Chart



* Data derived from interview questionnaire (self reported by study participants).

Silica Exposure Variable Flow Chart



Solvent Exposure Variable Flow Chart

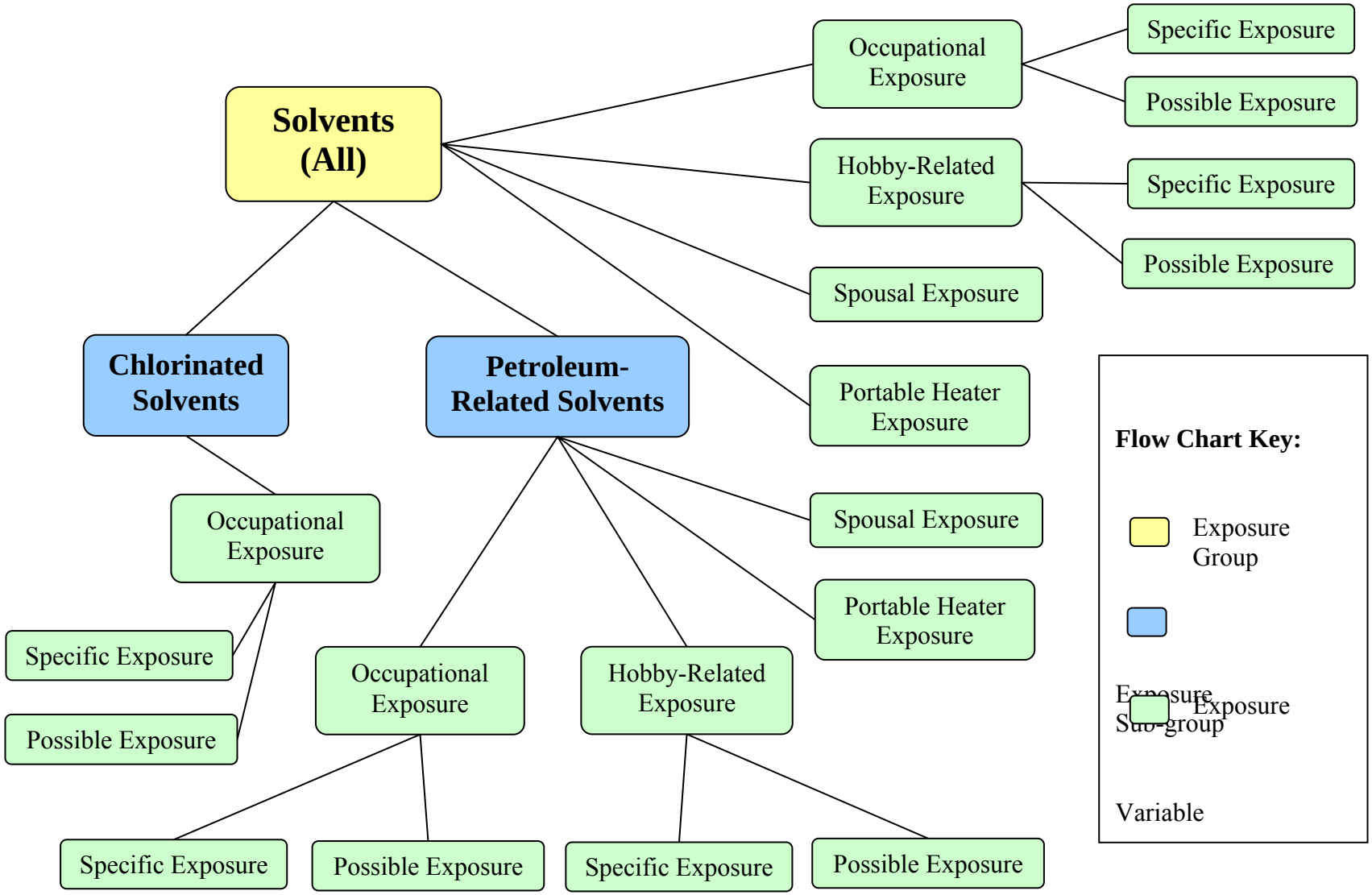


Figure 9
South Boston Scleroderma and Lupus Health Study
Petroleum Release Sites in South Boston, MA (n=106)

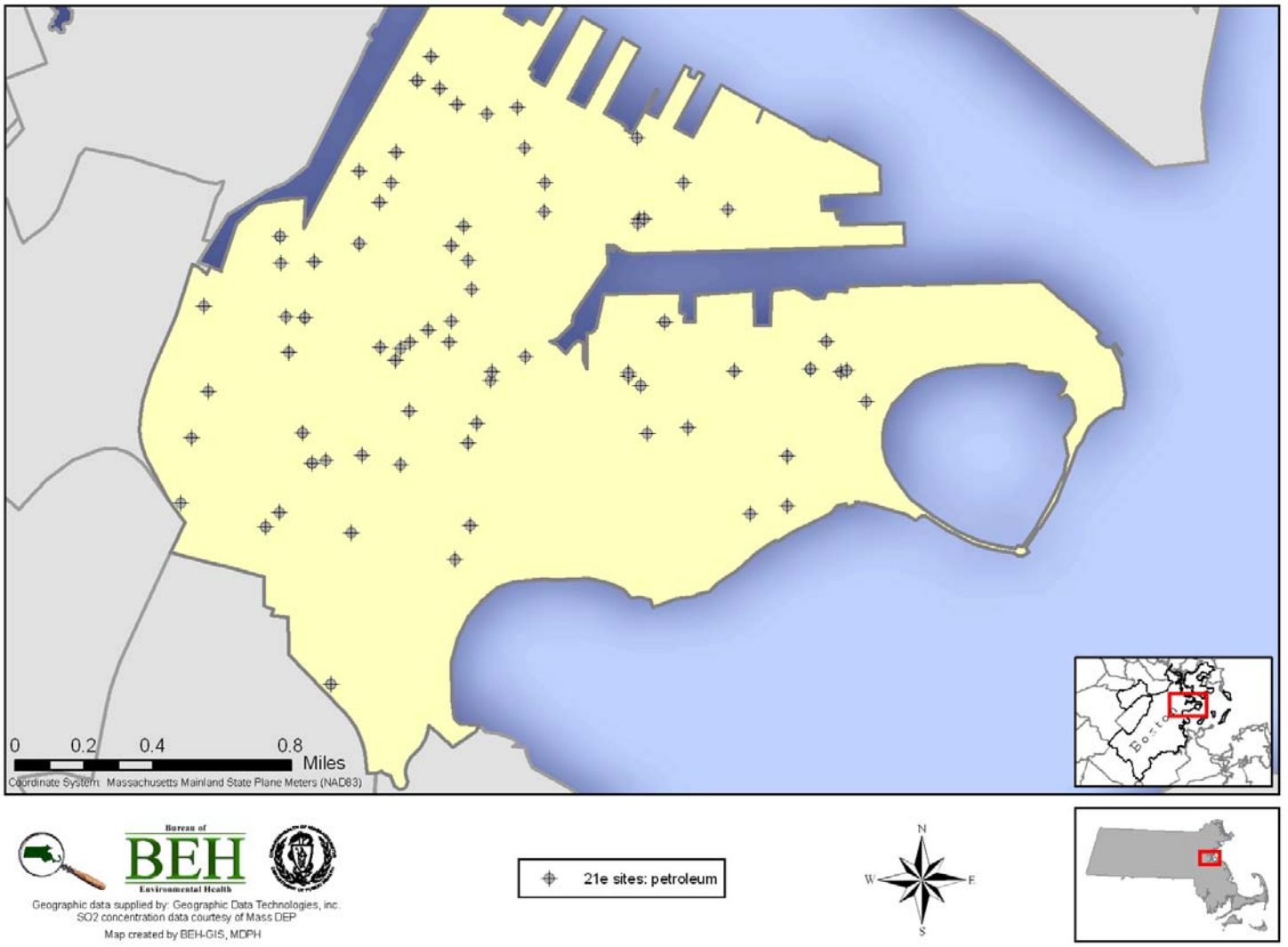


Figure 10
South Boston Scleroderma and Lupus Health Study
Other Hazardous Material Release Sites in South Boston, (n=44)

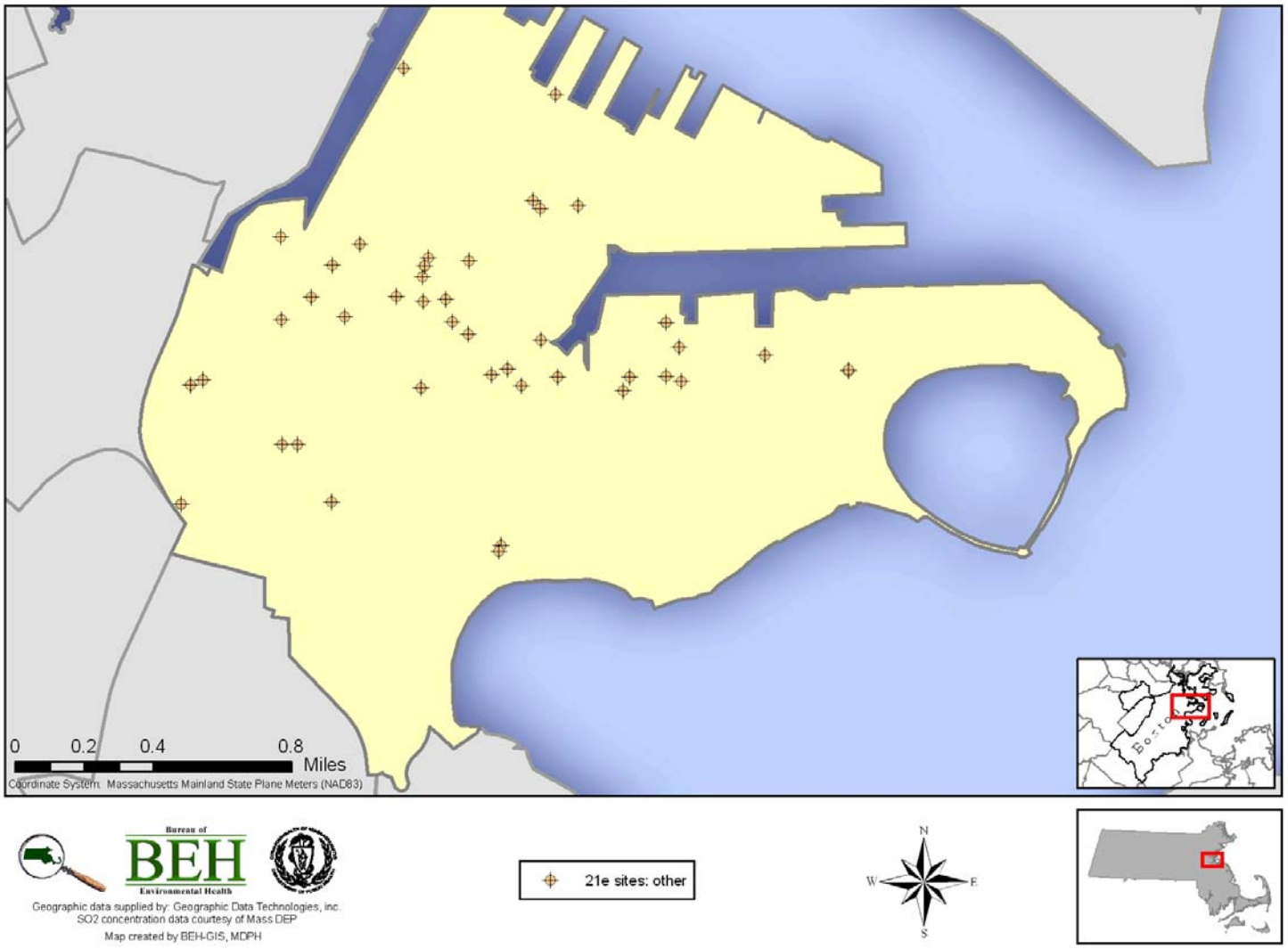


Figure 11
South Boston Scleroderma and Lupus Health Study
Modeled SO2 Concentrations Across South Boston

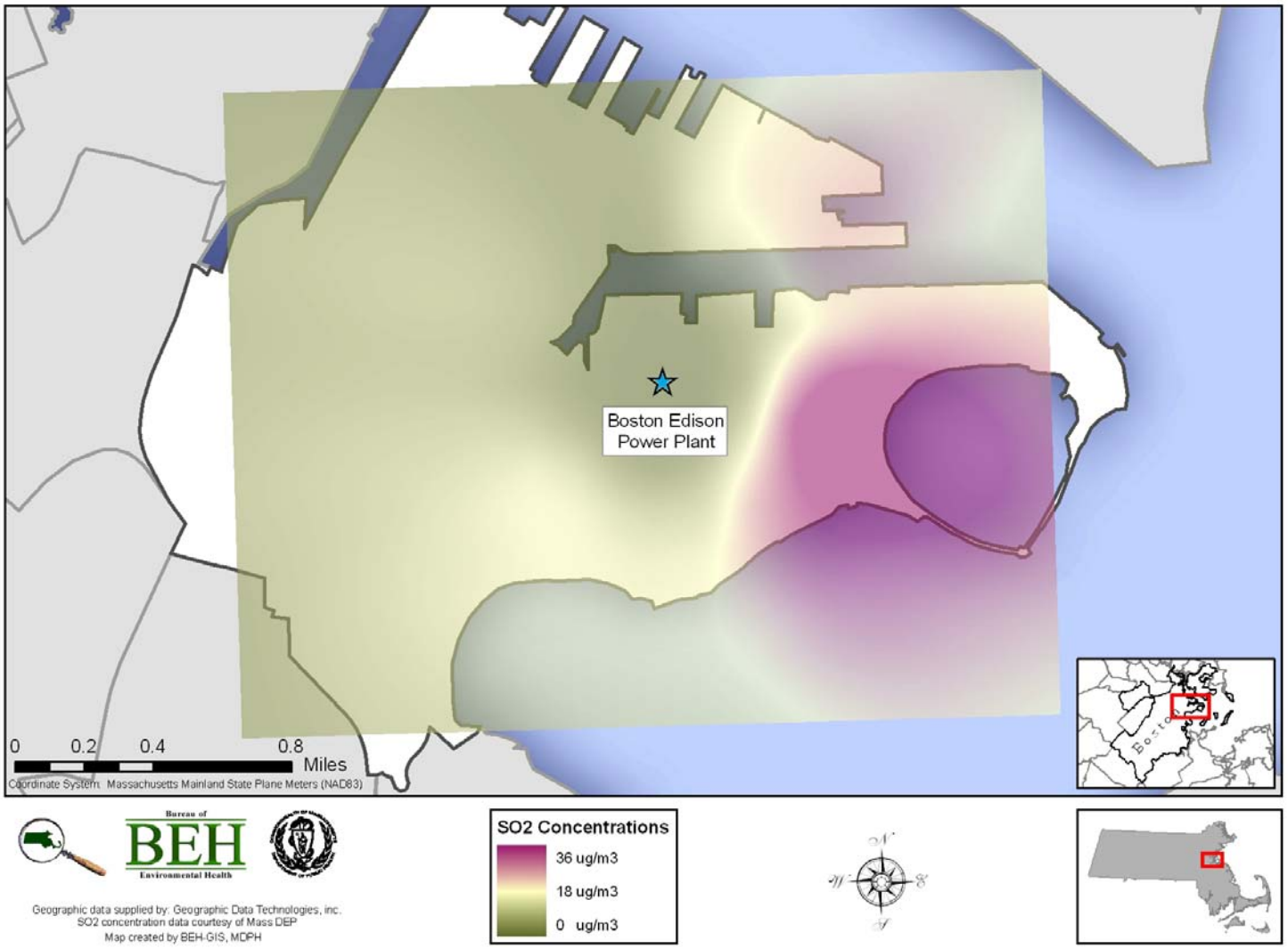
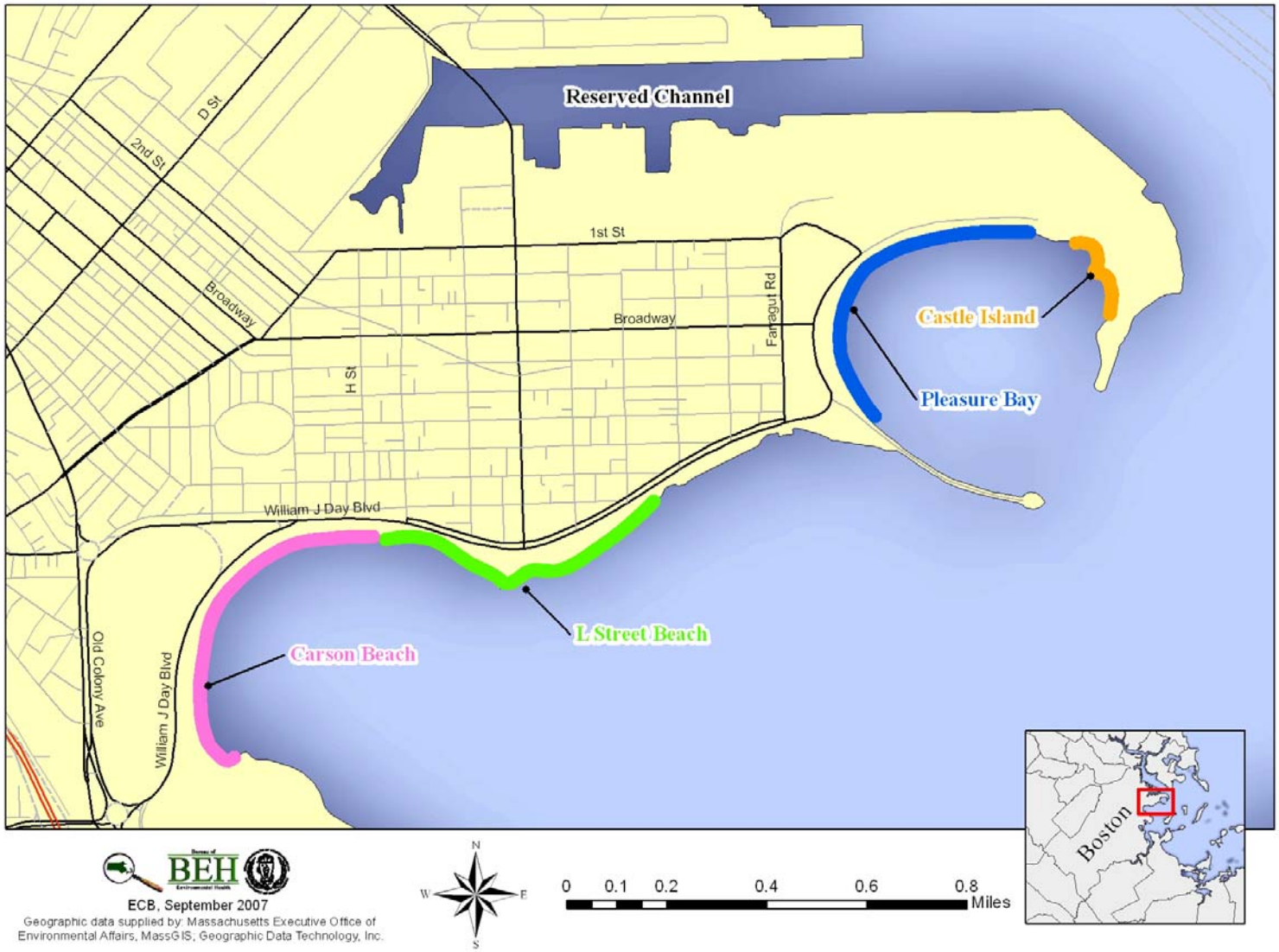


Figure 12
South Boston Scleroderma and Lupus Health Study
Geographic Location of Beaches in South Boston



Tables

Table 1: ICD Codes for Lupus, Scleroderma, and Mixed Connective Tissue Disease

ICD-8	
695.4	lupus erythematosus
701.0	circumscribed scleroderma
734.1	systemic lupus erythematosus
710.1	systemic sclerosis
716.0	dermatomyositis
734.9	other and specified diffuse diseases of connective tissue
ICD-9	
695.4	lupus erythematosus
701.0	circumscribed scleroderma
710.0	systemic lupus erythematosus
710.1	systemic sclerosis
710.2	sicca syndrome
710.3	dermatomyositis
710.4	polymyositis
710.8	other specified diffuse diseases of connective tissue
710.9	unspecified diffuse connective tissue disease
ICD-10	
L93	lupus erythematosus
L94.0	circumscribed scleroderma
M32.1, M32.8, M32.9	systemic lupus erythematosus
M34	systemic sclerosis
M35	sicca syndrome
M33.2, M33.1, M33.9	dermatopolymyositis
M35.8	other specified diffuse diseases of connective tissue
M35.9	unspecified diffuse connective tissue disease

Table 2: Distribution of Cases and Corresponding Controls

Case-Control Match Ratio	Total Case Count	SSc Case Count	SLE Case Count
1:6	1	0	1
1:5	4	1	3
1:4	25	14	11
1:3	7	3	4
1:2	3	2	1
1:1	1	1	0
Total Number of Controls	**154**	**75**	**79**

Table 3: Frequency of Country of Origin - Study Participants

		Cases (%)	Controls (%)	Total	% Total
US		39 (95.1)	147 (95.5)	186	95.5
Foreign (Total)		2 (4.9)	6 (3.9)	8	4.0
Countries	Ireland	1 (2.4)	1 (0.6)	2	1.0
	Italy	1 (2.4)	1 (0.6)	2	1.0
	Canada	0 (0)	1 (0.6)	1	0.5
	Germany	0 (0)	1 (0.6)	1	0.5
	Other	0 (0)	2 (1.3)	2	1.0
Unknown		0 (0)	1 (0.6)	1	0.5

Insufficient cell size for Chi Square (χ^2) analysis

Table 4: Frequency of Country of Origin - Study Participants' Parents

		Mother				**Father**			
		Cases (%)	Controls (%)	Total	% Total	Cases (%)	Controls (%)	Total	% Total
US		33 (80.5)	124 (80.5)	157	80.5	31 (75.6)	116 (75.3)	147	75.4
Foreign (Total)		7 (17.1)	30 (19.5)	37	19.0	8 (19.5)	37 (24.0)	45	23.0
Countries	Ireland	3 (7.3)	12 (7.8)	15	7.7	4 (9.8)	15 (9.7)	19	9.7
	Italy	2 (4.9)	3 (1.9)	5	2.6	2 (4.9)	5 (3.2)	7	3.6
	Canada	1 (2.4)	5 (3.2)	6	3.1	1 (2.4)	6 (3.9)	7	3.6
	Scotland	0 (0)	2 (1.3)	2	1.0	0 (0)	1 (0.6)	1	0.5
	Lithuania	0 (0)	2 (1.3)	2	1.0	0 (0)	2 (1.3)	2	1.0
	Poland	1 (2.4)	1 (0.6)	2	1.0	1 (2.4)	2 (1.3)	3	1.5
	Germany	0 (0)	1 (0.6)	1	0.5	0 (0)	1 (0.6)	1	0.5
	England	0 (0)	0 (0)	0	0.0	0 (0)	1 (0.6)	1	0.5
	Other	0 (0)	4 (2.6)	4	2.1	0 (0)	4 (2.6)	4	2.1
Unknown		1 (2.4)	0 (0)	1	0.5	2 (4.9)	1 (0.6)	3	1.6

Mother's country of origin U.S. vs. foreign Chi-Square (χ^2) p-value=0.7764. Father's country of origin U.S. vs. foreign Chi-Square (χ^2) p-value=0.6291.

Table 5: Frequency of Country of Origin - Study Participants' Grandparents*

		Maternal Grandparents				Paternal Grandparents			
		Cases (%)	Controls (%)	Total	% Total	Cases	Controls	Total	% Total
US		34 (41.5)	123 (39.9)	157	40.0	21 (25.6)	112 (36.4)	133	34.0
Foreign (Total)		42 (51.2)	171 (55.5)	213	55.0	49 (59.8)	180 (58.4)	229	59.0
Countries	Ireland	17 (20.7)	79 (25.6)	96	25.0	23 (28.0)	93 (30.2)	116	30.0
	Italy	9 (11.0)	20 (6.5)	29	7.0	13 (15.9)	20 (6.5)	33	8.5
	Canada	7 (8.5)	24 (7.8)	31	8.0	3 (3.7)	27 (8.8)	30	7.5
	Scotland	1 (1.2)	6 (1.9)	7	2.0	3 (3.7)	3 (1.0)	6	2.0
	Lithuania	1 (1.2)	10 (3.2)	11	3.0	0 (0)	6 (1.9)	6	2.0
	Poland	1 (1.2)	10 (3.2)	11	3.0	4 (4.9)	9 (2.9)	13	3.0
	Germany	0 (0)	4 (1.3)	4	1.0	0 (0)	7 (2.3)	7	2.0
	England	1 (1.2)	6 (1.9)	7	2.0	1 (1.2)	4 (1.3)	5	1.0
	Other	5 (6.1)	12 (3.9)	17	4.0	2 (2.4)	11 (3.6)	13	3.0
Unknown		6 (7.3)	14 (4.5)	20	5.0	12 (14.6)	16 (5.2)	28	7.0

* Category includes all grandparents (i.e., n=390 for each maternal and paternal grandparents)

Table 6: Frequency of Irish Ancestry

			Cases (%)	Controls (%)	Total	% Total
Any Family Member†	Yes		16 (39.0)	70 (45.5)	86	44.1
	No		25 (61.0)	84 (54.5)	109	55.9
Parent*	Yes (Total)		4 (9.8)	15 (9.7)	19	22.0
		One	1 (2.4)	3 (1.9)	4	4.5
		Both	3 (7.3)	12 (7.8)	15	17.5
	No		12 (29.3)	55 (35.7)	67	78.0
Grandparent*	Yes (Total)		16 (39.0)	70 (45.5)	86	100.0
		One	2 (4.9)	17 (11.0)	19	22.0
		Two	6 (14.6)	15 (9.7)	21	24.5
		Three	3 (7.3)	16 (10.4)	19	22.0
		Four	5 (12.2)	22 (14.3)	27	31.5
	No		0 (0)	0 (0)	0	0.00

† Chi-Square (χ^2) p-value = 0.4623.

*Frequencies only calculated for study participants who reported having an Irish ancestry (n=86); Insufficient cell size for chi-square analysis.

Table 9: Family History* of Autoimmune/Rheumatic Disease Diagnoses†

		Cases (%)	Controls (%)	Odds Ratio	95% Confidence Interval	
Any Family Member	**Yes**	**25 (61.0)**	**65 (42.2)**	**2.1**	**1.1**	**4.3**
	No	**16 (39.0)**	**89 (57.8)**			
Parent	Yes	19 (46.3)	46 (29.9)	2.0	1.0	4.1
	No	22 (53.7)	108 (70.1)			
Mother	Yes	16 (39.0)	41 (26.6)	2.5	0.8	7.3
	No	25 (61.0)	113 (73.4)			
Father	Yes	6 (14.6)	10 (6.5)	1.8	0.9	3.4
	No	35 (85.4)	144 (93.5)			
Sibling	Yes	13 (31.7)	39 (25.3)	1.4	0.7	2.9
	No	28 (68.3)	115 (74.7)			

* Family history includes a diagnosis among biological mother, father, sister or brother. Includes one mother-daughter case pair.

† Diagnoses include Rheumatoid Arthritis (RA), Raynaud's Disease, Systemic Lupus Erythematosus (SLE), Scleroderma (SSc), Mixed Connective Tissue Disease (MCTD) or Thyroid Disease.

Table 10: Frequency of Any Parent Reporting Specific Autoimmune/Rheumatic Diseases (n=390)

	n	% Total
Rheumatoid Arthritis	46	12.0
Raynaud's Disease	3	1.0
Systemic Lupus Erythematosus	3	1.0
Scleroderma	1	0.0
Mixed Connective Tissue Disease	3	1.0
Thyroid Disease	28	7.0

Table 11: Disease Outcome by Biological Parent Diagnoses of Autoimmune/Rheumatic Disease Diagnosis

Diagnosis of:	Odds Ratio	95% Confidence Interval	
Any Disease*	2.0	1.0	4.1
Any disease except RA†	**2.4**	**1.1**	**5.3**
Any disease except Thyroid Disease‡	1.5	0.7	3.2
SSc, SLE, MCTD §	3.0	0.6	13.8
Rheumatoid Arthritis or Thyroid Disease	1.8	0.9	3.6
Rheumatoid Arthritis	1.2	0.5	2.8
Thyroid Disease	2.1	0.9	5.2

NA = Not Analyzed

***** Diagnoses include Rheumatoid Arthritis (RA), Raynaud's Disease, Systemic Lupus Erythematosus (SLE), Scleroderma (SSc), Mixed Connective Tissue Disease (MCTD) or Thyroid Disease.

† Diagnoses include Raynaud's Disease, Scleroderma (SSc), Systemic Lupus Erythematosus (SLE) or Mixed Connective Tissue Disease (MCTD) or Thyroid Disease.

‡ Diagnoses include Rheumatoid Arthritis (RA), Raynaud's Disease, Systemic Lupus Erythematosus (SLE), Scleroderma (SSc) or Mixed Connective Tissue Disease (MCTD).

§ Diagnoses include Systemic Lupus Erythematosus (SLE), Scleroderma (SSc) or Mixed Connective Tissue Disease (MCTD).

Table 12: Frequency of Medical Diagnoses (Ever versus never had a diagnosis)

		Cases (%)	Controls (%)	Odds Ratio	95 % Confidence Interval	
Cancer	Yes	10 (24.4)	29 (18.8)	1.4	0.6	3.2
	No	31 (75.6)	125 (81.2)			
Parkinson's disease	Yes	0 (0)	1 (0.6)	NA (Zero Cell)	---	---
	No	41 (100.0)	153 (99.4)			
Tuberculosis	Yes	1 (2.4)	2 (1.3)	1.9	0.2	21.5
	No	40 (97.6)	152 (98.7)			
Heart Arrhythmia	Yes	4 (9.8)	25 (16.2)	0.6	0.2	1.7
	No	36 (87.8)	128 (83.1)			
	Unknown	1 (2.4)	1 (0.6)			
Rheumatoid Arthritis	**Yes**	**10 (24.4)**	**11 (7.1)**	**4.2**	**1.6**	**10.7**
	No	**31 (75.6)**	**143 (92.9)**			
Epilepsy	Yes	1 (2.4)	1 (0.6)	3.8	0.2	62.5
	No	40 (97.6)	153 (99.4)			
Hypertension	Yes	7 (17.1)	23 (14.9)	1.0	0.4	2.6
	No	33 (80.5)	127 (82.5)			
	Unknown	1 (2.4)	1 (0.6)			

Table 13: Frequency of Medication Use

		Cases (%)	Controls (%)	Odds Ratio	95% Confidence Interval	
Prescription Medicine to Treat Pain	Yes	29 (70.7)	93 (60.4)	1.7	0.8	3.7
	No	11 (26.8)	61 (39.6)			
	Unknown	1 (2.4)	0 (0)			
Medication to Treat a Psychotic Disorder?	Yes	10 (24.4)	19 (12.3)	2.4	1.0	5.6
	No	30 (73.2)	134 (87.0)			
	Unknown	1 (2.4)	1 (0.6)			
Penicillamine*	Yes	0 (0)	2 (18.2)	NA (Zero Cell)	---	---
	No	9 (90.0)	9 (81.8)			
	Unknown	1 (10.0)	0 (0)			
Chlorpromazine†	Yes	0 (0)	2 (10.5)	NA (Zero Cell)	---	---
	No	7 (70.0)	16 (84.2)			
	Unknown	3 (30.0)	1 (5.3)			

*Penicillamine is used in treatment of Rheumatoid Arthritis. Frequency counts include only persons who reported ever being diagnosed with Rheumatoid Arthritis (n=21).

† Chlorpromazine is used in treatment of some psychotic disorders. Frequency counts include only persons who reported ever being diagnosed with a psychotic disorder (n=29).

Table 14: Frequency of Herbal Remedies/Dietary Supplements

		Cases (%)	Controls (%)	Odds Ratio	95% Confidence Interval	
Alfalfa Products	Yes	0 (0)	6 (3.9)	NA (Zero Cell)	---	---
	No	40 (97.6)	148 (96.1)			
	Unknown	1 (2.4)	0 (0)			
L-Tryptophan	Yes	2 (4.9)	3 (1.9)	2.6	0.4	16.0
	No	39 (95.1)	151 (98.1)			
Appetite Suppressants*	Yes	2 (4.9)	18 (11.7)	0.4	0.1	1.8
	No	38 (92.7)	136 (88.3)			
	Unknown	1 (2.4)	0 (0)			

*Appetite Suppressant use defined as for three months or longer.

Table 15: Frequency of Medical Implants

		Cases (%)	Controls (%)	Odds Ratio	95% Confidence Interval	
Catheter	Yes	12 (29.3)	37 (24.0)	1.3	0.6	2.8
	No	29(70.7)	116 (75.3)			
	Unknown	0 (0)	1 (0.6)			
Pins, Screws, Wires, Rods or Plates	Yes	5 (12.2)	20 (13.0)	1.0	0.3	2.7
	No	35 (85.4)	134 (87.0)			
	Unknown	1 (2.4)	0 (0)			
Dental Implants	Yes	1 (2.4)	12 (7.8)	0.3	< 0.1	2.4
	No	39 (95.1)	142 (92.2)			
	Unknown	1 (2.4)	0 (0)			
Artificial Joints	Yes	2 (4.9)	8 (5.2)	0.9	0.2	4.6
	No	39 (95.1)	146 (94.8)			
Shunt to Drain Fluid	Yes	1 (2.4)	6 (3.9)	0.6	0.1	5.3
	No	40 (97.6)	148 (96.1)			
Artificial Arteries, Veins or Ligaments	Yes	1 (2.4)	3 (1.9)	0.3	0.1	12.8
	No	39 (95.1)	151 (98.1)			
	Unknown	1 (2.4)	0 (0)			
Intraocular Lens	Yes	0 (0)	4 (2.6)	NA (Zero Cell)	---	---
	No	41 (100.0)	150 (97.4)			
Pacemaker	Yes	0 (0)	3 (1.9)	NA (Zero Cell)	---	---
	No	41 (100.0)	151 (98.1)			
Medication Pump	Yes	0 (0)	2 (1.3)	NA (Zero Cell)	---	---
	No	41 (100.0)	152 (98.7)			

Table 16: Frequency of Number of Pregnancies (n=182)

		Cases (%)	Controls (%)	Total	% Total
Yes (Total)		32 (84.2)	111 (77.6)	143	79.0
Number of Pregnancies	1	5 (13.2)	20 (14.0)	25	14.0
	2	3 (7.9)	25 (17.5)	28	15.5
	3	12 (31.6)	21 (14.7)	33	18.0
	4	4 (10.5)	15 (10.5)	19	10.5
	≥ 5	8 (21.1)	30 (21.0)	38	21.0
No		6 (15.8)	33 (22.4)	39	21.0

C p-value = 0.3422.

Table 17: Disease Outcome by Reproductive Factors (n=182)

		Cases (%)	Controls (%)	Odds Ratio	95% Confidence Interval	
Pregnancy	Yes	32 (84.2)	111 (77.6)	1.6	0.6	4.1
	No	6 (15.8)	33 (22.4)			
Age at First Pregnancy ≤ 20 years*	Yes	8 (25.0)	26 (23.4)	1.1	0.4	2.7
	No	24 (75.0)	84 (75.7)			
	Unknown	0 (0)	1 (0.9)			
Oral Contraception	Yes	17 (44.7)	69 (48.9)	1.2	0.5	2.6
	No	15 (39.5)	72 (51.1)			
	Unknown	6 (15.8)	3 (2.1)			
Estrogen	Yes	2 (5.3)	19 (13.7)	0.4	0.1	1.7
	No	34 (89.5)	120 (86.3)			
	Unknown	2 (5.3)	5 (3.5)			
Hysterectomy	Yes	10 (26.3)	32 (22.2)	1.3	0.5	2.8
	No	28 (73.7)	112 (77.8)			

* Analyzed for only females who had ever been pregnant (n=143).

Table 18: Descriptive Statistics for Pregnancies (n=143)

		n	Mean	Minimum	Maximum	Wilcoxon Rank Sum p-value
Number of Pregnancies	Study Population	143	3.5	1	15	0.50
	Cases	32	3.8	1	10	
	Controls	111	3.5	1	15	
Age at First Pregnancy	Study Population	142*	24	15	42	0.11
	Cases	32	23	15	33	
	Controls	110	25	16	42	

* One participant did not provide sufficient information to calculate age at first pregnancy.

Table 19: Descriptive Statistics for Reproductive Markers

		n	Mean	Minimum	Maximum	Wilcoxon Rank Sum p-value
Age of Menarche	Study Population	178*	13	9	18	0.99
	Cases	34	13	9	17	
	Controls	144	13	9	18	
Age of Menopause	Study Population	96†	45	26	55	0.21
	Cases	20	44	32	55	
	Controls	76	46	26	55	

* Four participants did not report sufficient information to calculate age of menarche.
† Seven participants who reported having gone through menopause did not report sufficient information to calculate age of onset of menopause.

Table 20: Frequency of Menopause* and Age of Onset (n=163)†

		Cases (%)	Controls (%)	Total	% Total
Yes		18	66	84	53.7
Age Category	30-34	2	2	4	2.4
	35-39	0	3	3	1.2
	40-44	7	20	27	16.2
	45-49	6	13	19	11.5
	50-54	3	26	29	17.5
	≥ 55	0	2	2	1.2
No		17	61	78	46.7
Unknown		0	1	1	0.6

Chi Square (χ^2) p-value = 0.9549 for ever/never gone through natural menopause.
* Menopause is defined as having a natural menopause; natural meaning that menopause occurred in a female who has never had a hysterectomy or if the female did have a hysterectomy her age at the time of menopause was younger than her age when the hysterectomy occurred.
† Seven participants who reported having gone through menopause did not report sufficient information to calculate age of onset of menopause. Twelve additional females were removed from the analyses because their date of hysterectomy either preceded or corresponded with their date of menopause.

Table 21: Descriptive Statistics for Length of Oral Contraceptives and Estrogen Use (Years)

		n	Mean	Minimum	Maximum	Wilcoxon Rank Sum p-value
Length of Oral Contraceptives Use	Study Population	84*	5.4	1	18	0.57
	Cases	17	4.8	1	17	
	Controls	67	5.6	1	18	
Length of Estrogen Use	Study Population	21	3.9	1	17	0.57
	Cases	2	3.0	3	3	
	Controls	19	3.9	1	17	

* Two participants who reported use of oral contraceptives did not provide sufficient information to calculate the length of oral contraceptive use.

Table 22: Frequency of Smoking

		Cases (%)	Controls (%)	Chi-Square p-value	Odds Ratio	95% Confidence Interval	
Smoking*	Yes	25 (61.0)	95 (61.7)	NA	1.0	0.5	2.1
	No	15 (36.6)	59 (38.3)				
	Unknown	1 (2.4)	0 (0)				
Smoking†	Current	16 (40.0)	42 (27.3)	0.20	2.3‡	0.9‡	6.0‡
	Former	8 (20.0)	49 (31.8)				
	Non-Smoker	16 (40.0)	63 (40.9)				
Packs of Cigarettes per Day§	< 1 pack	8 (32.0)	44 (46.3)	0.44	NA	NA	NA
	1 to 2 packs	14 (56.0)	42 (44.2)				
	≥ 2 packs	3 (12.0)	9 (9.5)				
Household Member who Smoked¶	Yes	37 (90.2)	133 (86.4)	NA	1.5	0.5	4.5
	No	4 (9.8)	21 (13.6)				

NA = Not Analyzed
* Smoking is defined as ever having smoked on a regular basis for six months or longer.
† Smoking status at index date: current, former or non-smoker (n=194). Former defined as having quit smoking at least one year prior to the index date.
‡ Odds ratio and 95% confidence interval were calculated for current versus former smoking status prior to the index date.
§ Calculated for only persons who reported a history of smoking (n=120). One pack = 20 cigarettes.
¶ Ever lived in a home with someone (other than yourself) who smoked?

Table 23: Descriptive Statistics of Smoking

		n	Mean	Minimum	Maximum	Wilcoxon Rank Sum p-value
Age Started Smoking*	**Study Population**	**118†**	**17**	**9**	**33**	**0.04**
	Cases	**24**	**16**	**11**	**33**	
	Controls	**94**	**17**	**9**	**33**	
Number of Years as a Smoker‡	Study Population	114†	17	1	43	0.86
	Cases	23	19	1	42	
	Controls	91	17	1	43	
Cumulative Exposure to Smoking‡ §	Study Population	114†	6,645	55	36,135	0.52
	Cases	23	7,353	183	22,630	
	Controls	91	6,466	55	36,135	
Number of Household Members who Smoked¶	Study Population	195	2	0	13	0.84
	Cases	41	2	0	8	
	Controls	154	2	0	13	

* Calculated for all study participants who reported ever having smoked on a regular basis form 6 months or longer. One participant was removed from the analysis as the age in which they started smoking was 15 years greater than the next oldest reported age (n=119).

† One participant did not report sufficient information to calculate age started smoking, number of years as a smoker and cumulative exposure to smoking.

‡ Calculated for only study participants with a history of smoking at the index date (i.e., current and former categories) (n=115).

§ Cumulative exposure in packs per year = (# years smoked prior to the index date)*((# cigarettes per day*365)/20).

¶ Ever lived in a home with someone (other than yourself) who smoked?

Table 24: Frequency of Alcohol Consumption

		Cases (%)	Controls (%)	Chi-Square p-value	Odds Ratio	95% Confidence Interval	
Alcohol[*]	Yes	37 (90.2)	137 (89.0)	NA	1.1	0.4	3.6
	No	4 (9.8)	17 (11.0)				
Alcohol[†]	Current	31 (75.6)	112 (73.2)	0.95	1.1[‡]	0.2[‡]	4.2[‡]
	Former	3 (7.3)	12 (7.8)				
	Non-Drinker	7 (17.1)	29 (19.0)				
Alcoholic Drinks per Week[§]	< 4 drinks	26	77	0.23	NA	---	---
	4 to 10 drinks	7	32				
	> 10 drinks	2	19				

NA = Not Analyzed

[*] Alcohol consumption is defined as ever having consumed 12 or more drinks in one year.

[†] Alcohol consumption status at index date: current, former or non-drinker. Former defined as having quit drinking at least one year prior to the index date. One person who reported being a drinker did not report sufficient information to determine drinking status at index date (n=194).

[‡] Odds ratio and 95% confidence interval were calculated for drinking history (i.e., current or former drinker) prior to the index date

[§] Calculated for only persons who reported a history of drinking. Eleven participants did not report sufficient information to calculate the number of drinks consumed per week (n=163). One Drink = 1 beer, 1 glass of wine or one shot of 1 oz liquor.

Table 25: Descriptive Statistics of Alcohol Consumption

		n	Mean	Minimum	Maximum	Wilcoxon Rank Sum p-value
Age Started Drinking[*]	Study Population	167[†]	20	11	60	0.53
	Cases	35	21	13	60	
	Controls	132	20	11	48	
Number of Years as a Drinker[‡]	Study Population	150[§]	19	1	53	0.25
	Cases	32	17	1	45	
	Controls	118	19.5	1	53	

[*] Calculated for only participants who reported ever having consumed 12 or more drinks in one year (n=174).

[†] Seven participants did not report the age in which they first started drinking (n=167).

[‡] Number of years as a drinker prior to the index date was calculated for only study participants with a history of drinking at the index date (i.e., current and former categories) (n=158).

[§] Eight participants did not report sufficient information to calculate the number of years as a drinker prior to the index date (n=150).

[¶] Cumulative exposure in drinks per year = (# years drinking prior to the index date)*(# drinks per week*52).

Table 26: Frequency of Cosmetic Procedures

		Cases (%)	Controls (%)	Odds Ratio	95% Confidence Interval	
Acrylic Nails*	Yes	12 (31.6)	63 (44.1)	0.6	0.3	1.3
	No	26 (68.4)	80 (55.9)			
Breast Implants*†	Yes	0 (0)	2 (1.4)	NA (Zero Cell)	---	---
	No	38 (100.0)	141 (98.6)			
Collagen Shots	Yes	0 (0)	1 (0.6)	NA (Zero Cell)	---	---
	No	41 (100.0)	153 (99.4)			
Permanent Hair Dye‡	Yes	17 (41.5)	63 (40.9)	1.0	0.5	2.1
	No	23 (56.1)	87 (56.5)			
	Unknown	1 (2.4)	4 (2.6)			
Semi-Permanent Hair Dye‡	Yes	10 (24.4)	31 (20.1)	1.3	0.6	2.9
	No	30 (73.2)	119 (77.3)			
	Unknown	1 (2.4)	4 (2.6)			

NA = Not Analyzed

* Question only asked to female study participants (n=181).

† Breast Implants includes all types of implants: saline, silicone, double lumen etc.

‡ Use of permanent and semi-permanent hair dye is defined as having ever used permanent or semi-permanent hair dye prior to index date.

Table 27: Frequency of Silica Exposures

		Cases (%)	Controls (%)	Odds Ratio	95 % Confidence Interval	
Occupational Exposure*	Yes	11 (26.8)	35 (22.7)	1.3	0.6	2.7
	No	30 (73.2)	119 (77.3)			
	Yes	0 (0)	4 (2.7)	NA (Zero Cell)	---	---
	No	41 (100.0)	150 (97.4)			
Possible‡	Yes	11 (26.8)	31 (20.1)	1.5	0.7	3.2
	No	30 (73.2)	123 (79.9)			
Hobby Exposure*	Yes	26 (63.4)	70 (45.5)	2.1	1.0	4.2
	No	15 (36.6)	84 (54.5)			
	Yes	1 (2.4)	9 (5.8)	0.4	0.1	3.3
	No	40 (97.6)	145 (94.2)			
Possible‡	**Yes**	**25 (61.0)**	**61 (39.6)**	**2.4**	**1.2**	**4.8**
	No	16 (39.0)	93 (60.4)			
Scouring Powders	Yes	5 (12.2)	14 (9.1)	1.4	0.5	4.1
	No	36 (87.8)	140 (90.9)			
Spousal Exposure	Yes	4 (9.8)	28 (18.2)	0.5	0.2	1.5
	No	37 (90.2)	126 (81.8)			
Total Number of Silica Exposure Categories§	One	19 (46.3)	65 (42.2)	1.5§	0.7§	3.2§
	Two	6 (14.6)	25 (16.2)			
	Three	5 (12.2)	8 (5.2)			
	Four	0 (0)	2 (1.3)			
	None	11 (26.8)	54 (35.1)			

* Category includes both possible and specific exposures.

† Specific refers to an exposure that was confirmed by the participant (e.g., Yes, I worked in fiberglass manufacturing and yes, I used crushed quartz, sand and/or silica.).

‡ Possible is defined as having worked in an occupation or participated in a hobby where exposure was possible (e.g., Yes, I worked in fiberglass manufacturing but did not use crushed quartz, sand and/or silica).

§ The total number of silica exposures refers to the number of exposure categories (i.e., occupational, hobby, scouring powders and spousal) in which a participant was classified as exposed. Because there was insufficient cell size to calculate a Chi-Square p-value, an odds ratio and 95% confidence interval were calculated for ever versus never having a silica exposure (i.e., all persons with any number of silica exposures versus those with no silica exposure).

Table 28: Sources of Possible Hobby/Home Improvement Related Silica Exposures

		Cases (%)	Controls (%)	Odds Ratio	95 % Confidence Interval	
Pottery and Ceramics	Yes	10 (24.4)	34 (22.1)	1.5	0.7	3.6
	No	21 (51.2)	109 (70.8)			
	Unknown	10 (24.4)	11 (7.1)			
Stone Sculpting	Yes	0 (0)	0 (0)	NA (Zero Cell)	---	---
	No	41 (100.0)	154 (100.0)			
	Unknown	0 (0)	0 (0)			
Removal/ Installation of Dry Wall	Yes	6 (14.6)	29 (18.8)	0.7	0.3	1.9
	No	35 (85.4)	125 (81.2)			
	Unknown	0 (0)	0 (0)			

Table 29: Frequency Counts of Reported Exposure Type by Total Number of Silica Exposures Classification

		n†	Total Count	Count by Type of Silica Exposure			
				Occupational	Hobby	Spousal	Scouring Powders
Total Number of Exposures Reported*	One	84	84‡	9	60	15	0
	Two	31	62‡	22	22	10	8
	Three	13	39‡	13	12	5	9
	Four	2	8‡	2	2	2	2
Totals		130	193	46 (24%)	96 (50%)	32 (17%)	19 (9%)

* The total number of silica exposures refers to the number of exposure categories (i.e., occupational, hobby, scouring powders and spousal) in which a participant was classified as exposed.

† n = number of respondents

‡ Total count = n*(total number of silica exposures reported)

Table 30: Frequency of Solvent Exposures

		Cases (%)	Controls (%)	Odds Ratio	95 % Confidence Interval	
Occupational Exposure*	Yes	15 (36.6)	64 (41.6)	0.8	0.4	1.7
	No	26 (63.4)	90 (58.4)			
	Yes	8 (19.5)	33 (21.4)	0.9	0.4	2.1
	No	33 (80.5)	121 (78.6)			
Possible‡	Yes	7 (17.1)	31 (20.1)	0.8	0.3	2.0
	No	34 (82.9)	123 (79.9)			
Hobby Exposure*	Yes	41 (100.0)	154 (100.0)	NA (Zero Cell)	---	---
	No	0 (0)	0 (0)			
	Yes	41 (100.0)	153 (99.4)	NA (Zero Cell)	---	---
	No	0 (0)	1 (0.6)			
Possible‡	Yes	0 (0)	1 (0.6)	NA (Zero Cell)	---	---
	No	41 (100.0)	153 (99.4)			
Portable Heater	Yes	8 (19.5)	26 (16.9)	1.2	0.5	2.9
	No	33 (80.5)	128 (83.1)			
Total Number of Solvent Exposure Categories§	One	20 (48.8)	75 (48.7)	NA	---	---
	Two	18 (43.9)	65 (42.2)			
	Three	3 (7.3)	13 (8.4)			
	Four	0	1 (0.6)			

* Category includes both possible and specific exposures.

† Specific refers to an exposure that was confirmed by the participant (e.g., Yes, I worked in dry cleaning manufacturing and yes, I used perc).

‡ Possible is defined as having worked in an occupation or participated in a hobby where exposure was possible (e.g., Yes, I worked in dry cleaning but I did not use perc).

§ Total number of solvent exposures refers to the number of exposure categories (i.e., occupational, hobby, residential portable heater and spousal) in which a participant was classified as exposed. There was insufficient cell size to calculate a Chi-Square p-value.

Table 31: Frequency of Hobby Related Solvent Exposure (Activities)

		Cases (%)	Controls (%)	Odds Ratio	95% Confidence Interval	
Print Making or Silk Screening	Yes	1 (2.4)	9 (5.8)	0.4	0.1	3.3
	No	40 (97.6)	145 (94.2)			
Developed Photographs	Yes	2 (4.9)	6 (3.9)	1.3	0.3	6.5
	No	39 (95.1)	148 (96.1)			
Painted with Oil or Acrylic Paints	Yes	19 (46.3)	47 (30.5)	2.0	1.0	4.0
	No	22 (53.7)	107 (69.5)			
Refinished Furniture	Yes	10 (24.4)	46 (29.9)	0.8	0.3	1.7
	No	31 (75.6)	108 (70.1)			
Built Models	Yes	2 (4.9)	14 (9.1)	0.5	0.1	2.4
	No	39 (95.1)	140 (90.9)			
Automotive Repair	Yes	2 (4.9)	3 (1.9)	2.6	0.4	16.0
	No	39 (95.1)	151 (98.1)			
Dyed Textiles	Yes	0 (0)	5 (3.2)	NA (Zero Cell)	---	---
	No	41 (100.0)	149 (96.8)			
Painted	Yes	33 (80.5)	124 (80.5)	1.0	0.4	2.4
	No	8 (19.5)	30 (19.5)			
Remove/Install Walls	Yes	6 (14.6)	29 (18.8)	0.7	0.3	1.9
	No	35 (85.4)	125 (81.2)			

Table 32: Frequency of Hobby Related Solvent Exposure (Compound Use*)

		Cases (%)	Controls (%)	Odds Ratio	95% Confidence Interval	
Epoxy-based glues, resins or paints	Yes	3 (7.3)	26 (16.9)	0.4	0.1	1.4
	No	35 (85.4)	121 (78.6)			
	Unknown	3 (7.3)	7 (4.5)			
Silicone-based glues or sealants	**Yes**	**1 (2.4)**	**28 (18.2)**	**0.1**	**< 0.1**	**0.9**
	No	**37 (90.2)**	**123 (79.9)**			
	Unknown	**3 (7.3)**	**3 (1.9)**			
Silicone resins	Yes	0 (0)	1 (0.6)	NA (Zero Cell)	---	---
	No	40 (97.6)	148 (96.1)			
	Unknown	1 (2.4)	5 (3.2)			
Silicone rubber, oils or greases	Yes	0 (0)	66 (42.9)	NA (Zero Cell)	---	---
	No	40 (97.6)	146 (94.8)			
	Unknown	1 (2.4)	2 (1.3)			
Paint stripper, remover or thinner	Yes	3 (7.3)	16 (10.4)	0.7	0.2	2.5
	No	38 (92.7)	138 (89.6)			
Paints, varnishes or lacquers	Yes	4 (9.8)	14 (9.1)	1.1	0.3	3.5
	No	37 (90.2)	140 (90.9)			
Kerosene	Yes	3 (7.3)	14 (9.1)	0.8	0.2	3.0
	No	37 (90.2)	140 (90.9)			
	Unknown	1 (2.4)	0 (0)			
Mineral spirits, white spirits, naptha or stoddard solvents	Yes	3 (7.3)	5 (3.2)	2.4	0.6	10.7
	No	36 (87.8)	146 (94.8)			
	Unknown	2 (4.9)	3 (1.9)			

* Refers to ever having used any of the following compounds in a hobby or home improvement project other than the hobbies/home improvement projects asked about in Table 35.

Table 33: Frequency of Petroleum-Related Exposures

		Cases (%)	Controls (%)	Odds Ratio	95 % Confidence Interval	
Occupational Exposure*	Yes	11 (26.8)	32 (20.8)	1.4	0.6	3.1
	No	30 (73.2)	122 (79.2)			
	Yes	5 (12.2)	10 (6.5)	2.0	0.6	6.2
	No	36 (87.8)	144 (93.5)			
Possible‡	Yes	6 (14.6)	22 (14.3)	1.0	0.4	2.7
	No	35 (85.4)	132 (85.7)			
Hobby Exposure*	Yes	37 (90.2)	133 (86.4)	1.5	0.5	4.1
	No	4 (9.8)	21 (13.6)			
	Yes	28 (68.3)	96 (62.3)	1.3	0.6	2.7
	No	13 (31.7)	58 (37.7)			
Possible‡	Yes	9 (22.0)	37 (24.0)	0.9	0.4	2.0
	No	32 (78.0)	117 (76.0)			
Portable Heater	Yes	8 (19.5)	26 (16.9)	1.2	0.5	2.9
	No	33 (80.5)	128 (83.1)			
Total Number of Petroleum-Related Exposures§	One	18 (43.9)	95 (61.7)	0.9§	0.3§	3.0§
	Two	19 (46.3)	39 (25.3)			
	Three	0 (0)	6 (3.9)			
	Four	0 (0)	0 (0)			
	None	4 (9.8)	14 (9.1)			

* Category includes both possible and specific exposures.

† Specific refers to an exposure that was confirmed by the participant (e.g., Yes, I worked in automotive repair/maintenance and yes, I used gasoline.).

‡ Possible is defined as having worked in an occupation or participated in a hobby where exposure was possible (e.g., Yes, I worked in automotive repair/manufacturing but I did not use gasoline.).

§ Total number of exposures refers to the number of exposure categories (i.e., occupational, hobby, residential portable heater) in which a participant was classified as exposed. Because there was insufficient cell size to calculate a Chi-Square p-value, an odds ratio and 95% confidence interval were calculated for ever versus never having a petroleum-related exposure (i.e., all persons with any number of petroleum-related exposures versus those with no petroleum-related exposure).

Table 34: Frequency Counts of Reported Exposure Type by Total Number of Petroleum-Related Exposures Classification

		n†	Total Count	Count by Type of Petroleum Distillate Exposure		
				Occupational	Hobby	Portable Heater
Total Number of Exposures Reported*	One	113	113‡	4	106	3
	Two	58	116‡	33	58	25
	Three	6	18‡	6	6	6
Totals		177	247	43 (17%)	170 (69%)	34 (14%)

* The total number of petroleum-related exposures refers to the number of exposure categories (i.e., occupational, hobby, portable heater) in which a participant was classified as exposed.
† n = number of respondents
‡ Total count = n*(total number of silica exposures reported)

Table 35: Frequency of Residential Exposures

		Cases (%)	Controls (%)	Odds Ratio	95% Confidence Interval	
Basement Level Residence	Yes	2 (4.9)	20 (13.0)	0.3	0.1	1.5
	No	39 (95.1)	134 (87.0)			
Portable Heater	Yes	8 (19.5)	26 (16.9)	1.2	0.5	2.9
	No	33 (80.5)	128 (83.1)			

Table 36: Frequency of Chlorinated Solvent Exposures

		Cases (%)	Controls (%)	Odds Ratio	95 % Confidence Interval	
Occupational Exposure*	Yes	9 (22.0)	46 (29.9)	0.7	0.3	1.5
	No	32 (78.0)	108 (70.1)			
Specific†	Yes	1 (2.4)	5 (3.2)	0.8	0.1	6.6
	No	40 (97.6)	149 (96.8)			
Possible‡	Yes	8 (19.5)	41 (26.6)	0.7	0.3	1.6
	No	33 (80.5)	113 (73.4)			

* Category includes both possible and specific exposures.
† Specific refers to either an occupational or hobby related exposure that was confirmed by the participant (e.g., Yes, I worked in printing/publishing and yes, I used benzene.).
‡ Possible is defined as having worked in an occupation or participated in a hobby where exposure was possible (e.g., Yes, I worked in printing/publishing but I did not use benzene.).

Table 37: Univariate Analysis of SSc/SLE Risk and Residential Proximity within 30 Feet of Hazardous Waste Sites in South Boston (Residence at Index Date)

	Odds Ratio	95% Confidence Interval	
Hazardous Waste Site w/Petroleum Compounds	1.3	0.2	8.5
Hazardous Waste Site w/Compounds Other than Petroleum	---	---	---
Any Hazardous Waste Site	1.3	0.2	8.5

Table 38: Univariate Analysis of SSc/SLE Risk and Residential Proximity within 500 Feet of Hazardous Waste Sites in South Boston (Residence at Index Date)

	Odds Ratio	95% Confidence Interval	
Hazardous Waste Site w/Petroleum Compounds	0.4	0.2	1.0
Hazardous Waste Site w/Compounds Other than Petroleum	0.5	0.1	3.1
Any Hazardous Waste Site	0.5	0.2	1.1

Table 39: Univariate Analysis of SSc/SLE Risk and Residential Proximity within 30 Feet of Hazardous Waste Sites in South Boston (Longest South Boston Residence)

	Odds Ratio	95% Confidence Interval	
Hazardous Waste Site w/Petroleum Compounds	---	---	---
Hazardous Waste Site w/Compounds Other than Petroleum	---	---	---
Any Hazardous Waste Site	---	---	---

Table 40: Univariate Analysis of SSc/SLE Risk and Residential Proximity within 500 Feet of Hazardous Waste Sites in South Boston (Longest South Boston Residence)

	Odds Ratio	95% Confidence Interval	
Hazardous Waste Site w/Petroleum Compounds	0.8	0.5	1.2
Hazardous Waste Site w/Compounds Other than Petroleum	0.4	0.1	2.7
Any Hazardous Waste Site	0.8	0.5	1.2

Table 41: Univariate Analysis of SSc/SLE Risk and Historical Exposure to Emissions from Boston Edison Power Plant Based on Residential History (High versus Low Impact Area)

		Cases	Controls	Odds Ratio	95% Confidence Interval	
Residence at Index	High	21	71	1.2	0.4	3.8
	Low	4	16			
Longest Residence	High	35	119	1.9	0.7	5.3
	Low	5	31			

Table 42: Frequency of Swimming

		Cases (%)	Controls (%)	Odds Ratio	95 % Confidence Interval	
Pleasure Bay	Yes	28 (68.3)	103 (66.9)	1.2	0.6	2.7
	No	11 (26.8)	50 (32.5)			
	Unknown	2 (4.9)	1 (0.6)			
Castle Island	Yes	17 (41.5)	55 (35.7)	1.3	0.7	2.7
	No	23 (56.1)	99 (64.3)			
	Unknown	1 (2.4)	0 (0)			
L Street Beach	Yes	28 (68.3)	112 (72.7)	1.0	0.4	2.1
	No	11 (26.8)	42 (27.3)			
	Unknown	2 (4.9)	0 (0)			
Carson Beach	**Yes**	**32 (78.0)**	**82 (53.2)**	**3.5**	**1.5**	**8.0**
	No	**8 (19.5)**	**71 (46.1)**			
	Unknown	**1 (2.4)**	**1 (0.6)**			
Reserve Channel	Yes	4 (9.8)	7 (4.5)	2.5	0.7	9.0
	No	32 (78.0)	139 (90.3)			
	Unknown	5 (12.2)	8 (5.2)			
Pleasure Bay and/or Castle Island	Yes	23 (56.1)	66 (42.9)	1.9	0.9	3.9
	No	16 (39.0)	87 (56.5)			
	Unknown	2 (4.9)	1 (0.6)			
L Street and/or Carson Beach	Yes	15 (36.6)	51 (33.1)	1.2	0.6	2.5
	No	25 (61.0)	103 (66.9)			
	Unknown	1 (2.4)	0 (0)			

Table 43: Frequency of Recreational Park Use

		Cases (%)	Controls (%)	Odds Ratio	95 % Confidence Interval	
M Street Park	Yes	25 (61.0)	87 (56.5)	1.3	0.6	2.6
	No	15 (36.6)	65 (42.2)			
	Unknown	1 (2.4)	2 (1.3)			
Marine Park	Yes	18 (43.9)	78 (50.6)	0.8	0.4	1.6
	No	21 (51.2)	74 (48.1)			
	Unknown	2 (4.9)	2 (1.3)			
Columbia Park	Yes	26 (63.4)	87 (56.5)	1.4	0.7	2.9
	No	14 (34.1)	65 (42.2)			
	Unknown	1 (2.4)	2 (1.3)			

Table 44: Unmatched Multivariate Regression Analysis of Risk of SSc/SLE and Possible Risk Factors (Complete Model)

Regression Model Covariates	Odds Ratio	95% Confidence Interval	
Family History of Autoimmune Disease	1.9	0.9	4.1
Previous Diagnosis of Rheumatoid Arthritis	3.4	1.3	9.3
Use of medication for Psychotic Disorder	2.0	0.8	5.2
Possible Hobby-related Silica Exposure	2.3	1.1	4.4

Table 45: Unmatched Multivariate Regression Analysis of Risk of SSc/SLE and Possible Risk Factors (Final Model)

Regression Model Covariates	Odds Ratio	95% Confidence Interval	
Previous Diagnosis of Rheumatoid Arthritis	4.4	1.7	11.5
Possible Hobby-related Silica Exposure	2.4	1.1	5.0

Table 46: Matched Multivariate Regression Analysis of Risk of SSc/SLE and Possible Risk Factors (Complete Model)

Regression Model Covariates	Odds Ratio	95% Confidence Interval	
Family History of Autoimmune Disease	2.0	0.9	4.5
Previous Diagnosis of Rheumatoid Arthritis	3.5	1.3	9.8
Use of medication for Psychotic Disorder	1.9	0.7	5.0
Possible Hobby-related Silica Exposure	2.5	1.1	5.6

Table 47: Matched Multivariate Regression Analysis of Risk of SSc/SLE and Possible Risk Factors (Final Model)

Regression Model Covariates	Odds Ratio	95% Confidence Interval	
Previous Diagnosis of Rheumatoid Arthritis	4.0	1.5	11.0
Possible Hobby-related Silica Exposure	2.6	1.2	5.7

Table 48: Matched Multivariate Regression Analysis of Risk of SSc/SLE and Residential Proximity to Hazardous Waste Sites Based on Longest South Boston Residence

Regression Model Covariates	Odds Ratio	95% Confidence Interval	
Family History of Autoimmune Disease	1.8	0.9	3.9
Previous Diagnosis of Rheumatoid Arthritis	4.2	1.5	11.9
Hazardous Waste Site w/Petroleum Compounds (30 Feet)	< 0.1	---	---
Hazardous Waste Site w/Petroleum Compounds (500 Feet)	0.7	0.4	1.2

Table 49: Matched Multivariate Regression Analysis of Risk of SSc/SLE and Historical Exposure to Emissions from Boston Edison Power Plant Based on Longest South Boston Residence

Regression Model Covariates	Odds Ratio	95% Confidence Interval	
Family History of Autoimmune Disease	2.0	0.9	4.2
Previous Diagnosis of Rheumatoid Arthritis	4.4	1.6	12.2
Longest Residence in High versus Low Impact Area	2.3	0.8	6.6

Table 50a: Prevalence and Incidence of SSc in South Boston versus Medical Literature

Estimate (Cases per 100,000)	Population		n	South Boston	95% Confidence Interval		Medical Literature
Prevalence[§]	Overall		10	33.4	18.3	61.4	27.6 [1]
	Females	White	10	72.8	40.0	133.8	37.1 [1]
		Black	*	NC	NC	NC	43.4 [1]
		Asian	*	NC	NC	NC	†
		Hispanic	*	NC	NC	NC	†
	Males	White	*	NC	NC	NC	7.8 [1]
		Black	*	NC	NC	NC	10.4 [1]
		Asian	*	NC	NC	NC	†
		Hispanic	*	NC	NC	NC	†
Annual Incidence [‡]	Overall		12	1.13	0.58	1.98	0.96-1.93 [1, 2, 3]
	Females	White	12	2.27	1.18	3.98	1.28-2.7 [1, 2]
		Black	*	NC	NC	NC	3.11 [1]
		Asian	*	NC	NC	NC	†
		Hispanic	*	NC	NC	NC	†
	Males	White	*	NC	NC	NC	0.97 [1]
		Black	*	NC	NC	NC	0.62 [1]
		Asian	*	NC	NC	NC	†
		Hispanic	*	NC	NC	NC	†

1 Mayes 2003

2 Laing et al. 1997

3 Steen et al 1997

* n < 5

§ Point prevalence was estimated for December 31, 2000.

‡ Incidence rates were calculated for the period 1970-2000.

NC = not calculated

† Limited data available

Table 50b: Prevalence and Incidence of SLE in South Boston versus Medical Literature

Estimate (Cases per 100,000)	Population		n	South Boston	95% Confidence Interval		Medical Literature
Prevalence§	Overall		8	26.7	13.7	52.6	14.6-149.5 [1, 2, 3, 4]
	Females	White	7	50.9	25.1	104.9	164.4-203.1 [4]
		Black	*	NC	NC	NC	406.3-693.7 [4]
		Asian	*	NC	NC	NC	138.7-244.5 [4]
		Hispanic	*	NC	NC	NC	92.7-103.2 [4]
	Males	White	*	NC	NC	NC	†
		Black	*	NC	NC	NC	†
		Asian	*	NC	NC	NC	†
		Hispanic	*	NC	NC	NC	†
Annual Incidence‡	Overall		15	1.41	0.79	2.33	1.51-5.56 [3]
	Females	White	14	2.65	1.45	4.46	1.1-3.9 [3]
		Black	*	NC	NC	NC	3.0-11.42 [3]
		Asian	*	NC	NC	NC	†
		Hispanic	*	NC	NC	NC	†
	Males	White	*	NC	NC	NC	0.30-0.42 [3]
		Black	*	NC	NC	NC	0.8-2.50 [3]
		Asian	*	NC	NC	NC	†
		Hispanic	*	NC	NC	NC	†

1 Hochberg 1990

2 Ward 2004

3 Danchenko et al. 2006

4 Chakravarty et al. 2007

* n < 5

§ Point prevalence was estimated for December 31, 2000.

‡ Incidence rates were calculated for the period 1970-2000.

NC = not calculated

† Limited data available