THE BURDEN OF DISEASE AMONG PATIENTS OF THE CAROLINA LUPUS STUDY: HUMANISTIC, CLINICAL AND ECONOMIC FACTORS

by

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SCHOOL OF GRADUATE STUDIES

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DEDICATION

To my late family members; Sheena, Uncle Tommy, Cousin Blake, godmother Callender, Brother Graves, and Uncle Oscar. This is for your unwavering support throughout my attainment of personal, educational, and military goals. I feel your spirits and will never forget you. I miss you and will always love you. *Merci*

The Road Not Taken
Robert Frost

Two roads diverged in a yellow wood,
And sorry I could not travel both
And be one traveller, long I stood
And looked down one as far as I could
To where it bent in the undergrowth;

Then took the other, as just as fair,
And having perhaps the better claim,
Because it was grassy and wanted wear;
Though as for that the passing there
Had worn them really about the same,

And both that morning equally lay
In leaves no step had trodden black.
Oh, I kept the first for another day!
Yet knowing how way leads on to way,
I doubted if I should ever come back.

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I --
I took the one less traveled by,
And that has made all the difference.

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The Burden of Disease among Patients of
The Carolina Lupus Study:
Humanistic, Clinical and Economic Factors

ABSTRACT

by

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Objectives: To quantify differences in health-related quality of life, 5-year mortality risk, and direct and indirect costs between SLE patients early in the course of disease and controls, and to assess the association, among patients, between demographic and clinical characteristics and these outcomes.

Methods: Multiple dimensions of the burden of disease were measured in an inception cohort of 265 SLE patients and 355 controls. The study includes two data collection periods: the baseline study (1997-1999) and follow-up study (2001).

Results: Using a previously validated 8-item short form health-related quality of life instrument (SF-8), physical component scores were 7.7 points lower ($p < 0.0001$), and mental component scores were 1.8 points lower ($p = 0.07$) in cases compared with controls, adjusting for age, sex, race, state and education. Among cases, physical component scores of the 16-29 year olds and 30-49 year olds were 5.6 and 4.1 points higher, respectively, compared with the 50 and older group. Survival rates were

significantly reduced in cases: by 60 months after diagnosis, 8.7% of cases compared with 0.28% of controls had died (p<.0001). Predictors of mortality in cases included age, gender, and ethnicity, with a hazards ratio of 1.04 (95% CI 1.01, 1.06) per one-year increment in age, 2.5 (95% CI 1.0, 5.9) for males compared with females, and 2.0 (95% CI 0.89, 4.6) for African-Americans and other minorities compared with whites. Annual mean direct costs for health care was $12,375 (sd 13723) in cases compared with $3,718 (sd 6135) in controls (p <.0001); differences were also seen in the median costs ($8,008 compared with $2,207 in cases and controls, respectively). Predictors of higher costs among cases were low education level (less than high school), renal disease and serositis. Forty-seven cases (24%) compared with 8 (3%) controls reported they had stopped working because of their health, resulting in an average indirect cost of lost wages of $5113 compared to $750 in cases and controls, respectively.

Conclusions: Significant differences in quality of life scores, mortality risk, direct and indirect costs demonstrate the multidimensional burden of SLE.

CHAPTER 1: Introduction, Background and Aims

Description and Epidemiology of Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic, disabling autoimmune disease of unknown etiology that involves multiple organ systems. Patients with SLE typically develop immune abnormalities that include self-reactive T cells and autoantibodies to a number of nuclear and other cellular antigens. Diagnosis of SLE is facilitated by 11 clinical and laboratory criteria developed for the classification of SLE by the American College of Rheumatology. (Tan, Cohen et al. 1982) (Hochberg 1997)

The clinical expression of the disease is quite diverse, and may include constitutional symptoms (fever, weight loss, fatigue), extensive rashes, a high risk of renal failure, neuropsychiatric involvement resulting in seizures, psychosis, and peripheral neuropathy, and hematologic disorders. The clinical course of SLE involves periods of flares and remission, and therapy may include extensive use of corticosteroids and other immunosuppressants. The disease process and effects of long-term drug therapy cause significant morbidity including frequent hospitalizations, increased risk of cerebrovascular disease, and increased susceptibility to infections.

Although the cause of SLE remains unknown, many observations have suggested a role of genetic and environmental factors. Deapen et al. found that of 107 twin pairs meeting the American College of Rheumatology 1982 revised criteria for the diagnosis of SLE, 24% of 45 monozygous pairs and 2% of 62 dizygous pairs were concordant.(Deapen, Escalante et al. 1992) A recent study by Eroglu and Kohler reported that 7 of 14 sib pairs (50%) who had concordant SLE had identical HLA genetic types. Both studies provide evidence that genetic factors have a role in the development and

expression of SLE (Eroglu and Kohler 2002), but genetics do not solely determine risk for this disease.

Jacobson *et al.* summarized data from 16 studies and estimated the mean prevalence of SLE to be 23.8/100,000 population in the United States. Their estimated pooled incidence of SLE was 7.3 per 100,000 person years.(Jacobson, Gange et al. 1997) A study by Uramoto and colleagues of SLE among residents of Rochester, Minnesota showed that the age- and sex-adjusted incidence of SLE was 5.56 per 100,000 person years during 1980-92, compared with 1.51 per 100,000 person years during 1950-79.(Uramoto, Michet et al. 1999) Increased recognition of milder disease contributed to this significant increase in incidence, but the authors thought it was unlikely to account for the entire increase in incidence.

There is a greater preponderance of most autoimmune diseases in females compared with males in both experimental animals and in humans. (Ansar Ahmed, Penhale et al. 1985) SLE predominately affects women (9:1 compared to men) and often decreases in activity in postmenopausal women.(Lahita 1993) Sex hormones (androgens, oestrogens and progestogens) may be potent regulators of cytokine levels and disease activity (Lahita 1993), and may influence the onset and severity immune-mediated pathologic conditions by modulating lymphocytes, acting on several nonclassic target sites such as the immune system itself (nonthymic lymphoid organs), the central nervous system, the macrophage-macrocyte system, and the skeletal system.

There is a consensus of several studies showing a higher incidence of SLE in minorities. In the United States, the highest incidence of SLE is among Native Americans of the Crow, Arapahoe, and Sioux tribes (Morton, Gershwin et al. 1976), African

Americans (McCarty, Manzi et al. 1995), and Asians in Hawaii(Maskarinec and Katz 1995), with incidence rates approximately 2-3 times higher in these groups compared with whites. Several studies have also reported an earlier age at diagnosis (difference in mean age approximately 6-7 years) in minorities.(McCarty, Manzi et al. 1995) (Cooper, Parks et al. 2002) (Alarcón, Friedman et al. 1999) In a large, racially balanced cohort of 184 black patients and 174 white patients, Ward found race to be an important factor influencing the prevalence of 9 of 24 clinical features of SLE. Blacks more commonly manifested anti-Sm and anti-RNP antibodies, discoid skin lesions, and proteinuria and were more likely than whites to have had psychosis, serositis, and urinary cellular casts (Ward and Studenski 1990). The results of Ward's study were replicated separately by Alarcón (Alarcón, Friedman et al. 1999) and Cooper (Cooper, Parks et al. 2002) who also showed that black SLE patients exhibited Sm and RNP antibodies, discoid skin lesions, proteinuria and serositis more commonly than whites. Other studies have also reported higher rates for the development of lupus nephritis among blacks and Hispanic (Bastian, Roseman et al. 2002).

BACKGROUND AND SIGNIFICANCE

SF-36 and SLE

The Medical Outcomes study (MOS) short form Health Survey (SF-36) has been used to assess Health-Related Quality of Life (HRQoL) among lupus patients. Some studies examined the relationship between health-related quality of life and disease activity and damage. For SLE, disease activity is customarily measured with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the Systemic Lupus Activity

Measure (SLAM). Damage is measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index (SDI). Several studies have reported associations between higher physical health scores (Da Costa, Dobkin et al. 2000), (Wang, Shi et al. 2001) or mental health scores (Thumboo, Fong et al. 2000) and lower disease activity or damage, as well as psychosocial factors such as learned helplessness and emotional coping (Da Costa, Dobkin et al. 2000), (Thumboo, Fong et al. 2000).

Mortality and SLE

Prognosis, as measured by mortality rates, is worse among black SLE patients compared with whites. Some of this difference may be explained by differences in socioeconomic status, access to healthcare, or co-morbid conditions (Ginzler, Diamond et al. 1982), (Ward and Studenski 1990), (Petri, Perez-Gutthann et al. 1991). In an analysis of SLE mortality during 1979-1998, significant age, sex, and race-specific disparities were seen in SLE death rates. SLE-related death rates increased by approximately 70% during the study period among black women aged 45-64 years. Death rates for white women increased minimally at approximately 7% (2002).

Costs and SLE

Ann Clarke was one of the first researchers to analyze SLE costs. Her research not only looked at SLE costs in Canada, but the United States and the United Kingdom as well. In her 1993 study she reported that indirect costs were responsible for 54% of total costs, and hospitalizations among SLE patients were four times more frequent than the general population of Quebec. Higher 1989 creatinine values and poorer levels of

physical functioning were the best predictors of higher costs (Clarke, Esdaile et al. 1993). In an abstract published in 1993 in *Arthritis and Rheumatism*, annual medical costs of 74 SLE patients from Johns Hopkins Medical Institutions were analyzed. African Americans compared to whites had higher inpatient, physician and total costs. Females had higher outpatient and medication costs, and patients with hypertension had higher inpatient and physician costs. Patients with higher activity and damage scores also had higher costs (Finn 1993). This study was based on patients seen at a tertiary care referral center with varying years of duration.

In summary, SLE is uncommon, but not rare. An overwhelming number of epidemiological studies have reported that African-American women are at highest risk, at least 2 to 3-fold higher than white women. Significant morbidity and mortality risk is associated with SLE, and these risks also disproportionately affect African-American women. With the increased survival of SLE patients, there has been a change in the cause of death. Renal failure was once the leading cause of death for SLE, but it has now been replaced by cardiovascular disease, particularly accelerated atherosclerosis. Medical costs incurred by SLE patients are significantly greater than those of the general population. There are few comprehensive studies, however, that examine the burden of SLE along various dimensions from inception. From a theoretical standpoint, this study is the first to use major components of the highly validated ECHO model to assess burden of SLE along multiple scopes to include a lower quality of life, premature death, higher medical costs, and loss of work ability (Kozma, Reeder et al. 1993). I will compare these measures between SLE cases early in the disease course (approximately 4 years after

diagnosis) to data from a population-based control group. I will also assess the extent to which demographic factors (race and age) influence these measures.

1.1 Health-Related Quality of Life in Systemic Lupus Erythematosus

1.1.1 Health-Related Quality of Life Measurement Instruments

The Medical Outcomes Study Short Form 36 Health Survey (SF-36) is an internationally used measure of Quality of Life. The SF-36 includes 8 domains: General Health (GH – 5 questions), Physical Functioning (PF – 10 questions), Role Physical (RP – 4 questions), Bodily Pain (BP – 2 questions), Vitality (VT – 4 questions), Social Functioning (SF – 2 questions), Mental Health (MH – 5 questions), Role Emotional (RE – 3 questions). The composite physical component scale and mental component scale can be derived from these subscales.

Although the SF-36 is used throughout the world because it is brief, comprehensive, readily available, and psychometrically sound, it may be considered too lengthy for many large-scale population studies. The SF-36 is also the foundation of several smaller scales (SF-20, SF-12, SF-8) that measures life quality as a result of disease. Developed by QualityMetric Dynamic Health Assessment, the SF-8 Health Survey is a generic multipurpose short-form survey of health status comprised of 8 questions that measure 8 domains. It has three versions, which include the 4-week, 1-week, and the 24-hour versions. These questions discriminate better and/or cover a wider range of scores than individual SF-36 questions measuring the same concept (Ware 2001).

1.1.2 Studies of Health-Related Quality of Life in Lupus

Since there is no disease-specific instrument for SLE, researchers have customarily used the SF-36 or its derivatives and concentrated on the domains most relevant to the disease or condition under study. Thumboo *et al.* evaluated the validity and reliability of the SF-36 in a multiracial cohort of Asian patients with lupus in Singapore (Thumboo, Fong et al. 2000). Subscales of the SF-36 showed high internal consistency, with Cronbach's alpha coefficient ranging from 0.84 to 0.94 and an acceptable test-retest reliability with Spearman's rank correlation >0.70. In a cross section study of Chinese SLE patients, the SF-36 showed high internal consistency (alpha = 0.72-0.91) and good reliability, with correlations exceeding 0.70 for 7 scales and mean scale score differences of < 2 points for 6 scales (Thumboo, Fong et al. 1999).

In the United Kingdom, Stoll *et al.* investigated the metric properties and validity of the assessment of health-related quality of life by the MOS Short Form 36 (SF-36) in SLE patients. This cross-sectional study consisted of 150 patients with a mean age of 39.7 years. They were 95% female and attended two specialist lupus clinics between November 1994 and April 1995. Like the above studies, it was internally consistent (Cronbach's coefficient alpha > or = 0.71) and proven to possess construct, discriminatory, and criterion validity (Stoll, Gordon et al. 1997).

Composite physical component and mental component summary scores of the SF-36 have been used in clinical studies in SLE. Thumboo et al. reported 6-month improvements in both summary scores due to modifiable psychosocial, disease, and therapy related factors, but cited evidence that while physical component summary and mental component summary scores can demonstrate physical and mental health cross-

sectionally, they are not as sensitive to changes in health-related quality of life as are individual SF-36 domains (Thumboo, Fong et al. 2000).

Although the SF-36 has been used in studies of SLE, there are limited published data addressing the effect of demographic (e.g. ethnicity, age) variables on SF-36 health-related quality of life measures in this patient population. Devins et al. reported ethnoracial differences in psychosocial health scores among white, black, and Asian SLE female patients employing widely used instruments. This measure was a composite based on principal components analysis of four psychosocial measures (Affect Balance Scale, Center for Epidemiologic Studies Depression Scale, Health Assessment questionnaire and Rheumatology Attitudes Index). It differed significantly across the three groups with whites reporting the highest, and blacks the lowest levels (Devins and Edworthy 2000). Older age at diagnosis was associated with improved mental health scores over a 6 month study period in 90 ethnically diverse patients (Thumboo, Fong et al. 2000). Rinaldi *et al.* compared health-related quality of life in 126 Italian SLE patients and 96 controls using the SF-36. As expected, summary scores were lower in patients (mean difference 14.74 points in the physical component summary scale and 9.72 points in the mental component summary scale). In all subscales, mean scores were also lower in SLE patients than in controls and were statistically significant for all subscales except role physical and social functioning. Among demographic variables for SLE patients, physical component summary scale was lower in age groups 35-44 years ($p=0.04$), and 45-54 years ($p=0.0001$), and the mental component summary score was lower in ages 45-54 years ($p=0.001$) compared with the 25-34 year group (Rinaldi, Doria et al. 2004).

1.2 Mortality Risk in Systemic Lupus Erythematosus

In the mid-1950's Merrell and Shulman reported a 5-year survival rate of 51% in 99 clinic-based SLE patients in the United States (Merrell and Shulman 1955). Due in part to earlier diagnosis and in part to the use of immunosuppressant medications, SLE survival rates seem to have increased significantly since this early report. Infections, atherosclerotic and cardiovascular diseases, active systemic lupus erythematosus, end stage renal disease and malignancy are the leading causes of death attributed to SLE in the United States. This spectrum of clinical complication is seen in males and females and in all ethnic groups. There is some variability however, with infection and renal-related mortality more common in younger patients, and cardiovascular disease and cancer deaths seen more frequently in older patients (Ward, Pyun et al. 1995).

Studies that examine patients immediately after diagnosis are called inception studies. When studies examining survival trends of patients are not measured from time of diagnosis, mortality is underestimated since patients who die soon after the onset of SLE are missed. Non-inception cohorts can also overestimate mortality rates since patients with mild disease may be lost to observation soon after diagnosis (Trager and Ward 2001). Trager and Ward reviewed inception and non-inception cohort studies of SLE survival dating from 1955 to 2000. The inception cohorts (and near-inception cohorts, that is, studies identifying patients within 2-3 years of diagnosis) identified by Trager and Ward or published subsequent to their review are summarized in Table 1.2.1. For most of the studies, investigators reported a survival rate of 90% or higher. Michet *et al.'s* Mayo Clinic study conducted in 1985 reported the lowest 5-year survival of all inception cohorts at 76% (Michet, McKenna et al. 1985).

Many of the inception cohorts are fairly small (< 100 patients), and thus we have limited data regarding the association between demographic and clinical factors and mortality risk early in the disease course. Inception and non-inception studies that analyzed survival in relation to racial or ethnic group, age, and renal disease are summarized in Table 1.2.2. An increased mortality risk in African-American SLE patients (compared with whites) has been demonstrated in numerous studies, but this excess risk is attenuated in most studies that adjust for socioeconomic factors. Mortality risk may be increased among older patients, but the available data on this issue are not consistent and have not been limited to patients early in the disease course. An increased mortality risk among men has also been reported in several studies with the most recent study by Manger reporting a relative risk of mortality among men of 3.5 compared to women (Manger, Manger et al. 2002). However, the number of men in these studies (approximately 10%) is relatively small, so estimates for risk differences are often imprecise, and the potential influence of other factors (race and age) has not been examined often. Lupus nephritis, one of the most serious complications of SLE occurs more often in younger patients. Some studies suggest that mortality risk may be higher in patients with renal damage, but few studies have examined the potential confounding effects of race, age, and nephritis on survival.

Table 1.2.1 Inception and Near-Inception Cohort Studies of Mortality Risk in SLE

Reference Location, Period	Patients (n) and description	Deaths (n)	Survival (%) 5 yr	10 yr	15 yr
(Fessel 1974) San Francisco 1965-73	n = 74; 81% white, 9% black, 9% Asian; median group age at diagnosis 15-44 years; median follow-up 8 years	5		90+	
(Michet, McKenna et al. 1985) Minnesota 1950-79	n = 25; mean age at diagnosis 42 years; median follow-up not presented	8	75	63	
(Ginzler, Diamond et al. 1982) US, 9 sites 1965-76	n = 1103; 32% African-American; mean age at diagnosis 32 years, median follow-up 44 months	8	77	71	
(Jonsson, Nived et al. 1989) Sweden 1981-86	n = 38; median age at diagnosis 40 years; mean follow-up 4 years	9	97		
(Gudmundsson and Steinsson 1990) Iceland 1975-88	n = 76; mean age at diagnosis 46.6 years; median follow-up = 7 years	17	84	78	
(Pistiner, Wallace et al. 1991) Los Angeles 1970-89	n = 256; 72% white, 11% black, 8% Hispanic; mean age at diagnosis 33 years; mean follow-up 6 years; middle class, private practice	26	97	93	83
(Ward, Pyun et al. 1995) North Carolina 1969-83	n = 408; 48% black, 52% white; mean age at diagnosis 37 years; median follow-up = 11 years	144	82	71	63
(Alarcón, Williams et al. 1991) Salt Lake City 1982	n = 57; 38 followed for 5 years	4	92		

(Uramoto, Michet et al. 1999)8 Minnesota 1980-97	n = 48; 94% white, 6% other mean age at diagnosis 47 years; mean follow-up 8 years	---	93*	74*	

Table 1.2.1 (continued)

Reference Location, Period	Patients (n) and description	Deaths (n)	Survival (%) 5 yr	 10 yr	 15 yr
(Peschken and Esdaile 2000) Manitoba, Canada 1980-96	n = 226; 19% North American Indian, 69% whites, 7% East Asians, 2% African American; mean age at diagnosis 35 years; mean follow-up 7.5 years	31	97	92	87
(Mok, Lee et al. 2000) Hong Kong 1992-99	n = 186; mean age at diagnosis 34 years; mean follow-up 45 months	9	93		
(Alarcón, McGwin et al. 2001) Alabama, Texas 1994-97	n = 288 38% African American, 31% white, 31% Hispanic	34			
(Kasitanon, Louthrenoo et al. 2002) Thailand 1986-2000	n = 349; mean age at diagnosis 32 years; median follow-up = 24 months	52	84	75	

*Estimated from graph

Table 1.2.2 Summary of Cohort Studies with Data on Associations Between Ethnicity, Age, Gender or Renal Disease and Survival in SLE

***Reference*(s)** Site, n, % minorities, inception or prevalent cohort, main covariates	***Results***
Ethnicity	
(Ginzler, Diamond et al. 1982) 9 sites in US, n=1103, 32% Blacks, incident cohort, insurance status	5 year survival Blacks 73%, Whites 80%; 10 year survival Blacks 68%, Whites 90%, p = 0.02 (univariate) but no racial difference when stratified by insurance
(Reveille, Bartolucci et al. 1990) Texas, n=389, 52% Blacks prevalent cohort insurance status	10 year survival: Blacks 82%, Whites 90%, p = < 0.05 (univariate). Multivariate analysis at any time during the course of SLE, present at or within 6 months of diagnosis for increasing age, Black, and thrombocytopenia, p <0.05. Racial difference in survival (~ 5%) also seen within insurance type strata – not statistically significant in public/no insurance group, but small n
(Pistiner, Wallace et al. 1991) Los Angeles, n = 464, 11% Blacks, inception cohort, middle class, private practice	No difference by race, but data not shown; small sample size for Blacks (n=51)
(Ward, Pyun et al. 1996) North Carolina n=408, 48% Blacks, inception cohort, insurance status and census tract income	In Studenski's paper, 5 year survival: Black 80%, White 93%, p = 0.002 (univariate); insurance-adjusted p-value = 0.01 but risk ratios not given; in the later analysis by Ward , ~ 10% difference survival at 5, 10, and 15 years in Blacks compared with Whites, p = 0.005 (univariate) but no association when adjusted for insurance and income Adjusted hazard ratio = 0.95 (0.57, 1.59)
(Alarcón, McGwin et al. 2001) Alabama and Texas, n = 288, 42% Blacks, 28% Hispanics, prevalent cohort	5 yr number of deaths; 10-Hispanics, 18-Blacks, 6- Whites (p<0.05). Ethnic survival rates reported graphically, but not significantly different.

Table 1.2.2 (continued)

***Reference*(s)** Site, n, % minorities, inception or prevalent cohort, main covariates	***Results***
Age	
(Reveille, Bartolucci et al. 1990) Texas, n=389, 52% Blacks prevalent cohort, insurance status	Increasing age at SLE onset associated with increased mortality risk
(Alarcón, McGwin et al. 2001) Alabama, Texas 1994-97	Older age mortality risk
(Manger, Manger et al. 2002) Erlangen-Nurenberg, Germany, n=338, 100% German prevalent cohort; death, end stage renal disease, and thromboembolic events	Age>40 at disease onset associated with increased mortality risk (RR=3.5, p<0.0001)
Gender	
(Pistiner, Wallace et al. 1991) Los Angeles, n = 464, 11% Blacks, inception cohort, middle class, private practice	Pistiner: Women survived longer (p=0.003). Wallace: 5, 10, 15 yr survival for females vs. males; 89%, 80%, 75% vs. 77%, 75%, and 58%, respectively (p<0.005).
(Manger, Manger et al. 2002) Erlangen-Nurenberg, Germany, n=338, 100% German prevalent cohort; death, end stage renal disease, and thromboembolic events	Male sex (p<0.001, RR=3.5)
(Bellomio, Spindler et al. 2000) Tucuman, Argentina; n=366, 12% males; multi-center study/established cohort; heart involvement, hyperlipidemia and renal damage	Male sex, univariate: RR=2.31, 95% CI 1.1-4.7, p=0.01

Table 1.2.2 (continued)

***Reference*(s)** Site, n, % minorities, inception or prevalent cohort, main covariates	***Results***
Gender (continued)	
(Ward, Pyun et al. 1995) Duke University Medical Center (NC), n=408, 48% Blacks, inception cohort, insurance status and census tract income	Ward: No significant difference in cause of death between males and females. Studenski: No significant effect of sex (p=0.0985).
(Blanco, Gomez-Reino et al. 1998) Madrid, Spain, n=306, 100% European Spanish patients; observational cohort	Multivariate analyses: male gender, nephropathy and central nervous system involvement associated w/ worse survival
Nephritis (renal)	
(Karsh, Klippel et al. 1979) Maryland, n=428, 68 deaths, large series cohort	Multivariate analyses: renal damage RR= 2.62
(Ward, Pyun et al. 1996) North Carolina, n=408, 48% Blacks, inception cohort, insurance status and census tract income	Nephritis RR=2.19, 95% CI 1.27-3.76, p=.005 adjusted for age, sex, race, SES
(Manger, Manger et al. 2002) Erlangen-Nurenberg, Germany, n=338, 100% German, prevalent cohort	Nephritis at disease onset; p<0.05, RR=1.6,
(Blanco, Gomez-Reino et al. 1998) Madrid, Spain, n=306, 100% European Spanish patients; observational cohort	Multivariate analyses: male gender, nephropathy and central nervous system involvement associated w/ worse survival

Table 1.2.2 (continued)	
***Reference*(s)** Site, n, % minorities, inception or prevalent cohort, main covariates	***Results***
(Bellomio, Spindler et al. 2000) Tucuman, Argentina; n=366, 12% males; multi-center study/prospective cohort; heart involvement, hyperlipidemia and renal damage	Multivariate analyses: nephritis RR=2.62, 95% CI 1.13-6.10, p=0.025 Kidney biopsy (WHO Class) III-IV; univariate: RR=2.48, 95% CI 1.1-3.0, p=0.001.

1.3 Economic Costs of Systemic Lupus Erythematosus

1.3.1 Direct Costs: Health Care Utilization

There have been few studies of the direct or indirect costs of SLE, and no studies have compared costs to those incurred by a population-based control group. In a comparison of health care expenditures between SLE patients in Stanford, CA and Montreal, Quebec, Gironimi reported that the direct health care costs for American SLE patients were more than doubled those of Canadian patients ($10,530 versus $5,271 in 1991 US dollars) (Gironimi, Clarke et al. 1996). Several years later, Clarke analyzed the overall annual resource utilization of SLE patients in Canada, the United States, and the United Kingdom. Utilization amongst the three were similar after adjusting for demographics, disease duration, activity, damage, social support, health status, patient satisfaction, and age and sex adjusted country-specific SF-36 general population norms. Expenditures totaled $4853, $5285, and $4760 for Canada, United States, and United Kingdom, respectively (Clarke, Petri et al. 1999).

One of the first published Canadian studies conducted by Ann Clarke identified substantial predictors of medical costs for SLE patients. Direct costs were shown to arise

from organic complications which induce functional disability. Indirect costs were shown to be potentially amenable to psychological or social interventions and may be more easily modified than the determinants of direct costs, thereby improving patient outcome while simultaneously reducing disease costs (Clarke, Esdaile et al. 1993). An unpublished study (except for an abstract based on a poster presentation) (Finn 1993) reported annual medical costs of 74 SLE patients from Johns Hopkins Medical Institution. African-Americans compared to whites had higher inpatient, physician and total costs, but indirect costs were not assessed. This study was based on patients seen at a tertiary care referral center with varying years of duration.

1.3.2 Indirect Cost

Partridge *et al* studied the risk factors for early work disability in SLE. A sample of 159 patients was drawn from a multi-center study of outcomes in SLE. These patients had been employed at the time of study enrollment. After a mean follow-up time of 3.4 years, 40% of the patients were no longer working, and job modification was extensive. Univariate analysis showed that predictors (measured at enrollment) associated with an increased risk of work disability included lower education, receiving Medicaid or having no health insurance, having jobs requiring higher physical demands, having and income below the poverty level and having greater disease activity at diagnosis (Partridge, Karlson et al. 1997).

Gordon et al reviewed the methods of several studies assessing the economic burden of lupus by disease activity, chronic damage, and health related-quality of life, (Gordon and Clarke 1999) recommending that a thorough economic review of lupus must include the above themes. In addition, she believes that extensive information, using

clinic-based populations, community cohorts, and national surveys, should be used in assessing the economic burden of lupus. Few American studies exist which determine direct or indirect costs of lupus patients from the patient's perspective.

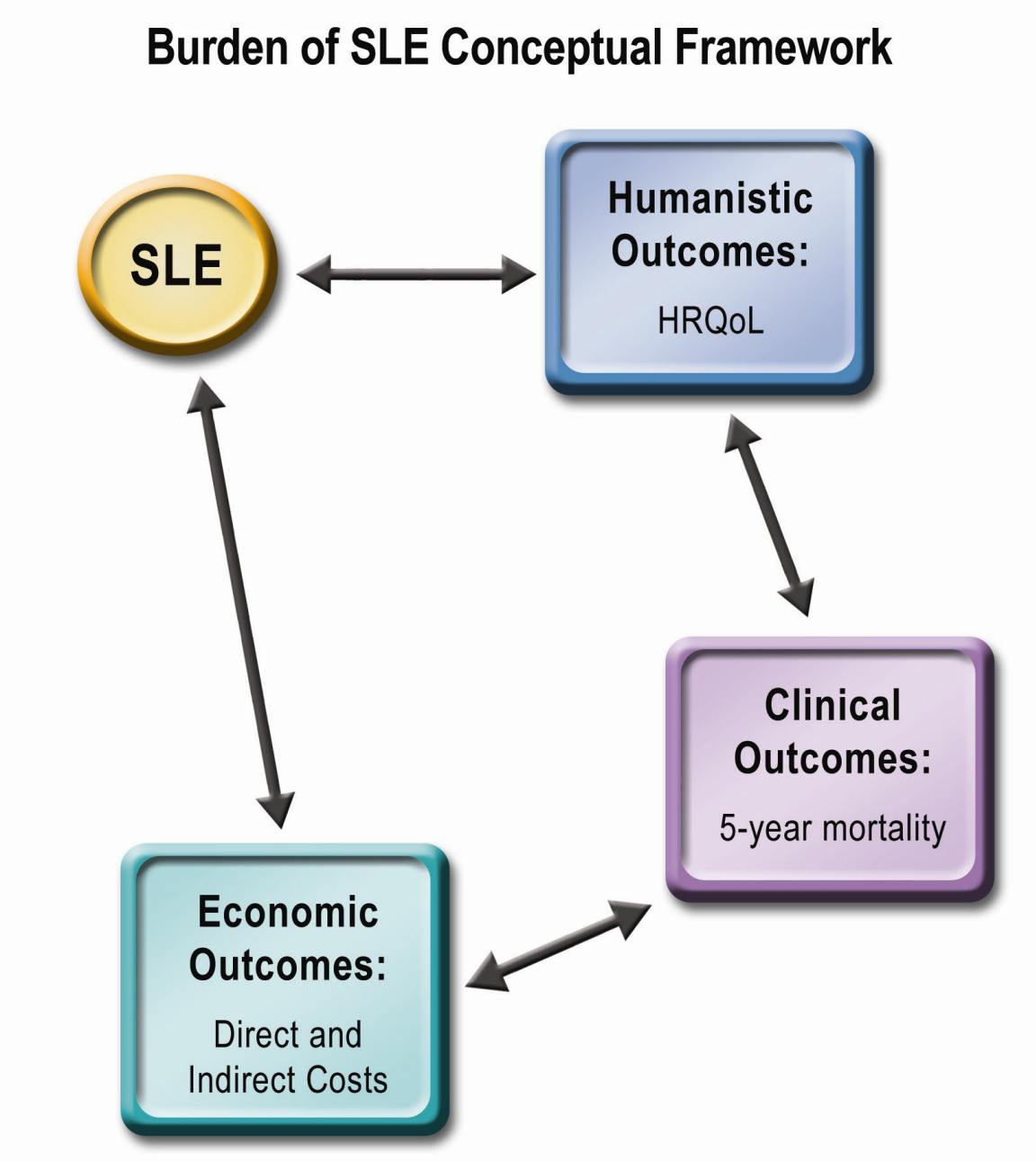
Factors attributable to racial/ethnic differences in total medical (direct and indirect) costs amongst patients of several chronic diseases have been reported to be a result of racial/ethnic bias and discrimination in the US health care system, problems with cultural sensitivity and effective communication, and access to high-quality health care providers. These differences not only result in significant health disparities, but significant racial differences in costs incurred. Differences in costs due to age are attributable to disproportionate rates of unemployment by age. In 2001 Americans 50 years old and older accounted for almost 28% of those non-institutionalized Americans who were not contributing to the labor force for various reasons to include unemployment, retirement and disability (US Bureau of Labor Statistics).

1.4 Conceptual Framework

Systemic lupus erythematosus (SLE) is a chronic, disabling autoimmune disease. Short-term (5-year) mortality from SLE is thought to have improved since the 1950's but data from inception-based cohort studies are limited. In addition, few studies are available examining other consequences of SLE, such as ability to work, quality of life, and direct costs of health care utilization. The available studies are mostly drawn from tertiary care centers, and have not included comparable data from a control group representing the source population of the patients.

The goal of this dissertation is to examine the multifaceted burden of SLE along multiple dimensions (health-related quality of life, mortality, employment-related impact, and direct and indirect costs) using data from a population-based case-control study of recently diagnosed SLE patients in a 60 county area of North Carolina and South Carolina (The Carolina Lupus Study). The multifaceted burden of SLE will be elucidated by a modified Economic, Clinical and Humanistic Outcomes (ECHO) framework (Figure 1.1) which explains the underlying relationship between disease, health outcomes, and decisions about medical care interventions (Kozma, Reeder et al. 1993). The goals of the study are to quantify the burden of disease by comparing outcomes in patients and a population-based control group, and to assess the influence of specific demographic and clinical features on the likelihood of worse outcomes among patients.

Figure 1.1 Burden of Systemic Lupus Erythematosus (SLE) Conceptual Framework



1.5 Specific Aims

The specific aims of this study are:

Aim 1: *To quantify the differences in health related quality of life (summary physical and mental health component scores and domain scores) between SLE patients early in the course of disease and controls using health-related quality of life scores(SF-8) from the follow-up assessment period.*

Aim 2: *To quantify the differences in 5-year mortality risk between SLE patients early in the course of disease and controls based upon data collected at baseline assessment.*

Aim 3: *To quantify the differences in direct and indirect costs (i.e., costs of health care utilization, and costs associated with job loss) between SLE patients in the course of disease and controls based upon data provided at the follow-up assessment.*

In addition, demographic predictors of each of these outcomes (lower quality of life, increased mortality risk, increased direct and indirect costs) among patients will be examined.

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CHAPTER 2: Estimating the Humanistic Burden of Carolina Lupus Patients

2.1 Methods

2.1.1 Study Population

The Carolina Lupus Study is a population-based case-control study of SLE based in 60 contiguous counties in eastern and central North Carolina and South Carolina. Eligible patients were drawn from 30 of the 40 community-based rheumatologists and the four university-based rheumatology practices in the study area. Lupus diagnosis was based on fulfillment of the revised American College of Rheumatology classification criteria (Hochberg 1997) diagnosed between January 1, 1995 and July 31, 1999, age >= 18 years at study enrollment, residence within the study area during at least 6 months of the year prior to diagnosis, and the ability to speak and understand English. Investigators received 285 referrals of eligible patients based on medical record data pertaining to the diagnostic criteria. Ninety-three percent (n=265) of referrals comprise cases. The median time from diagnosis to study interview was 13 months, and 75% of patients were interviewed within 20 months of diagnosis. Approximately 50% of cases were referred from community-based rheumatology practices. The study protocol was approved by the review boards at all participating institutions.

Controls were identified through driver's license records and frequency matched to cases by age, sex, and state. Of 1873 potential control subjects, 813 were contacted for telephone screening of which 163 refused screening and 46 were not eligible (i.e., because of change of address or death). One hundred twenty-nine were eligible but

deferred, 120 were eligible but declined to participate, and 355 (75% of the screened and eligible and not deferred) completed the study interview.

Sixty percent of the SLE patients in the Carolina Lupus Study are African-American and 34% are white. Ninety-one percent are female, 30% have some college experience, 33% are between 25 and 34 years old, and 77% live in North Carolina. Twenty-eight percent of population-based controls are African-American and 65% are white, reflecting the racial distribution of the source population. Thirty-six percent have some college, 29% are between 25 and 34 years old, and 71% live in North Carolina (Table 2.1.1). These patients and controls comprise our baseline assessment, or initial period of data collection.

The 2001 follow-up study included 198 cases and 299 controls. Among those who were alive at time of contact, participation rates in the 2001 follow-up interview were similar in cases and controls (82% and 84%, respectively). Similar proportions of cases and controls could not be located (9% and 10%, respectively), and were located but did not participate (9% and 6% of cases and controls, respectively). The median time since diagnosis was 4 years at time of follow-up interview.

Table 2.1.1 Baseline Assessment Demographic Characteristics of Cases and Controls in the Carolina Lupus Study

	Cases	(n=265)	Controls	(n=355)	Chi-square
	n	(%)	n	(%)	
Sex					NS
Female	240	90.6	321	90.4	
Male	25	9.4	34	9.6	
Ethnicity					p<.0001
African-American	160	60.4	99	27.9	
White	89	33.6	230	64.8	
Other[a]	16	6.0	26	7.3	
Education					p<.0001
less than high school	59	22.3	32	9.0	
completed high school	66	24.9	77	21.7	
some college	80	30.2	130	36.6	
completed college	60	22.6	116	32.7	
Age (years)[b]					NS
15-24	43	16.2	44	12.4	
25-34	86	32.5	103	29.0	
35-44	49	18.5	76	21.4	
45-54	46	17.4	72	20.3	
55-64	24	9.1	35	9.9	
65-81	17	6.4	25	7.0	
State					.07
North Carolina	205	77.4	252	71.0	
South Carolina	60	22.6	103	29.0	

[a] Includes Native Americans, Asians and Hispanics
[b] At diagnosis for cases or corresponding reference age for controls

2.1.2 Data Collection and Analysis

The study includes two data collection periods, the baseline assessment at enrollment (1997-1999) and the follow-up assessment conducted in 2001 (Figure 2.1). Baseline is defined as the initial period where the patient enrolled in the study irregardless to when they were diagnosed with SLE. In the baseline study, data were collected using a

structured 60-minute in-person interview (1997-1999). Demographic information (date of birth, education level, race) was obtained at this time. Medical records of 256 cases were reviewed to obtain data on clinical features of SLE, and 244 cases provided serum for an autoantibody profile. The 2001 follow-up interview obtained information from cases and controls via a 45-minute and 15-minute telephone interview, respectively. Control interviews were shorter because some sections specific to the clinical course of SLE were not included.

The 2001 follow-up included the SF-8 health-related quality of life assessment for cases and controls. The eight questions and the related domains used in the follow-up of the Carolina Lupus Study are shown in Table 2.1.2. Single domain items cannot represent thoroughly the content captured by the items in a multi-item scale. For this reason, summary scores are more appropriate to use when measuring quality of life using the SF-8.

Health-related quality of life summary scores were calculated applying a summated, algebraic algorithm using a norm-based scoring (NBS) method. Mean SF-36, Version 2 (SF-36 v2) scale scores from the 2000 general population sample were assigned to each SF-8 item response category. These values were provided by Ware et al. from Table 4.1 (Scale Values Used to Score SF-8 Response Categories) (Ware and Kosinski 2001) and are representative of nearly 13,000 assessments that were completed via the internet, by personal interview on the telephone or using mail-out and mail-back methods. Summary scores were computed by multiplying the final scores on all eight items by their respective weights (physical weights for the Physical Component

Summary-8 and mental weights for the Mental Component Summary-8) and then summing.

Using norm-based scoring, all scores have the same mean and standard deviation (mean = 50, SD =10). To achieve 50/10 scoring for the Physical Component Summary-8 and Mental Component Summary-8, the respective intercept or constant is added to the sum of all the physical products and mental products, respectively. Norm-based scoring of the SF-8 allows for easier interpretation. The general population norm is built into the scoring algorithm. All scores above or below 50 can be interpreted as above or below the general population. Standard deviation scores for each scale are equalized at 10, making it easier to see exactly how far above or below the mean the score is in standard deviation units.

I compared the frequency distribution among cases and among controls of each item in the SF-8 health-related quality of life instrument. I also examined the box-plots of the summary scores for the two subscales (physical health and mental health components) by case-control status. The formal statistical analysis used Chi-square statistics to assess the differences between cases and controls in the individual items. I also used the Student's *t* test procedure to assess the crude (unadjusted) difference in means of the summary scores between groups. The linear regression (PROC REG; ls means) procedure was used to compare mean summary scores between cases and controls, adjusting for the matching factors used in sample selection (age, sex, and state) and other demographic factors (race, education). I compared the unadjusted to the fully-adjusted estimated effects. I also repeated the analyses, dropping specific variables (e.g., race, education) to see which variables were acting as confounders in the analysis.

Figure 2.1 Data Sources: Carolina Lupus Baseline and Follow-up Assessments

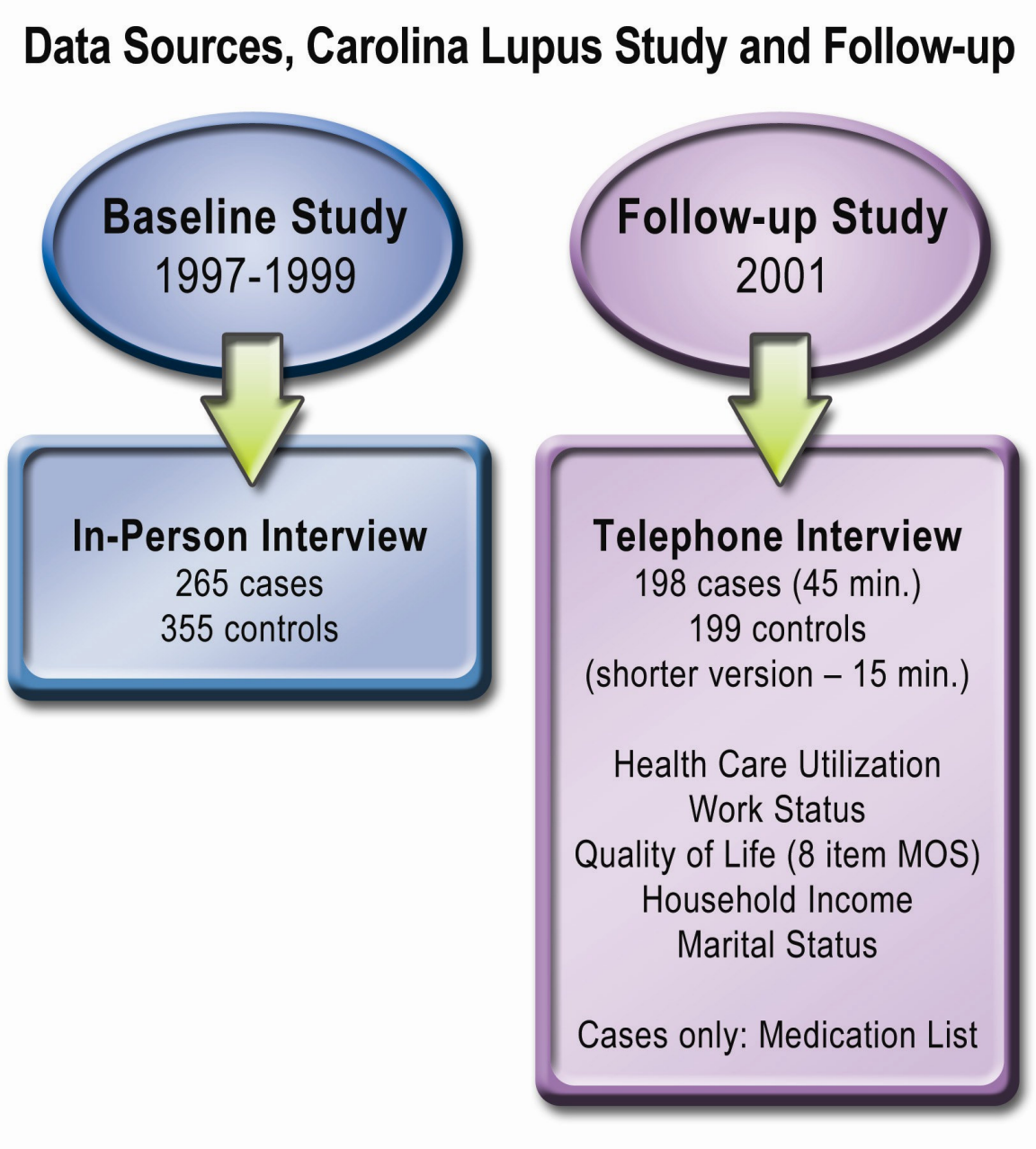


Table 2.1.2 Content of the SF-8 Health Related Quality of Life Instrument

Domain	Question	Response Categories
General Health	Overall, how would you rate your health during the past 4 weeks?	very poor, poor, fair, good, very good, excellent
Physical Function	During the past 4 weeks, how much did physical health problems limit your usual physical activities (such as walking or climbing stairs)?	could not do physical activity, quite a lot, somewhat, very little, not at all
Role Physical	During the past 4 weeks, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?	could not do daily work, quite a lot, some, a little bit, none
Bodily Pain	How much bodily pain have you had during the past 4 weeks?	very severe, severe, moderate, mild, very mild, none at all
Vitality	During the past 4 weeks, how much energy did you have?	none, a little, some, quite a bit, very much
Social Function	During the past 4 weeks, how much did your physical health or emotional problems limit your usual social activities with family or friends?	could not do social activities, quite a lot, somewhat, very little, not at all
Mental Health	During the past 4 weeks, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?	extremely, quite a lot, moderately, slightly, not at all
Role Emotional	During the past 4 weeks, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities?	could not do daily activities, quite a lot, somewhat, very little, not at all

2.2 Results

2.2.1 Quality of Life Differences between Cases and Controls

In case and control comparisons, significant differences were seen in 7 of the 8 individual SF-8 domains, with a greater degree of limitation seen in cases. Domain scores between cases and controls were significantly different at the p<.0001 level for physical functioning, general health, vitality, social functioning, role physical, and bodily pain, and the case-control difference for role emotion was significant at the p<.0035 (Figure 2.2.1). The mental health domain was the only area where there were no significant differences between cases and controls.

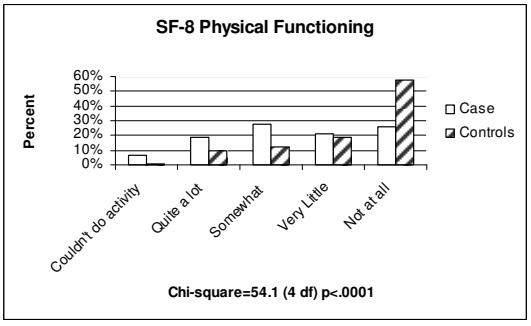
Physical component summary and mental component summary scores (mean summary and standard deviations) for controls are similar to those reported from the general US population (mean=50, standard deviation=10). Cases had a mean difference of 8.1 points in physical component summary and 2.1 points in mental component summary scores, respectively, compared with controls (Figure 2.2.2). The mean (standard deviation, sd) physical component summary was 41.38 (sd 11.07) in cases and 49.49 (sd 10.48) in controls (p<.0001). Mental component summary scores were 47.35 (sd 10.42) and 49.49 (sd 9.06) for cases and controls, respectively (p=.03).

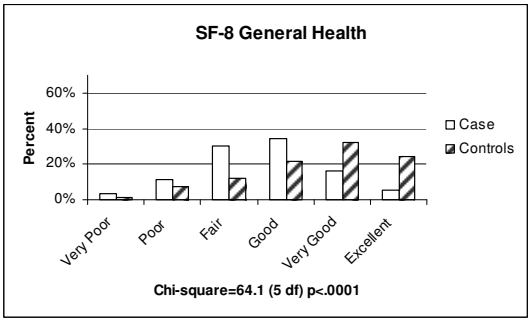
Several models were tested to determine the difference in summary scores between cases and controls, adjusting for the matching variables and other demographic factors. The age variable was tested as a continuous and group variable, and the education variable was modeled both as a one category and 4-level variable. In the final model (adjusting for age as a continuous variable, sex, state, race and education (as a 4-level variable), a 7.7 point lower physical component summary score was seen in cases

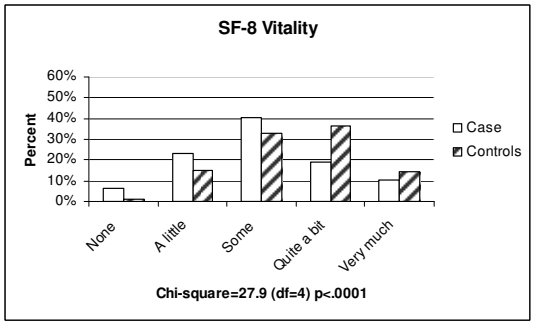
compared to controls (mean score 41.6 for cases and 49.3 for controls). Mental component summary scores between cases and controls were marginally significantly different using all forms of the age variable (p=.07) with a 1.8 point difference between case and control means (47.5 and 49.3, respectively, in cases and controls) adjusting for sex, state, race and education.

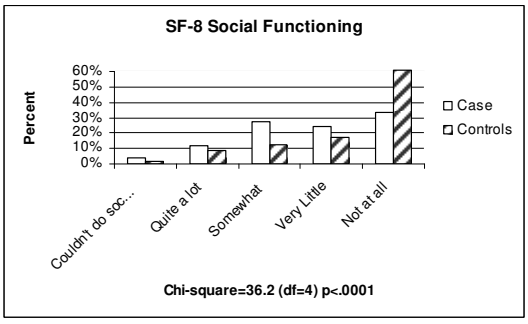
Among cases, physical component summary scores were significantly different ($p<0.02$) by age, with decreasing scores seen with increasing age (Table 2.2.1). Cases ages 16-29 years old had a 5.5 point higher physical component score compared to those 50 and older. Also, physical component scores were 4 points higher among cases 30-49 years old. No significant differences by any of the demographic variables were seen for the mental component summary scores.

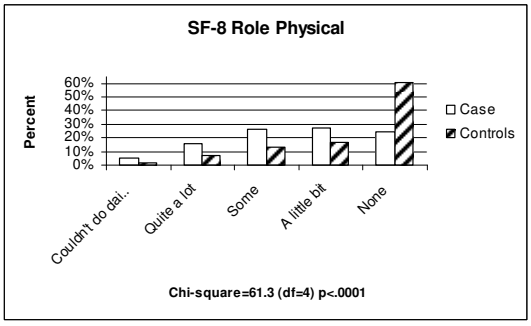
Figure 2.2.1 SF-8 Domain Summary Scores between Cases (n=197) and Controls (n=250)

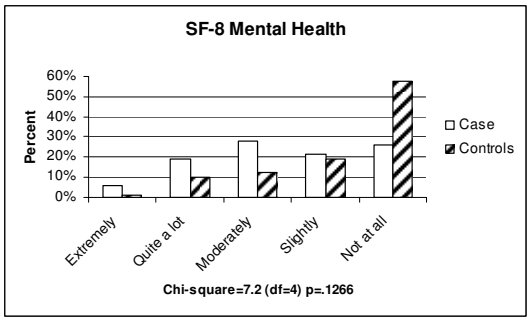


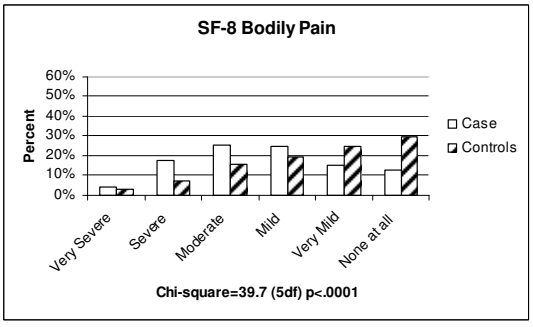












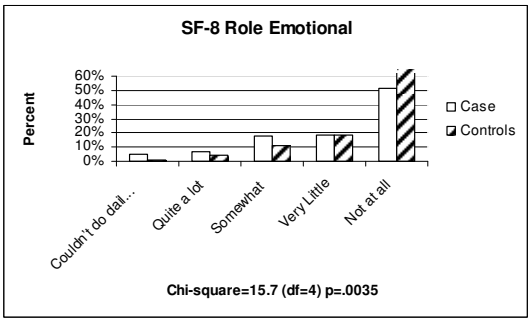


Figure 2.2.2 SLE Patients SF-8 Physical Summary Scores

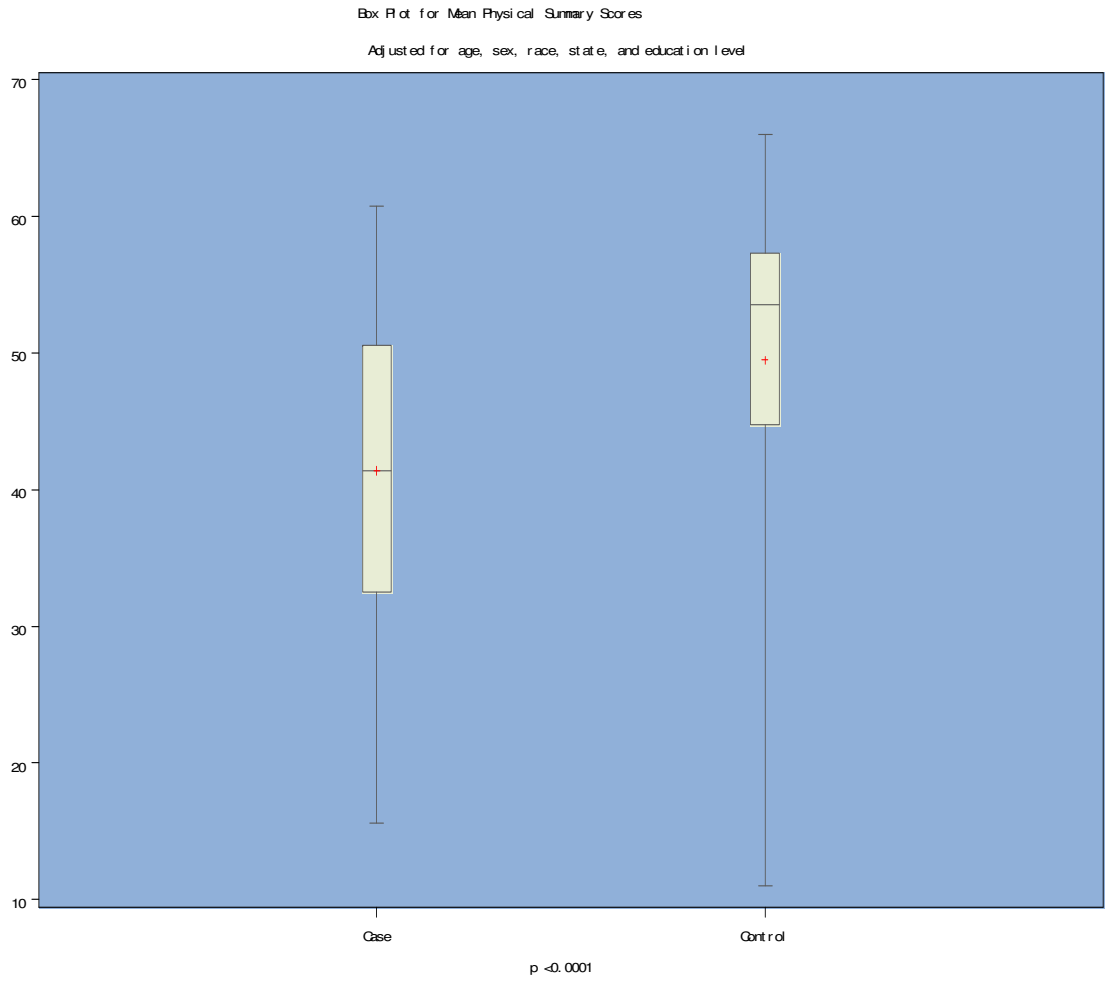


Figure 2.2.3 SLE Patients SF-8 Mental Summary Scores

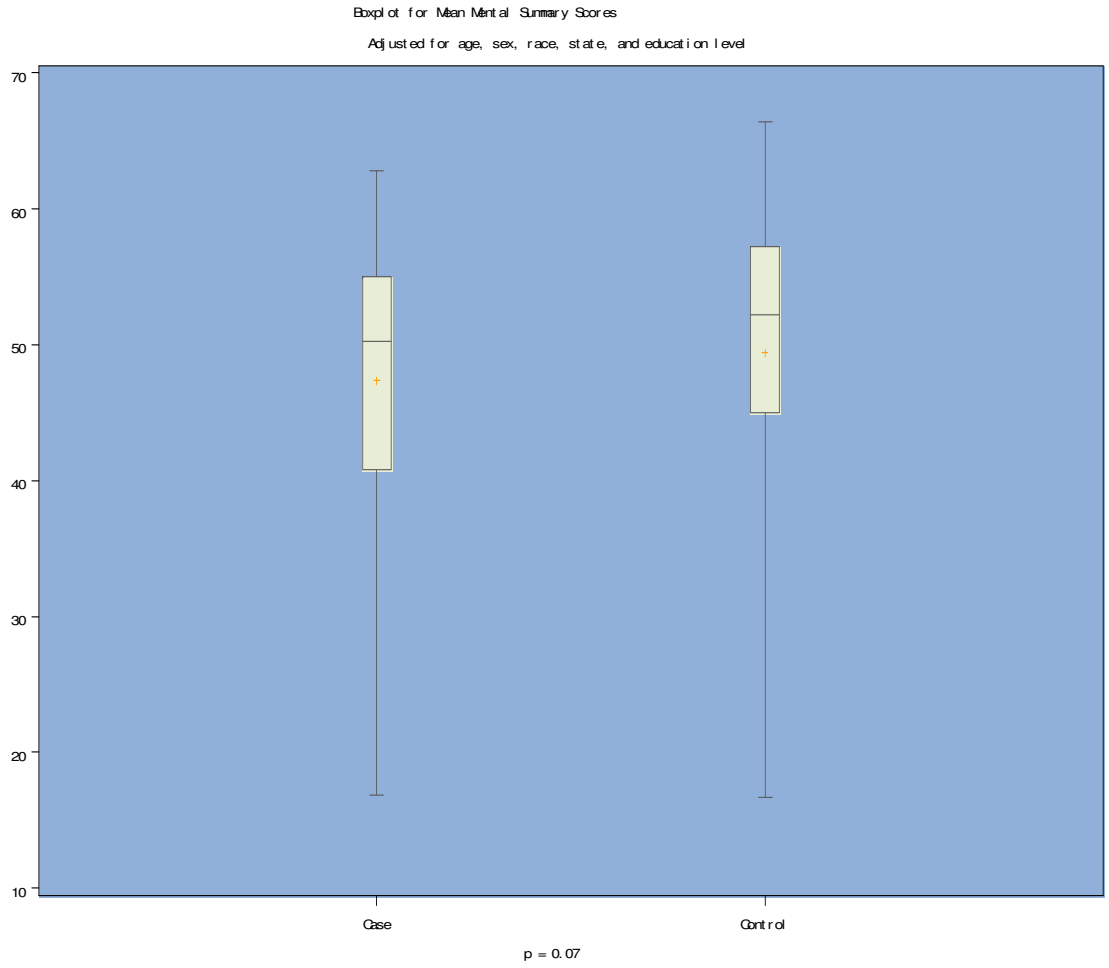


Table 2.2.1 SLE Patients Differences in SF-8 Summary Component Scores by Demographic Factors

	Physical Component Score			Mental Component Score		
	mean	(sd)	p-value	mean	(sd)	p-value
African Americans and other minorities	41.8	(11.4)	.53	47.6	(9.9)	.60
Whites	40.7	(10.5)		46.8	(11.3)	
<30 years	44.0	(11.3)	**0.02**	45.8	(10.7)	.48
30-49 years	42.5	(10.6)		48.2	(9.3)	
≥ 50 years	38.4	(11.1)		47.0	(11.9)	
Female	41.3	(11.2)	.88	47.4	(10.2)	.97
Male	41.8	(10.4)		47.3	(12.7)	
North Carolina	40.9	(11.1)	.19	47.3	(10.3)	.92
South Carolina	43.4	(11.0)		47.5	(11.0)	
<HS	40.3	(12.4)	.50	45.8	(11.8)	.60
HS	40.8	(11.6)		48.9	(8.9)	
Some college	40.9	(10.6)		47.2	(10.4)	
Completed college	43.5	(10.3)		47.1	(10.9)	

2.3 Discussion

Health-related quality of life scores on 7 of the 8 individual SF-8 domains were lower in SLE cases, approximately 4 years after diagnosis, compared with age- and sex-matched controls. Adjusting for age, race and other demographic factors, the mean physical component score was 7.7 points lower ($p < .00001$), and the mean mental component summary score was 1.8 points lower ($p = 0.07$) in cases compared with controls. Among cases, physical component summary scores were significantly different ($p<0.02$) by age, with decreasing scores seen with increasing age, but there was no differences by any of the demographic variables in the mental component summary scores.

Ware et al developed the SF-8 single-item scales to measure the eight health concepts defined and measured by the SF-36. In its development, it was hypothesized that each SF-8 scale would substantially converge with its corresponding scale in the SF-36 Health Survey. Also, each scale was hypothesized to discriminate between its hypothesized health concept and other concepts in the SF-36. Very high correlations between the two physical and mental summary measures (PCS- 8 and PCS -36) and very low correlations between measures of different concepts were hypothesized and proven resulting in excellent content, convergent, and discriminate validity for the SF-8. However, each of the SF-8 scales and the 2 summary scores were expected to differ not only in terms of their performance across various tests of validity, but also have different interpretations (McHorney, Kosinski et al. 1994).

Thumboo measured 6-month change in composite physical and mental component scores, but reported that changes in health-related quality of life scores were not as

sensitive to changes as are individual SF-36 (Thumboo, Fong et al. 2000). Therefore, this analysis not only examined summary scores between cases and controls, but looked at individual domain differences between lupus patients and controls in addition to demographic differences among patients. This approach is in contrast to Devins' ethnoracial study which reported differences in psychosocial health scores among white, black and Asian female patients only using complex principal components analysis (Devins and Edworthy 2000).

The SF-8 was used in the 2001 follow-up study in order to maximize the amount of time in the interview that could be used for other sections (e.g., work history, health care utilization), but a limitation of this analysis is the SF-8's brevity. Only one item for each of the eight health concepts are used to compute a score. Because of its brevity, the SF-8 is best primarily used to compare composite summary scores and not individual domain scores. Scales this short have been shown to be less precise than well-constructed multi-item scales (McHorney, Ware et al. 1992). Scores estimated from the SF-8 can not only be less precise, but cover a narrower range of scores compared to the SF-36, the scale from which it is derived. Despite these limitations, the SF-8 scales and summary measures rarely missed differences in physical or mental health status captured by the SF-36 scales and summary measures (Ware and Kosinski 2001).

Another limitation to this analysis is the inability to compare pre and post health-related quality of life scores. During the baseline assessment study, only 2 measures of the SF-36 quality of life scale were obtained and the follow-up used the SF-8. Changes in health-related quality of life of Carolina Lupus patients from baseline to follow-up would have been of major interest to researchers. Further research in minimally significant

differences could have been performed if the same scales had been used at both collection periods.

This study is the first to use the SF-8 to assess quality of life amongst SLE patient. There exists no disease-specific measure of health-related quality of life for SLE patients. Unlike previous studies of health-related quality of life in SLE patients using the SF-36, this study was not designed to measure differences between pre- and post- health-related quality of life scores. This is the first study to measure health-related quality of life summary and domain differences between SLE cases early in the diseases course and controls as well as trends in scores by select demographic characteristics among cases. The degree of difference in individual domains, physical component scores and mental component scores has not been previously studied. The physical and mental component summary scores for controls of this study are similar to those reported from the general US population (mean=50, standard deviation=10) (Ware and Kosinski 2001), providing some assurance of the appropriateness of the sampling and implementation process, and suggests that we can generalize the results amongst this study's controls to the general US population.

The SF-8 has proven to be a very useful tool in assessing quality of life among SLE patients and their age and sex-matched controls. The significant quality of life domain and summary mean score differences between cases and controls elucidate the significant burden of disease among cases.

Future research is needed to elucidate the contributions to the impact on the decreased physical domain and summary scores in SLE patients, in contrast to the relative stability of the mental component scores among patients and controls. It would be

interesting to compare this observation to those in other chronic diseases assessed in relation to matched controls from the general population. Additional SLE research using the SF-8 should include larger sample sizes amongst cases allowing for the inclusion of interaction variables when performing multivariable regression analyses without the risk of reducing the study's power. The SF-8 provides highly validated domain, physical and mental component normative scores by gender, education level and race subgroups. These group-specific control scores can be utilized for comparisons to future multi-site or meta-analyses which will allow for results to be more appropriately generalized to several sub-populations while conducting health outcomes research.

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CHAPTER 3: Estimating the Clinical Burden of Carolina Lupus Patients

3.1 Methods

3.1.1 Study Population and Data Collection

As was described in Section 2.1.1., the Carolina Lupus Study is a population-based case-control study of SLE conducted in eastern and central North Carolina and South Carolina. Adult patients diagnosed between January 1, 1995 and July 31, 1999 were eligible, and the median time from diagnosis to study interview was 13 months. Approximately 50% of cases were referred from community-based rheumatology practices and 50% from university-based rheumatology practices in the study area. Controls were identified through driver's license records and frequency matched to cases by age, sex, and state. The study protocol was approved by the review boards at all participating institutions.

Sixty percent of the SLE patients in the Carolina Lupus Study are African-American and 34% are white and 91% are female. Because of the matching criteria the sex-distribution of controls is similar to cases, but the racial distribution of controls matching the source population is 28% African-American and 65% white.

Tracing of the study participants occurred in 2001 and 2004 as part of the steps taken for follow-up studies. The most recent information on vital status (known live, known died, or lost contact) based upon baseline assessment was used for the survival analysis.

3.1.2 Analysis of Mortality Risks

For preliminary survival analyses, the Kaplan-Meier survival probabilities and curves were computed for both cases and controls using the Lifetest procedure in SAS. Schoenfeld residuals and the log of time dependent covariates were used to test the proportional hazards assumption (Cox 1972). Follow-up time was calculated from date at diagnosis for cases (and the corresponding referent date for controls) to date of death or last known contact. I also repeated the analyses using the date of enrollment (study interview) for cases and controls. Individuals who were not found during the 2001 or the 2004 tracing efforts did not contribute any time in this analysis. Based on the review of information about all referred patients, there were few known losses between diagnosis and study enrollment, and the results for this analysis were similar to that which began follow-up at time of diagnosis/referent date. For all survival curves, the log-rank test and associated probability was used to test for stratum differences. I used proportional hazards modeling (PROC PHREG in SAS) to model the association between case-control status, adjusting for demographic factors. However, the limited number of deaths among controls (only 3 observed) presents a limitation to the interpretation of the results.

I also used proportional hazards modeling (PROC PHREG in SAS) to model the association between demographic factors and the presence of renal disease and the mortality risk among cases. This procedure makes no assumptions about the shape of the distribution of survival times, allows for time-dependent covariates, is appropriate for both discrete-time and continuous-time data, easily handles left truncation, can stratify on categorical control variable, and most importantly, can be extended to nonproportional hazards. Schoenfeld residuals were computed using the PROC PHREG and PROC

GPLOT SAS commands to detect possible departures from the proportional hazards assumptions. Schoenfeld residuals are independent of time. Although ad hoc and subjective, a plot that shows a relationship with time is substantiation against the proportional hazards assumption (Schoenfeld 1980).

3.2. Results

3.2.1 Mortality Risk Differences

There were 18 deaths among cases and 1 among controls at the time of the 2001 follow-up. Fourteen additional deaths were identified among cases and 2 among controls through follow-up mailings and telephone tracing until 2004. The immediate cause of death amongst both groups included liver failure, intercerebral hemorrhage, anoxic brain injury, cerebrovascular disease, lung cancer, sepsis, cardio respiratory arrest, and pulmonary embolism.

At 60 months (5 years) post-diagnosis, 8.7% of cases had died compared with 0.28% of controls ($p<.0001$) (Figure 3.1.1), so post-diagnosis 5-year survival rates (standard error, se) were 90.4% (se .02) and 99.7% (se .003) for cases and controls, respectively. Similar results were seen in the analysis beginning at study enrollment with 9.8% of cases and 0.56% of controls dying within 5 years of study enrollment ($p<.0001$) (Figure 3.1.2). Survival rates for cases and controls were 89.0% (se .02) and 99.0% (se .01), respectively. Using Cox proportional hazards modeling, the unadjusted hazards ratio was 13.1 (95% confidence interval, CI, 4.0, 42.9) for cases compared with controls beginning at diagnosis, and 11.0 (95% CI 3.4, 36.0) beginning at study enrollment. There

was little change in these estimates when adjusting for individual covariates (age, race, sex, or education).

The plots of the log of the negative log of the estimated survivor function against log time (LLS) of cases and controls were approximately parallel on visual examination, suggesting that the proportional hazard assumptions were met for survivor estimates at months of follow-up after diagnosis and at baseline. The time dependent covariates case status*log of time post- diagnosis and case status*log time at study enrollment, reported chi-squared and p-values of 1.57; p=0.21 and 1.99; p=0.16, respectively, confirming that there was no violation of the proportionality assumption.

Amongst cases Schoenfeld residuals were modeled and plotted for age (continuous), race, sex, education, state and renal involvement status. The only variable which reported a possible violation of the proportion hazards assumption was age. Inspection of the graph (Figure 3.1.3) shows that the residuals had a slight tendency to decrease with increasing time ($p = 0.0031$). The continuous age variable was then categorized into 3 groups (<30 years, 30-49 years, and $\geq$ 50 years) where the proportional hazards assumptions were retested using the Schoenfeld residuals. The proportional hazards assumptions were no longer violated ($p= 0.14$).

Significant survival between-group differences were only found between males and females with survival rates of 83.13% (se .08) and 91.15% (se .02), respectively. Differences in survival across education, race, and nephritis involvement groups are shown in Figures 3.1.4-3.1.7.

The results from the proportional hazards unadjusted and adjusted models are shown in Table 3.1.1. For each 1-year increment in age, the risk of death was estimated

to increase by 4%. Males had a 2.6 increased risk of death compared to females. Patients who did not complete high school were 4 times more likely to die compared to those who completed college. In controls, the risk of death was estimated to increase by 16% for each 1-year increment in age (95% confidence interval, 1.02-1.3).

Figure 3.1.1 Case and Control Survival Estimates from SLE Diagnosis

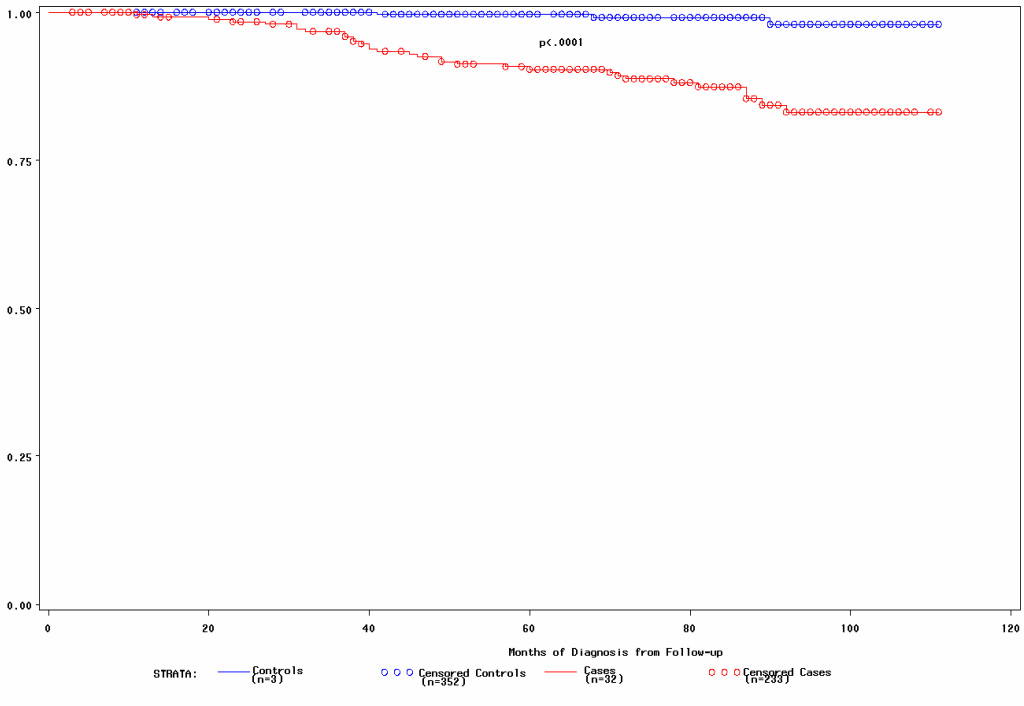


Figure 3.1.2 Case and Control Survival Estimates from Baseline Assessment

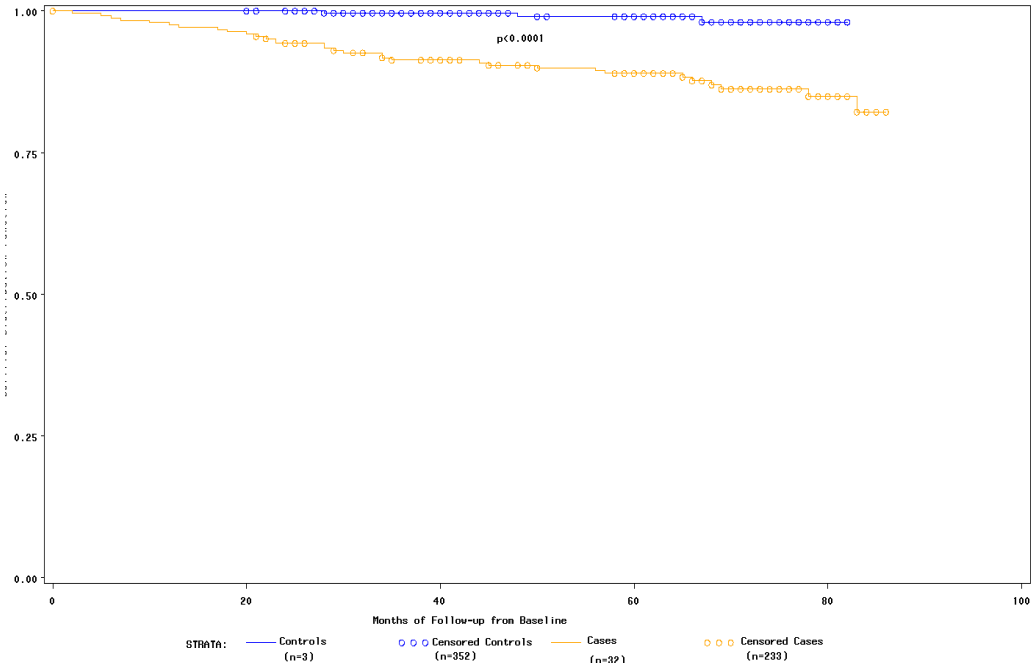
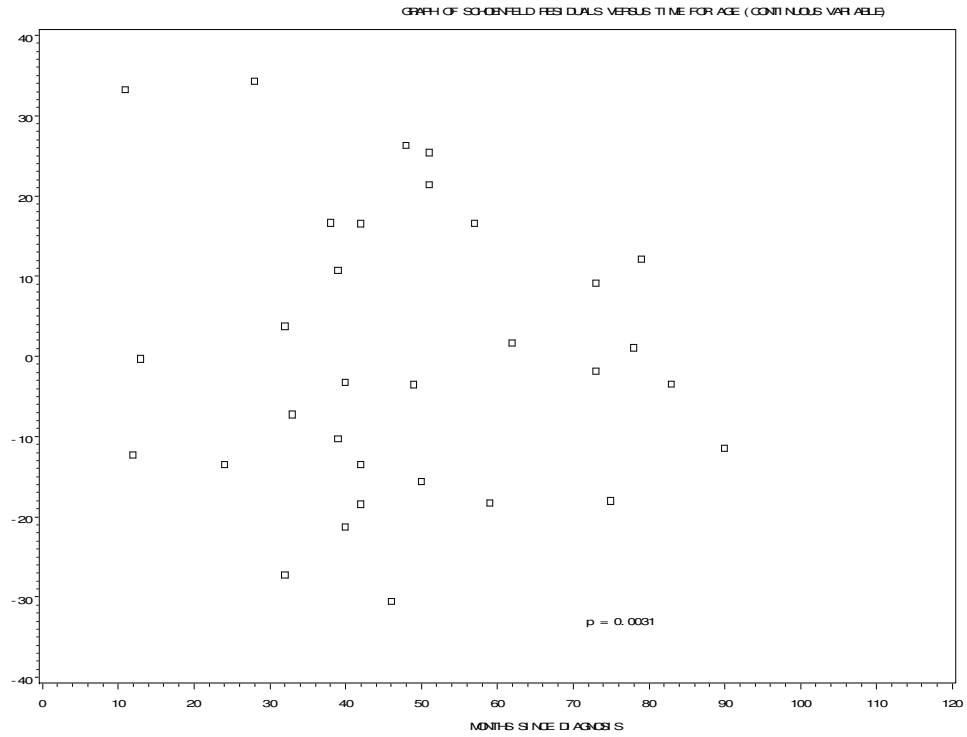

1.00
0.75
0.50
0.25
0.00
p<0.0001
0
20
40
60
80
100
Months of Follow-up from Baseline
STRATA:
Controls
(n=3)
Censored Controls
(n=352)
Cases
Censored Cases
(n=233)

Figure 3.1.3 Schoenfeld Residuals for Age Amongst Cases



Scatter of residuals slightly decline with time suggesting there may be some departure from proportionality for the AGE (continuous) variable amongst cases (n=32).

Figure 3.1.4 Case Survival Estimates from Diagnosis by Sex

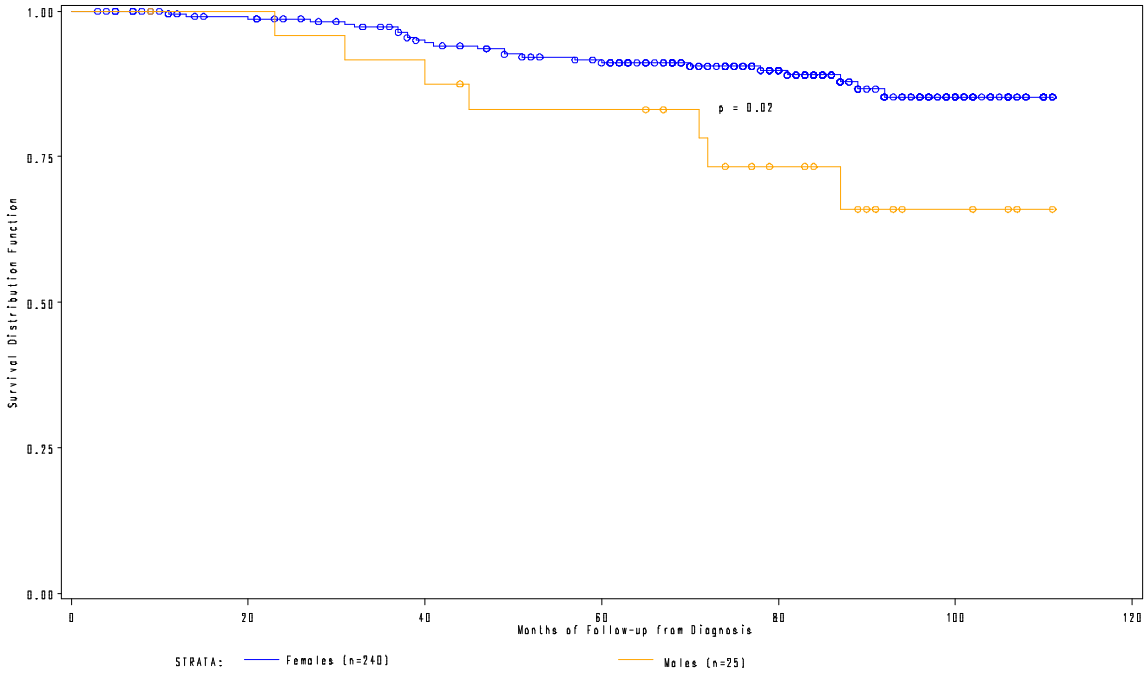


Figure 3.1.5 Case Survival Estimates from Diagnosis by Age Group

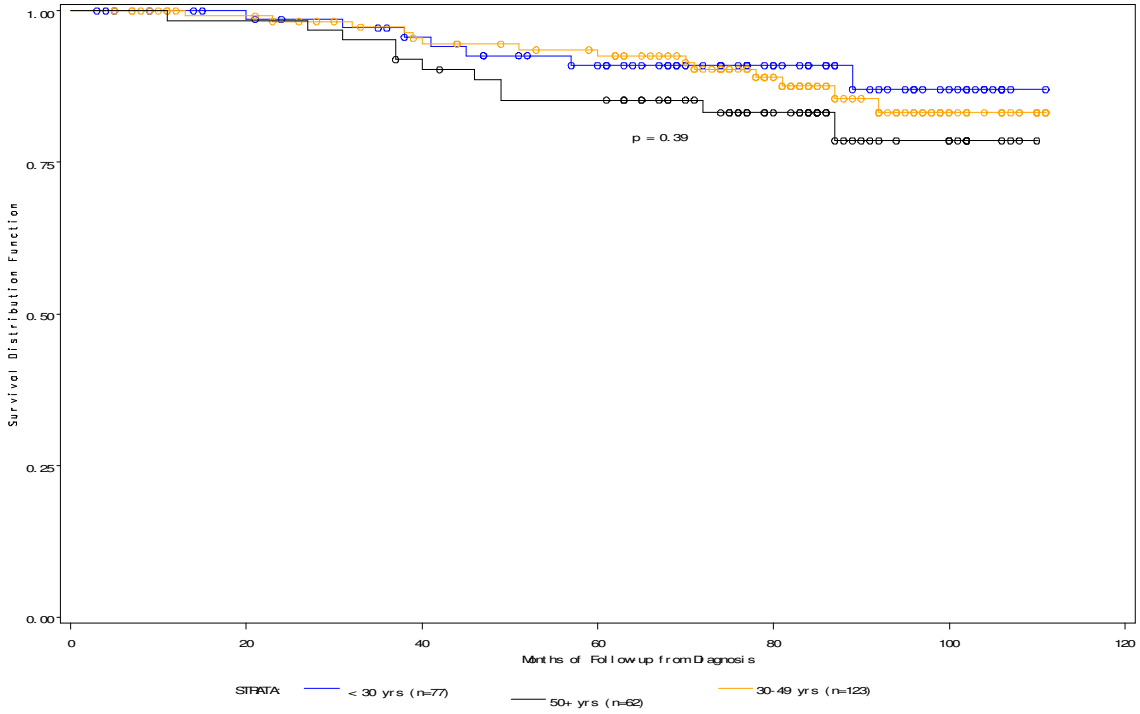


Figure 3.1.6 Case Survival Estimates from Diagnosis by Race

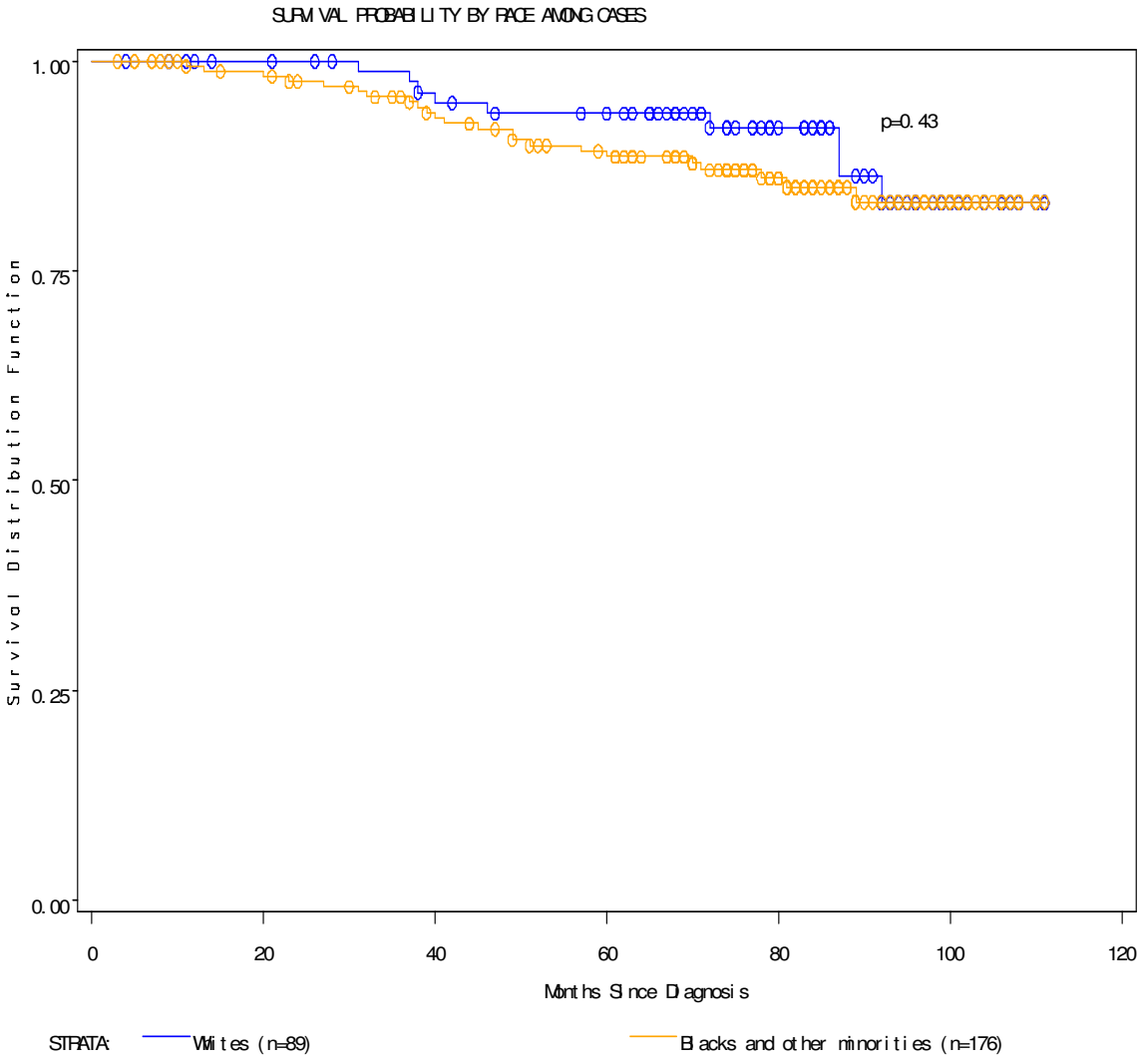


Figure 3.1.7 Case Survival Estimates from Diagnosis by Renal Involvement

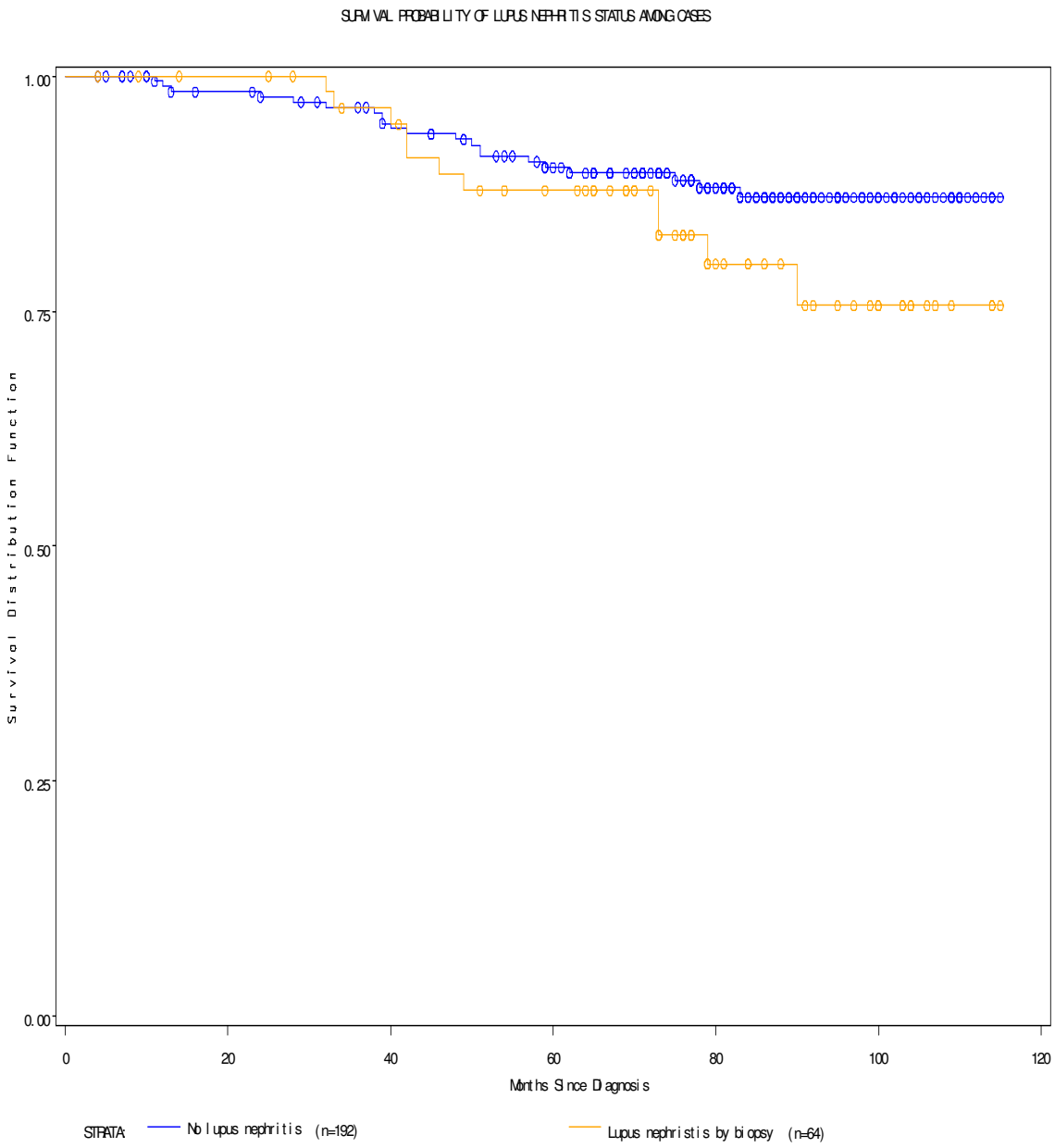


Table 3.1.1 Associations Between Demographic Variables and Mortality Risk among SLE Cases from Time of Diagnosis

	Unadjusted		Full Model*	
	Hazard Ratio	**(95% CI)**	**Hazard Ratio**	**(95% CI)**
Age (per year)	1.03	(1.01, 1.05)	1.03	(1.01, 1.06)
Gender				
males	2.6	(1.1, 6.1)	2.5	(1.0, 5.9)
females	1.0	(referent)	1.0	(referent)
Race				
African-Americans and others	1.4	(0.63, 2.9)	2.0	(.89, 4.6)
whites	1.0	(referent)	1.0	(referent)
Education				
did not complete high school	1.5	(0.49, 4.6)	.99	(0.31, 3.1)
completed high school	1.8	(0.59, 4.9)	1.5	(0.50, 4.7)
some college	1.7	(0.59, 5.5)	1.7	(0.58, 4.9)
completed college	1.0	(referent)	1.0	(referent)
Renal disease†				
present	1.4	(0.67, 3.0)	1.7	(0.78, 3.9)
absent	1.0	(referent)	1.0	(referent)

*Full model adjusts for age (per year), gender, and race.

† Renal disease lupus nephritis based on kidney biopsy

3.3 Discussion

As expected, SLE patients had significantly lower survival compared to their age, sex, and state-matched controls. The 5-year mortality risk was 9.6% in cases compared with less than 1% in controls. Among cases, there was no association between ethnicity and nephritis to mortality risk. Increased risk was seen in men and with increasing age. These results highlight the burden of SLE, even early in the disease and even with currently available treatments.

An increased risk with increasing age was reported in seen study and also found by Reveille, Alarcón, and Manger (Reveille, Bartolucci et al. 1990) (Alarcón, McGwin et al. 2001) (Manger, Manger et al. 2002). The increased mortality risk seen in this study in male compared with female SLE patients were similar to research conducted by Pistiner and Wallace who reported a longer survival amongst women and a 5-year survival rate for females vs. males of 80% vs. 75% ($p<.005$), respectively (Pistiner, Wallace et al. 1991). Studies in Germany and Argentina also reported a higher mortality risk amongst men compared to females (RR=3.5; $p<.001$ and RR=2.3; $p<.01$) (Manger, Manger et al. 2002). At baseline assessment, males only represented 9% of cases and controls. It is possible that selection bias may be the reason for the reported higher mortality among men. Due to the smaller number of men in the general population with SLE, those who are being treated by rheumatologists may be more likely to have higher severity and disease activity. Since SLE has long been labeled as a "woman's" disease, males with the disease may only seek (or be referred to) a specialist's services at a more advanced stage, when it is less likely to be misdiagnosed. Also, men have higher rates of cardiovascular

disease, hypertension and other comorbidities which when combined with the often deleterious effects of SLE medications make them more susceptible to morbidity and mortality compared to females.

3.4 References

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CHAPTER 4: Estimating the Economic Burden of Carolina Lupus Patients

4.1 Methods

4.1.1 Study Population and Data Collection

As was described in Section 2.1.1 and 3.1.1., the Carolina Lupus Study is a population-based case-control study of SLE conducted in eastern and central North Carolina and South Carolina. Community and university-based rheumatology practices referred recently diagnosed patients to the study, with approximately 50% of cases coming from each source. Controls were identified through driver's license records and frequency matched to cases by age, sex, and state. The study protocol was approved by the review boards at all participating institutions. Sixty percent of the SLE patients in the Carolina Lupus Study are African-American and 34% are white and 91% are female. The racial distribution of controls was similar to that of the source population, with 28% African-American and 65% white.

In 2001, a follow-up study was conducted. Participation rates were similar in cases and controls (n=198 cases, 82%, and n=299 controls, 84%). The median time since diagnosis was 4 years at time of follow-up interview. The 2001 follow-up study included sections pertaining to health care utilization in the past 12 months, and current work status and changes in work status since diagnosis (and corresponding referent date for controls. The specific data collected is described more fully in the following sections.

4.1.2 Analysis of Health Care Utilization Costs

The analysis of health care utilization costs was based only upon data provided by cases and controls during the follow-up interview assessment (Figure 2.1). The 2001 follow-up interview obtained detailed information about health care utilization from cases and controls. Health care utilization facilities use included hospitalizations, total nights in the hospital, nursing/convalescent home use, hospital emergency room visit, and outpatient surgery. Additional questions asked about ancillary services (number of x-rays, number of blood tests) and physician visits in the past 12 months.

Table 4.1.1 provides sources for the direct and indirect costs, cost components and per unit costs used in this analysis. Per unit costs were calculated for each service. Sources were selected based on complimentary access and comparability to the data collected in the follow-up study. Where possible, several databases for each service were compared. Regardless of the year of the source of cost data, all costs were adjusted to December 2001 costs using the Medical Consumer Price Index.

Hospitalization costs were calculated on a per-night basis using data from the 2001 Medical Expenditure Panel Survey Household Component hospital inpatient stays dataset. It provides national estimates of the level and distribution of health care use and expenditures and contains variable and frequency distributions for a total of 25,096 persons who participated in the survey. Mean cost per hospital stay for the southern census region was calculated by subtracting the total zero night stays facility and doctor expenses from the total hospital inpatient facility expenses including zero nights. The difference was divided by the difference of the number of zero-night hospital stays from the number of nights in hospital for discharges.

Average cost estimates for nursing/convalescent home and in-home nursing/personal care help were obtained from the 1999 Centers of Disease and Control and Prevention, National Center for Health Statistics, and National Nursing Home Survey. The 1999 estimates were converted to 2001 rates using the Consumer Price Index inflation converter. Average emergency room and estimates were obtained from the 2001 Medical Expenditure Panel Survey Household Component (MEPS HC) hospital emergency room visit dataset. The southern geographic area charges were derived by dividing the emergency room facility and doctor visit charges by the number of emergency room visits. Average 2001 total charge for lower gastrointestinal endoscopy was used as a proxy for average outpatient surgery charges due to its number one ambulatory surgery and outpatient visit ranking for 2001. X-ray averages were obtained by averaging the Unites States' Top 3 X-rays (chest, extremity and skull) using costs from a North Carolina family medicine office. Blood test costs were obtained by averaging the 2005 costs for CBC and lipid panel. The 2005 rates were converted to 2001 rates using the Consumer Price Index inflation converter.

To address the issue of skewness amongst the total annual cost for cases and controls, those health services which reported a median or mode of 0 were separated from the total annual cost formula. The natural logarithm was taken of the remaining services which were used in linear regression to predict factors associated with an increase or decrease in magnitude of the new partial total annual cost variable. Due to such a large percentage of health services being omitted during the partial analysis, I ultimately decided to conduct linear regression using all 10 original health services. This was the

optimal approach due to the fact that although 5 out of the 10 health services had medians or modes of 0, no health service reported a total annual cost of zero.

Table 4.1.1 Source of Cost Data – Health Care Utilization and Job Loss

Service	Source of Cost Data	Per unit cost
Total nights in hospital	2001 Medical Expenditure Panel Health Component Survey Query (MEPSnet/HC) Hospital Inpatient Stays	$1387.84/night: South
Nursing/convalescent home	1999 *Health* Report: CDC, National Center for Health Statistics, National Nursing Home Survey	$3263/ month: South
In-home nursing/personal care help (weeks)	2001 Medical Expenditure Panel Health Component Survey Query (MEPSnet/HC) Home Health Care	$67.82/day: South
Hospital ER visits	2001 Medical Expenditure Panel Health Component Survey Query (MEPSnet/HC) Hospital Emergency Room Visits	$876.28/ visit: South
Outpatient Surgery	Agency for Health Care Administration; 2001 Ambulatory Payment Class	$1796/ surgery
X-rays	NC Family Medicine Radiology practice	$143/x-ray (average of top 3-chest, extremity and skull)
Blood tests	Quest Diagnostics, Inc.	**$74** (average) $34 -CBC $114 – Lipid panel
Prescription meds (past 30 days)	2000 Scott-Levin source Prescription Drug and Diagnosis Audit, 2001 *Drug Topics*	Cases: $73.90/month (average cost of top 10 drugs used) Controls: $50.72/month (average of generic and brand Top 10 drugs)
Primary Care MD (PC) Medical Specialist (MS)	2001 Medicare Physicians/ Supplier summarized Report	**PC** SC: $59.30 NC: $62.20 **MS** SC: $59.24 NC: $66.42
Change in work status	2001 US Department of Labor, Bureau of Labor Statistics	Amt. ($)/year by state

4.1.3 Analysis of Prescription Costs

Cases and controls were asked how many prescription medicines were taken in the past 30 days. For cases, a list of all prescription medicines for any reason was also obtained. For those patients who had their prescription bottles available during the time of the interview, they were asked to read the name on each label. If the prescriptions bottles were not handy during the interview, cases were asked to respond "yes", "no" or "don't know" to a list of drugs commonly taken for lupus. Controls were not asked for a listing of their medications. Drug use among controls were obtained from the 2001 list of the top 200 brand-name and generic drugs listing (by total retail dollars), published by the January 1, 2002 edition of *Drug Topics*. Average costs were derived from the top 10 generic and brand-name drugs.

The Top 10 medications reported by patients were used as a proxy for lupus medication costs (Table 4.1.2). The average prices were obtained from the prescription price checker (http://www.drugstore.com/). If a medication had more than 1 dosage, the median dosage was used and converted to a monthly cost. For controls, only the number of prescription medications taken in the past 30 days was obtained. The 2001 Top 10 (by total retail dollars) brand-name and generic drugs from *Drug Topics* 2001 "Top 200" list (http://www.drugtopics.com/drugtopics/article/articleList.jsp?categoryId=7604) was used to obtain medication prices for controls. Similar to the methodology used for cases to calculate costs, the prescription price checker was used to calculate monthly costs for controls.

Table 4.1.2 Most Common Prescriptions Among Carolina Lupus Study Patients

Rank	Medication	No. of times reported*
1	Prednisone	76
2	Plaquenil	57
3	Hydroxychloroquine	33
4	Prevacid	18
5	Prilosec	18
6	Vioxx	18
7	Celebrex	17
8	Folic_Acid	17
9	Premarin	17
10	Imuran	15
11	Atenolol	14
12	Norvasc	14
13	Coumadin	13
14	Fosamax	13
15	Furosemide	12
16	Synthroid	12
17	Darvocet	11
18	Amitriptyline	10
19	Lasix	10
20	Lipitor	10
21	Lotensin	10

*among 199 patients in follow-up study, based on listing of all prescription medications taken in the past 30 days.

4.1.4 Analysis of Physician Costs

Primary care and medical specialist costs for services were obtained from the 2001 Medicare Physicians/Supplier reimbursement report for CPT code 99213. The nature of problem for this code is defined as moderate or low severity for an established outpatient visit meeting 2 of 3 key components amongst evaluation and management of 1) expanded problem focused history 2) expanded problem focused exam and 3) low complexity medical decision with a physician time of 15 minutes. For North Carolina and South Carolina patients the Medicare reimbursement rate was multiplied by a factor of 2 which is customarily done by medical offices to charges for insured and private pay patients. Separate costs were derived for primary care and medical specialists.

4.1.5 Analysis of Job Loss (Indirect Costs)

The baseline questionnaire included a job history for all jobs held at least 12 months from age 16 to the time of the baseline interview, including part-time and seasonal work. Information was collected on various aspects of work history, job titles, main activities or job duties, hours worked per week and months per year. This information was used to define the job held during diagnosis year for cases. Controls were only asked those questions regarding the number of hours they worked for the year in question and the previous year.

The 2001 follow-up questionnaire asked about work status in the preceding year. Cases and controls who previously worked before diagnosis and reference year, respectively, but who were not working at the follow-up assessment, were asked to indicate the reason they were no longer working. Choices included health reasons, stoppage due to supervisor/coworker conflicts, being laid off, there no longer being a need to work, and non-health retirement.

I first examined the frequency distribution among cases and among controls of the "job loss" outcome variable, and the health-related absences due to health using PROC FREQ (chi-square option) and PROC UNIVARIATE commands, respectively. Unadjusted logistic regression (PROG logistic descending) was then used to identify those covariates individually associated with loss of job, which were then examined as potential confounders of the association between case-control status and loss of job because of health.

For patients and controls no longer working because of health, estimates for lost wages were calculated based on the given job title and description. Job titles were

matched with employment descriptions from the 2001 U.S. Department of Labor; Bureau of Labor Statistics Occupational Employment Statistics report. Median hourly and weekly salaries were recorded for each participant who provided a job title using the appropriate state chart. Descriptive statistics were computed for annual salary loss for cases and controls using the SAS "PROC UNIVARIATE" procedure among all participants who had left work because of health (to see the extent to which there were differences in the salaries of the jobs that cases had left compared with the jobs that controls had left). I then compared the salary loss average across all participants (so that if there had been no loss of job because of health, the salary loss was computed as "0") using "PROC NPAR1WAY" to ascertain case-control differences using non parametric procedures.

4.2 Results

4.2.1 Direct Costs

Health utilization costs between cases and controls were significantly different for 9 out of the 10 health services used to compare 2001 patient direct health care costs. The mean total direct cost for cases and controls were $12,375 and $3,718, respectively ($p<.0001$) (Table 4.2.1). Among cases, the biggest components of direct costs were prescription medication ($5,061) and in-patient hospitalization costs ($2,685) which represented 41% and 22%, respectively, of total direct costs. Similar in percentage of total direct costs to that for cases, prescription costs accounted for 41% of direct costs ($1,533) for controls, and in-patient hospitalization attributed to 16% of direct costs ($608). Annual median costs for in-patient hospitalization, nursing home, in-home nursing, emergency room, and outpatient surgery were $0 for both cases and controls (Table 4.2.1). For cases, nursing home and primary care physician costs were very small contributors of direct costs. Nursing home and in-home nursing care were also small contributors of direct costs for controls.

Due to the skewness in the distribution of the cost data, the natural logarithm was used to achieve a more normal distribution so that parametric methods could be used to detect differences between cases and controls and predict factors associated with changes in cost. Geometric means between cases and controls were significantly different ($p<.0001$). Figure 4.2.1 shows the histogram of the transformed costs for cases and controls. This graph shows the normal distribution shape which satisfies the major assumption for subsequent advanced statistical analyses.

Total direct costs were correlated to in-patient hospital ($r = 0.81$; $p<.0001$), out-patient surgery ($r = 0.53$; $p<.0001$), specialist ($r = 0.54$; $p<.0001$) and medication prescription ($r = 0.62$; $p<.0001$) costs. Similar correlations were seen among controls: total direct costs were correlated to in-patient hospital ($r = 0.65$; $p<.0001$), out-patient surgery ($r = 0.53$; $p<.0001$), and medication prescription ($r = 0.72$; $p<.0001$) costs.

Among cases, unadjusted and adjusted demographic and clinical variables were modeled to determine relative predictors of transformed costs (Table 4.2.2 and Table 4.2.3). Patients in the less than high school group were associated with a 56% increase in total costs compared to those who completed college ($p=.04$). Serositis was associated with a 37% increase in total costs ($p = 0.04$) and renal involvement was associated with a 36% increase in costs ($p = 0.07$). Neurological problems (seizures and/or psychosis) was associated with a 66% increase in costs ($p = 0.07$). Adjusting for race, age at follow-up, and sex, reported significant increases in costs grew even larger. Patients in the less than high school group were associated with a 63% increase in total costs compared to those who completed college ($p = 0.03$), and serositis was associated with a 40% increase in costs ($p = 0.02$).

Table 4.2.1 Annual health utilization costs for cases and controls, in 2001 US $

	Costs in Cases (n=198)			Costs in Controls (n=299)			
Health Service	Mean (sd)	Median (Min, Max)	% of Direct Costs	Mean (sd)	Median (Min, Max)	% of Direct Costs	p-value
Hospital nights	2685 (7125)	0 (0, 48574)	22	608 (2521)	0 (0, 27757)	16	0.0001
Nursing home	29 (265)	0 (0, 3263)	0.2	3 (74)	0 (0, 816)	0.1	0.17
In-home nursing	403 (2687)	0 (0, 24687)	3	18 (184)	0 (0, 2374)	.5	0.04
ER*	818 (1555)	0 (0, 10515)	7	202 (607)	0 (0, 5258)	5	<.0001
Outpatient Surgery	1370 (5759)	0 (0, 71840)	11	493 (1339)	0 (0, 12572)	13	0.03
X-rays*	200 (309)	143 (0, 1716)	2	106 (199)	0 (0, 1144)	3	0.0002
Blood tests*	643 (952)	296 (0, 7252)	5	180 (545)	74 (0, 7326)	5	<.0001
Rx	5061 (3654)	4434 (0, 22170)	41	1533 (3674)	609 (0, 60255)	41	<.0001
Primary Care Physician	318 (373)	187 (0, 2488)	0.4	191 (226)	609 (0, 2301)	5	<.0001
Medical Specialist	841 (946)	531 (0, 6775)	7	241 (435)	66 (0, 3653)	7	<.0001
Total Direct Costs	12375 (13723)	8008 (0, 93629)	100`	3718 (6135)	2207 (0, 61383)	100`	<.0001

*Data for only 196 cases and 250 controls were available.
`Rounded total

Figure 4.2.1 Histogram of logarithm total costs for cases (n=198) and controls (n=299), in 2001 US $

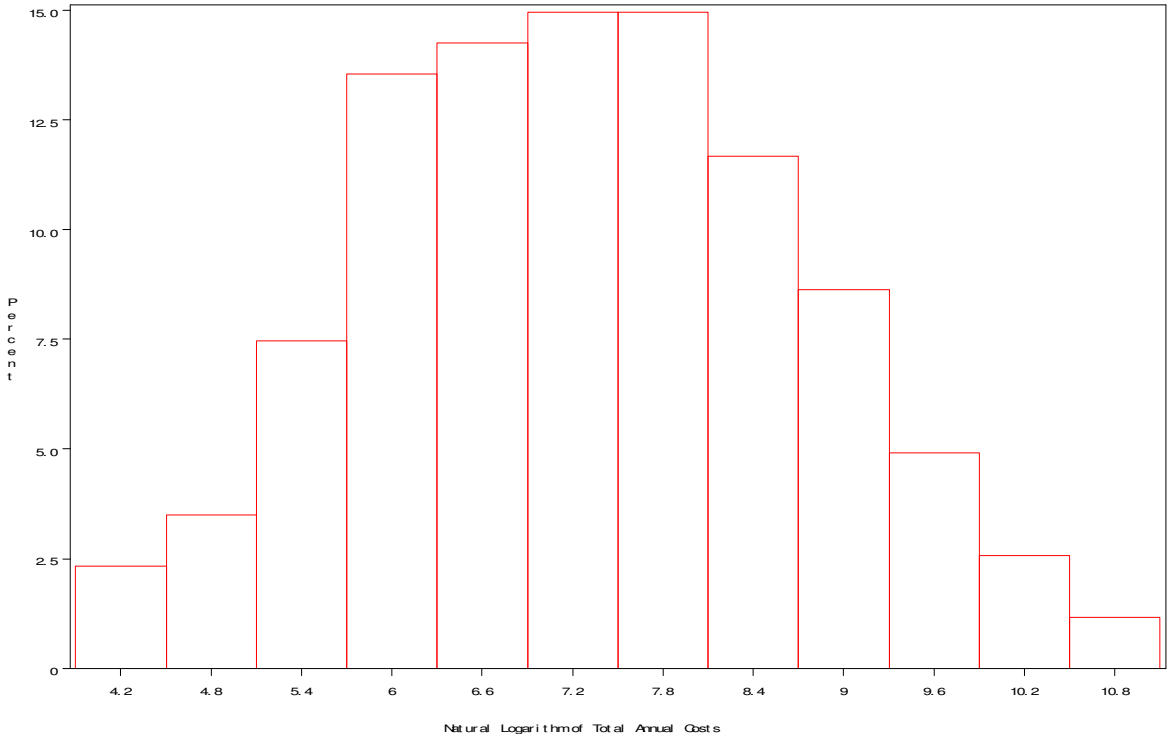

Table 4.2.2 Demographic Predictors of the Logarithm of Total Costs in 2001 dollars amongst SLE Patients (n=198)

Dependent Variable: **Log-transformed Total Cost**	**Unadjusted**		**Full Model***	
	β (S.E)	**p-value**	**β (S.E)**	**p-value**
Age (per year)	-0.01 (0)	0.24	-0.005 (0.006)	0.39
Gender				
males	-0.35 (.29)	0.23	-0.26 (0.30)	0.38
females	referent			
Race				
African-Americans and others	0.20 (.18)	0.27	0.13 (0.19)	0.48
whites	referent			
Education				
did not complete high school	0.56 (.27)	**0.04**	0.63 (0.28)	**0.03**
completed high school	0.32 (.25)	0.19	0.34 (0.25)	0.18
some college	0.37 (.23)	0.12	0.38 (0.23)	0.10
completed college	referent		referent	
State				
North Carolina	0.01 (0.21)	0.96	0.03 (0.19)	0.87
South Carolina	referent		referent	
Type of Rheumatology Practice				
University	0.02 (0.17)	0.93	-0.02 (0.18)	0.89
Community	referent		referent	

*Full model adjusts for age (per year), gender, and race.

Table 4.2.3 Clinical Predictors of the Logarithm of Total Costs in 2001 dollars amongst SLE Patients (n=198)

Dependent Variable: **Log-transformed Total Cost**	**Unadjusted**		**Full Model***	
	β (S.E)	**p-value**	**β (S.E)**	**p-value**
Arthritis				
present	0.23 (.20)	0.24	0.29 (0.33)	0.15
absent	referent		referent	
Pericarditis				
present	0.45 (.25)	0.08	0.42 (0.25)	0.10
absent	referent		referent	
Pleuritis				
present	0.26 (.18)	0.14	0.29 (0.18)	0.10
absent	referent		referent	
Renal disease†				
present	0.36 (.20)	0.07	0.34 (0.22)	0.12
absent	referent		referent	
Seizures or psychosis				
present	0.66 (.36)	0.07	0.60 (0.36)	0.10
absent	referent		referent	
Serositis				
present	0.37 (.17)	**0.04**	0.40 (0.17)	**0.02**
absent	referent		referent	
Thrombocytopenia				
present	0.27 (.27)	0.32	0.32 (0.28)	0.27
absent	referent		referent	

*Full model adjusts for age (per year), gender, and race.
† Renal disease lupus nephritis based on kidney biopsy

4.2.2 Indirect Costs

In the 2001 follow-up study, 51 cases (26%) and 22 controls (7%) reported they had stopped working since diagnosis/referent year (Table 4.2.4). The biggest difference in reasons given for having stopped work was because of health, with 92% of cases compared with 36% of controls who were no longer working indicating this as a reason. Among participants who were working, however, there was little difference in the amount worked (in hours per week of months per year). Twenty-one percent of cases, compared

with 11% of controls, reported an absence from work because of health of 15 or more days during the last year. In the entire period from diagnosis (or corresponding reference year for controls), 28% of cases compared with 9% of controls were unable to work for a period of 2 or more months.

For unadjusted results using logistic regression, cases were 10 times more likely than controls to have had job loss because of health (odds ratio = 10.03, 95% CI 4.8, 21.0). College graduates were less likely to quit their jobs due to health compared to non college graduates (odds ratio = 0.3, 95% CI .13, 0.67). After adjusting for race, education level and gender, cases were 8 times more likely to quit their jobs for health reasons compared to controls (odds ratio = 8.38, 95% CI 3.9, 18.0). Among cases, college graduates were less likely to quit their jobs due to health compared to non college graduates (odds ratio = 0.31, 95% CI 0.11, 0.83). After adjusting for race, college graduates were still less likely to quit their jobs due to health compared to non college graduates (odds ratio = 0.35, CI .15, 0.80).

The average salary was somewhat lower in cases compared with controls who were no longer working because of health, but the difference was not statistically significant ($p = 0.4$). The annual mean salary was $21,540 (sd 11215) among the 47 cases and $24,909 (sd 9399) among the 9 controls who had stopped working for this reason. Median salary levels were also lower in the cases ($17,971, compared with $21,785 in controls). When averaged across the full follow-up sample (199 cases and 298 controls), the average annual cost of wages lost due to illness was $5,113 and $749 in cases and controls, respectively ($p<.0001$).

Table 4.2.4 Work Status of Cases and Controls

		Patients (n = 198)		Controls (n=299)	
		N	(%)	N	(%)
Working 10+ hrs/week at diagnosis		141	(71)	222	(74)
Work status at follow-up					
Reasons Stopped Working (total n) (could choose more than 1 reason)		51	(26)	22	(7)
	Did not like job, supervisor	0	(0)	2	(9)
	Job ended, laid off	4	(8)	6	(27)
	No longer needed to work	1	(2)	6	(73)
	Retired (other than health)	2	(4)	3	(14)
	Health	47	(92)	8	(36)
Hours per week (median)		40		40	
24 or less		12	(12)	20	(11)
Months per year (median)		12		12	
3 or less		12	(12)	19	(10)
Days lost last year because of health (median)		10		6	
15 or more days		21	(21)	24	(11)
Unable to work more than 2 months since diagnosis		25	(28)	14	(9)

4.3 Discussion

Among 9 out of 10 of the health services used to calculate total costs, cases incurred significantly more costs than controls. Only with nursing home costs were there no differences in costs between the two groups. There are no published studies which compare medical expenditure costs of SLE patients to matched-controls. However, in an effort to highlight the significant cost disparity between the US population who suffers from arthritis and other rheumatic conditions compared to those without any chronic conditions, Yelin *et al* calculated estimates of the total medical care expenditures with arthritis and other rheumatic conditions from data derived from the 1997 Medical Expenditures Panel Survey (MEPS). They reported that arthritic conditions accounted for a mean of $4865, and persons with no chronic conditions only accounted for $500 in 1997 total mean expenditures. The type of health care expenditures used to calculate expenditures included office-based and hospital outpatient, ER, home healthcare, prescriptions dental visits and other medical supplies and equipment expenditures to calculate health care expenditures (Yelin, Cisternas et al. 2004). Similar to the methods utilized in Yelin's study, I used data from the Medical Expenditures Panel Survey (2001) to calculate in-patient hospital stay, in-home nursing and ER costs, but I used the data to calculate cost-per patient.

Prescription costs and in-patient hospital stays accounted for the largest percentages of total costs for cases (41% vs. 22%). In a study comparing health care expenditures between SLE patients in Stanford, CA and Montreal, Quebec, Gironimi reported that 35% of 1991 direct costs incurred by US patients were for diagnostic

procedures/therapeutics followed by hospital care at 25%. Prescription medications accounted for 10% of all direct costs in this cohort (Gironimi, Clarke et al. 1996). Total direct costs for the US cohort were $10,530. Those services which comprise the largest percent of direct costs are for services which a patient has little or no flexibility in reducing to save costs.

I identified lower education, serositis, nephritis, and neurological involvement as predictors of direct cost among SLE patients. Currently there are no US studies which examine predictors of costs between SLE cases and matched-controls. Ann Clarke, one of the leading SLE cost analyst in the world, performed the first prospective SLE cost-identification study and identified various components of cost. Direct 1989 costs, serum creatinine value, and level of physical functioning explained 20% to 26% of the variance in the model. When costs were divided into low and high direct costs, stepwise linear regression revealed that the level of support, creatinine value, employment/education interaction, level of physical functioning, and marital status were the strongest predictors of cost by accounting for 19% of the cost variance. Amongst the high direct cost group, disease duration and level of social support explained 42% of the cost variance (Clarke, Esdaile et al. 1993). Seven years later, Sutcliffe in his tri-nation study (co-authored with Clarke) reported that disease activity and end-organ damage were positively associated with direct costs, and that age and technical competence were negatively associated with direct costs (Sutcliffe, Clarke et al. 2001). Results from these studies suggest kidney involvement as one of the major causes of in-patient hospitalization, thus significantly contributing to overall health expenditures.

Forty-seven cases (24%) compared with 8 (3%) controls reported they had stopped working because of their health, and the differences between these groups in absences due to health was also quite strong (e.g., 21% of cases compared with 11% of controls reported losing 15 or more days of work due to illness in the past year). These statistics elucidate the overwhelming inability of patients to work due to physical limitations.

The mean salary between cases and controls who no longer worked as a result of health reasons were similar. However, further analysis reported that the actual job loss created by the individual no longer being in the workforce was considerable. Cases reported a job loss mean of $5,113 compared to a mean of only $750 for controls (Figure 4.2.3). This is an illustration of the considerable impact SLE patients absence has on the workforce with implications to non-market work in the home. These mean values of job loss are an underestimate of the actual loss of productivity due to the disproportionate number of women who are affected by SLE. Clarke reported on how the long term job absenteeism and diminished non-labor did not use gender neutral wages and jeopardize resources for women's diseases like lupus (Clarke, Penrod et al. 2000).

The limitations of this cost analysis are those which are typical to any health care medical cost analysis. The most obvious is recall bias. Costs were based upon responses given by patients and controls of services they utilized over the preceding 12-month period. Because of the per person cost analysis approach of this study, a value for each health care cost had to be determined. There are many sources which provide this information in aggregate. Due to the large number of specific health components, no one source existed to obtain this information on a per-person basis. As a result, the variability

in cost estimates for each type of medical service varies. An attempt was made to limit variability in costs as much as possible. Figures provided by the Medical Expenditure Panel did provide geography-specific values. The southern geographic area (the geographic area of Carolina Lupus patients and controls) were used for all three components where MEPS values were available (in-patient hospitalization, in-home nursing and ER costs). Some costs were only available for specific years, as a result figures had to be converted to 2001 US dollar values using the Consumer Price Index medical conversion rates.

Despite the labor-intensive methodology for identifying a cost-person amount for each type of health care service, the total costs estimates were different by only $1000-$2000 based upon adjustments to total costs calculated in limited previous US studies, and adjusted for 2001 figures. More importantly, cost data was derived from highly validated national databases which easily allow one to calculate costs on a per-person basis. Since Carolina Lupus participants represented only two states, the geographic sub-cost analysis was extremely useful, and conversions to 2001 figures weren't necessary for many of the cost data sources since they just happened to be reported in the same year of interest for this study.

In a time of rising medical costs, patients, providers, and insurers are constantly trying to institute cost cutting measures across the board. One area which warrants much attention is number of service used within a specific period. One of the major advantages to this study is that cost were calculated with one only needing to know the number of services used for the period of interest. Despite the condition and length of period, one can apply the same algorithm to calculate costs for any chronic and even acute disease as

long as the quantity and duration of health service use is available. The most complex calculations and those likely to produce a more variable figure were prescription costs which calculated costs by a ranking of the most common prescriptions used by cases compared to a ranking of the top generic and brand named drugs for controls. This procedure is still much easier methodology than trying to calculate a per unit prescription cost which is used in Canada and the United Kingdom. Future research could implement sensitivity analysis to examine the effect of various costs.

There still remains much debate on how to handle non-normal cost data. Many researchers endorse a transformation of the skewed data, while others suggest retaining the original data and making inferences using confidence intervals obtained by bootstrapping methods. Another group recommends using the median and making inferences via non-parametric methods (Mann-Whitney U test). I chose the former approach and accept the disadvantages of difficulty in the interpretation of results. Despite the above limitations, total mean cost differences in health care and missed work/job loss confirm the major multifaceted disparity experienced by lupus patients.

4.4 References

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Discussion

This study elucidated the humanistic, clinical and economic burden experienced by SLE patients through the identification of significant differences in health-related quality of life, 5-year mortality, and job loss between SLE patients and matched-controls using select information obtained from baseline and follow-up assessment interviews.

In order to identify directions for future research, it is imperative to highlight briefly those factors which may have limited the robustness of results found in this study. These specific issues include the study design matching methodology for controls and the use of limited clinical information to assess 5-year mortality and costs differences between cases and controls and among patients.

Cases and Age-, Sex-, and State-Matched Controls

Table 2.1.1 reported that 60% of the cases and only 28% of age-, sex-, and state-matched controls at baseline assessment were African American. The racial distribution of the controls reflects the racial distribution of the study area from which the cases were drawn; the increased prevalence of African-Americans among the cases is clear evidence of the disproportionate impact of SLE on this group. Also, among the cases, there was a 6-year younger mean age at diagnosis among African Americans and other minorities compared to whites ($p < 0.01$), and African-American patients more commonly presented with discoid lupus, proteinuria, anti-Sm and anti-RNP autoantibodies with an odds ratios higher than 3.0 (Cooper, Parks et al. 2002). This sampling frame, based on the study area population, allowed the examination of the effect of race as a risk factor, and the extent to

which other factors contribute to the observed association between risk of SLE and ethnicity. All analyses of risk factors were first in separate race-strata (African Americans and other minorities, whites) to determine if the observed associations were similar in the two groups, and ethnicity was also assessed as a possible confounder. However, the relatively small number of African-American controls (total n at baseline = 99, total n at follow-up = 60), limited the statistical power for the race-specific analyses, particularly for relatively uncommon exposures. Given the importance of race in the incidence and expression of this disease, further research involving SLE population-based cases and controls could plan for a larger sampling frame for minority groups (for example, by using a 2:1 or higher control:case selection frame for African-Americans, and 1:1 for whites). This would effectively oversample African-Americans controls compared to a random sample, and allow for greater statistical power and precision of the observed associations within this group. With a larger sample of controls you can do more within race analyses, which is important if the severity of disease differs significantly by race. This would allow you to identify important risk factors within a race group whereas analyses with a smaller control sample could result in spurious results due to sparse strata.

Comorbidities

This study concentrated on a few clinical features typically present in lupus patients. In addition to the presence of arthritis, nephritis, serositis, thrombocytopenia, neurological involvement, and a host of autoantibodies, other comorbidities reported included headaches, hypertension, cardiovascular disease, and malignancies. Use of the

variables may have provided additional information regarding factors associated with mortality and higher costs amongst SLE patients. However, in the analyses focusing on differences between cases and controls, adjusting for any of these comorbidities may be "over-adjusting" to the extent that these comorbidities are the result of SLE.

Markus prospectively studied the association between migraines in his 90 SLE patient and 90 age- and sex-matched controls to phospholipids autoantibodies. Not only was there a significant difference in the presence of migraine among cases compared to controls [31(34%) vs 15(16%); $p<0.05$], but an association between migraines and SLE disease activity was also reported (Markus and Hopkinson 1992). This study identified yet another component, SLE disease activity, available in the Carolina Lupus that could have been included to provide additional important clinical information on SLE patients. A later studied conducted by Sfikakis indicated that headache was not specifically related to SLE severity. He further cautioned researchers that accepting headaches as a neurological manifestation of SLE in the absence of seizures or overt psychosis may result in overestimation of the disease status (Sfikakis, Mitsikostas et al. 1998). Perhaps the use of migraines or headaches in general could have provided information as to the actual role of headaches if it had been used, especially since Markus used similar matching covariates to identify controls.

A recent study by Ward identified factors associated with in-hospital mortality amongst 3839 SLE patients in California who were diagnosed from 1996 to 2000. Using a relatively new type of analysis, random forests, Ward identified the Charlson Index, respiratory failure, and the SLE Comorbidity Index as important predictors of mortality amongst 109 SLE patients (Ward, Pajevic et al. 2006). Future studies with the Carolina

Lupus Study could utilize the existing and highly validated SLE Comorbidity Index. This is yet another tool not used which could have been useful in the identification of the multifaceted burden of SLE.

The implications of these results suggest a need for newer treatment and therapies for patients to improve lower quality of life and survival rates amongst patients. In addition there is a need to evaluate health policies to reduce the extraordinary physical and mental strain SLE places on the patient, family, workforce, and insurance industry.

The results presented here are novel in that this is the first analysis of an US SLE and matched control population to examine costs and their predictors. The identification of the most appropriate, validated health services sources should be used as a model to examine the economic per-person burden of other chronic diseases.

Health-related quality of life and survival rates are improving for SLE patients. However, there is still room for improvement in decreasing the disparities between patients and controls. There are few US studies which thoroughly review the varied indirect costs (change in job status and financial repercussions) associated with SLE. More research needs to examine what these results mean to the groups who suffers from this disease disproportionately; women. More specifically, gender and racial interactions should be reviewed.

Future implications suggest research on SLE using as much available data as possible, specifically to include disease activity, disease severity, and comorbidities from the Carolina Lupus Study, that would allow one to further identify and compare the multidimensional burden to an even larger population of several studies that have been reported in the literature.

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Appendix A (Publication)

Lack of recording of systemic lupus erythematosus in the death certificates of lupus patients

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Objective. To determine to what extent the diagnosis of systemic lupus erythematosus (SLE) in deceased lupus patients is underreported in death certificates, and the patient characteristics associated with such an occurrence.

Methods. The death certificates of 76 of the 81 deceased SLE patients from two US lupus cohorts (LUMINA for Lupus in Minorities: Nature vs Nurture and CLU for Carolina Lupus Study), including 570 and 265 patients, respectively, were obtained from the Offices of Vital Statistics of the states where the patients died (Alabama, Georgia, North Carolina, South Carolina, Tennessee and Texas). Both cohorts included patients with SLE as per the American College of Rheumatology criteria, aged¸16 yr, and disease duration at enrolment of ·5 yr. The median duration of follow-up in each cohort at the time of these analyses ranged from 38.1 to 53.0 months. Standard univariable analyses were performed comparing patients with SLE recorded anywhere in the death certificate and those without it. A multivariable logistic regression model was performed to identify the variables independently associated with not recording SLE in death certificates.

Results. In 30 (40%) death certificates, SLE was not recorded anywhere in the death certificate. In univariable analyses, older age was associated with lack of recording of SLE in death certificates [mean age (standard deviation) 50.9 (15.6) years and 39.1(18.6) yr among those for whom SLE was omitted and included on the death certificates, respectively, P=0.005]. Patients without health insurance, those dying of a cardiovascular event and those of Caucasian ethnicity were also more likely to be in the non-recorded group. In the multivariable analysis, variables independently associated with not recording SLE as cause of death were older age [odds ratio=(95% confidence interval) 1.043 (1.005–1.083 per yr increase); P=0.023] and lack of health insurance [4.649 (1.152–18.768); P=0.031].

Conclusions. A high proportion of SLE diagnoses are not recorded in death certificates. Older patients and those without health insurance are more prone to have SLE not recorded. These findings do have implications for the assessment of the impact of this disease in epidemiological studies conducted using vital statistics records.

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Appendix B (Abstracts)

IN ONE THIRD OF DECEASED LUPUS PATIENTS, SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) IS NOT RECORDED IN THE DEATH CERTIFICATE: IMPLICATIONS FOR EPIDEMIOLOGICAL STUDIES.
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The University of Alabama at Birmingham (UAB)[1], Case Western Reserve University[2] and NIEHS/NIH/DHHS[3]
Abstract of the American College of Rheumatology Annual Meeting
October 16-21, 2004

"Understanding the Burden of Disease: New Results from the Carolina Lupus Study"
Presented by: Dr. Glinda Cooper & **Robert Campbell, Jr**., Pre-doctoral Fellow
Epidemiology Branch, Environmental & Molecular Epidemiology Section
National Institutes of Environmental Health Sciences (NIEHS)
Seminar and Video
October 7, 2004

PREVALENCE OF DISABILITY AMONG LUPUS PATIENTS AND CONTROLS: THE IMPACT OF LUPUS ACROSS MULTIPLE DIMENSIONS OF HEALTH"
*GS Cooper, **R Campbell**, CG Parks, M Dooley, GS Gilkeson, B St. Clair, EL Treadwell*
Abstract of the 36th Annual Meeting for the Society for Epidemiologic Research/Poster Presentation
June 11-14, 2003