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Timing and Predictors of Incident Cardiovascular Disease in Systemic Lupus Erythematosus: Risk Occurs Early and Highlights Racial Disparities

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Abstract

Objectives: Systemic lupus erythematosus (SLE) affects Black people two to three times more frequently than non-Black people and is associated with higher morbidity and mortality. Four predominantly non-Black SLE cohorts highlighted that cardiovascular disease (CVD) is no longer primarily a late complication of SLE. This study assessed the timing and predictors of incident CVD in a predominantly Black population-based SLE cohort.

Methods: Incident SLE cases from the population-based Georgia Lupus Registry were validated as having a CVD event through review of medical records and matching with the Georgia Hospital Discharge Database and the National Death Index. The surveillance period for an incident CVD event was over a 15-year period, starting from two years prior to SLE diagnosis.

Results: Among 336 people with SLE (75% Black), 56 (17%) had an incident CVD event. The frequency of CVD events peaked in the second and eleventh year after SLE diagnosis. There was 7-fold higher risk of incident CVD over the entire 15-year period, 19-fold in the first 12 years, in Black compared to non-Black people with SLE. Black people with SLE ($p<0.0001$) and those with discoid rash (HR 3.2, 95% CI 1.4–7.1) had higher risk of incident CVD events.

Conclusion: The frequency of incident CVD events peaked in the second and the eleventh year after SLE diagnosis. Being Black or having a discoid rash were strong predictors of an incident CVD event. Surveillance for CVD and preventive interventions, directed particularly towards Black people with recent SLE diagnoses, are needed to reduce racial disparities.

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Keywords

SLE; Incident cardiovascular disease; Early risk; Racial disparities; Predictors

INTRODUCTION

Systemic lupus erythematosus (SLE) is a leading cause of mortality in young women, with a three- to five-fold higher mortality rate and an accelerated risk of cardiovascular disease (CVD) compared with the general population.[1–3] Previously, a bimodal distribution of mortality in SLE was observed, with deaths early in the disease course related to active SLE or infection and deaths later (>10 years) associated with CVD.[4] Also previously reported was a 16 to 52-fold higher risk of CVD in younger patients with SLE compared with healthy controls, with risk peaking around year 10.[5] More recently, four predominantly non-Black cohorts challenged the paradigm of CVD being mostly a late complication of SLE.[6–9] These studies also reported a higher risk of CVD around the time of SLE diagnosis.[6,7]

It is important to examine findings in communities of color given the significant racial disparities that exist, particularly in Black women. SLE afflicts Black women at a three-fold higher rate and at a significantly younger age compared with non-Black women.[10,11] Black women have a three-fold higher risk of developing nephritis compared with White women with SLE.[12] Black people with SLE have a three times higher risk of developing end stage renal disease (ESRD) compared with White people with SLE (15.3% vs. 4.5%).[10] Black women with SLE have three times higher risk of early death compared with Black women from the general population.[13] Moreover, Black people in the general population have higher rates of fatal coronary heart disease and stroke than White people after controlling for age.[14,15] However, most SLE studies of CVD have been in predominantly White cohorts,[5–7,16–18] limiting the generalizability of the findings.[11–13] This study assessed the timing and predictors of incident CVD events in a population-based cohort of predominantly Black people with incident SLE over a 15-year period.

METHODS

The Georgia Lupus Registry (GLR) is a Centers for Disease Control and Prevention supported population-based registry of residents of Atlanta, Georgia, meeting classification criteria for SLE. The GLR methods are described in detail elsewhere.[11] Briefly, the Georgia Department of Public Health (GA DPH) designated Emory University as its agent, allowing investigators to utilize the public health surveillance exemption to the Health Insurance Portability and Accountability Act Privacy Rule to obtain protected health information, including review of medical records, without written consent and ascertain cases on a population level.[19] The GLR protocol was reviewed and approved by the Institutional Review Boards at Emory University and the GA DPH (IRB #: IRB00003656).

The primary sources of case ascertainment included hospitals, rheumatologists, nephrologists and dermatologists in/around the catchment area. Administrative databases were queried for billing codes for SLE and related conditions. Other sources included

laboratories and queries of other population databases. Medical records were abstracted and regular data quality assessments were conducted.

SLE Case Validation:

Incident SLE cases were identified in the years 2002–2004 and defined as meeting either the 1997 update of the 1982 American College of Rheumatology (ACR) revised classification criteria for SLE or meeting three ACR criteria with a documented SLE diagnosis by the patient's board-certified rheumatologist.[20,21]

End-Stage Renal Disease (ESRD):

Validated SLE cases were matched with the United States Renal Data System database for 2002–2015 to capture ESRD after SLE diagnosis.

Race and Ethnicity:

Race/ethnicity was defined as reported in medical and administrative records and included physician or patient self-identified Black, White, Asian, and Hispanic groups. Very few sites reported race and ethnicity as separate categories, or included other racial/ethnic groups or mixed race. Less than 5% Hispanic ethnicity was recorded; thus groups were analyzed by race only (Supplementary File A).

CVD Event Ascertainment and Validation:

Incident SLE cases from the GLR from 2002–04 were matched to the Georgia Hospital Discharge Database from 2000–17 and the National Death Index 2002–2017 capturing all hospitalizations throughout the state and deaths across the nation. Surveillance for CVD events started 2 years prior to SLE diagnosis and continued for 13 years after diagnosis. CVD-related hospitalizations and deaths were identified following published algorithms using the first three codes for billing at hospitalization or cause of death.[22,23] CVD events were defined as: 1) ischemic heart disease, including myocardial infarction, coronary artery revascularization, abnormal stress test or echocardiogram, ≥50% abnormal angiogram and events documented by a cardiologist,[24,25] 2) cerebrovascular disease including thrombotic and ischemic stroke, and transient ischemic attack (TIA),[26] and 3) peripheral vascular disease (PVD), including abnormal ankle-brachial index, abnormal peripheral angiography, limb ischemia undergoing bypass or angioplasty, or documented by a surgeon. [27,28] Patients with baseline CVD were excluded and only the first event was included in the analysis.

Analysis—Descriptive results were reported as means ± standard deviations for normally distributed data or medians with ranges for data that were not normally distributed. The 15-year surveillance period was divided into three, based on the distribution of CVD events: Pre-SLE (2 years before SLE diagnosis until SLE diagnosis), Initial (SLE diagnosis through the 10th year after diagnosis) and Late (the 11th through the 13th year after SLE diagnosis) Periods (Figure 1).

We annualized rates of incident CVD events over the 15-year surveillance period. A particular period of incident CVD events was defined by the start of a unique peak followed by a downward trend. Trends over time were compared with each other using interrupted

time series analysis (ITSA).[29] We estimated coefficients using the Newey-West model and one-lag in each model and used the Cumby-Huizinga test for autocorrelation to confirm the correct model with lag one using STATA version 15.[30]

We categorized our data by age groups and sex similar to NHANES (2009–12) to calculate age-group and sex-specific rates of CVD and CVD subtypes in our lupus cohort. We then compared these rates with published rates of CVD subtypes categorized by age group and sex in general population over a 4-year period.[31] Additionally, we compared 7-year race-specific incidence of MI by age-group and sex in our lupus cases with the 7-year published incidence of MI (2005–12) and the annual rate of race-specific stroke in lupus vs. the healthy population.[31]

We examined Kaplan-Meier survival analyses by racial groups. We focused on two follow-up periods with accelerated risk of CVD occurrence derived from ITSA analysis: 1) the first 12-year follow-up period (Pre-SLE and Initial Periods, years −2 through 10 from SLE diagnosis) and 2) the full 15-year surveillance period. In these two periods, we examined predictors of incident CVD events using univariable and multivariable Cox proportional hazard models. Factors studied included sociodemographics, ESRD, and ACR criteria within one year of SLE diagnosis (Table 1).[21] ACR criterion with a p-value <0.1 in the univariable models, along with sociodemographics and ESRD were included in the multivariable analyses. We performed Schoenfeld residual analyses to verify that proportional hazards model assumptions were not violated for covariates.[32] We performed competing risk analysis to compare cumulative incidence of CVD events/deaths with cumulative incidence of non-CV deaths in our cohort. Lastly, we performed a separate analysis stratified by race to compare CVD events in Black with non-Black people with SLE.

We analyzed two racial groups: Black and non-Black. Non-Black people were mostly White along with a few Asian and Hispanic people. We performed a sensitivity analysis by excluding patients who did not report ethnicity and another sensitivity analysis stratifying Black and White racial groups and excluding the relatively few individuals from other groups. Additionally, we calculated e-values to quantify how extreme the bias from the unmeasured confounders would need to be to remove the effect of race on CVD incidence.[33] Statistical software R v3.4.1 was used.

RESULTS

Cohort Characteristics

Among 336 people with SLE, 87% were female with a mean age at SLE diagnosis of 40 ± 17 years, of whom 75% identified as Black, 22% White and 3% Asian (Table 1 & Supplementary Table B). ACR SLE classification criteria within one year of diagnosis are shown in Table 1.

Timing of Incident CVD Events

Figure 1 shows incident CVD event frequencies spanning 15 years of surveillance by CVD event type. A total of 56 patients with SLE (17%) had incident CVD: 33 were cerebrovascular disease, 20 were IHD, and three were PVD. The highest frequency of

incident CVD occurred in the second year after SLE diagnosis, with 7 of 9 events being cerebrovascular disease. A total of 36 CVD events (including 5 CVD-related deaths) occurred in the first 12 years (years −2 through 10). Mean ages at SLE diagnosis and incident CVD event were 45±17 and 49±17 years. All but one event occurred in Black persons with SLE. Thirty one were women and 5 were men. A total of 20 CVD events (including 1 CVD-related death) occurred in the final three years of surveillance (years 11 through 13) with mean ages at SLE diagnosis and incident CVD of 39±16 and 51±16 years. Seventeen CVD events occurred in Black persons while 3 events occurred in White persons with SLE. Eighteen were women and 2 were men.

Using a 4-year follow-up we noted that the rate of stroke was higher in women and men with SLE <40 years old (2% and 3.9%) compared with published rates of stroke in the healthy population (0.7% and 0.02%). (Supplementary Table C). However, we did not note higher rates of IHD in our cohort as most IHD events occurred later in our cohort.[31] We found two times higher incidence of MI (4.3 vs. 2.3 per 1000 person years) and seven times high annual stroke rate in Black women with lupus <55 years old compared with healthy Black peers (23 vs. 2.9 per 1000 persons) (Supplementary Table D).

Determination of CVD Event Periods

Using ITSA (Supplementary Figure E), three event periods emerged visually. Despite a visual breakpoint in year 2, this did not reach statistical significance (p-value = 0.06). Thus, the event periods were assigned as the first 12 years of surveillance (years −2 through 10) and the final 3 years of surveillance (years 11 through 13).

Kaplan-Meier (KM) Survival Analysis by Racial Groups

KM survival analyses examined differences in the timing of incident CVD stratified by race across the 15-year surveillance period showing significantly accelerated incident CVD in Black compared with non-Black people with SLE (p-value <0.0001) (Figure 2). Our sensitivity analysis stratifying Black vs. White racial groups was similar (p-value <0.0001, data not shown). Finally, using competing risk analysis, we noted no statistical difference between cumulative incidence of CVD events including CV related deaths vs. cumulative incidence of non-CVD related deaths in our cohort (p-value = 0.97, Supplementary File F).

Multivariable Cox Modelled Predictors of Incident CVD in SLE

In the first 12-year surveillance period (years −2 through 10), incident CVD event rates in Black people with SLE were 19-fold higher compared with non-Black people with SLE (Adjusted HR 19, 95% CI 3–142; Table 2). Age ≥65 years at SLE diagnosis, renal disorder and discoid rash were other predictors of CVD events. To estimate bias from unmeasured confounders, we found an e-value of 35 (e-values = 34.8), meaning confounders need to be associated with a 35-fold increase in CVD incidence for the causal effect of Black race on CVD to be truly null.

In the 15-year surveillance period, multivariable analysis (Table 3) showed that Black people with SLE had a seven-fold higher risk of incident CVD events over 15 years (Adjusted HR 7.3, 95% CI 2.4–22.0). Other multivariable predictors were age ≥65 years at SLE diagnosis,

renal disorder or ESRD (Adjusted HR 2.1, 95% CI 1.1–4.1), and discoid rash (Adjusted HR 3.2, 95% CI 1.4–7.1). An e-value of 14 (e-values 14.1) was found for this period.

Next, in a smaller Cox model stratified by race, discoid rash (Adjusted HR 3.1, 95% CI 1.4–6.9, Table 4; only Black patients: Adjusted HR 2.3, 95% CI 1.2–4.4, data not shown), renal disorder or ESRD (Adjusted HR 2.1, 95% CI 1.1–4.0), and age ≥65 years at SLE diagnosis remained strong predictors of incident CVD (Table 4).

DISCUSSION

To our knowledge, this is the first study that examined the risk, timing, and predictors of incident CVD events in a predominantly Black population-based incident SLE cohort. Incident CVD events occurred in 17% of our cohort over 15 years, with the highest frequency of CVD events in the second and the eleventh year after SLE diagnosis. We found that people identified as Black had the highest risk of incident CVD events, and we found discoid rash was a new predictor of incident CVD in SLE. We found a 19-fold higher incident CVD risk in Black people with SLE in the first 12 years of surveillance. Additionally, we found that the incidence of MI and annual stroke rate in Black women with SLE <55 years old were 2–7 times higher than peers.[31] Our study highlights racial disparities with a high rate of incident CVD events around the time of SLE diagnosis, particularly in Black patients, and points to discoid rash as a potential novel risk factor.

CVD-Related Morbidity and Mortality in SLE and Current Gaps in CVD Prevention

With advances in early diagnosis and treatment, the overall prognosis of SLE disease has dramatically improved, yet CVD remains a major cause of morbidity and mortality in SLE.[34] Relative to their peers, CVD is more common in premenopausal women with SLE, with a 50-fold higher CVD risk in ages 35–45,[5] and up to 16-fold higher risk of CVD-related mortality in patients <45 years.[5,34] A Medicaid study reported marked racial and ethnic variations in CVD events with 31% higher stroke occurrence in Black people with SLE compared to White people.[35] Yet, there is limited information on other population- and disease-based predictors, or on event timing to guide CVD prevention efforts in SLE.[34,36] Our study identifies patients with SLE who are at highest CVD risk to support further studies to implement and test CVD prevention efforts.

Timing of Accelerated CVD Risk in SLE

Historically, accelerated CVD risk was considered to be a late complication in SLE.[4,5,37–39] Multiple studies reported a median SLE duration of 7–10 years prior to incident CVD events. [4,5,37–39] However, recent studies reported SLE as an independent CVD risk factor and noted a key role of inflammatory cytokines and subclinical inflammation in accelerating atherosclerosis around the time of SLE diagnosis.[34,40] Bartels et al. reported that the risk of CVD was two-fold higher even two years before SLE diagnosis in a cohort of predominantly non-Black patients with SLE.[7] Similar studies in predominantly non-Black cohorts reported that the risk of CVD starts early, up to two years before SLE diagnosis, reaching 2–6 fold.[6–9]

Our study highlights that incident CVD events peaked twice, during the second and the eleventh years after SLE diagnosis. The early CVD peak in our study could depict

accelerated and premature atherosclerosis due to systemic inflammation from SLE or anti-phospholipid antibody mediated hypercoagulability leading to direct and indirect vascular intima damage.[6–9] Our findings in a predominantly Black SLE population-based cohort add to prior reports in predominantly non-Black populations, and challenge the paradigm that CVD is predominantly a late complication of SLE.[6–9] Therefore, these findings support clinical and public health efforts to implement CVD prevention early as well as late in the course of SLE disease, particularly in Black people with SLE.

Racial Disparities in CVD in SLE

CVD, including heart disease and stroke, is leading cause of death in the U.S. and the largest cause of reduced life expectancy in Black adults, making it an important focus in SLE, which disproportionately afflicts Black people.[10,11] Prior multiethnic SLE cohorts have reported high CVD event rates in Black people. For example, the Hopkins SLE cohort reported a 2.7-fold higher observed CVD event rate vs. expected CVD event rate using Framingham risk calculation in Black people with lupus (RR 2.8, 95% CI 2.0–3.5).[18] Likewise, the LUMINA multiethnic SLE cohort reported a higher CVD event rate in Black people (42%) compared to other racial/ethnic groups (37% in White people, 20% in Hispanic ethnicity), which approached but did not reach statistical significance (p-value = 0.07).[41] Moreover, a Medicaid study highlighted that Black race predicted 31% higher stroke risk compared with White people with SLE.[35] Our study supports these findings and is among the first to report striking racial disparities in incident CVD in SLE: 19-fold higher incident CVD risk in Black people during the first 12 years of surveillance. The comparator rate in our cohort was 5%, similar to the rates previously reported in other predominantly White SLE cohorts (1.6%[6], 3.6%[42], 9%[5,7]). We were unable to control for traditional risk factors, in our cohort which could have confounded some of our findings. However, based on our e-values, unmeasured confounders, including traditional risk factors, would have to be associated with a 35-fold increase in incident CVD in Black people with lupus, to explain our observed hazards ratio.[33] Previous studies have reported that traditional risk factors conferred only a 2- to 5-fold increase in risk of CVD events in people with lupus.[43] Moreover, recent studies in SLE and non-SLE patients have shown that Black race alone predicts 31–60% higher CVD occurrence, even after controlling for traditional CVD risk factors, further supporting our findings.[35,44]

Additionally, we found that the incidence of MI and annual rate of stroke in Black women with SLE <55 years old were 2–7 times higher than healthy peers.[31] Thus, based on these findings and the magnitude of our 19-fold CVD risk estimate in Black people with SLE, we believe that traditional risk factors alone would insufficiently explain the heightened CVD risk, particularly in young Black people with SLE in our cohort. Moreover, observed disparities remain unchanged from previous studies, thus, calling for investigations of timely preventive strategies, particularly in young Black women.

Predictors of CVD in SLE

There has been limited research on the role of discoid rash as a predictor of CVD. What is known is that Black people have five-fold higher incidence of discoid lupus than non-Black people with lupus.[45] Historically, discoid rash was considered to have better SLE prognosis,

with lower prevalence of nephritis.[46] One study of 155 patients with subacute and chronic cutaneous lupus erythematous (CCLE) reported a higher risk of stroke compared with a matched, non-cutaneous SLE cohort, even after controlling for smoking.[47] A Danish cohort reported a 1.3-fold higher risk of CVD in patients with CCLE with or without SLE, suggesting that chronic cutaneous inflammation may be a driver of low-grade systemic inflammation resulting in atherosclerosis.[48] Our study reported a strong association between the presence of discoid rash within the first year of diagnosis and CVD, independent of race, which supports previous findings that discoid rash may serve as a predictor of incident CVD in SLE.

Next, consistent with previous studies, we found that renal disorder or ESRD was a strong predictor of CVD supporting that severe renal inflammation could lead to direct and indirect damage to the vasculature contributing towards accelerated atherosclerosis.[18] Age >65 years at the time of SLE diagnosis was another strong predictor of incident CVD in our study. Our study and others note that despite milder SLE in late onset SLE, such groups face higher early CVD risk and mortality compared to peers.[7] This could be due to delays in diagnosing SLE due to late onset of symptoms or due to age accelerated CVD.[7]

Strengths of this study include the use of a large, predominantly Black, population-based incident registry with validated SLE cases and incident CVD events over 15 years of surveillance. We also acknowledge limitations. First, a few CVD events could be missed due to migration or unavailability of records. Second, White people with SLE were under-represented in our cohort however CVD rate in our cohort was similar to previously published CVD rates in other predominantly White SLE cohorts. Other racial groups were included in non-Black racial group due to small sample size. However, our sensitivity analysis stratified by White vs. Black racial groups revealed similar findings. Third, we did not individually match our cohort with the general population. Fourth, data for traditional CVD risk factors and anti-phospholipid syndrome (APS) were unavailable. Hydroxychloroquine and glucocorticoid use were not uniformly documented. We acknowledge that unmeasured APS, hydroxychloroquine, and other traditional risk factors may be confounders. Thus, we provided e-values that showed confounders need to be associated with a 35-fold increase in CVD incidence for the effect of Black race on CVD to be truly null. Further, a recent study highlighted that Black patients with lupus were 66% less likely to have clinically significant APS antibody profiles compared to White patients.[49] Finally, smoking status, a risk factor for both discoid rash and CVD, was not uniformly available, and the association between discoid rash and CVD could have been confounded by smoking exposure.

To summarize, this study contributes new information that the burden of CVD was 19-fold higher in Black people with SLE. CVD risk starts early during the second year after SLE diagnosis. Finally, we found discoid rash was a new potential predictor of future CVD events in SLE, which warrants further validation and mechanistic research. Future CVD prevention may focus on at-risk populations (young, Black, age ≥65 years) and disease characteristics such renal disease, discoid rash, with more aggressive screening and management of CVD risk factors to reduce disparities in lupus outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CDC Disclaimer:

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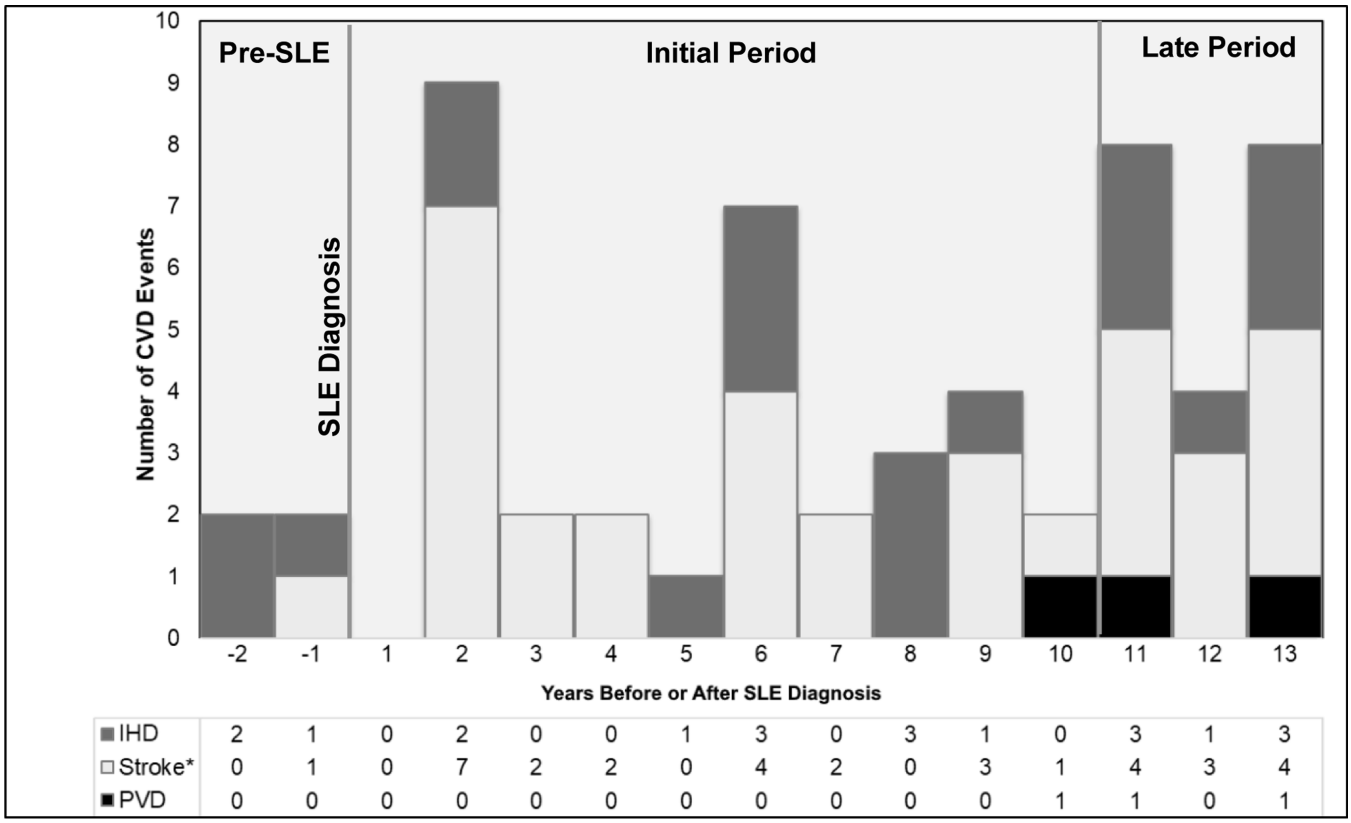


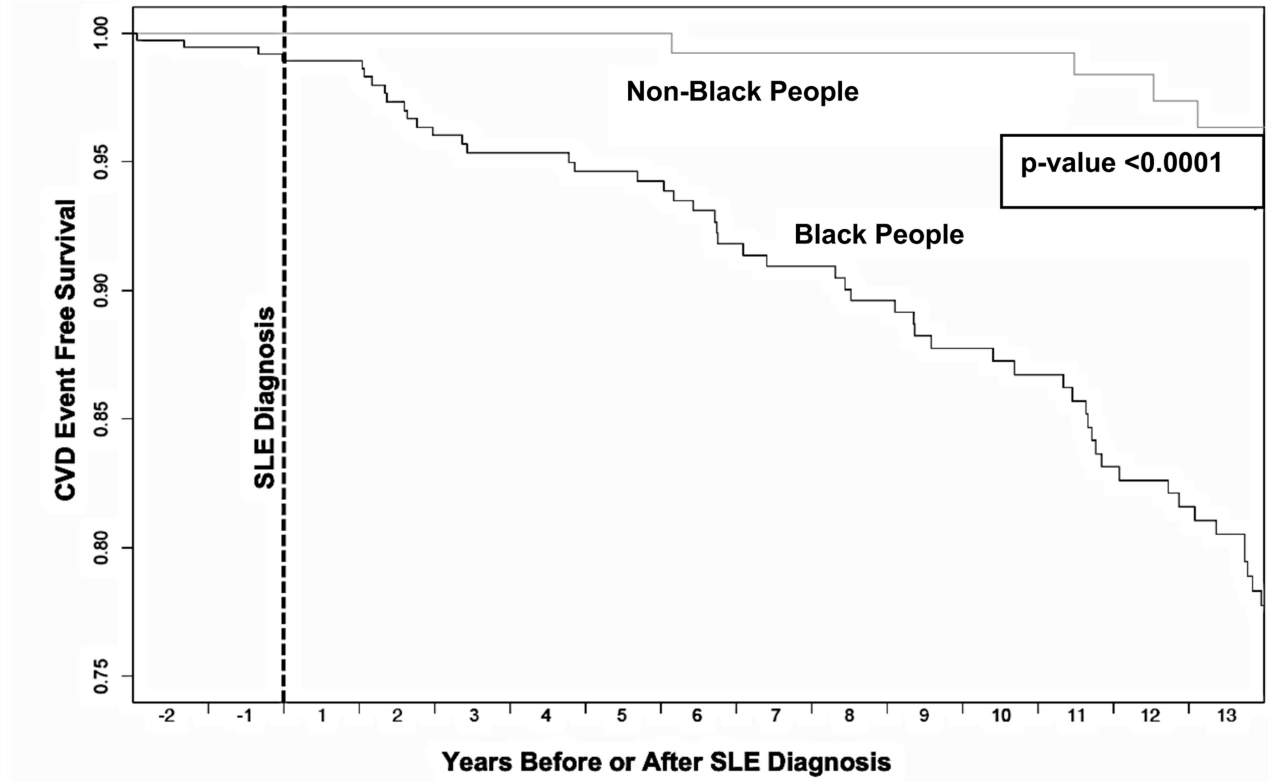
Figure 1.

Incident cardiovascular disease (CVD) events among 336 people with lupus over 15 years (from 2 years before through 13 years after SLE diagnosis), by CVD subtype.

Footnote: * Stroke includes Cerebrovascular Accident and Transient Ischemic Attack.

IHD=Ischemic Heart Disease; PVD=Peripheral Vascular Disease.

Bar heights reflect annual incident CVD. CVD subtypes are shown in color legend.



Number at risk

Time	Start	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13
Black	253	251	250	234	218	208	202	199	190	183	179	168	164	156	152	142
Non-Black	83	83	83	83	83	83	83	83	82	82	82	82	76	70	69	68

Figure 2.

Incident CVD event-free survival by Kaplan-Meier stratified by racial groups

Footnote: x-axis represents years before or after SLE diagnosis

Table 1.

Demographics and manifestations of 336 people with incident systemic lupus erythematosus from the Georgia Lupus Registry, 2002–2004

Characteristic	n (%)
Demographics	
Racial groups	
White	72 (22)
Black	253 (75)
Asian *	11 (3)
Age at SLE diagnosis, mean years ± SD	40 ± 17
<19	28 (8)
19 to <35	104 (31)
35 to <50	113 (34)
50 to <65	63 (19)
≥ 65	28 (8)
Sex	
Female	292 (87)
Male	44 (13)
ACR criteria within one year of diagnosis *	
Malar rash	64 (20)
Discoid rash	48 (14)
Photosensitivity	61 (19)
Oral ulcers	75 (22)
Arthritis	220 (66)
Serositis	118 (35)
Renal disorder	103 (31)
Neurologic disorder	31 (9)
Hematologic disorder	282 (84)
Immunological disorder	231 (69)
Antinuclear antibody	321 (96)
Other	
End stage renal disease (by 2015)	36 (11)

* Includes one patient with unknown race.

Table 2.

Cox proportional hazards model predictors of incident cardiovascular disease events over the 12-year surveillance period (2 years before through 10 years after SLE diagnosis)

Variables	Unadjusted Hazard Ratio (95% CI)	p value	Adjusted* Hazard Ratio (95% CI)	p value
Demographic				
Racial groups				
Non-Black	ref	ref	ref	ref
Black	**14.0 (2.0-102.0)**	**0.01**	**19.0 (3.0–142.0)**	**0.005**
Age at SLE Diagnosis (years)				
<19	ref	ref	ref	ref
19 to <35	0.4 (0.1–1.4)	0.4	0.5 (0.1–1.7)	0.3
35 to <50	1.0 (0.3–2.9)	0.8	1.4 (0.5–4.5)	0.5
50 to <65	0.9 (0.3–3.0)	0.8	1.4 (0.4–5.0)	0.6
≥65	1.5 (0.4–6.0)	0.8	**6.7 (1.6–29.0)**	**0.01**
Sex				
Male	ref	ref	ref	ref
Female	0.9 (0.4–2.4)	0.9	1.1 (0.4–2.9)	0.8
ACR criteria within one year of diagnosis or ESRD ** **(Yes vs. No)**				
Malar Rash	0.5 (0.2–1.5)	0.1	-	-
Discoid Rash	**2.3 (1.1-4.7)**	**0.03**	**3.5 (1.6–8.0)**	**0.002**
Photosensitivity	0.6 (0.2–1.6)	0.3	-	-
Oral Ulcers	1.2 (0.5–2.5)	0.7	-	-
Arthritis	0.8 (0.4–1.5)	0.4	-	-
Serositis	1.3 (0.7–2.6)	0.5	-	-
Renal Disorder or ESRD	**2.2 (1.1–4.0)**	**0.02**	**2.6 (1.3–5.0)**	**0.01**
Neurologic Disorder	1.4 (0.5–4.0)	0.5	-	-
Hematologic Disorder	1.3 (0.5–2.6)	0.6	-	-
Immunological Disorder	1.6 (0.7–3.5)	0.3	-	-
Antinuclear Antibody	1.6 (0.2–12.0)	0.6	-	-
ACR Criteria Total (>4 vs. ≤4)	1.2 (0.9–1.4)	0.2	-	-

*Hazard Ratios adjusted for age, sex, racial groups, and ACR criteria within 1 year of SLE diagnosis with p <0.1 on univariable analysis.

**ACR Criteria results from a Multivariable Cox Proportional Hazards Model that included ESRD. Results reported for criterion with p<0.1 on univariable analysis. All ACR criteria were within 1 year of SLE diagnosis. ESRD was through years 2002–2015. All hazard ratios for variables with significant p values (<0.05) are shown in bold. Abbreviations: ESRD=end stage renal disease. Ref=reference. SLE=systemic lupus erythematosus. ACR=American College of Rheumatology.

Table 3.

Cox proportional hazards model predictors of incident cardiovascular disease events over the 15-year surveillance period (2 years before through 13 years after SLE diagnosis)

Variables	Unadjusted Hazard Ratio (95% CI)	p value	Adjusted* Hazard Ratio (95% CI)	p value
Demographic				
Racial groups				
Non-Black	ref	ref	ref	ref
Black	**5.4 (2.0-15.0)**	**0.0011**	**7.3 (2.4–22.0)**	**0.0004**
Age at SLE Diagnosis (years)				
<19	ref	ref	ref	-
19 to <35	0.6 (0.2–1.7)	0.3	0.7 (0.2–1.8)	0.4
35 to <50	1.5 (0.6–3.7)	0.4	1.8 (0.7–5.1)	0.3
50 to <65	0.7 (0.2–2.3)	0.6	1.2 (0.4–3.8)	0.8
≥65	2.0 (0.6–6.7)	0.2	**9.0 (2.4–33.0)**	**0.001**
Sex				
Male	ref	ref	ref	ref
Female	1.1 (0.5–2.3)	0.9	1.4 (0.6–3.2)	0.4
ACR criteria within one year of diagnosis or ESRD ** **(Yes vs. No)**				
Malar Rash	1.0 (0.5–1.9)	0.9	-	-
Discoid Rash	**2.1 (1.1-3.8)**	**0.02**	**3.2 (1.4–7.1)**	**0.005**
Photosensitivity	0.9 (0.5–1.8)	0.8	-	-
Oral Ulcers	1.1 (0.6–2.0)	0.8	-	-
Arthritis	1.1 (0.6–2.0)	0.7	-	-
Serositis	**1.7 (1.01–2.9)**	**0.047**	1.2 (0.6–2.4)	0.52
Renal Disorder or ESRD	**1.9 (1.1-3.3)**	**0.014**	**2.1 (1.1–4.1)**	**0.03**
Neurologic Disorder	1.2 (0.5–3.0)	0.7	-	-
Hematologic Disorder	1.3 (0.6–2.8)	0.46	-	-
Immunological Disorder	**2.2 (1.1-4.3)**	**0.03**	2.1 (0.9–4.5)	0.07
Antinuclear Antibody	1.3 (0.3–5.1)	0.8	-	-
ACR Criteria Total (>4 vs. ≤4)	**1.3 (1.1–1.5)**	**0.002**	1.0 (0.8–1.3)	0.92

*Hazard Ratios adjusted for age, sex, racial groups, and ACR criteria within 1 year of SLE diagnosis with p <0.1 on univariable analysis.

**ACR Criteria results from a Multivariable Cox Proportional Hazards Model that included ESRD. Results reported for criterion with p<0.1 on univariable analysis. All ACR criteria were within 1 year of SLE diagnosis. ESRD was through years 2002–2015. All hazard ratios for variables with significant p values (<0.05) are shown in bold. Abbreviations: ESRD=end stage renal disease. Ref=reference. SLE=systemic lupus erythematosus. ACR=American College of Rheumatology.

Table 4.

Cox model predictors of incident cardiovascular disease events in Black vs. non-Black people with SLE over 15 years

Variables	Adjusted* Hazard Ratio (95% CI)	p value
SLE Diagnosis Age <19 years	Ref	-
Age 19 - <35 years	0.6 (0.2–1.8)	0.38
Age 35 - <50 years	1.8 (0.7–5.1)	0.25
Age 50 - <65 years	1.2 (0.4–3.8)	0.81
Age ≥65 years	**8.8 (2.4–32.1)**	**0.0011**
Male	Ref	-
Female	1.4 (0.6–3.1)	0.41
Discoid Rash (Yes)	**3.1(1.4–6.9)**	**0.005**
ACR Criteria Total (>4) vs. ≤4	0.98 (0.8–1.3)	0.9
Serositis (Yes)	1.0 (0.7–2.3)	0.82
Renal Disorder or ESRD ** **(Yes)**	**2.1 (1.1–4.0)**	**0.03**
Immunological Disorder (Yes)	2.1 (0.93–4.5)	0.07

* Hazard Ratios adjusted for age, sex, and ACR criteria within 1 year of SLE diagnosis with p <0.1 on univariable analysis, and stratified by racial groups.

ACR Criteria with p<0.1 on univariable analysis included in Multivariable Cox Proportional Hazards Model Stratified by Racial groups. CI=Confidence Interval; ESRD=End Stage Renal Disease; Ref=Reference; SLE=systemic lupus erythematosus; ACR=American College of Rheumatology.

** All ACR criteria within the first year of SLE diagnosis. ESRD was through 2002–2015. All hazard ratios for variables with significant p values (<0.05) on multivariable analysis are shown in bold.