Published in final edited form as:

Transl Res. 2009 February ; 153(2): 51–59. doi:10.1016/j.trsl.2008.11.006.

Differences in Subclinical Cardiovascular Disease between African American and Caucasian Women with Systemic Lupus Erythematosus

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Abstract

Racial differences exist in disease rates and mortality in both cardiovascular disease (CVD) and Systemic Lupus Erythematosus (SLE). The objective of this cross-sectional study was to compare the frequency of and risk factors for subclinical CVD in African-American (AA) and Caucasian women with SLE and no prior CVD events.

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*Funding

This work was supported by grants from the National Institutes of Health (NIH) T32-AR07611, F32-AR51681, K23-AR054418, and Mary Kirkland Center for Lupus Research and Rheumatism, Inc. (ER);

**NIH K24-AR02318, P60-AR30692, P60-AR48098, NCRR/GCRC M01-RR00048 (RRG);

†NIH R01-AR046588, K24-AR002213 (SM);

††NIH K23 AR051044, American College of Rheumatology/REF Physician Scientist Development Award (AHK).

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Traditional CVD risk factors and SLE-related factors were assessed in 309 SLE women. Subclinical CVD was assessed by carotid ultrasound to measure intima-medial thickness (IMT) and plaque, and electron beam computed tomography (EBCT) to measure coronary artery calcium (CAC).

AA had less education, higher body mass index, blood pressure, lipoprotein(a), CRP, fibrinogen, and ESR, but lower albumin; more and longer duration of corticosteroid use; higher SLE disease activity and damage; and more had dsDNA antibodies compared to Caucasian women, after adjustment for age and study-site. More AA had carotid plaque (adjusted OR 1.94, 95%CI 1.03, 3.65) and higher carotid IMT (0.620 vs. 0.605mm, $p=0.07$) compared with Caucasians, but similar CAC. Multivariate analysis included risk factor variables significantly different between the racial groups and associated with plaque: blood pressure, current corticosteroid use, SLE disease activity and damage. All factors contributed, but no individual risk factor fully accounted for the association between race and plaque.

In conclusion, the presence of carotid plaque was higher in AA compared with Caucasian women with SLE, in contrast to studies of non-SLE subjects, where AA have similar or less plaque than Caucasians. A combination of SLE-related and traditional CVD risk factors explained the racial difference in plaque burden.

Keywords

Systemic Lupus Erythematosus; Race; Cardiovascular Disease

Introduction

Cardiovascular disease (CVD) is the leading cause of death for women in the general population in the United States [1], primarily affecting postmenopausal women. There is increasing recognition of the elevated risk of accelerated CVD in Systemic Lupus Erythematosus (SLE) women, including those who are premenopausal [2,3].

Traditional CVD risk factors are important in SLE patients [2,4-6], but several studies have suggested that lupus disease itself may be an important risk factor for CVD in these patients [7-9]. These observations support the hypothesis that traditional CVD risk factors do not fully account for the elevated and premature risk seen in SLE patients and that other factors related to SLE, i.e. inflammatory and immune mediators, as well as thrombotic factors such as antiphospholipid antibodies, may also be important in the development of these complications. Atherosclerosis is now accepted to be an inflammatory disease and the role that inflammation plays in atherosclerosis has raised a putative mechanism that may underlie the increased risk of CVD reported in SLE patients.

In the general population, racial differences exist in both CVD events and subclinical CVD, which can be measured noninvasively by imaging various vascular beds, including the carotid and coronary arteries. These subclinical markers are predictive of events and are reflective of systemic atherosclerotic burden [10-13].

Racial differences also exist in SLE disease rates and severity. Compared with Caucasians, African Americans (AAs) have a higher incidence rate [14-16] and prevalence [16,17] of SLE, as well as worse survival [18-20]. Although socioeconomic status is an important determinant in predicting survival, several studies have demonstrated that race, itself, is an independent risk factor for mortality in SLE patients [18,19]. The Systemic Lupus International Collaborating Clinics Group, a multicenter international cohort, confirmed the increased risk of mortality in Black/AA race [21].

Based on these findings, we hypothesize that the racial differences in SLE disease is related to higher rates of underlying subclinical CVD in AA SLE patients compared with Caucasians. There is little known about racial differences with respect to subclinical CVD in SLE women. The objective of this study was to compare traditional and SLE related risk factors for CVD and to compare various measures of subclinical CVD, including carotid IMT, carotid plaque, and coronary calcification in AA and Caucasian women with SLE and no history of clinical CVD events.

Methods

Study population

A total of 309 SLE women, all meeting at least 4 classification criteria for SLE, age ≥ 18 , and without a history of clinical CVD events [which included myocardial infarction (MI), angina, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG) surgery, cerebrovascular accident (CVA), or transient ischemic attack (TIA)], were enrolled from the Chicago Lupus Database and the Pittsburgh Lupus Registry for the purposes of this study. The Chicago Lupus Database is a cohort of 508 participants and the Pittsburgh Lupus Registry includes 983 participants who meet the 1982 or updated 1997 American College of Rheumatology classification for SLE [22,23]. In Chicago, all eligible women, aged ≥ 18 years were invited to participate, with the first 180 women to respond being enrolled in SOLVABLE (Study of Long-term Vascular and Bone Outcomes in Lupus Erythematosus). In Pittsburgh, all eligible women from the original cardiovascular study ($n=286$), aged ≥ 18 years, without a history of clinical CVD events were invited to participate in HEARTS (Heart Effects on Atherosclerosis and Risk of Thrombosis in Systemic Lupus Erythematosus). Identical protocols were utilized for both SOLVABLE and HEARTS.

For this analysis, only AA and Caucasian women who had not experienced a confirmed myocardial infarction or stroke, and without a physician diagnosis of angina or transient ischemic attack event at baseline were included, 150 women from SOLVABLE and 159 women from the HEARTS study.

Data Collection

Participant visits included interview, examination, blood and urine collection, carotid artery B-mode ultrasound and electron beam computed tomography (EBCT) of the coronary arteries. This research was carried out according to the principles of the Declaration of Helsinki and the institutional review boards of Northwestern University, University of Illinois at Chicago, and University of Pittsburgh approved the protocols. All study participants provided informed consent prior to enrollment.

Data were collected using identical protocols at both sites for the SOLVABLE and HEARTS studies. A self-administered questionnaire was administered followed by interview and physical examination by a trained physician during the study visit. All specialized laboratory tests (e.g. lipid, inflammatory markers, antiphospholipid antibodies) for both sites were performed at the same laboratory. All sonographers were trained at the University of Pittsburgh Ultrasound Research Laboratory. All imaging tests for subclinical CVD were read at one site. Carotid ultrasounds were read at the University of Pittsburgh Ultrasound Research Laboratory and EBCT's were read at the University of Pittsburgh Cardiovascular Institute.

Traditional CVD risk factors

Information on age, demographics, and self-reported race/ethnicity, education level, smoking history, family history of CVD (MI and CVA), history of hypertension, diabetes and hypercholesterolemia, current estrogen use, current aspirin use, and menopause status was

obtained from the questionnaire. Although education level is not a direct measure of socioeconomic status (SES) and access to care, we used this variable as a surrogate for SES. Data on current income level were collected, but several subjects refused to answer this question in the questionnaire and a decision was made to exclude the income level variable given that the missing data points would render the results difficult to interpret accurately. Menopause status was confirmed by FSH measurements if the subject's status was uncertain (e.g. irregular menses or hysterectomy without oophorectomy). Blood pressure was measured twice and the mean of the two measurements was used for analysis. Height, weight, and waist/hip measurements were obtained. Laboratory tests included fasting lipids (total cholesterol, high-density lipoprotein cholesterol (HDLc)) and triglycerides), homocysteine, glucose, insulin, and lipoprotein(a) which were measured in the Lipid Laboratory at the University of Pittsburgh Graduate School of Public Health and Prevention. The Friedewald equation was used to estimate low-density lipoprotein cholesterol (LDLc), unless the triglyceride level was >400, in which case, LDLc was measured directly. Plasma glucose levels were determined by enzymatic assay, and plasma insulin levels were measured by radioimmunoassay. C-reactive protein (CRP) was measured using immunonephelometric assay at the Laboratory for Clinical Biochemistry Research at the University of Vermont.

SLE-related factors

Validated measures of lupus disease activity, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), as well as disease damage, Systemic Lupus International Collaborating Clinics Damage Index (SLICC-DI), were completed by trained physicians. Disease duration was calculated using the date the subject fulfilled the 4th ACR classification criteria for lupus. Participants provided information on corticosteroid treatment (current use and duration of treatment), as well as current use of hydroxychloroquine and immunosuppressants (cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, and tacrolimus). Renal disease was defined as being present if the subject had fulfilled ACR classification criteria for lupus renal involvement (greater than 0.5 gm/day or 3+ proteinuria and/or the presence of cellular casts) or had a renal biopsy with evidence of WHO Class IIb, III, IV or V lupus nephritis. Antiphospholipid antibodies: anticardiolipin (ACL) antibodies (IgG and IgM; Incstar, Stillwater, MN) and lupus anticoagulant (partial thromboplastin time or Russell's viper venom time with mix) were measured at the Coagulation Laboratory at University of Pittsburgh Medical Center. ACL IgG was considered positive if the result was >10 units and ACL IgM was considered positive if >15 units, as per laboratory standards. C3, C4, and native double stranded DNA (dsDNA) antibodies (*Crithidia luciliae*) were measured locally at each site. dsDNA was dichotomized and considered positive if the titer was $\geq 1:10$. Inflammatory markers included fibrinogen (modified clot-rate assay), which was measured at the Laboratory for Clinical Biochemistry Research at the University of Vermont, albumin (dye binding assay) measured at the Lipid Laboratory in the University of Pittsburgh Graduate School of Public Health and Prevention, and ESR (standard Westergren's method) measured locally at each site.

Subclinical Cardiovascular Disease Outcome Measures

Subclinical CVD was measured in the carotid arteries using B-mode ultrasound by centrally trained sonographers. Carotid plaque was defined as a distinct area protruding into the vessel lumen that was at least 50% thicker than the surrounding areas and was measured at 8 sites (bilateral internal carotid, external carotid, common carotid and carotid bulb). The outcome measure used for analysis was the presence or absence of plaque (plaque index ≥ 1 versus plaque index = 0). Intima-medial thickness (IMT) was measured using specialized reading software across 1 cm segments of both the right and left sides of the near and far walls of the distal common carotid artery and the far wall of the carotid bulb and internal carotid artery. The mean of all average IMT readings across the 8 sites were used as the outcome measure for

analysis. The reproducibility of carotid duplex scanning using this technique has been previously documented in both the Pittsburgh SLE cohort and a non-SLE population [5,24]. The carotid duplex scans obtained at both sites were read.

In the coronary arteries, electron beam computed tomography (EBCT) scanning was performed to measure vascular calcium, using the Imatron C150 Ultrafast CT Scanner. Calcium scores were calculated with a densitometric program available on the Imatron C-150 scanner, using the Agatston method. The outcome measures used for analyses were the absence or presence of coronary calcium. EBCT's were also read centrally.

Statistical Methods

For univariate analyses, t-tests were used to compare means between the two racial groups for continuous variables that were normally distributed, Wilcoxon's rank sum test was used to compare the intergroup differences for nonparametric continuous variables, and unadjusted odds ratios were calculated for the two groups for dichotomous variables. For multivariate analyses, linear regression was used to compare adjusted differences in means and quantile regression was used to compare adjusted differences in medians between the two racial groups with adjustment for age and study site. Logistic regression was used to calculate age and study site adjusted odds ratio for the two groups. Adjustment was performed for age since age is strongly related to subclinical CVD as well as many of the other variables, and by study site in order to account for any unidentifiable confounding factors between the two sites. Carotid IMT was analyzed as a continuous variable, while carotid plaque and coronary calcification were dichotomized as absent versus present, given the skewing of the data caused by the large number of subjects with zero values for both of these measures.

Results

There were 309 SLE women that were included in the analysis from both sites, Sixty-three were AA and 246 were Caucasian. AA women were significantly younger compared to the Caucasian women (44.6 ± 10.3 vs. 47.6 ± 10.6 yrs, $p < 0.05$), but this difference in age was no longer significant after adjustment for study site.

Traditional CVD Risk Factors: (Table 1)

The AA women had higher mean body mass index (BMI) (29.5 vs. 27.1 kg/m²) and diastolic blood pressure (DBP) (77.8 vs. 74.7 mmHg) than Caucasian women, with the differences remaining significant after adjustment for age and study site. Systolic blood pressure (SBP) was higher in AAs, after adjustment for age and study site. AAs were only slightly less educated with an adjusted mean difference of less than 1 year of education. Of the traditional CVD risk factors measured in the laboratory, only lipoprotein(a) and CRP differed between the two races, with AAs having higher levels compared with Caucasians.

Lupus related factors: (Table 1)

AAs had higher disease activity, (mean SLEDAI scores 4.4 vs. 2.6), higher damage (mean SLICC-DI 2.4 vs. 1.2), more current corticosteroid use (61.9% vs. 36.3%), longer mean duration of corticosteroid use (10.9 vs. 9.2 years), and higher frequency of dsDNA antibody positivity compared with Caucasians. There were no differences in current hydroxychloroquine use, current immunosuppressant use, with all immunosuppressants combined as well as evaluated individually (data for individual immunosuppressants not shown), or renal disease. AAs also had more inflammation, with higher fibrinogen and ESR, and lower albumin, but did not differ from Caucasians with regard to antiphospholipid antibodies.

Subclinical Cardiovascular Outcomes: (Table 2)

Compared with Caucasians, more AAs had carotid plaque (43.5% vs. 29.6%, adjusted OR 1.94, 95% CI 1.03, 3.65) and AAs had higher carotid IMT, with an age and study site adjusted mean difference of 0.024mm, which was borderline significant (p 0.07). The racial difference in carotid plaque persisted despite adjustment for years of education (adjusted OR 2.02, 95% CI 1.06, 3.87). There were no significant differences in the presence of coronary calcium (45.0% vs. 42.1%, adjusted OR 1.55, 95% CI 0.81, 2.98) between the AA and Caucasian SLE women.

Multivariate Analysis: (Table 3)

We performed multivariate analyses examining the association of carotid plaque and race, with adjustment for multiple risk factors. The models were adjusted a priori for age and study site. The risk factor covariates were selected for inclusion in this model if they differed significantly between the 2 races and were also associated with plaque with $p < 0.20$, when added individually into a model that included race, age, and study site. If variables were redundant, only one was chosen to avoid collinearity (e.g. DBP was included but SBP excluded, current corticosteroid use was included but duration of use excluded). Adjustment for DBP, corticosteroid use, SLEDAI, and SLICC-DI only modestly altered the odds ratio when each covariate was added individually (see Table 3). When all covariates were included in the model simultaneously, the odds ratio for plaque in AA women compared to Caucasian women was 1.29 (95% CI 0.64, 2.58). Interestingly, the only traditional cardiovascular risk factor covariates that met criteria for inclusion into the model was blood pressure – systolic and diastolic, with all others being lupus related factors.

Discussion

This study is the first to investigate racial differences in subclinical CVD at various vascular beds in SLE women. We found that AA women with SLE are 2 times more likely to have carotid plaque than Caucasians. In our study the traditional risk factors that were more prevalent in AA lupus women included higher blood pressure, BMI, CRP, and lipoprotein(a) levels. Education level was slightly lower in AAs. For lupus related factors, AAs had more disease activity, disease damage, corticosteroid use, duration of corticosteroid use, presence of dsDNA antibodies, and higher levels of inflammatory markers than Caucasian women with SLE. A combination of lupus related factors and traditional CVD risk factors generally explained the racial differences in plaque burden.

It is well known that AAs have an increased rate of adverse cardiovascular events and related mortality compared with Caucasians in the general population [1]. Despite this increased risk of clinical events, AAs do not necessarily have more subclinical disease compared with Caucasians. Many studies suggest that patterns of atherosclerotic CVD may be different between AAs and Caucasians.

In the general population, AAs have consistently been reported to have higher IMT in the carotid arteries than Caucasians, particularly in the common carotid artery [25-27]. In our study, we detected a similar trend towards AA SLE women having higher IMT compared with Caucasians, with an adjusted mean difference of 0.024mm (p 0.07).

In contrast, studies of racial differences in coronary artery calcification have been conflicting. Many studies have reported that AAs in the general population have a lower burden of coronary artery calcification [28-33]. One large physician referral based population study reported a higher prevalence rate of coronary artery calcium in AA women as compared with Caucasian women [34], yet several other studies were not able to demonstrate any differences in coronary

calcification between AA and Caucasian women [28,35,36]. It has been suggested that the prevalence of coronary calcium increases with age, with Caucasians having a higher rate of progression with increasing age, resulting in larger racial differences in older populations [37,38]. Most of these latter studies had younger cohorts, which may explain the lack of racial differences seen in coronary calcification. In our study of relatively young women, we also found no significant differences in coronary artery calcification in AAs compared with Caucasians.

Carotid plaque has also generally been reported to be more frequent in Caucasians compared with AAs in the general population. One early study demonstrated that Caucasians have a higher prevalence of occlusive atherosclerotic disease in the extracranial arteries while AAs have more disease in the intracranial vessels [39]. In the general population and the diabetic population, AA women were found to have less carotid plaque burden than Caucasian women [26,27]. In contrast, we found that carotid plaque was seen more frequently in AA compared with Caucasian women with SLE.

The reason for these differences in the prevalence of subclinical CVD between those in the general population and the lupus women in our study is not known. It is possible that the relative role of important risk factors may be contributing to differences seen in our population compared with the reports from the general population. There may be differences in traditional CVD risk factors between our SLE population and the general population, or it may be that the addition of lupus related factors may be affecting the risk of developing subclinical disease at different rates. Alternatively, there may be synergistic effects of the lupus related factors in combination with the traditional risk factors that may be driving the differential risk between the racial groups in both populations. The combination of SLE related risk factors and hypertension in the AA SLE women, as seen in this study, may be contributing to the greater risk of subclinical CVD among AA SLE women, as well as the increased risk of mortality in these women. In order to explore these potential explanations, we are collecting data on healthy controls to further characterize and compare the risk factors and prevalence of subclinical CVD in the SLE women and age-race matched healthy controls from the general population.

Although not specifically designed to study racial differences in subclinical CVD, two earlier studies have reported an absence of racial differences in the prevalence of carotid plaque. [9, 40]. The findings described in these studies are in contrast to the results of our study, and may be explained by several differences in methodology. In our study, only asymptomatic patients without a history of clinical CVD were included, whereas 25 of 204 subjects had a history of clinical CVD (MI, angina, CVA or TIA) in Roman, et al.'s study, and 5% had a CVA and 4% had an MI in Maksimowicz-McKinnon, et al.'s study. There is insufficient information provided to estimate the prevalence of angina or TIA amongst the latter cohort. Furthermore, in the latter study, only 14% of their subjects had plaque, which is in contrast to 45% in our subjects and 37% in Roman et al.'s subjects. Plaque was defined similarly in both Roman et al.'s and our studies, but the latter study does not describe the criteria which were used to determine the presence of plaque. Roman, et al. compared "Whites" versus "non-Whites", and inclusion of other non-AA subjects in the "non-White" category may have precluded detecting differences in subclinical carotid disease. Lastly, the two previous studies included male lupus subjects, who were excluded from our study.

Several studies have examined risk factors for subclinical CVD in SLE patients, but none have systematically studied racial differences in risk factors in SLE patients. Traditional CVD risk factors including male sex, hyperlipidemia, hypertension, post-menopausal status, obesity, smoking and diabetes mellitus were found to be predictive of clinical and subclinical CVD in SLE patients [2-6,40]. Carotid plaque has been associated with both traditional CVD risk factors, including older age [4,5,41], higher systolic blood pressure [5,41], higher LDL c [5],

and lower HDL3 cholesterol [41], as well as SLE related factors, including older age at diagnosis [9], longer duration of SLE [9], higher damage index score [9], less aggressive immunosuppressive therapy [9], longer duration of prednisone use [5], and cumulative prednisone dose [4].

We recognize that our study has several limitations that should be taken into consideration when evaluating the results. The study population consisted of relatively fewer AA women than Caucasian women. Therefore, we did not have adequate power to fully determine the associations between risk factors and the various measures of subclinical disease within the AA group.

Furthermore, we excluded women with clinical CVD. In the Pittsburgh original cardiovascular study, 17.6% of Caucasians and 32.3% of AAs had a history of cardiovascular events, and in SOLVABLE, 7% of Caucasians and 8% of AAs had a history of baseline cardiovascular events. Exclusion of women with clinical events may have introduced bias, as a higher proportion of AA subjects were excluded due to having clinical events compared with Caucasians. Despite excluding a higher proportion of AA subjects, we were still able to demonstrate a difference in the presence of carotid plaque between the two races.

Although bias may have been introduced by the exclusion criteria, the focus of our study was asymptomatic women, which we a priori determined was important for the purposes of a prospective study to determine the true incidence of clinical CVD, as well as for the purposes of a cross sectional analysis where clinical disease may influence health behaviors and thus risk factor exposure. Particularly, since atherosclerosis is a chronic inflammatory disease that may lead to activation of inflammatory and endothelial cells in the diseased areas, increases in measured markers of inflammation may be reflective of the total burden of atherosclerosis in all arterial beds, rather than as a risk factor contributing to CVD. We attempted to overcome this limitation by excluding women with the greatest burden of atherosclerosis, ie. those patients with known clinical CVD. Nevertheless, the cross-sectional nature of this study precludes us from making any conclusions on CVD prediction based on the various risk factors. We plan on following this cohort longitudinally which will allow us to overcome this limitation in the future.

Another limitation in this study is that antiphospholipid antibodies were measured at one occasion at the study visit due to the cross-sectional study design and may have led to misclassification. Although 2 serial positive measurements are necessary for the diagnosis of antiphospholipid syndrome, the purpose in this cross-sectional study was not to study the correlation between race and antiphospholipid syndrome, but antiphospholipid positivity at the baseline visit. We hope to address this issue in the future, as our study is a longitudinal one, with subjects returning for regular follow-up visits. We are confident that in the longitudinal analyses we will be able to address the issue of association between race and antiphospholipid positivity (with at least 2 positive measurements) and/or syndrome (by including clinical criteria).

However, given these limitations, the results support our findings that in SLE women without clinical CVD, AAs were more likely to have carotid plaque than Caucasians. The CVD risk factors associated with racial differences in plaque for our study were a combination of both lupus related and traditional ones, which would provide a potential explanation for the differential findings in our study of SLE women compared with the general population. Further longitudinal investigation of both racial groups in women with and without SLE will provide valuable information regarding the relative role of lupus related factors in the progression of subclinical CVD and incidence of clinical CVD events.

Acknowledgements

The authors would like to thank the lupus research staff at Northwestern University and University of Pittsburgh, including Charmayne Dunlop-Thomas, MS, Penny Shaw, RN, BSN, Rodlescia Sneed, MPH, and Sue Cunanan; carotid ultrasound technicians, Bonnie Kane, BS, RDCS, and Beverly Smulevitz, BS; EBCT technician Susan Jeziorny, R.T. (R, CT); and Dr. Russell Tracy's Laboratory at the University of Vermont for CRP and fibrinogen measurements.

References

1. Ferdinand KC. Coronary artery disease in minority racial and ethnic groups in the United States. *Am J Cardiol* 2006;97(2A):12A–19A.
2. Ward MM. Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. *Arthritis Rheum* 1999;42(2):338–46. [PubMed: 10025929]
3. Manzi S, Meilahn EN, Rairie JE, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol* 1997;145(5):408–15. [PubMed: 9048514]
4. Doria A, Shoenfeld Y, Wu R, et al. Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. *Ann Rheum Dis* 2003;62(11):1071–7. [PubMed: 14583570]
5. Manzi S, Selzer F, Sutton-Tyrrell K, et al. Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. *Arthritis Rheum* 1999;42(1):51–60. [PubMed: 9920014]
6. Petri M, Perez-Gutthann S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. *Am J Med* 1992;93(5):513–9. [PubMed: 1442853]
7. Asanuma Y, Oeser A, Shintani AK, et al. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;349(25):2407–15. [PubMed: 14681506]
8. Esdaile JM, Abrahamowicz M, Grodzicky T, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum* 2001;44(10):2331–7. [PubMed: 11665973]
9. Roman MJ, Shanker BA, Davis A, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;349(25):2399–406. [PubMed: 14681505]
10. Arad Y, Spadaro LA, Goodman K, et al. Predictive value of electron beam computed tomography of the coronary arteries. 19-month follow-up of 1173 asymptomatic subjects. *Circulation* 1996;93(11):1951–3. [PubMed: 8640967]
11. Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. *Am J Epidemiol* 1997;146(6):483–94. [PubMed: 9290509]
12. Craven TE, Ryu JE, Espeland MA, et al. Evaluation of the associations between carotid artery atherosclerosis and coronary artery stenosis. A case-control study *Circulation* 1990;82(4):1230–42.
13. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 1999;340(1):14–22. [PubMed: 9878640]
14. McCarty DJ, Manzi S, Medsger TA Jr, Ramsey-Goldman R, LaPorte RE, Kwok CK. Incidence of systemic lupus erythematosus. Race and gender differences. *Arthritis Rheum* 1995;38(9):1260–70. [PubMed: 7575721]
15. Hochberg MC. The incidence of systemic lupus erythematosus in Baltimore, Maryland, 1970-1977. *Arthritis Rheum* 1985;28(1):80–6. [PubMed: 3966940]
16. Siegel M, Holley HL, Lee SL. Epidemiologic studies on systemic lupus erythematosus. Comparative data for New York City and Jefferson County, Alabama, 1956-1965. *Arthritis Rheum* 1970;13(6):802–11. [PubMed: 5495391]
17. Fessel WJ. Systemic lupus erythematosus in the community. Incidence, prevalence, outcome, and first symptoms; the high prevalence in black women. *Arch Intern Med* 1974;134(6):1027–35. [PubMed: 4433183]

18. Reveille JD, Bartolucci A, Alarcon GS. Prognosis in systemic lupus erythematosus. Negative impact of increasing age at onset, black race, and thrombocytopenia, as well as causes of death. *Arthritis Rheum* 1990;33(1):37–48. [PubMed: 2302266]
19. Studenski S, Allen NB, Caldwell DS, Rice JR, Polissson RP. Survival in systemic lupus erythematosus. A multivariate analysis of demographic factors. *Arthritis Rheum* 1987;30(12):1326–32. [PubMed: 3435564]
20. Walsh SJ, Algert C, Gregorio DI, Reisine ST, Rothfield NF. Divergent racial trends in mortality from systemic lupus erythematosus. *J Rheumatol* 1995;22(9):1663–8. [PubMed: 8523342]
21. Bernatsky S, Boivin JF, Joseph L, et al. Mortality in systemic lupus erythematosus. *Arthritis Rheum* 2006;54(8):2550–7. [PubMed: 16868977]
22. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25(11):1271–7. [PubMed: 7138600]
23. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40(9):1725. [PubMed: 9324032]
24. Sutton-Tyrrell K, Wolfson SK Jr, Thompson T, Kelsey SF. Measurement variability in duplex scan assessment of carotid atherosclerosis. *Stroke* 1992;23(2):215–20. [PubMed: 1561650]
25. D'Agostino RB Jr, Burke G, O'Leary D, et al. Ethnic differences in carotid wall thickness. The Insulin Resistance Atherosclerosis Study. *Stroke* 1996;27(10):1744–9. [PubMed: 8841322]
26. Freedman BI, Hsu FC, Langefeld CD, et al. The impact of ethnicity and sex on subclinical cardiovascular disease: the Diabetes Heart Study. *Diabetologia* 2005;48(12):2511–8. [PubMed: 16261310]
27. Manolio TA, Burke GL, Psaty BM, et al. Black-white differences in subclinical cardiovascular disease among older adults: the Cardiovascular Health Study. CHS Collaborative Research Group. *J Clin Epidemiol* 1995;48(9):1141–52. [PubMed: 7636516]
28. Bild DE, Detrano R, Peterson D, et al. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2005;111(10):1313–20. [PubMed: 15769774]
29. Budoff MJ, Yang TP, Shavelle RM, Lamont DH, Brundage BH. Ethnic differences in coronary atherosclerosis. *J Am Coll Cardiol* 2002;39(3):408–12. [PubMed: 11823077]
30. Doherty TM, Tang W, Detrano RC. Racial differences in the significance of coronary calcium in asymptomatic black and white subjects with coronary risk factors. *J Am Coll Cardiol* 1999;34(3):787–94. [PubMed: 10483961]
31. Lee TC, O'Malley PG, Feuerstein I, Taylor AJ. The prevalence and severity of coronary artery calcification on coronary artery computed tomography in black and white subjects. *J Am Coll Cardiol* 2003;41(1):39–44. [PubMed: 12570942]
32. Newman AB, Naydeck BL, Whittle J, Sutton-Tyrrell K, Edmundowicz D, Kuller LH. Racial differences in coronary artery calcification in older adults. *Arterioscler Thromb Vasc Biol* 2002;22(3):424–30. [PubMed: 11884285]
33. Tang W, Detrano RC, Brezden OS, et al. Racial differences in coronary calcium prevalence among high-risk adults. *Am J Cardiol* 1995;75(16):1088–91. [PubMed: 7762490]
34. Budoff MJ, Nasir K, Mao S, et al. Ethnic differences of the presence and severity of coronary atherosclerosis. *Atherosclerosis* 2006;187(2):343–50. [PubMed: 16246347]
35. Jain T, Peshock R, McGuire DK, et al. African Americans and Caucasians have a similar prevalence of coronary calcium in the Dallas Heart Study. *J Am Coll Cardiol* 2004;44(5):1011–7. [PubMed: 15337212]
36. Khurana C, Rosenbaum CG, Howard BV, et al. Coronary artery calcification in black women and white women. *Am Heart J* 2003;145(4):724–9. [PubMed: 12679771]
37. Kawakubo M, LaBree L, Xiang M, et al. Race-ethnic differences in the extent, prevalence, and progression of coronary calcium. *Ethn Dis* 2005;15(2):198–204. [PubMed: 15825965]
38. Orakzai SH, Orakzai RH, Nasir K, et al. Subclinical coronary atherosclerosis: racial profiling is necessary! *Am Heart J* 2006;152(5):819–27. [PubMed: 17070140]
39. Caplan LR, Gorelick PB, Hier DB. Race, sex and occlusive cerebrovascular disease: a review. *Stroke* 1986;17(4):648–55. [PubMed: 3526645]

40. Maksimowicz-McKinnon K, Magder LS, Petri M. Predictors of Carotid Atherosclerosis in Systemic Lupus Erythematosus. *J Rheumatol*. 2006
41. Selzer F, Sutton-Tyrrell K, Fitzgerald SG, et al. Comparison of risk factors for vascular disease in the carotid artery and aorta in women with systemic lupus erythematosus. *Arthritis Rheum* 2004;50(1):151–9. [PubMed: 14730611]

Abbreviations

SLE	systemic lupus erythematosus
CVD	cardiovascular disease
AA	African-Americans
IMT	intima-medial thickness
EBCT	electron beam computed tomography
CAC	coronary artery calcium
MI	myocardial infarction
PTCA	percutaneous transluminal coronary angioplasty
CABG	coronary artery bypass graft surgery
CVA	cerebrovascular accident
TIA	transient ischemic attack
HDLc	high-density lipoprotein cholesterol
LDLc	low-density lipoprotein cholesterol
CRP	C-reactive protein
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC-DI	Systemic Lupus International Collaborating Clinics Damage Index
ACL	anticardiolipin

BMI	body mass index
SBP	systolic blood pressure
DBP	diastolic blood pressure

Table 1

Unadjusted and Adjusted* Differences in Means and Odds Ratios for Traditional Cardiovascular Disease (CVD) Risk Factors, Systemic Lupus Erythematosus Related Risk Factors, Thrombotic Factors and Inflammatory Markers between African American and Caucasian Women with Systemic Lupus Erythematosus

	AA (n 63)	Caucasian (n 246)	Unadjusted		Adjusted*				
			Mean Difference	OR	p value	Mean Difference	OR	p value	
Traditional CVD Risk Factors									
Patient Characteristics									
Age, years	44.6 ±10.3	47.6 ±10.6	-3.0	---	0.048	-0.9	---	0.522	
Education, years	14.8 ±2.4	15.1 ±2.7	-0.3	---	0.431	-0.8	---	0.023	
Current Smoking, %	15.9	8.1	---	2.1	0.069	---	2.2	0.069	
Family History of CVD, %	42.9	50.2	---	0.7	0.299	---	0.8	0.530	
Menopausal, %	44.4	49.6	---	0.8	0.466	---	1.9	0.140	
Current Estrogen, %	7.9	10.6	---	0.7	0.536	---	0.9	0.827	
Current ASA, %	9.5	14.6	---	0.6	0.295	---	0.6	0.225	
Hypertension [†]	60.3	35.4	---	2.8	<0.001	---	3.7	<0.001	
Diabetes [†]	11.1	5.7	---	2.1	0.134	---	2.2	0.118	
Hypercholesterolemia [†]	25.4	25.8	---	1.1	0.851	---	1.1	0.838	
Physical Factors									
Body Mass Index, kg/m ²	29.5 ±6.8	27.1 ±6.8	2.4	---	0.014	2.9	---	0.004	
Waist Hip Ratio	0.85 ±0.1	0.84 ±0.1	0.01	---	0.749	0.01	---	0.618	
Systolic BP, mmHg	122.9 ±18.5	119.0 ±17.4	3.8	---	0.126	5.8	---	0.016	
Diastolic BP, mmHg	77.8 ±11.4	74.7 ±9.4	3.1	---	0.028	4.3	---	0.003	
Laboratory Values									
Lipoprotein a, mg/dl	60.9 ±39.6	40.0 ±39.6	21.3	---	<0.001	20.5	---	0.001	
Total Cholesterol, mg/dl	189.9 ±37.6	190.9 ±40.9	-0.99	---	0.865	0.37	---	0.949	
HDLc, mg/dl	55.6 ±15.1	55.8 ±16.0	-0.16	---	0.943	-0.69	---	0.765	
LDLc, mg/dl	111.8 ±33.1	109.4 ±33.6	2.4	---	0.624	3.5	---	0.471	
Median Triglycerides ^{††} , mg/dl	108 (69, 149)	109 (82, 154)	-1.0	---	0.209	0.2	---	0.983	
Glucose, mg/dl	89.0 ±13.6	92.3 ±20.1	-3.3	---	0.228	-2.8	---	0.318	

	AA (n 63)	Caucasian (n 246)	Unadjusted		Adjusted*			
			Mean Difference	OR	p value	Mean Difference	OR	p value
Insulin, <i>mU/l</i>	16.8 ±13.6	15.1 ±12.5	1.7	---	0.366	2.2	---	0.254
Median CRP ^{††} , <i>mg/L</i>	2.7 (1.1, 6.5)	1.9 (0.7, 4.7)	0.8	---	0.110	1.2	---	0.017
Homocysteine, <i>μmol/L</i>	11.3 ±3.3	10.5 ±4.0	0.7	---	0.200	0.5	---	0.359
SLE Related Factors								
SLEDAI	4.4 ±4.5	2.6 ±2.7	1.8	---	<0.001	1.2	---	0.006
SLICC-DI	2.5 ±2.3	1.3 ±1.5	1.2	---	<0.001	1.4	---	<0.001
Disease Duration, <i>years</i>	14.4 ±8.8	14.4 ±8.0	0.03	---	0.978	1.6	---	0.152
Duration of CS Use <i>years</i>	10.9 ±8.6	9.2 ±7.9	1.6	---	0.249	2.9	---	0.034
Current CS, %	61.9	36.3	---	2.9	<0.001	---	3.1	<0.001
Current HCQ, %	65.1	58.1	---	1.3	0.317	---	0.9	0.833
Current immunosuppressant use [‡] , %	30.2	22.0	---	0.3	0.271	---	0.4	0.379
Renal Disease,%	31.7	24.8	---	1.4	0.265	---	1.3	0.396
C3, <i>mg/dl</i>	98.8 ±28.1	100.5 ±25.8	-1.7	---	0.652	-0.4	---	0.912
C4, <i>mg/dl</i>	21.7 ±8.8	19.6 ±7.4	2.1	---	0.061	2.5	---	0.026
dsDNA (<i>crithidia</i>), %	50.8	24.4	---	3.2	<0.001	---	2.2	0.014
Thrombotic Factors								
LAC, %	16.7	15.9	---	1.1	0.899	---	1.5	0.403
ACL IgG, %	18.0	17.8	---	1.0	0.971	---	1.4	0.439
ACL IgM, %	12.0	18.2	---	0.6	0.303	---	0.6	0.301
Antiphospholipid antibodies ^{**} , %	36.5	32.9	---	1.2	0.616	---	0.2	0.508
Inflammatory Markers								
Median Fibrinogen, <i>mg/dl</i>	362 (294, 390)	320 (246, 383)	42	---	0.004	52.1	---	0.002
ESR, <i>mm/hr</i>	25.0 ±19.8	14.1 ±14.1	10.9	---	<0.001	10.1	---	<0.001

	AA (n 63)	Caucasian (n 246)	Unadjusted		Adjusted*	
			Mean Difference	OR	Mean Difference	OR
				p value		p value
Albumin, g/dl	4.0 ± 0.6	4.4 ± 0.5	-0.4	---	-0.3	---
				<0.001		<0.001

* Adjusted for age and study site

Results reported as mean±SD for continuous variables, median (interquartile range) for continuous variables with non-normal distribution, and % for categorical variables. Differences in means and medians (if data not normally distributed) were calculated for continuous variables and odds ratios (OR) were calculated for categorical variables.

^{ff} Results for triglycerides, CRP and fibrinogen reported as Median (interquartile range)

† Self-reported history of hypertension, diabetes and hypercholesterolemia

[‡]Immunosuppressants included: cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, and FK506

*† Antiphospholipid antibodies considered positive if any one of the 3 antiphospholipid antibodies were positive (Lupus anticoagulant, ACL IgG, or ACL IgM). ACL IgG positive if >10 units and ACL IgM positive if >15 units, as per University of Pittsburgh Coagulation Laboratory standards.

AA = African American; CVD = cardiovascular disease; ASA = aspirin; BP = blood pressure; HDLc = high density lipoprotein cholesterol; LDLc = low density lipoprotein cholesterol; CRP = C-reactive protein; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SLICC-DI = Systemic Lupus International Collaborating Clinics Damage Index; CS = Corticosteroid; HCQ = Hydroxychloroquine; dsDNA = double stranded DNA antibodies; LAC = lupus anticoagulant; ACL = anticardiolipin antibodies; ESR = erythrocyte sedimentation rate

Table 2
Comparison of Carotid Plaque, Coronary Calcification (CAC), and Intima-Medial Thickness (IMT) between African American and Caucasian Women with Systemic Lupus Erythematosus

Subclinical Markers of CVD	AA	Caucasian	Unadjusted			Adjusted*		
			Mean Difference	OR	p value	Mean Difference	OR	p value
Plaque >0, %	43.5	29.6	---	1.83	0.038	---	1.94	0.041
CAC >0, %	45.0	42.1	---	1.12	0.689	---	1.55	0.189
IMT, mm	0.620 ±0.125	0.605 ±0.110	0.015	---	0.354	0.024	---	0.070

* Adjusted for age and study-site
Differences in mean calculated for continuous variables and odds ratios (OR) calculated for categorical variables.
CVD = Cardiovascular disease; AA = African American; CAC = coronary artery calcium; IMT = intima-medial thickness

Table 3
Multivariate Adjusted Odds Ratio for Carotid Plaque in African American Compared with Caucasian Women with Systemic Lupus Erythematosus

Adjusting Variables	Odds Ratio for Plaque in AA versus Caucasians	95% Confidence Interval
Age and Study Site	1.94	1.03, 3.64
+ Diastolic Blood Pressure alone	1.68	0.87, 3.21
+ Corticosteroid Use alone	1.73	0.90, 3.31
+ SLEDAI alone	1.79	0.94, 3.41
+ SLICC-DI alone	1.57	0.81, 3.10
+ Diastolic Blood Pressure, Corticosteroid Use, SLEDAI, SLICC-DI	1.29	0.64, 2.58

Risk factor variables were selected for inclusion into the model if they differed significantly between the 2 races and were also associated with plaque with a p value < 0.20 when added individually into a model that included race, age, and study site. Odds ratios for plaque are shown with each explanatory risk factor variable added individually and then when added simultaneously into a model that includes age and study site. AA = African American; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SLICC-DI = Systemic Lupus International Collaborating Clinics – Damage Index