Lupus 21st Century 2022 Meeting Abstract

Cardiovascular Disease and Lupus

502 PSYCHOLOGICAL STRESS AND CARDIOVASCULAR HEALTH IN JUVENILE LUPUS AND DERMATOMYOSITIS

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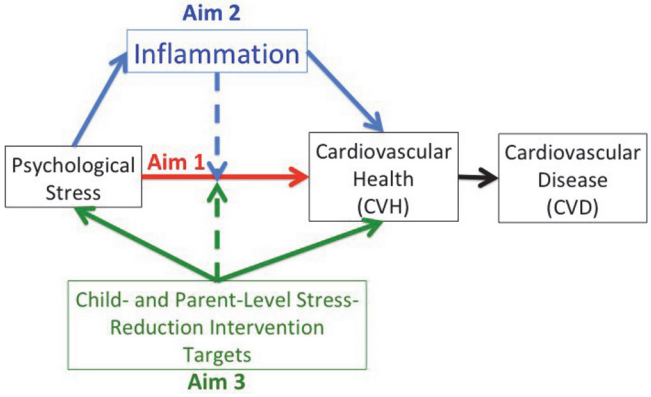
Background The American Heart Association (AHA) has defined 7 protective factors comprising ideal cardiovascular health (CVH), a positive health construct whose maintenance in childhood and young adulthood predict markedly reduced rates of cardiovascular disease (CVD) events in middle-age. In the general population, suboptimal CVH is observed in 58% of individuals by young adulthood and is associated with increased carotid intimal media thickness (cIMT) - a predictor of CVD. For youth with juvenile systemic lupus erythematosus (JSLE) and juvenile dermatomyositis (JDM), risk of premature CVD is even more pronounced. The Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial demonstrated that carotid intimal media thickness (cIMT) progresses faster in JSLE than familial dyslipidemia. Both traditional CVD risk factors and disease-related variables (e.g. chronic inflammation, endothelial dysfunction) likely underlie why patients with JSLE and JDM follow worse CVH trajectories than the general population. Potentially augmenting the impact of biological disease- related variables on CVH in youth with JSLE and JDM is psychological stress, which can negatively impact long-term CVH trajectories by triggering systemic inflammation and endothelial dysfunction. Children with rheumatic diseases experience significant psychological stress related to their health condition, with up to half of JSLE and JDM patients warranting professional mental health referral. We hypothesize that the high stress and inflammation of JSLE/JDM create a "perfect storm" that leads to early loss of CVH, compounding CVD risk. Stress is a modifiable risk factor amenable to intervention, but optimal intervention targets have not yet been identified in JSLE/JDM.



Abstract 502 Figure 1 Conceptual model showing that stress and inflammation deplete CVH while stress- reduction can preserve CVH. As CVH is depleted, CVD risk increases over the life course.

Methods We are conducting a 2-site (Duke, UNC) prospective observational study with the following three aims: (1) Prospectively assess the association of psychological stress and CVH indicators in JSLE/JDM patients; (2) Prospectively quantify the mediating effect of inflammation on psychological stress and CVH in JSLE/JDM patients; and (3) Identify optimal stress-reduction intervention targets that moderate the impact of psychological stress on CVH in JSLE/JDM patients (figure 1).

Results Data/specimen collection is ongoing, with 53 participants enrolled in the study to date and planned follow up for 1 year for study participants. Cross-sectional analyses of baseline data are planned in early 2023, followed by analysis of the full longitudinal dataset in late 2023/early 2024.

Conclusions Successful completion of this study will produce quantitative support for a novel, generalizable framework relating stress, inflammation, and CVH in JSLE/JDM and other pediatric-onset rheumatic diseases. Additionally, preliminary study data will inform development and pilot testing of stress-reduction interventions to improve CVH in JSLE/JDM.

Lay Summary Juvenile lupus (JSLE) and dermatomyositis (JDM) patients are at high risk of cardiovascular disease. The American Heart Association has defined 'cardiovascular health' (CVH) as the factors that can protect against heart attack, stroke, and other cardiovascular diseases. Studies show that JSLE/JDM patients have worse CVH than children and adolescents who do not have these conditions.

Recent studies show that stress can worsen CVH, partly by increasing inflammation, but this has not been studied yet in JSLE/JDM. In this study, we will assess stress, inflammation, and CVH in JSLE/JDM patients over 1 year to determine if stress triggers inflammation and worsens CVH. We will also evaluate factors that might prevent stress from negatively affecting inflammation and CVH.

503 STRESS AND DISCRIMINATION PREDICT CARDIOVASCULAR DISEASE IN A POPULATION-BASED COHORT WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background/Purpose Stress is known to contribute to the development of atherosclerosis in the general population. African American (AA) people are more likely to experience psychosocial and environmental stressors and are three times more likely to develop systemic lupus erythematosus (SLE) than White people.

Cardiovascular disease (CVD) is a leading cause of SLE morbidity and mortality. However, the increased CVD risk is not completely attributable to disease activity and traditional risk factors. We examined if psychosocial stress predicts CVD in SLE.

Methods Georgians Organized Against Lupus (GOAL) is a population-based cohort of validated SLE patients in Atlanta, Georgia supported by the Centers for Disease Control and Prevention. Sociodemographic information, disease factors, CVD risk factors and social determinants of health measures were collected at baseline in 2016. Potential CVD events were identified by participant report and by matching with the

Georgia Hospital Discharge Database for CVD-related codes. Associated medical records were reviewed by study physicians and adjudicated for CVD events (myocardial infarction, angina, transient ischemic attack, thrombotic stroke, and/or peripheral vascular disease) using validated algorithms. After participants with prevalent CVD events through 2016 were identified, CVD-naïve participants were surveilled for incident CVD events from 2017-2021. We analyzed 2 validated measures of psychosocial stress, Perceived Stress Scale (PSS) and Everyday Discrimination Scale (EDS). Univariate and

Abstract 503 Table 1 Baseline Characteristics of Participants with Systemic Lupus Erythematosus

Factors	Category	Overall (n=599)	Incident CVD		
			No (n=486)	Yes (n=113)	P- value
Socio-Demographics					
Age, years (mean ± SD)		46.8 ± 13.7	44.9 ± 13.2	54.5 ± 13.2	**<0.001**
Age at diagnosis, years (mean ± SD)		32.1 ± 11.9	31.4 ± 12.1	35.1 ± 10.9	**0.003**
Disease duration, years (mean ± SD)		14.7 ± 9.8	13.6 ± 9.2	19.4 ± 10.7	**<0.001**
Education, years (mean ± SD)		14.7 ± 3.0	14.7 ± 3.1	14.6 ± 2.9	0.70
Gender, n (%)	Male	35 (5.8)	30 (6.2)	5 (4.4)	0.48
	Female	564 (94.2)	456 (93.8)	108 (95.6)	
Race, n (%)	AI/AN[1]	1 (0.2)	1 (0.2)		0.21
	Asian	9 (1.5)	9 (1.9)		
	African American	472 (78.8)	378 (77.8)	94 (83.2)	
	NH/PI[2]	1 (0.2)		1 (0.9)	
	White	115 (19.2)	97 (20.0)	18 (15.9)	
	Other	1 (0.2)	1 (0.2)		
Latino/Hispanic Ethnicity, n (%)	Yes	31 (5.2)	27 (5.6)	4 (3.5)	0.37
Marital status, n (%)	Currently Married	235 (39.3)	194 (40.0)	41 (36.3)	**0.012**
	Ever Married	153 (25.6)	112 (23.1)	41 (36.3)	
	Never Married	210 (35.1)	179 (36.9)	31 (27.4)	
Poverty, n (%)[3]	Yes	224 (37.5)	188 (38.8)	36 (32.1)	0.19
Work Status, n (%)	Employed	251 (42.6)	229 (48.0)	22 (19.6)	**<0.001**
	Off work force	138 (23.4)	103 (21.6)	35 (31.3)	
	Unemployed	200 (34.0)	145 (30.4)	55 (49.1)	
Insurance, n (%)	Medicare/Medicaid	278 (46.6)	206 (42.7)	72 (63.7)	**<0.001**
	None	80 (13.4)	71 (14.7)	9 (8.0)	
	Private	238 (39.9)	206 (42.7)	32 (28.3)	
Disease Severity					
Disease activity (SLAQ)[4] (mean ± SD)		15.6 ± 9.1	15.2 ± 9.2	17.6 ± 8.9	**0.011**
Organ damage (BILD)[5] (mean ± SD)		2.1 ± 2.0	1.8 ± 1.9	3.2 ± 2.3	**<0.001**
Hydroxychloroquine, n (%)	No	159 (27.1)	122 (25.6)	37 (33.6)	0.089
	Yes	427 (72.9)	354 (74.4)	73 (66.4)	
Glucocorticoids, n (%)	No	274 (49.6)	226 (50.2)	48 (47.1)	0.56
	Yes	278 (50.4)	224 (49.8)	54 (52.9)	
Glucocorticoid dose, mg[6] (mean ± SD)		10.4 ± 15.9	9.6 ± 10.8	14.1 ± 28.9	0.07
Glucocorticoid duration, years (mean ± SD)		9.7 ± 8.4	9.2 ± 7.8	11.9 ± 10.3	**0.035**
CVD Traditional Risk Factors					
Hypercholesterolemia, n (%)	Yes	108 (18.0)	79 (16.3)	29 (25.7)	**0.019**
Hypertension, n (%)	Yes	325 (54.3)	239 (49.2)	86 (76.1)	**<0.001**
Diabetes, n (%)	Yes	53 (8.8)	38 (7.8)	15 (13.3)	0.066
Chronic Kidney Disease, n (%)	Yes	30 (5.0)	24 (4.9)	6 (5.3)	0.87
Smoker, n (%)	Yes	151 (25.2)	115 (23.7)	36 (31.9)	0.071
Obesity, n (%)	Yes	249 (41.6)	181 (37.2)	68 (60.2)	**<0.001**
Physical Inactivity	Yes	433 (72.3)	339 (69.8)	94 (83.2)	**0.004**
Family History, n (%)	Yes	104 (17.4)	74 (15.2)	30 (26.5)	**0.004**
Poor Diet, n (%)	Yes	53 (8.8)	42 (8.6)	11 (9.7)	0.71
Alcohol, n (%)	Yes	141 (23.5)	117 (24.1)	24 (21.2)	0.52
Social Determinants of Health					
Cohen perceived stress scale (mean ± SD)		6.1 ± 3.2	5.8 ± 3.2	7.4 ± 2.8	**<0.001**
Everyday discrimination scale (mean ± SD)		1.7 ± 0.6	1.6 ± 0.6	2.0 ± 0.6	**<0.001**

Baseline=2016; [1] AI/AN- American Indian/Alaska Native; [2] NH/PI- Native Hawaiian or other Pacific Islander; [3] below 100% of the Federal poverty level; [4] Systemic Lupus Activity Questionnaire; [5] Self-Administered Brief Index of Lupus Damage; [6] prednisone equivalent. CVD=cardiovascular disease.

multivariate Cox regression analyses were used to evaluate the ability of PSS or EDS to predict incident CVD.

Results Out of 780 participants, 179 (23%) were adjudicated as having had prevalent CVD events through 2016. Two individuals died before reaching 2017. The majority of the remaining 599 CVD-naïve participants were AA (472, 78.8%) or White (115, 19.2%). From 2017-2021, 113 (18.9%) participants were adjudicated as having had an incident CVD event, with a mean time to event of 27.6 months (SD 16.9, range 0.7-60). The proportion of African American participants with incident CVD (94/472) was 19.9% compared to 15.7% in White participants (18/115), though not statistically significant. Those with incident CVD were older, had longer duration of SLE, were less employed, and had more federal insurance than those without CVD. They also had more SLE activity and organ damage, longer glucocorticoid use, and more traditional CVD risk factors. There were no differences in race, ethnicity, and poverty status.

Multivariate Cox regression analyses showed the PSS and EDS (table 3. Models 1 and 2) were independent predictors of incident CVD events. Race, glucocorticoid duration, and hydroxychloroquine did not predict incident CVD in either model.

Abstract 503 Table 2 Univariable Cox Regression Analysis of Cardiovascular Disease

Risk Factors at Baseline	Coeff. (±SE)	HR (95%CI)	P-value
Socio-Demographics			
Age (per 10 years ↑)	0.047 ± 0.007	1.60 (1.40-1.83)	**<0.001**
Age at diagnosis (per 10 years ↑)	0.022 ± 0.007	1.25 (1.08-1.45)	**0.003**
Disease duration (per 5 years ↑)	0.048 ± 0.008	1.27 (1.18-1.38)	**<0.001**
Education (per 3 years ↑)	-0.014 ± 0.031	0.96 (0.80-1.15)	0.66
Female Gender	0.314 ± 0.457	1.37 (0.56-3.35)	0.49
African American Race (ref: White)	0.254 ± 0.257	1.29 (0.78-2.13)	0.32
Latino/Hispanic Ethnicity	-0.441 ± 0.509	0.64 (0.24-1.75)	0.39
Marital Status (ref: Currently Married)			
Ever Married	0.461 ± 0.221	1.59 (1.03-2.44)	**0.037**
Never Married	-0.210 ± 0.238	0.81 (0.51-1.29)	0.38
Poverty[1]	-0.286 ± 0.202	0.75 (0.51-1.12)	0.16
Work Status (ref: Employed)			
Off work force	1.191 ± 0.272	3.29 (1.93-5.61)	**<0.001**
Unemployed	1.267 ± 0.252	3.55 (2.16-5.82)	**<0.001**
Insurance (ref: Private)			
Medicare/Medicaid	0.748 ± 0.213	2.11 (1.39-3.21)	**<0.001**
None	-0.206 ± 0.377	0.81 (0.39-1.70)	0.58
Disease Severity			
Disease activity (SLAQ[2], per 3 units ↑)	0.024 ± 0.010	1.08 (1.02-1.14)	**0.013**
Organ damage (BILD[3], per unit ↑)	0.224 ± 0.032	1.25 (1.18-1.33)	**<0.001**
Glucocorticoids	0.125 ± 0.198	1.13 (0.77-1.67)	0.53
Glucocorticoid dose (per 10 mg ↑)	0.008 ± 0.005	1.08 (0.99-1.19)	0.093
Glucocorticoid duration (per 5 years ↑)	0.036 ± 0.013	1.19 (1.05-1.36)	**0.008**
Hydroxychloroquine	-0.375 ± 0.202	0.69 (0.46-1.02)	0.063
CVD Traditional Risk Factors			
Hypercholesterolemia	0.500 ± 0.215	1.65 (1.08-2.52)	**0.02**
Hypertension	1.096 ± 0.221	2.99 (1.94-4.61)	**<0.001**
Diabetes	0.509 ± 0.277	1.66 (0.97-2.86)	0.066
Chronic Kidney Disease	0.122 ± 0.420	1.13 (0.50-2.57)	0.77
Smoker	0.367 ± 0.202	1.44 (0.97-2.14)	0.069
Obesity	0.803 ± 0.192	2.23 (1.53-3.25)	**<0.001**
Physical inactivity	0.715 ± 0.252	2.05 (1.25-3.35)	**0.004**
Family History	0.610 ± 0.213	1.84 (1.21-2.79)	**0.004**
Poor Diet	0.100 ± 0.317	1.10 (0.59-2.06)	0.75
Alcohol	-0.164 ± 0.230	0.85 (0.54-1.33)	0.48
Social Determinants of Health			
Cohen perceived stress scale (per unit ↑)	0.131 ± 0.029	1.14 (1.08-1.21)	**<0.001**
Everyday discrimination scale (per unit ↑)	0.772 ± 0.129	2.16 (1.68-2.78)	**<0.001**

Baseline=2016; [1] below 100% of the Federal poverty level; [2] Systemic Lupus Activity Questionnaire; [3] Self- Administered Brief Index of Lupus Damage. CVD=cardiovascular disease; Coeff=coefficient; SE=standard error; HR=hazard ratio; CI=confidence interval.

Abstract 503 Table 3 Multivariable Cox Regression Analysis of Cardiovascular Disease

Risk Factors	Model 1		Model 2	
	HR (95%CI)	P-value	HR (95%CI)	P-value
Social Determinants of Health				
Perceived stress scale (per unit ↑)	1.23 (1.14-1.32)	**<0.001**		
Everyday discrimination scale (per unit ↑)			2.83 (2.05-3.90)	**<0.001**
Socio-Demographics				
Age (per 10 years ↑)	1.50 (1.20-1.88)	**<0.001**	1.43 (1.13-1.80)	**0.002**
Disease duration (per 5 years ↑)	1.14 (1.01-1.29)	**0.036**	1.11 (0.98-1.25)	0.1
Female gender	0.80 (0.27-2.36)	0.68	1.19 (0.40-3.57)	0.76
African American race (ref: White)	1.27 (0.69-2.34)	0.45	0.71 (0.38-1.33)	0.29
Marital status (ref: Currently Married) Ever Married	1.05 (0.65-1.71)	0.84	0.94 (0.58-1.54)	0.82
Never Married	1.28 (0.74-2.21)	0.37	1.07 (0.62-1.84)	0.82
Work status (ref: Employed) Off work force	1.51 (0.73-3.11)	0.26	2.21 (1.08-4.52)	**0.031**
Unemployed	1.98 (1.02-3.85)	**0.043**	3.00 (1.51-5.94)	**0.002**
Insurance (ref: Private)				
Medicare/Medicaid	0.71 (0.38-1.32)	0.28	0.69 (0.37-1.29)	0.25
None	0.65 (0.28-1.55)	0.34	0.46 (0.16-1.26)	0.13
Disease Severity				
Disease activity (SLAQ[1], per 3 units ↑)	0.94 (0.87-1.03)	0.17	0.95 (0.87-1.03)	0.18
Organ damage (BILD[2], per 1 unit ↑)	1.22 (1.10-1.35)	**<0.001**	1.23 (1.11-1.37)	**<0.001**
Glucocorticoid duration (per 5 years ↑)	1.13 (0.97-1.33)	0.11	1.09 (0.93-1.28)	0.29
Hydroxychloroquine	0.88 (0.56-1.38)	0.57	1.01 (0.63-1.60)	0.98
CVD Traditional Risk Factors				
Hypercholesterolemia	0.86 (0.52-1.42)	0.56	1.03 (0.63-1.69)	0.91
Hypertension	1.67 (1.00-2.79)	0.051	1.99 (1.16-3.41)	**0.013**
Diabetes	0.75 (0.40-1.40)	0.37	0.74 (0.40-1.38)	0.34
Smoker	0.99 (0.63-1.56)	0.96	0.93 (0.59-1.48)	0.76
Obesity	1.97 (1.27-3.07)	**0.003**	1.74 (1.10-2.76)	**0.018**
Physical inactivity	1.70 (0.99-2.92)	0.054	1.93 (1.11-3.36)	**0.02**
Family History	1.11 (0.68-1.81)	0.67	1.16 (0.71-1.90)	0.56

[1] Systemic Lupus Activity Questionnaire; [2] Self-Administered Brief Index of Lupus Damage. CVD=cardiovascular disease; HR=hazard ratio; CI=confidence interval.

Conclusions The burden of CVD remains very high in this SLE cohort. This is the first study in SLE to find that psychosocial stressors (perceived stress and discrimination) independently predict incident CVD events controlling for race/ethnicity, traditional CVD risk factors, and other sociodemographic and disease- related factors. High stress is known to contribute to the development of atherosclerosis in the general population. The disproportionate burden of negative social determinants of health in communities of color may be a significant driver of CVD and other disparities described in SLE. Further research into related causal pathways, mitigating factors, and biologic mechanisms is needed.

Lay Summary The burden of cardiovascular disease (CVD) remains very high in this systemic lupus erythematosus (SLE) cohort. This is the first study in SLE to find that psychosocial stressors (perceived stress and discrimination) independently predict incident CVD events controlling for race/ethnicity, traditional CVD risk factors, and other sociodemographic and disease-related factors. High stress is known to contribute to the development of atherosclerosis in the general population. The disproportionate burden of negative social determinants of health in communities of color may be a significant driver of CVD and other disparities described in SLE. Further research into related causal pathways, mitigating factors, and biologic mechanisms is needed.

Lupus 21st Century 2022

504 PERSONALIZING CARDIOVASCULAR RISK PREDICTION FOR SLE PATIENTS

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Objective The risk of cardiovascular disease (CVD), including myocardial infarction (MI) and stroke, is increased in SLE patients and is underestimated by current prediction algorithms designed for the general population including the 10-year atherosclerotic cardiovascular disease (ASCVD) risk score. The American College of Cardiology/American Heart Association now considers systemic inflammatory diseases such as SLE as risk enhancers for CVD. The purpose of this study was to develop an SLE-specific prediction tool to provide a more accurate estimate of CVD risk by including both traditional and SLE-related CVD risk factors.

Methods We included SLE patients enrolled in the Brigham and Women's Hospital SLE Cohort and collected one-year baseline data on traditional CVD risk factors, demographic and clinical features from the electronic medical record at cohort enrollment. Disease activity was rated using a modified physician global assessment (PGA) tool and SLE-related variables including autoantibodies, complement levels, and SLE manifestations were also collected. All subjects were required to have one or more visits for SLE during the baseline period. A up to ten-year follow-up period for CVD events began day +1 at end of baseline period (index date). The primary outcome was first major adverse cardiovascular events (MACE) defined as composite of first myocardial infarction (MI), stroke, or cardiac death, in the follow-up period. These were identified by ICD-9/10 codes and adjudicated by medical record review by board-certified cardiologists as either definite or probable events (not meeting all the criteria for MI or stroke definition). The secondary outcome was boarded to include first event of: carotid artery occlusion or stenosis, transient ischaemic attack, atrial fibrillation/flutter, heart failure, peripheral vascular disease, or angina pectoris. We excluded subjects with CVD events prior to the index date. Three Cox regression risk prediction models that categorized patients into low risk <7.5% risk, moderate risk 7.5-20%, and >20% risk over 10 years were derived: 1) primary outcome with definite/probable events, 2) combined model 1 and secondary outcomes, and 3) primary outcome with definite events only. We performed least absolute shrinkage and selection operator (LASSO) regression for variable selection and required one of the candidate predictors to be the 10-year ASCVD risk score. We assessed model performance using integrated time-dependent area under the curve, Harrell's C statistic, optimism corrected C- statistic, integrated discrimination (IDI), and net reclassification index (NRI) using bootstrap resampling.

Results We included 1243 patients; 93.0% female and mean age of 41.6 (SD 13.3) years. There were 90 definite and probable MACEs (46 MIs, 36 strokes, and 19 cardiac deaths) and 211 secondary events over the follow-up period. The variables selected included: ASCVD risk score, disease activity (PGA at most recent baseline visit), disease duration, creatinine level, presence of anti-dsDNA, anti-RNP, lupus anticoagulant, anti-Ro60/SSA, and low C4 (table 1). Models 1 (primary outcomes with definite and probable events) and 3 (primary outcomes with definite events only) performed similarly and outperformed model 2 (combination of model 1 and secondary events) (table 2). Model performance improved in comparing risk predicted by ASCVD risk score alone vs. ASCVD risk score combined with selected SLE variables by LASSO regression for models 1 and 2, particularly at year 1. For these models, the number of SLE patients who were classified as high risk (>20%) more than doubled

Abstract 504 Table 1 Beta Coefficients of ASCVD risk score and SLE Variables Selected by LASSO regression

Variable	Model 1 (Primary Outcome, Definite + Probable Events)	Model 2 (Combined Model 1 and Secondary Events)	Model 3 (Primary Outcome, Definite Events Only)
Model with ASCVD risk score only			
ASCVD	6.42	5.09	6.51
Model with ASCVD risk score and SLE-Selected Variables			
ASCVD	5.44	4.58	5.40
Disease activity	0.31	0.33	0.34
Disease Duration	0.04	0.02	0.04
Creatinine Level	0.17	0.23	0.17
Anti-dsDNA Positive	0.35	0.03	0.33
Anti-RNP Positive	0.22	0.12	0.41
Lupus Anticoagulant	0.47	0.30	0.40
Anti-Ro60/SSA Positive	0.31	0.23	0.15
Low C4	0.49	0.40	0.51

Abbreviations: ASCVD, atherosclerotic cardiovascular disease