

# Association between depression and coronary artery calcification in women with systemic lupus erythematosus

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**Objectives.** To determine the associations between depression, cardiovascular risk factors and coronary artery calcification (CAC) in women with SLE and controls.

**Methods.** CAC was measured using electron-beam CT (EBCT). Traditional, inflammatory and lupus-related risk factors as well as depressive symptoms (Center for Epidemiologic Studies Depression Scale—CES-D) were measured at a single study visit in 161 women with SLE and 161 age- and race frequency-matched female healthy controls.

**Results.** Women with SLE reported more depressive symptoms than controls, with 27% of SLE and 15% of controls having CES-D scores suggestive of clinical depression. SLE women were more likely to have CAC, as well as more severe CAC compared with controls. Among the SLE women, depression was associated with greater than 2-fold odds of having any CAC [odds ratio (OR) 2.48; 95% CI 1.05, 5.87;  $P=0.04$ ], independent of traditional risk factors (age, hypertension and triglycerides) and inflammatory markers. However, when BMI was included among the covariates, the association between depression and CAC was attenuated, indicating the potential mediating role of BMI. Depression was not a risk factor for CAC in controls.

**Conclusions.** In women with SLE, depression was associated with CAC. This association was mediated by BMI. Depression and adiposity may add to the inflammatory burden of SLE, thus contributing to cardiovascular disease risk.

**KEY WORDS:** Systemic lupus erythematosus, Calcified tissue, Cardiovascular, Depression, CT scanning, Adipose tissue, Psychosocial factors, Risk factors, Inflammation.

## Introduction

Cardiovascular disease (CVD) is one of the major contributors to morbidity and mortality in women with SLE. Young women with lupus (aged 35–44 years) are 50 times more likely to have an acute myocardial infarction (AMI) than age-matched women from the Framingham study [1]. Women with SLE also experience higher than expected rates of hypertension and stroke [2–4]. Markers of subclinical atherosclerosis such as carotid artery plaque and coronary artery calcification (CAC) are more prevalent in SLE patients than in controls [5, 6], are present at younger ages, and may be predictive of future cardiac events [7].

To address the problem of early atherosclerosis in SLE requires identification of contributors. The contributing risk factors to early atherosclerosis in SLE are complex and may be interrelated, suggesting that this risk is likely multi-factorial [8, 9]. Identified potential contributors include traditional CVD risk factors, those related to SLE disease pathogenesis and treatment and inflammation- or immune-mediated factors [3]. Traditional risk factors for CVD, such as hyperlipidaemia, hypertension and BMI are common in SLE and are associated with carotid plaque [2, 10], coronary artery disease [11] and coronary calcium [12]. Antibodies frequently identified in patients with lupus (LAC, aPL auto-antibodies) were found to predict carotid artery plaque in SLE women [13]. Duration of SLE, age and homocysteine levels were identified as independent contributors to CAC [14]. Serum levels

of the pro-inflammatory cytokine IL-6 were also identified as a contributor to CAC after adjustment for traditional and SLE-related variables [15]. Although the individual risk factors are not consistent across studies, it appears that markers associated with a pro-inflammatory state in SLE are associated with CVD risk in this group.

Depression and psychological stress are associated with increased inflammation in healthy persons [16] and in RA patients [17]. Depression has been linked to increased levels of the inflammatory markers CRP and IL-6, [18] as well as increased platelet activity and hypercoagulable states [19] that are thought to contribute to atherosclerosis [20, 21]. Women with a history of recurrent major depression had greater than 2-fold risk for CAC than those without depression [22]. In addition, depression predicted coronary heart disease events over an 8-year follow-up period in older adult women without known CVD at baseline [23] and over a 10-year follow-up in a younger female cohort [24].

Depression may represent another piece of the CVD risk factor puzzle in SLE. Depression is prevalent in SLE. A recent report found a current major depressive episode in 22.5% of SLE patients [25]. Compared with the general population, women with SLE are more likely to be hospitalized for severe depression (standardized incidence rate 2.80) [26]. Depressive symptoms are higher in SLE than controls [27], and self-reported mental health is lower than that of controls [28] and RA patients [29]. Given the painful, unpredictable and often disabling nature of SLE, depressive symptoms may be an understandable psychosocial consequence of the illness. In addition, medication side effects may contribute to depressive symptoms in SLE. Although depression has been linked to inflammation and atherosclerosis in the CVD literature, the potential contribution of depression to atherosclerosis in SLE has not been investigated.

The aim of the present study was to investigate the associations between depressive symptoms and CVD risks in a group of women with SLE and a comparison group of healthy control women of similar age and race. We hypothesized that depression and CAC would be greater among SLE patients than controls,

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and that depression would be associated with subclinical atherosclerosis, specifically, CAC.

## Patients and methods

### Study population

The SLE and healthy women (control) participants in this study were enrolled in the Heart Effects on Atherosclerosis and Risk of Thrombosis in SLE (HEARTS) funded by the National Institutes of Health. The purpose of the HEARTS study was to compare prevalence and risk factors for CAC in SLE women and healthy controls. The SLE women were without prior history of CVD events [30] and were non-selectively recruited from the Pittsburgh Lupus Registry, which at the time of enrolment included 983 living participants. The registry includes patients seen either at inpatient or outpatient facilities at the University of Pittsburgh Medical Center or by practising rheumatologists within the Pittsburgh, PA metropolitan area. Thus, the SLE patients are a community-based sample with mild to severe SLE but with minimal tertiary care centre referral bias. All SLE women were required to fulfil 1982 or 1997 ACR revised criteria for the classification of definite or probable SLE [31, 32] and be over the age of 18 years.

The HEARTS control participants were women without prior cardiac events who were recruited using voter registration lists, and were similar to the SLE women in age ( $\pm 5$  years), race and area of residence. All participants completed informed consent procedures. The study was approved by the University of Pittsburgh's Institutional Review Board.

### Procedures

The study procedures included an interview, completion of a validated depression questionnaire [Center for Epidemiologic Studies Depression Scale (CES-D)], physical examination and laboratory and imaging studies [electron-beam computed tomography (EBCT)]. Each participant completed the study procedures during a single study visit. Data for this cross-sectional study were collected between March 2002 and September 2005.

### Traditional cardiovascular risk factors

Information on age, race, education level, household income, smoking habits, family history of CVD (MI, stroke or sudden death of a first-degree relative before the age of 60 years), menopausal status and BMI were collected. Blood pressure was determined and hypertension was defined as systolic blood pressure (SBP)  $\geq 140$  mmHg systolic or  $\geq 90$  mmHg diastolic or the use of anti-hypertensive therapy. Fasting blood samples were obtained for standard laboratory testing of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, insulin and glucose levels. Insulin resistance was calculated using the homeostatic model (HOMA-IR) formula [7, 33]:

$$\frac{\text{Insulin (mU/l)} \times \text{glucose (nmol/l)}}{22.5}$$

### Inflammatory markers

Laboratory assessments of inflammatory markers were conducted using blood samples from the single study visit. Assays were run in batches to reduce analytical variability. Soluble E-selectin (sE-selectin) and soluble intercellular adhesion molecule-1 (sICAM-1) were measured by commercial assays (Parameter Human sE-selectin Immunoassay and Human sICAM-1 Immunoassay; both from R&D systems, Minneapolis, MN, USA). High-sensitivity CRP (hsCRP) was quantified by automated particle-enhanced immunonephelometry (BN-II, Siemens Healthcare Diagnostics, Deerfield, IL, USA). Fibrinogen was measured

using an automated clot-rate assay (Diagnostica Stago STA-R, Parsippany, NJ, USA) [34, 35] (R.P.T., University of Vermont).

### SLE-related factors

Two rheumatologists specializing in lupus (A.H.K. and S.M.) assessed SLE disease activity and cumulative organ damage due to SLE at the study visit. Lupus measures included the revised SLAM (SLAM-R) [36], the SLEDAI [37] and the SLICC damage index [38] with the vascular items removed. We also collected information regarding individual criteria for SLE diagnosis and history of steroid use.

### Psychosocial assessment

Participants completed the CES-D [39] during the study visit. The CES-D [39] is a validated 20 item self-report instrument used extensively in community samples and medically ill groups, including SLE [27, 40–42]. The CES-D items assess past week symptoms consistent with a depressive disorder. Clinically significant depression is defined as a CES-D score  $\geq 16$ .

### CAC

Presence of CAC was determined using EBCT (Imatron C-150 scanner, Imatron, San Francisco, CA, USA). About 30–40 3 mm slices starting at the aortic root to the apex of the heart were scanned in all participants at the same point during diastole (80% of the R-R interval in the ECG) during a single breath hold. The images were scored for calcification using the Agatston method [43]. Presence of CAC was defined as Agatston score  $> 0$ .

### Data analysis

The distributions of the continuous variables were examined by Q–Q plot, skewness/kurtosis test and the Shapiro–Wilk test of normality. Depending on the nature of the distributions, either two-sample *t*-test or Wilcoxon rank-sum tests were performed for comparison of SLE and controls. Differences in categorical variables were tested using two sample tests of proportions. In all tables, we report means and standard deviations for normally distributed variables, and median and interquartile range (IQR) for non-normally distributed continuous variables.

Logistic regression was used to evaluate associations between risk factors and presence or absence of CAC in SLE and controls. All assumptions related to single-predictor and multi-predictor logistic regression analysis were met.

In addition to determining whether depression was a contributor to CAC, we were interested in whether CVD risk factors mediated the depression and CAC association. Potentially mediating variables were first identified based on significant associations with both depression and CAC. A bias-corrected bootstrap CI for percentage decrease in the depression coefficient due to mediation and the equivalent proportion of treatment explained (PTE) was performed to determine that the attenuation was not due to chance.

To select variables for inclusion in multivariable models, we first chose risk factors that were found significant ( $P < 0.20$ ) in unadjusted single predictor models. Covariates were evaluated for multi-collinearity and were selected out or centred if necessary. Variables were retained if removing them changed the coefficient of the primary predictor, depression,  $> 10$ –15%. Variables were removed if their inclusion resulted in a large increase in the standard error of the coefficient of depression [44]. Only those covariates retained in the model at  $P < 0.10$  were included in final analyses. Final models were checked for interaction effects. Adequacy of multivariable models was evaluated using the specification link test and Hosmer–Lemeshow goodness-of-fit test. SPSS 15 (SPSS, Chicago, IL, USA) and STATA 9 (Intercooled Stata 9.1, StataCorp, College Station, TX, USA) were used to perform all statistical analyses.

## Results

Demographic characteristics and CVD risk factors of patients with SLE and controls are shown in Table 1. Total cholesterol was lower in the SLE group, as was LDL cholesterol and glucose, whereas homocysteine, hsCRP, sICAM-1, sE-selectin and hypertension were higher in SLE than in controls. Depressive symptoms were greater among SLE than controls, and a higher percentage of SLE was classified as depressed by CES-D compared with controls. In fact, when we evaluated risk factors for depression in the entire sample ( $n=322$ ), SLE patients were more likely to be depressed (OR 1.90; 95% CI 1.06, 3.39;  $P=0.03$ ), independent of other depression risk factors, which were BMI (OR 1.05; 95% CI 1.00, 1.09;  $P=0.03$ ) and sICAM-1 (OR 1.00; 95% CI 1.001, 1.006;  $P=0.02$ ).

### SLE characteristics

Disease-related characteristics of the SLE sample are provided in Table 2. The average duration of SLE diagnosis was 16 years, and current SLE disease activity was mild, on average. The majority of patients (110 of 161) had used steroids, with a median duration of 10 years of use.

### CAC and CVD risk factors in SLE women and controls

Women with SLE had higher CAC scores than controls ( $P < 0.01$ ) and were also more likely than controls to have any CAC (Table 1). Women with SLE had an increased odds of having any CAC compared with controls across all age groups (Fig. 1) (OR 1.68,  $P=0.034$ ).

Table 3 shows univariate associations between each of the CVD risk factors and CAC in the SLE and control groups. CAC was present in 48% of the SLE patients. In SLE, several traditional CVD risk factors were associated with CAC, including age, hypertension, adiposity and glucose metabolism factors. Inflammatory factors related to CAC were higher levels of hsCRP, sE-selectin and fibrinogen. Depression was more prevalent among SLE women with CAC (36.3%) than in those without CAC (17.9%) ( $P=0.009$ ). In terms of SLE disease characteristics, women with SLE who had any CAC, compared with those without CAC, had greater cumulative damage due to SLE and longer history of corticosteroid use. Among controls, the risk factors for CAC were nearly identical to those for SLE women, with the exception that sICAM-1 was associated with CAC, and depression was not associated with CAC in the controls.

The final multivariable model of risk factors associated with the presence of CAC in SLE included older age, hypertensive status, triglycerides and sE-selectin and depression (Table 4). However, when BMI, which is a risk factor for both depression and CAC, was included in the model, depression status was no longer an independent contributor to CAC (OR 1.72; 95% CI 0.61, 4.89;  $P=0.31$ ). This suggests that the association between CAC and depression in SLE is potentially mediated by adiposity. Inclusion of BMI in the multivariable model also attenuated the association between sE-selectin and CAC (OR 1.02; 95% CI 0.99, 1.04;  $P=0.17$ ).

For comparison, we constructed a multivariable model of CAC in controls (results not shown in table). The variables that remained in the model were age (OR 1.10; 95% CI 1.05, 1.16;  $P < 0.001$ ) and BMI (OR 1.11; 95% CI 1.03, 1.19;  $P=0.008$ ). Thus, BMI appears to be a critical risk factor for CAC in controls as well as in SLE.

## Discussion

Our study addressed the questions of whether depression is associated with CAC and CVD risk factors in women with SLE, and whether depression and CAC are greater in SLE women than

TABLE 1. Demographic, risk factor and depression characteristics of SLE women and controls<sup>a</sup>

	SLE women ( $n=161$ )	Controls ( $n=161$ )	<i>P</i> -value
Age, mean $\pm$ s.d., years	50.1 $\pm$ 10.0	51.0 $\pm$ 9.6	0.42
Caucasian race, <i>n</i> (%)	142 (88%)	145 (90%)	0.59
Education, median (IQR), years	14 (12–16)	14 (12–17)	0.15
SBP, median (IQR), mmHg	119 (107–133)	120 (110–135)	0.18
DBP, mean $\pm$ s.d., mmHg	76.6 $\pm$ 10.26	76.2 $\pm$ 9.8	0.77
Hypertension <sup>b</sup> , <i>n</i> (%)	<b>88 (55)</b>	<b>49 (31)</b>	<b>&lt;0.01</b>
BMI, median (IQR), kg/m <sup>2</sup>	27 (22.6–32.7)	26.9 (23.9–32.1)	0.33
Waist circumference, median (IQR), cm	84 (75–96)	82 (73–93)	0.30
Ever a smoker, <i>n</i> (%)	58 (36)	69 (43)	0.21
Homocysteine, median (IQR), mg/dl	<b>9.7 (8–11.9)</b>	<b>8.9 (7.6–10.3)</b>	<b>&lt;0.01</b>
Fasting serum glucose, median (IQR), mg/dl	<b>89 (83–96)</b>	<b>93 (88–101)</b>	<b>&lt;0.01</b>
Total cholesterol, median (IQR), mg/dl	<b>186 (161–215)</b>	<b>203 (176–221)</b>	<b>&lt;0.01</b>
HDL-C, median (IQR), mg/dl	53.6 (42.8–61.9)	56 (46.3–63.8)	0.07
LDL-C, median (IQR), mg/dl	<b>108 (87–127)</b>	<b>122 (101–141)</b>	<b>0.01</b>
Triglycerides, median (IQR), mg/dl	114 (76–158)	104 (74–140)	0.10
Lipid-lowering agents, <i>n</i> (%)	<b>15 (9)</b>	<b>5 (3)</b>	<b>0.02</b>
Aspirin, <i>n</i> (%)	20 (12.4)	13 (8)	0.20
HOMA-IR, median (IQR)	2.8 (1.9–4.1)	2.6 (2.1–3.8)	0.82
hsCRP, median (IQR), mg/dl	<b>2.51 (0.97–5.6)</b>	<b>1.62 (0.61–3.65)</b>	<b>0.02</b>
sICAM-1, median (IQR), ng/ml	<b>267.5 (235.4–319.6)</b>	<b>245 (211.9–275.9)</b>	<b>&lt;0.01</b>
sE-selectin, median (IQR), ng/ml	<b>47.1 (31.2–62.5)</b>	<b>36.6 (26.4–53.2)</b>	<b>&lt;0.01</b>
Fibrinogen, median (IQR), mg/dl	341.5 (275–393)	337 (308.5–382)	0.62
CES-D score, median (IQR)	<b>9 (5–16)</b>	<b>6 (3–11)</b>	<b>&lt;0.01</b>
CES-D $\geq 16$ , <i>n</i> (%)	<b>43 (27)</b>	<b>24 (15)</b>	<b>&lt;0.01</b>
CAC category, <i>n</i> (%)			<b>&lt;0.01</b>
0	<b>84 (52)</b>	<b>99 (61.5)</b>	
1–10	<b>31 (19.5)</b>	<b>30 (18.6)</b>	
11–100	<b>26 (16)</b>	<b>23 (14.3)</b>	
101–400	<b>13 (8.1)</b>	<b>6 (3.7)</b>	
>400	<b>7 (4.3)</b>	<b>3 (1.8)</b>	

Statistically significant differences ( $P < 0.05$ ) between SLE and controls are indicated in bold. <sup>a</sup>Median (IQR) is provided for skewed variables, mean  $\pm$  s.d. is provided for normally distributed variables, *n* (%) are provided for dichotomous variables. <sup>b</sup>Hypertensive status defined as blood pressure  $\geq 140/90$  mmHg or anti-hypertensive medication. DBP: diastolic blood pressure.

TABLE 2. SLE characteristics of patients ( $n=161$ )

SLE characteristics	Mean $\pm$ s.d.	Range
Disease duration, years	16.3 $\pm$ 7	5–47
SLAM-R	4.5 $\pm$ 2.9	0–15
SLEDAI	2.0 $\pm$ 2.3	1–14
SLICC/ACR Damage Index	1.4 $\pm$ 1.6	0–9
Number of ACR criteria, median (IQR)	5 (4–7)	
Skin (malar or discoid rash), %		48
Photosensitivity, %		68.6
Oral ulcer, %		60
Arthritis, %		92
Serositis, %		48
Renal, %		24.5
CNS, %		8
Haematological, %		54
Immunological, %		60
ANA positive, %		94

control women. We found that women with SLE had greater depressive symptoms and higher prevalence and severity of CAC than healthy women. Depressive symptoms were similar to those found in other SLE investigations using the CES-D [40, 42]. SLE women with depression (CES-D  $\geq 16$ ) were more than twice as likely to have CAC, independent of traditional CVD risk factors of age, hypertension, triglycerides and the inflammatory marker sE-selectin. This association between depression and CAC in SLE appears to be mediated by adiposity, however, because

the addition of BMI to the multivariable model attenuated the depression–CAC link. BMI, a measure of adiposity, was an important risk factor in controls as well as SLE.

There are several pathways that may contribute to the associations between depression, adiposity and calcification in SLE.

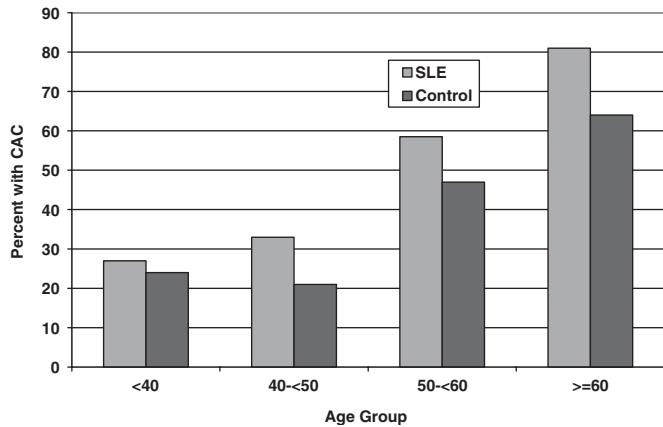


FIG. 1. Presence of CAC. Conditional logistic regression for overall difference in CAC for SLE and controls by age group: OR 1.68, *P* = 0.034.

Depression may influence lifestyle factors such as poor diet and sedentary habits, which may contribute to weight gain. Conversely, high BMI may lead to reduced activity levels and depressed mood. In addition, the pain and fatigue that are nearly universal in SLE may further promote sedentary behaviour, and lead to depressive features such as low energy and anhedonia. Depression and adiposity are both associated with increased levels of pro-inflammatory cytokines [45], thereby potentially contributing to CVD risk by increasing inflammation. Additionally, low mood is one of the behavioural manifestations of inflammation and immune activation [46], so reports of depressive symptoms may be partially due to an inflammatory milieu. In SLE, which is characterized by systemic immune activation and inflammation, depressive symptoms and adiposity appear to contribute to the existing inflammatory burden of the disease.

Studies of CVD risks in healthy adults support a pathway between depression, weight and inflammation. These factors may function in a positive feedback fashion, where the interactions between depression, increased BMI and inflammation promote a vicious cycle, propagating each of these risk factors and CVD risk. In a structural equation modelling study of physically healthy adults, half of whom were clinically depressed, depression was found to promote accumulation of weight, which was associated with release of pro-inflammatory cytokines [47]. Further support for this mechanism is provided by a large (*n* = 6814)

TABLE 3. Association of traditional risk factors, inflammatory markers, SLE disease characteristics and depression with CAC in SLE patients (*n* = 161) and controls (*n* = 161)

Traditional risk factors	SLE				Controls			
	CAC ( <i>n</i> = 77)	No CAC ( <i>n</i> = 84)	OR (95% CI)	<i>P</i> -value	CAC ( <i>N</i> = 62)	No CAC ( <i>N</i> = 99)	OR (95% CI)	<i>P</i> -value
Age, mean ± s.d., years	54.5 ± 9.7	46.5 ± 8.7	<b>1.09 (1.05, 1.14)</b>	<0.001	54.9 ± 9.6	48.6 ± 8.8	<b>1.08 (1.04, 1.12)</b>	<0.001
Caucasian race, %	83	93	0.38 (0.14, 1.05)	0.063	85.5	92.9	0.44 (0.16, 1.27)	0.132
Education, median (IQR), years	14 (12–15)	14 (12–16)	<b>0.85 (0.74, 0.97)</b>	<b>0.015</b>	13 (12–16)	15 (13–17)	<b>0.87 (0.76, 0.99)</b>	<b>0.033</b>
SBP, median (IQR), mmHg	128 (119–143)	109 (100.7–122.5)	<b>1.06 (1.04, 1.09)</b>	<0.001	129 ± 15.3	119.5 ± 17.1	<b>1.04 (1.02, 1.06)</b>	<b>0.001</b>
DBP, mean ± s.d., mmHg	79.5 ± 10.8	73.9 ± 9.0	<b>1.06 (1.02, 1.09)</b>	<0.001	79.3 (71.5–85)	73 (68–79.5)	<b>1.05 (1.02, 1.07)</b>	<0.001
Hypertension, %	72.7	38.1	<b>4.33 (2.22, 8.45)</b>	<0.001	45.9	22.1	<b>2.99 (1.49, 6.01)</b>	<b>0.002</b>
BMI, mean ± s.d.	31.6 ± 6.6	23.8 (21.3–27.5)	<b>1.28 (1.18, 1.38)</b>	<0.001	32 (26.1–37.3)	25 (22.7–29.1)	<b>1.21 (1.15, 1.27)</b>	<0.001
Waist circumference, mean ± s.d.	95.2 ± 15.2	78.1 ± 10.4	<b>1.11 (1.07, 1.15)</b>	<0.001	91 (81–102.5)	77 (71–86)	<b>1.09 (1.07, 1.12)</b>	<0.001
Ever a smoker, %	40.3	32.1	1.42 (0.75, 2.71)	0.285	47	40.4	1.31 (0.84, 2.06)	0.234
Homocysteine, median (IQR)	10.1 (8.8–12.5)	9.3 (7.6–11.2)	1.08 (0.99, 1.17)	0.077	8.85 (7.8–10)	9 (7.4–10.4)	1.04 (0.97, 1.12)	0.232
Fasting serum glucose, median (IQR)	90 (84–100)	89 (81.5–93)	<b>1.04 (1.01, 1.07)</b>	<b>0.005</b>	98 (93–105)	91 (87–98)	<b>1.07 (1.03, 1.11)</b>	<b>0.001</b>
Serum albumin, mean ± s.d.	4.5 ± 0.5	4.5 ± 0.5	0.82 (0.44, 1.53)	0.528	4.3 ± 0.42	4.4 ± 0.36	0.50 (0.21, 1.15)	0.105
Total cholesterol, mean ± s.d.	191.7 ± 38.8	185 (160.5–214)	1.00 (0.99, 1.00)	0.638	207.3 ± 39.3	199.4 ± 34.6	1.01 (0.997, 1.015)	0.185
HDL cholesterol, mean ± s.d.	51.7 ± 14.7	55 (44.6–62.5)	0.98 (0.96, 1.00)	0.076	53 (44.3–60.2)	56.6 (48.3–67.3)	0.98 (0.96, 1.00)	0.099
LDL cholesterol, mean ± s.d.	110.4 ± 36.6	107.5 (87–124)	1.00 (0.99, 1.01)	0.877	125.6 ± 36.6	120 ± 31.2	1.01 (.995, 1.015)	0.297
Triglycerides, median (IQR), mg/dl	127 (84–198)	103.5 (71–137)	<b>1.01 (1.00, 1.01)</b>	<b>0.002</b>	126.5 (93–170)	93 (69–130)	<b>1.01 (1.00, 1.016)</b>	<b>0.001</b>
Lipid-lowering agent, %	15.6	3.6	<b>4.98 (1.35, 18.41)</b>	<b>0.016</b>	2.5	0.6	6.76 (0.74, 61.9)	0.091
Aspirin, %	10.4	14.3	0.69 (0.27, 1.80)	0.456	12.9	5.1	2.79 (0.87, 8.94)	0.085
HOMA-IR, median (IQR)	3.7 (2.5–5.7)	2.3 (1.8–3.1)	<b>1.48 (1.19, 1.83)</b>	<0.001	3.5 (2.6–5.03)	2.36 (1.96–2.9)	<b>1.40 (1.14, 1.73)</b>	<b>0.001</b>
Inflammatory markers								
hsCRP, median (IQR)	3.8 (1.9–8.7)	1.4 (0.7–3.2)	<b>1.16 (1.06, 1.26)</b>	<b>0.001</b>	2.9 (1.1–9.5)	1.24 (0.52–2.6)	<b>1.17 (1.07, 1.28)</b>	<0.001
sICAM-1, median (IQR)	286.9 (242–333)	258.2 (224.7–305.6)	1.00 (0.99, 1.01)	0.207	267.2 (236–303)	235.2 (207–259)	<b>1.01 (1.00, 1.013)</b>	<b>0.005</b>
sE-selectin, median (IQR)	56.2 (42.6–67.5)	41.3 (28.4–51.9)	<b>1.03 (1.01, 1.04)</b>	<b>0.002</b>	41.8 (31.6–59)	34.9 (24.8–46.9)	<b>1.03 (1.01, 1.04)</b>	<b>0.002</b>
Fibrinogen, mean ± s.d.	360.6 ± 84.6	320.1 ± 84.9	<b>1.01 (1.00, 1.01)</b>	<b>0.004</b>	356 (311–404)	329.5 (301–370)	<b>1.01 (1.00, 1.01)</b>	<b>0.023</b>
Depression								
CES-D ≥ 16, %	36.3	17.9	<b>2.63 (1.28, 5.39)</b>	<b>0.009</b>	12.9	16.2	0.77 (0.30, 1.91)	0.573
SLE characteristics								
SLE duration, median (IQR), years	15 (12–20)	14 (11–20)	1.01 (0.97, 1.06)	0.612	–	–	–	–
ACR criteria (no.) <sup>a</sup> , median (IQR)	6 (4–7)	5 (4.5–7)	1.02 (0.84, 1.23)	0.837	–	–	–	–
SLICC damage index, modified <sup>b</sup> , median (IQR)	1 (0–3)	1 (0–2)	<b>1.43 (1.14, 1.80)</b>	<b>0.002</b>	–	–	–	–
SLEDAI score, median (IQR)	2 (0–4)	2 (0–2)	0.99 (0.86, 1.13)	0.880	–	–	–	–
SLAM score, median (IQR)	4 (0–6)	4 (2–6)	0.98 (0.88, 1.10)	0.754	–	–	–	–
Serum creatinine, median (IQR)	0.8 (0.7–0.9)	0.08 (0.7–0.9)	0.97 (0.41, 2.26)	0.937	–	–	–	–
Steroid use, ever, %	89.6	88	1.17 (0.43, 3.12)	0.761	–	–	–	–
Steroid use, median (IQR), years	10 (5–15)	8 (4–15)	<b>1.07 (1.01, 1.16)</b>	<b>0.032</b>	–	–	–	–

Mean and s.d. are presented for normally distributed variables, and median and IQRs are presented for skewed variables. Statistically significant ORs are indicated in bold. <sup>a</sup>SLE patients with and without CAC did not differ on any individual diagnostic criteria. <sup>b</sup>SLICC damage index was modified by removing vascular items.

TABLE 4. Multivariable logistic regression analysis of depression and risk factors with CAC in SLE ( $n=161$ )

Variable	Model without BMI			Model with BMI		
	Coefficient	OR (95% CI)	P-value	Coeff.	OR (95% CI)	P-value
Age	0.0919	1.10 (1.05, 1.15)	<0.001	0.0872	1.28 (1.04, 1.15)	0.001
Hypertension	1.154	3.17 (1.46, 6.91)	0.005	1.017	2.77 (1.12, 6.82)	0.027
Triglycerides	0.0087	1.09 (1.00, 1.02)	0.004	0.0083	1.01 (1.00, 1.02)	0.023
sE-selectin	0.0244	1.03 (1.01, 1.05)	0.014	0.0166	1.02 (.99, 1.04)	0.166
Depression	0.9075	2.48 (1.05, 5.87)	0.039	0.5441	1.72 (.61, 4.89)	0.307
BMI	–	–	–	0.2505	1.28 (1.16, 1.42)	<0.001

cross-sectional study [Multi-Ethnic Study of Atherosclerosis (MESA)] in which depression and other psychosocial factors were associated with inflammatory markers, with BMI presumably playing a mediating role [48]. However, in the MESA study, depression was not associated with CAC [49]. A prospective investigation of a female cohort determined that the influence of recurrent major depressive disorder on CAC was independent of adiposity as measured by BMI [22]. However, concurrent depressive symptoms were not associated with CAC, which is consistent with our result for control women without SLE.

The limitations of this study are its cross-sectional design, sample size limitations and assessment of current depressive symptoms rather than lifetime history of mood disorder diagnosis. History of mood disorder may more accurately assess the burden of depression on physiology. However, strong associations between symptoms and depression diagnosis [50] suggest that current depressive symptoms may reflect enduring depressive disposition. Vascular changes presumably develop over years, and a prospective design in which depressive symptoms, adiposity and inflammation are measured over time, and mood disorder diagnostic history is obtained, could clarify or strengthen the associations found in the current study and provide important clues regarding causality and possible mechanisms. Because of the cross-sectional design of the current study, it is not possible to determine whether depression plays a causal role in the development of adiposity and inflammation, or vice versa. Interestingly, depression may also reflect CNS involvement from lupus. Depressive symptoms have been linked to serum antibody to *N*-methyl-D-aspartate (NMDA) receptor NR2 [51] and cognitive impairment as assessed by neuropsychological testing [52, 53]. It is possible that depression may be a surrogate for lupus disease activity or severity.

The potential links between psychosocial factors and CVD in lupus remain largely unexplored. The present study provides support for the importance of depression assessment and suggests an association between depression and known CVD risk factors in SLE. Both depression and weight are modifiable risk factors. An important question for future investigation is whether treating depression can reduce CVD risk factors related to adiposity, and ultimately impact CVD outcomes.

#### Rheumatology key messages

- Depression was associated with CAC in women with SLE after risk factor adjustment.
- This association appears to be mediated by BMI.
- Depression and weight are modifiable risk factors that should be considered for assessment and intervention.

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