Published in final edited form as:
Arthritis Care Res (Hoboken). 2011 April ; 63(4): 542–549. doi:10.1002/acr.20426.

Cardiovascular and Disease Related Predictors of Depression in SLE

Laura J. Julian, PhD, **Chris Tonner, MPH**, **Ed Yelin, PhD**, **Jinoos Yazdany, MD MPH**, **Laura Trupin, MPH**, **Lindsey A. Criswell, MD MPH**, and **Patricia P Katz, PhD**

Abstract

OBJECTIVE—Depression and cardiovascular disease are common and debilitating comorbidities associated with systemic lupus erythematosus (SLE). In this study, history of cardiovascular events, cardiovascular risk factors and SLE disease related factors were evaluated as longitudinal predictors of depression in a large cohort of patients with SLE.

METHODS—Data derive from 663 adult participants in the 2004-2008 Lupus Outcomes Study, followed for up to 5 annual interviews. Multivariate logistic regression analyses using generalized estimating equations were used to determine predictors of the development of increased depressive symptom severity over a 12 month period (Center for Epidemiological Studies – Depression, CES-D, Score of 23 or greater), yielding 2,224 paired observations. Predictors included sociodemographics, traditional cardiovascular risk factors (reported presence of heart disease, history of stroke or myocardial infarction, hypertension, hypercholesterolemia, diabetes, obesity, smoking status, and family history), and SLE-specific risk factors (glucocorticoid use, renal involvement, disease duration, and disease activity).

RESULTS—Annual incidence of depression was 12% in this cohort. Multivariate predictors of new onset depression included younger age (age 20-39 OR 2.3; 1.3, 3.9; age 40-59 OR 1.8; 1.1, 2.7), Hispanic/ Latino ethnicity (OR 1.8; 1.2, 2.8) having some college education (OR 1.8; 1.1, 3.0), baseline CES-D(OR per point 1.1; 1.1, 1.2), presence of diabetes (OR 1.8; CI 1.1, 2.8), and baseline SLE disease activity (OR 1.2; CI 1.1, 1.4).

CONCLUSION—These results suggest that in addition to known sociodemographic factors, the presence of diabetes and SLE disease activity may play a role in the development of depression in SLE.

INTRODUCTION

Depression is a debilitating co-morbidity common among patients with systemic lupus erythematosus (SLE). Studies cite a broad range of prevalence rates of depression ranging from 17-75% (1-7); however recent estimates suggest that point prevalence rates of clinically significant symptoms and lifetime incidence of Major Depressive Disorder occur in approximately half of patients with SLE (8-12). In 1999, the American College of Rheumatology (ACR) developed a nomenclature system for 19 neuropsychiatric syndromes in SLE (NPSLE)(13), which included mood disorders of at least moderate severity. Since the development of this nomenclature system, there has been considerable debate about the inclusion of depression as an NPSLE manifestation, and the nomenclature system has been criticized as lacking specificity for SLE-specific central nervous system involvement (14-16). Using decision rules to estimate attribution of depression to SLE disease processes,

Corresponding Author: Laura J. Julian, PhD Department of Medicine University of California San Francisco 3333 California St., STE 270 San Francisco, CA 94143-0920 415/502-4587 (office) 415/476-9030 (fax) .

studies suggest that mood disorders are as likely to occur as a result of pathophysiological SLE processes as other reasons (e.g., psychosocial, impact of disease on quality of life, etc.) (17, 18).

A number of disease-related processes have been considered as potential etiological factors contributing to depression in SLE. Specific autoantibodies have been implicated including anti-ribosomal P autoantibodies (19), cross-reacting N-methyl D-aspartate (NMDA) autoantibodies (20), and antiphospholipid antibodies (21). Additionally, though few studies have evaluated specific markers of inflammation in relation to depression, a link has been observed between overall SLE disease activity, a potential proxy for inflammation, and depression (22, 23). Few studies have explored the role of cardiovascular disease and risk in the context of depression in SLE. One such study observed a cross-sectional relationship between subclinical markers of cardiovascular disease (i.e., coronary artery calcification) and depression in a well-described SLE cohort (24). Another study found an association between the presence of atherosclerosis and mood disorders in a Russian cohort of SLE patients (25).

Initially termed “atherosclerotic depression” (26), the vascular depression hypothesis posits that subclinical cerebrovascular disease can “predispose, precipitate, or perpetuate a depressive syndrome” (27). There has been considerable effort to understand vascular depression as a potential diagnostic subtype of Major Depressive Disorder, including clarifying the specific role of cardiovascular and cerebrovascular characteristics as risk factors for the development of depression (27-29). Vascular depression has been almost exclusively described in older adults as substantive cardiovascular/ cerebrovascular risk typically accumulates later in life. SLE is a condition characterized by strikingly high rates of cardiovascular disease and cerebrovascular disease in a relatively young population (30-32). Despite considerable evidence in the general population linking cardiovascular disease and risk factors to depression, relatively few studies have explored these relationships in SLE.

Cardiovascular disease has emerged as a major cause of morbidity and mortality in SLE (33-35). Traditional risk factors for cardiovascular disease, including tobacco use, hypertension, hyperlipidemia, and obesity have been observed to occur at higher rates in SLE compared to matched samples (31, 36, 37). However, other studies cite traditional cardiovascular risk factors in SLE occurring at similar rates when compared to age-matched peers (31, 38). It has become clear that these traditional cardiovascular risk factors do not fully explain the cardiovascular burden observed in SLE (39). Disease- and treatment-related factors may also be important contributors to the development of cardiovascular disease (40, 41). First, chronic inflammation is a key pathogenic mechanism for atherosclerosis and cardiovascular disease in SLE (30, 42), whether measured by specific biological markers (e.g., C-reactive protein), or when measured by proxy measures such as disease activity and damage (30, 43, 44). Other SLE-related factors include renal involvement (45, 46), and potentially treatment-related factors including chronic glucocorticoid use. Glucocorticoid use may be a reflection of active disease; however, this treatment also directly contributes to cardiovascular risk and disease (e.g., hypertension, diabetes mellitus, increased adiposity, etc.) (36, 47).

The purpose of this study was to explore the role of traditional (e.g., Framingham type) cardiovascular and SLE-specific risk factors as predictors of the longitudinal development of depression in a large observational cohort of adults with SLE followed over the course of five years. We aimed to test the impact of traditional and disease specific risk factors on the development of incident depression above and beyond that which can be predicted by sociodemographic characteristics known to be associated with depression in the general

population. An improved understanding of etiological factors associated with depression in SLE can point to targeted strategies for both prevention and intervention of depression.

SUBJECTS AND METHODS

A subset of participants were included in this study from the Lupus Outcomes Study (LOS), a prospective longitudinal study of 957 individuals with SLE whose diagnoses were confirmed by medical chart review prior to enrollment, using American College of Rheumatology (ACR) criteria (48). Details about enrollment and data collection for this study have been reported previously (49), and are briefly summarized here. Subjects were recruited through academic medical centers (25%), community rheumatology offices (11%), and non-clinical sources including patient support groups and conferences (26%), and other forms of media (38%). Initial subject recruitment occurred between 2002 and 2004; a second enrollment period began in 2006. Annual retention rates in the study have consistently exceeded 92%, including mortality. The principal data collection modality is an annual standardized telephone interview that averages 50 minutes in length and consists of validated measures of SLE disease activity and manifestations, general physical and mental health status, disability, employment, service utilization, and sociodemographic characteristics. This research protocol has been approved by the University of California San Francisco Committee on Human Research. All participants gave their informed consent to be part of the study.

Dependent Variable

Depressive symptom severity—The dependent variable is new onset “depression” over a twelve-month period. The Center for Epidemiological Studies – Depression (CES-D) scale, was used to evaluate depression status. The CES-D is a commonly used 20-item scale used to evaluate depressive symptom severity, with a score range of 0-60 (50). A CESD cut-score of ≥16 was suggested to identify individuals with “possible” depression; and a CESD cut-score of ≥ 23 has been suggested to identify individuals with “probable” depression (51). This higher cut-score has been consistent with other studies suggesting that a higher cut-score more accurately identifies persons with Major Depression (50, 52, 53). Therefore we defined incident depression as those cases crossing a more conservative threshold of ≥ 23 to identify patients with symptoms more consistent with a diagnosis of Major Depression. Although we recognize that the CESD is a measure of symptom severity and not diagnostic status, to maintain brevity we use the terms “depressed” or “depression” for patients who meet CESD score of 23 and above in this manuscript.

Independent Variables

Sociodemographic factors—Sociodemographic characteristics included in this study were age, sex, race/ethnicity (white, African American, Asian, and Hispanic/Latino, education (less than high school, high school, some college, and college educated), and poverty status (dichotomized as household income at or below versus above 125% of the Federal Poverty Threshold).

Depressive Symptom Severity—The CESD total score was also used as an independent variable in order to account for baseline levels of depressive symptoms not meeting criteria for our definition of depression. In this case, CESD severity would range from 0-22, as participants with a 23 or above would be excluded from a time 1 datapoint.

History of cardiovascular events and risk factors—The following cardiovascular events and risk factors were evaluated: reported history of heart disease (including angina and congestive heart failure), myocardial infarction, stroke, hypertension,

hypercholesterolemia, diabetes, obesity (defined as a body mass index >30), smoking status (current smoker and ever smoker versus never smoked), and family history of diabetes and/or hypertension,.

SLE-specific risk and disease factors—Disease activity was assessed using the Systemic Lupus Activity Questionnaire (SLAQ) a validated, self-report measure of disease activity in SLE which includes items assessing constitutional symptoms, mucocutaneous symptoms, musculoskeletal symptoms, among other disease activity domains (54, 55). Other SLE-related disease characteristics included disease duration (years), self-reported presence of renal involvement since the year prior to the beginning of study participation, and current treatment with glucocorticoids.

Study sample—The present analysis includes data from interviews conducted between 2004 and 2008, including participants interviewed for at least two consecutive years. To analyze predictors of incident depression, we created a unit of analysis consisting of pairs of consecutive observations, with the independent variables measured as of the first year of the pair (time 1), and depression status taken from the second year (time 2), an average of 12 months later. Thus, a participant can contribute one observation for every two consecutive interviews. If a participant had CESD scores ≥ 23 at all of the 5 waves, she/he was excluded from data analyses, leaving. 2327 observations, of which an additional 103 (5%) were excluded due to missing data. An individual excluded from the analysis in one paired-year observation due to a time 1 CES-D ≥23 or missing data could be included in a subsequent observation if a new time 1 CES-D score of <23 is present. The final sample included 2,224 observations among 663 LOS participants, an average of 3.4 observations per LOS participant.

Analysis—First, we ran a univariate model using generalized estimating equation (GEE) to fit a logistic regression model. Next, we ran a series of multivariate models using a GEE that simultaneously fits a logistic regression model (56). Collinearity thresholds were also considered. The first model examined the association of sociodemographic characteristics, time 1 depression symptom severity (CESD total score) and new onset depression. The second model built on the previous model by adding traditional cardiovascular risk and disease factors. The final model added SLE-specific risk and disease factors. All multivariate models include the time 1 CESD score, which could vary between 0 and 22 (mean 8.7±6.3) (since observations with a time 1 CESD score of 23 or greater had already been excluded). We present the results of these models using odds ratios with 95% confidence intervals.

As a sensitivity analysis we repeated the series of multivariate analysis substituting the variable SLAQ (a measure of disease activity) with a modified version of SLAQ. This modified version removes the SLAQ items that may overlap with our assessment of depression (i.e., depressed mood, fatigue, and forgetfulness).

RESULTS

Sample Characteristics and Bivariate Results

Twelve percent of observations were found to develop “depression” during the course of this study. Time 1 characteristics for the final sample are depicted in Table 1. The depression characteristics of the 663 participants were as follows: 467 (70%) never developed depression, 115 (17%) had one instance of depression, and 81 (12%) had more than one instance of depression. Univariate observational analyses of sociodemographics suggest that persons between the age of 40 and 59, persons with some college education, and persons

who identify their race/ethnicity as Hispanic/Latino(a) were more likely to develop depression compared to older adults or younger participants. The unadjusted analyses evaluating cardiovascular risk factors and SLE disease factors suggest that those with heart disease, history of myocardial infarction or stroke, diabetes, obesity (body mass index > 30), glucocorticoid use, renal involvement, a shorter disease duration, and increased disease activity were also more likely to develop depression at a subsequent interview compared to persons who remained non-depressed. Collinearity diagnostics suggested no evidence of shared variance that would preclude including all variables in the model.

Multivariate Results

Multivariate analyses predicting depression are depicted in Table 2. Model 1 included time 1 demographics and depressive symptoms. In this model, persons with less than a college education (OR 1.8; CI 1.1, 3.0), participants who were Hispanic/Latino(a) (OR 1.8; CI 1.2, 2.8), were more likely to become depressed. Time 1 CES-D symptom severity was also a significant predictor of new onset depression (OR per point 1.2; CI 1.1, 1.2).

Model 2 incorporated traditional cardiovascular risk factors in addition to time 1 demographics and depressive symptoms. In this model, both persons between the ages of 20-39 (OR 2.1; CI 1.2, 3.5) and 40-59 (OR 1.7; CI 1.1, 2.6) were more likely to develop depression, as were persons with some college education (OR 2.0; CI 1.2, 3.2), Hispanic/Latino(a) ethnicity (OR 1.8; CI 1.2, 2.8), and increased time 1 depressive symptom severity (OR 1.1; CI 1.1, 1.2). Of the cardiovascular characteristics, only the presence of diabetes emerged as being significantly related to the onset of depression (OR 1.8; CI 1.1, 2.7).

The final model incorporated SLE-specific characteristics (Model 3) in addition to demographics, time 1 depressive symptoms and traditional cardiovascular risk and disease related factors. In this model, younger age (20-39 years OR 2.4; CI 1.4, 4.2; 41-60 years OR 1.7; CI 1.1, 2.7), some college education (OR 1.8; CI 1.1, 3.0), time 1 depression symptom severity (OR 1.1, CI 1.1, 1.2), presence of diabetes (OR 1.7; CI 1.1, 2.7), and baseline assessment of SLE disease activity (SLAQ per 5 points OR 1.2; CI 1.1, 1.4) were associated with new onset depression.

Multivariate analyses of the final model were repeated with a modified SLAQ excluding overlapping symptoms with depression (e.g., depressed mood, fatigue, and forgetfulness). The results of this model were nearly identical to the original final model. Significant predictors included younger age (20-39 years OR 2.5; CI 1.4, 4.3; 40-60 OR 1.7, CI 1.1-2.7), some college educational attainment (OR 1.8; CI 1.1, 2.9), Hispanic ethnicity (OR 1.8; CI 1.2, 2.8), baseline depression symptom severity (OR 1.1; CI 1.1, 1.2), presence of diabetes (OR 1.7; CI 1.1, 2.6) and the modified SLAQ (OR 1.4; CI 1.2, 1.6). Therefore, to maintain psychometric integrity of the SLAQ measure, the original measure was retained in the model.

DISCUSSION

In this study, we sought to determine longitudinal predictors of depression in a large cohort of persons with SLE, with a particular focus on the role of cardiovascular risk factors and SLE related disease factors. In multivariate analyses, our hypotheses were partially supported. We found that in addition to sociodemographic factors, the presence of diabetes and SLE related disease activity were the strongest predictors of the development of depression in this cohort, and other traditional cardiovascular risk factors were not significant predictors of the development of depression.

The majority of the work evaluating the cardiovascular disease/ depression connection has described the pathway from depression to increased risk of developing or worsening cardiovascular disease (57). Although the previous study investigating this link by Greco and colleagues was cross-sectional, the authors hypothesize that depression contributes to subclinical markers of atherosclerosis in patients with SLE (24). Among older adults with substantive accumulation of cardiovascular risk and disease, the reverse pathway has also been explored, that of depression *precipitated by* cardiovascular and cerebrovascular disease (27). Given the fact that patients with SLE accumulate substantial cardiovascular burden at a relatively young age, we hypothesized that this pathway may be bidirectional in SLE and sought to explore this reverse pathway by evaluating traditional and disease-specific characteristics as risk factors for the longitudinal development of incident depression over the course of twelve months. In our multivariate analyses we observed that the presence of diabetes was the only traditional (i.e., Framingham type) factor associated with the development of depression.

Although the presence of diabetes was not a common comorbidity in our cohort of SLE patients, this relationship has also been observed in other populations (58), and suggests that SLE patients with diabetes may be a particularly vulnerable group at risk for the development of depression. Diabetes is also a serious, often difficult to manage chronic condition, and the burden of these two conditions may place an individual at an increased risk for depression. Additionally, the constellation of metabolic and cardiovascular risk factors characteristic of diabetes may contribute to vascular depression, whereas individual risk factors did not emerge as significant risk factors for depression in this study. Future studies evaluating specific aspects of diabetes and clinical cardiovascular risk indices and profiles are warranted to better understand the role of these factors in precipitating depression.

Disease activity emerged as the SLE-specific characteristic most robustly associated with incident depression. Although few longitudinal studies have been conducted investigating depression, our results are similar to other findings suggesting that depression scores appear to parallel disease activity over time (23, 59). It is possible that measures of SLE disease activity may reflect increased systemic inflammation contributing to the development of subclinical cardiovascular and cerebrovascular disease which may, in turn, precipitate the development of depression akin to the vascular depression hypothesis. Alternatively, there may exist a direct pathway between inflammation, in the form of increased cytokine production, and the development of depression (60). Finally, increased disease activity may be associated with a range of other down-stream effects (e.g., increased disability, decreased function) which may confer additional risk for depression.

Lower education, specifically participants who did not attain a college degree, was associated with the onset of depression in this cohort of patients with SLE, supporting earlier findings in the general population citing a potentially protective effect of increased education (61).In this study, the lowest level of educational attainment (i.e., high school or less) was not statistically significant in the multivariate analyses, but was significant in the bivariate analyses. We suspect that this lack of significance in the multivariate analyses is due to decreased power given our relatively small sample size for this lowest level of education. Increased education has been posited to be associated with social maturation and improved coping skills as well as increased social and occupational opportunities(61). Additionally, income and education are often used interchangeably as a marker of socioeconomic status. In this study, poverty was not associated with incident depression unlike our previous studies evaluating prevalent depression (62), suggesting that education and income constitute social determinants exerting unique effects on the development of depression.

Younger age was a risk factor for depression in this study, a finding that has been observed in other medical populations (63). This observation may also be a reflection of increased disease activity earlier in the course of the disease contributing to depression through one of the pathways described above. However, in the context of the vascular depression hypothesis, one would expect that older adults with SLE may have an increased cardiovascular/ cerebrovascular burden as a result of living with SLE for many years and may have increased rates of depression as they age, which we did not find in this study. This finding may also be attributed to a reporting bias, specifically decreased reporting of depressive symptoms among older adults (64). Additionally, this may be a survivor effect in that the older adults in our sample may be a generally healthier subset of older adults with SLE.

Participants who identified their race/ ethnicity as Hispanic/Latino(a) were more likely to develop depression as compared to whites. Other studies that have found increased depression symptom severity in Hispanics(65), and some observed predictors include greater exposure to stressful life events and in some cases limited social support(66). It is well-known that depression in Hispanic/Latino patients may be less likely to be detected by providers, and depression is undertreated in this group(67), as such leaving this group a potentially vulnerable subgroup with respect to depression and poor outcomes.

Finally, although the effect is modest, time 1 depressive symptom severity was a significant risk factor for incident depression. This finding is not surprising, and highlights the importance of monitoring patients with minor or sub-threshold depression in the clinic, as this is a particularly vulnerable group for the development of more severe depressive disorders (68).

This study is not without limitations. First, we sought to determine predictors of the development of “depression,” as defined in this study using cases that cross a threshold of the CESD, a measure of depression symptom severity, and not depressive disorder diagnostic status. Future studies employing a determination of diagnoses of Major Depressive Disorder are warranted. Related to this issue is the fact that incidence of depression was 12% per year, perhaps limiting our power to detect other significant effects. Future studies prospectively evaluating the development of depression in large sample of patients with lupus remain warranted in order to best understand the social and biological predictors. Second, interviews of health status and depression were conducted annually and like SLE, depression is a relapsing condition and incident or recurrent events within the one year lag period were not measured.

Third, with the exception of SLE diagnostic status, the data derived from this cohort is largely self-report. Although self-reported diagnoses of a number of health and treatment related factors have been validated and deemed reliable in epidemiological studies (e.g., hypertension) (69), it is possible that our patients are unaware of their health status across all traditional and SLE-specific risk factors. In addition, specific biological markers (e.g., inflammation, presence of antiphospholipid antibodies) are unavailable for analyses. Perhaps with this biological data, we would find more robust associations among a range of cardiovascular risk factors and depression. Related to this limitation, the SLAQ as our measure of disease activity was the most potent predictor of depression, and though we know that a 5 point increase in SLAQ score is clinically meaningful, there are not validated cut-points for the SLAQ to characterize disease severity or specific manifestations(55). Finally, psychosocial and functional predictors of depression were not evaluated in this study. It is quite possible that our markers of health status (e.g., increased disease activity) are associated with a host of psychosocial and functional sequelae (e.g., increased disability, decreased activity level) which would confer additional effects on the development of

depression. Our group and others have found increases in functional limitations as important predictors of depression in rheumatic disease and other chronic conditions(70-74). Future studies employing a blend of health status and psychosocial risk factors for depression are necessary to best elucidate etiological factors associated with depression in SLE. Despite these limitations, to our knowledge, this is the first study to evaluate longitudinally the development of depressive symptoms in a large cohort of patients with SLE. Additionally, this study is hypothesis generating, in that few studies have focused on the relationship among cardiovascular disease and risk, a major cause of morbidity and mortality in SLE, and the development of depression.

In conclusion, we found that in addition to younger age and less education, diabetes was the only traditional cardiovascular risk factor associated with the development of depression in controlled analyses. SLE related disease activity was also an important disease specific risk factor for the development of depression. This study points to potential preventative and interventional approaches including the targeting of modifiable risk factors which could result in improved depression outcomes in addition to improved overall health outcomes. Depression in the context of SLE, like many chronic conditions, is a substantial risk factor for a host of adverse personal outcomes for patients including decreased treatment adherence (75) and increased disability (59, 76). In addition to the personal costs of depression in SLE, mental health status has emerged as one of the most robust predictors of health care costs among patients with SLE (77). A number of effective treatments for depression are available and identifying patients at risk for significant depressive disorders could substantially improve the quality of life for patients with SLE.

Acknowledgments

We gratefully acknowledge funding support from the following sources: National Institute of Arthritis and Musculoskeletal and Skin Diseases; Grant Number: P60-AR-053308; National Institutes of Mental Health; Grant Number: K08-MH-072724; the Rosalind Russell Medical Research Center for Arthritis, University of California, San Francisco; and the State of California Lupus Fund.

REFERENCES

1. Ward MM, Lotstein DS, Bush TM, Lambert RE, van Vollenhoven R, Neuwelt CM. Psychosocial correlates of morbidity in women with systemic lupus erythematosus. J Rheumatol. 1999; 26:2153–2158. [PubMed: 10529132]
2. Omdal R, Waterloo K, Koldingsnes W, Husby G, Mellgren SI. Fatigue in patients with systemic lupus erythematosus: the psychosocial aspects. J Rheumatol. 2003; 30:283–287. [PubMed: 12563681]
3. Wekking EM. Psychiatric symptoms in systemic lupus erythematosus: an update. Psychosom Med. 1993; 55:219–228. [PubMed: 8475237]
4. Iverson GL. Psychopathology associated with systemic lupus erythematosus: a methodological review. Semin Arthritis Rheum. 1993; 22:242–251. [PubMed: 8484131]
5. Shapiro, H. Psychopathology in the patient with lupus. In: Wallace, DJ.; Hahn, BH., editors. Dubois' Lupus Erythematosus. 6th ed. Lippincott, Williams, & Wilkins; Philadelphia: 2002.
6. Hay EM, Black D, Huddy A, et al. Psychiatric disorder and cognitive impairment in systemic lupus erythematosus. Arthritis Rheum. 1992; 35:411–416. [PubMed: 1567490]
7. Hay EM, Huddy A, Black D, et al. A prospective study of psychiatric disorder and cognitive function in systemic lupus erythematosus. Ann Rheum Dis. 1994; 53:298–303. [PubMed: 8017982]
8. Kozora E, Thompson LL, West SG, Kotzin BL. Analysis of cognitive and psychological deficits in systemic lupus erythematosus patients without overt central nervous system disease. Arthritis Rheum. 1996; 39:2035–2045. [PubMed: 8961909]
9. Brey RL, Holliday SL, Saklad AR, et al. Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. Neurology. 2002; 58:1214–1220. [PubMed: 11971089]

10. Katz, P.; Yelin, E.; Trupin, L.; Rush, S.; Stein, J.; Spry, J. American College of Rheumatology. San Antonio, TX: 2004. Depression among adults with lupus. 2004
11. Bachen LA, Chesney MA, Criswell LA. Prevalence of mood and anxiety disorders in women with systemic lupus erythematosus. Arthritis Care & Research. 2009; 61:822–829. [PubMed: 19479699]
12. Nery FG, Borba EF, Viana VST, et al. Prevalence of depressive and anxiety disorders in systemic lupus erythematosus and their association with anti-ribosomal P antibodies. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2008; 32:695–700. [PubMed: 18077068]
13. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum. 1999; 42:599–608. [PubMed: 10211873]
14. Hanly JG. ACR classification criteria for systemic lupus erythematosus: limitations and revisions to neuropsychiatric variables. Lupus. 2004; 13:861–864. [PubMed: 15580983]
15. Ainiala H, Loukkola J, Peltola J, Korpela M, Hietaharju A. The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. Neurology. 2001; 57:496–500. [PubMed: 11502919]
16. Nived O, Sturfelt G, Liang MH, De Pablo P. The ACR nomenclature for CNS lupus revisited. Lupus. 2003; 12:872–876. [PubMed: 14714904]
17. Hanly JG, Su L, Farewell V, McCurdy G, Fougere L, Thompson K. Prospective study of neuropsychiatric events in systemic lupus erythematosus. J Rheumatol. 2009; 36:1449–1459. [PubMed: 19447937]
18. Hanly JG, Urowitz MB, Su L, et al. Prospective analysis of neuropsychiatric events in an international disease inception cohort of SLE patients. Ann Rheum Dis. 2009
19. Abdel-Nasser AM, Ghaleb RM, Mahmoud JA, Khairy W, Mahmoud RM. Association of anti-ribosomal P protein antibodies with neuropsychiatric and other manifestations of systemic lupus erythematosus. Clin Rheumatol. 2008; 27:1377–1385. [PubMed: 18481154]
20. Lapteva L, Nowak M, Yarboro CH, et al. Anti-N-methyl-D-aspartate receptor antibodies, cognitive dysfunction, and depression in systemic lupus erythematosus. Arthritis Rheum. 2006; 54:2505–2514. [PubMed: 16868971]
21. Morgan M, Downs K, Chesterman CN, Biggs JC. Clinical analysis of 125 patients with the lupus anticoagulant. Aust N Z J Med. 1993; 23:151–156. [PubMed: 8517839]
22. Nery FG, Borba EF, Hatch JP, Soares JC, Bonfá E, Neto FL. Major depressive disorder and disease activity in systemic lupus erythematosus. Comprehensive Psychiatry. 2007; 48:14–19. [PubMed: 17145276]
23. Ward MM, Marx AS, Barry NN. Psychological distress and changes in the activity of systemic lupus erythematosus. Rheumatology. 2002; 41:184–188. [PubMed: 11886968]
24. Greco CM, Kao AH, Sattar A, et al. Association between depression and coronary artery calcification in women with systemic lupus erythematosus. Rheumatology. 2009; 48:576–581. [PubMed: 19286698]
25. Lisitsyna TA, Vel'tishchev D, Seravina OF, et al. Prevalence of mental disorders in SLE patients: correlations with the disease activity and comorbid chronic conditions. Ter Arkh. 2009; 81:10–16. [PubMed: 19663185]
26. Krishnan KR, McDonald WM. Arteriosclerotic depression. Med Hypotheses. 1995; 44:111–115. [PubMed: 7596303]
27. Alexopoulos GS. The vascular depression hypothesis: 10 years later. Biol Psychiatry. 2006; 60:1304–1305. [PubMed: 17157096]
28. Krishnan KR. Towards a scientific taxonomy of depression. Dialogues Clin Neurosci. 2008; 10:301–308. [PubMed: 18979943]
29. Román GC. Vascular Depression: An Archetypal Neuropsychiatric Disorder. Biological Psychiatry. 2006; 60:1306–1308. [PubMed: 17157097]
30. Salmon JE, Roman MJ. Subclinical Atherosclerosis in Rheumatoid Arthritis and Systemic Lupus Erythematosus. The American Journal of Medicine. 2008; 121:S3–S8. [PubMed: 18926167]
31. Roman MJ, Shanker B-A, Davis A, et al. Prevalence and Correlates of Accelerated Atherosclerosis in Systemic Lupus Erythematosus. N Engl J Med. 2003; 349:2399–2406. [PubMed: 14681505]

32. Kao AH, Sabatine JM, Manzi S. Update on vascular disease in systemic lupus erythematosus. Current Opinion in Rheumatology. 2003; 15:519–527. [PubMed: 12960475]
33. Kaell AT, Shetty M, Lee BC, Lockshin MD. The diversity of neurologic events in systemic lupus erythematosus. Prospective clinical and computed tomographic classification of 82 events in 71 patients. Arch Neurol. 1986; 43:273–276. [PubMed: 3947277]
34. Sibley JT, Olszynski WP, Decoteau WE, Sundaram MB. The incidence and prognosis of central nervous system disease in systemic lupus erythematosus. J Rheumatol. 1992; 19:47–52. [PubMed: 1556699]
35. Bluestein, HG. Neuropsychiatric disorders in systemic lupus erythematosus. In: L, R., editor. Systemic Lupus Erythematosus. Wiley; New York: 1987.
36. Bessant R, Duncan R, Ambler G, et al. Prevalence of conventional and lupus-specific risk factors for cardiovascular disease in patients with systemic lupus erythematosus: A case-control study. Arthritis Rheum. 2006; 55:892–899. [PubMed: 17139666]
37. Asanuma Y, Oeser A, Shintani AK, et al. Premature Coronary-Artery Atherosclerosis in Systemic Lupus Erythematosus. N Engl J Med. 2003; 349:2407–2415. [PubMed: 14681506]
38. Frostegard J. SLE, atherosclerosis and cardiovascular disease. Journal of Internal Medicine. 2005; 257:485–495. [PubMed: 15910552]
39. 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; 44:2331–2337. [PubMed: 11665973]
40. Davis JM 3rd, Kremers H Maradit, Crowson CS, et al. Glucocorticoids and cardiovascular events in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. 2007; 56:820–830. [PubMed: 17330254]
41. Maxwell SR, Moots RJ, Kendall MJ. Corticosteroids: do they damage the cardiovascular system? Postgrad Med J. 1994; 70:863–870. [PubMed: 7870631]
42. Abou-Raya A, Abou-Raya S. Inflammation: A pivotal link between autoimmune diseases and atherosclerosis. Autoimmunity Reviews. 2006; 5:331–337. [PubMed: 16782558]
43. Bertoli AM, Vila LM, Reveille JD, Alarcon GS. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA): LXI. Value of C-reactive protein as a marker of disease activity and damage. J Rheumatol. 2008; 35:2355–2358. [PubMed: 19004040]
44. Yip GWK, Shang Q, Tam LS, et al. Disease chronicity and activity predict subclinical left ventricular systolic dysfunction in patients with systemic lupus erythematosus. Heart. 2009; 95:980–987. [PubMed: 19240052]
45. Chaiamnuay S, Bertoli AM, Roseman JM, et al. African-American and Hispanic ethnicities, renal involvement and obesity predispose to hypertension in systemic lupus erythematosus: results from LUMINA, a multiethnic cohort (LUMINAXLV). Ann Rheum Dis. 2007; 66:618–622. [PubMed: 17107981]
46. Toloza SM, Uribe AG, McGwin G Jr. et al. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA): XXIII. Baseline predictors of vascular events. Arthritis & Rheumatism. 2004; 50:3947–3957. [PubMed: 15593203]
47. Calvo-Alen J, Toloza SM, Fernandez M, et al. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA). XXV. Smoking, older age, disease activity, lupus anticoagulant, and glucocorticoid dose as risk factors for the occurrence of venous thrombosis in lupus patients. Arthritis Rheum. 2005; 52:2060–2068. [PubMed: 15986376]
48. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997; 40:1725. [PubMed: 9324032]
49. Yelin E, Trupin L, Katz P, et al. Work dynamics among persons with systemic lupus erythematosus. Arthritis Rheum. 2007; 57:56–63. [PubMed: 17266065]
50. Radloff LS. The CES-D scale: a self report depression measure for research in the general population. Applied Psychological Measurement I. 1977:385–401.
51. Pandya R, Metz L, Patten SB. Predictive Value of the CES-D in Detecting Depression Among Candidates for Disease-Modifying Multiple Sclerosis Treatment. Psychosomatics. 2005; 46:131–134. [PubMed: 15774951]

52. Haringsma R, Engels GI, Beekman ATF, Ph S. The criterion validity of the Center for Epidemiological Studies Depression Scale (CES-D) in a sample of self-referred elders with depressive symptomatology. International Journal of Geriatric Psychiatry. 2004; 19:558–563. [PubMed: 15211536]
53. Barrett J, Oxman T, Gerber P. Prevalence of depression and its correlates in a general medical practice. J Affect Disord. 1987; 12:167–174. [PubMed: 2955009]
54. Karlson EW, Daltroy LH, Rivest C, et al. Validation of a Systemic Lupus Activity Questionnaire (SLAQ) for population studies. Lupus. 2003; 12:280–286. [PubMed: 12729051]
55. Yazdany J, Yelin EH, Panopalis P, Trupin L, Julian L, Katz PP. Validation of the systemic lupus erythematosus activity questionnaire in a large observational cohort. Arthritis Rheum. 2008; 59:136–143. [PubMed: 18163398]
56. Hardin, JW.; Hilbe, JM. Generalized Estimating Equations. Chapman & Hall/ CRC; Boca Raton, FL: 2002.
57. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. Int J Geriatr Psychiatry. 2007; 22:613–626. [PubMed: 17236251]
58. Katon W, Russo J, Lin EHB, et al. Depression and Diabetes: Factors Associated With Major Depression at Five-Year Follow-Up. Psychosomatics. 2009; 50:570–579. [PubMed: 19996227]
59. Nery FG, Borba EF, Hatch JP, Soares JC, Bonfá E, Neto FL. Major depressive disorder and disease activity in systemic lupus erythematosus. Comprehensive Psychiatry. 48:14–19. [PubMed: 17145276]
60. Irwin MR, Miller AH. Depressive disorders and immunity: 20 years of progress and discovery. Brain, Behavior, and Immunity. 2007; 21:374–383.
61. Ladin K. Risk of Late-Life Depression Across 10 European Union Countries: Deconstructing the Education Effect. J Aging Health. 2008; 20:653–670. [PubMed: 18635752]
62. Trupin L, Tonner MC, Yazdany J, et al. The role of neighborhood and individual socioeconomic status in outcomes of systemic lupus erythematosus. J Rheumatol. 2008; 35:1782–1788. [PubMed: 18634153]
63. Strik JJMH, Lousberg R, Cheriex EC, Honig A. One year cumulative incidence of depression following myocardial infarction and impact on cardiac outcome. Journal of Psychosomatic Research. 2004; 56:59–66. [PubMed: 14987965]
64. Lyness JM, Cox C, Curry J, Conwell Y, King DA, Caine ED. Older age and the underreporting of depressive symptoms. J Am Geriatr Soc. 1995; 43:216–221. [PubMed: 7884106]
65. Bromberger JT, Schott LL, Kravitz HM, et al. Longitudinal Change in Reproductive Hormones and Depressive Symptoms Across the Menopausal Transition: Results From the Study of Women's Health Across the Nation (SWAN). Arch Gen Psychiatry. 67:598–607. [PubMed: 20530009]
66. Boutin-Foster C, Ogedegbe G, Peterson J, Briggs WM, Allegrante JP, Charlson ME. Psychosocial mediators of the relationship between race/ethnicity and depressive symptoms in Latino and white patients with coronary artery disease. J Natl Med Assoc. 2008; 100:849–855. [PubMed: 18672563]
67. Simpson S, Krishnan L, Kunik M, Ruiz P. Racial Disparities in Diagnosis and Treatment of Depression: A Literature Review. Psychiatric Quarterly. 2007; 78:3–14. [PubMed: 17102936]
68. Fogel J, Eaton WW, Ford DE. Minor depression as a predictor of the first onset of major depressive disorder over a 15-year follow-up. Acta Psychiatrica Scandinavica. 2006; 113:36–43. [PubMed: 16390367]
69. Vargas CM, Burt VL, Gillum RF, Pamuk ER. Validity of Self-Reported Hypertension in the National Health and Nutrition Examination Survey III, 1988-1991. Preventive Medicine. 1997; 26:678–685. [PubMed: 9327477]
70. Gitlin LN, Hauck WW, Dennis MP, Schulz R. Depressive Symptoms in Older African-American and White Adults with Functional Difficulties: The Role of Control Strategies. Journal of the American Geriatrics Society. 2007; 55:1023–1030. [PubMed: 17608874]
71. Katz PP, Julian LJ, Omachi TA, et al. The impact of disability on depression among individuals with COPD. Chest. 137:838–845. [PubMed: 19933374]

72. Margaretten M, Yelin E, Imboden J, et al. Predictors of depression in a multiethnic cohort of patients with rheumatoid arthritis. Arthritis Care & Research. 2009; 61:1586–1591. [PubMed: 19877099]

73. Katz PP, Yelin EH. Activity loss and the onset of depressive symptoms: do some activities matter more than others? Arthritis Rheum. 2001; 44:1194–1202. [PubMed: 11352254]

74. Katz PP, Yelin EH. The development of depressive symptoms among women with rheumatoid arthritis. The role of function. Arthritis Rheum. 1995; 38:49–56. [PubMed: 7818571]

75. Julian LJ, Yelin E, Yazdany J, et al. Depression, medication adherence, and service utilization in systemic lupus erythematosus. Arthritis Rheum. 2009; 61:240–246. [PubMed: 19177526]

76. Baker K, Pope J, Fortin P, et al. Work disability in systemic lupus erythematosus is prevalent and associated with socio-demographic and disease related factors. Lupus. 2009; 18:1281–1288. [PubMed: 19854811]

77. Panopalis P, Yazdany J, Gillis JZ, et al. Health care costs and costs associated with changes in work productivity among persons with systemic lupus erythematosus. Arthritis Rheum. 2008; 59:1788–1795. [PubMed: 19035422]

Table 1

Characteristics of SLE Participants

	All Participants at Time 1 n=663 n (%)
Age	
Age 20-39	195 (29)
Age 40-59	347 (52)
Age 60+	121 (18)
Female	589 (90)
Living below poverty	68 (10)
Race/ Ethnicity	
Hispanic	62 (9)
African American	54 (8)
Asian	75 (11)
Other	58 (9)
White	414 (62)
Education	
High school graduate or less	73 (11)
Some college	299 (45)
College graduate	166 (25)
Post graduate	125 (19)
Heart Disease	142 (21)
History of MI[b] or stroke	98 (15)
Hypertension	352 (53)
Hypercholesterolemia	158 (24)
Diabetes	54 (8)
Body Mass Index over 30	159 (34)
History of smoking	196 (30)
Current smoking	48 (7)
Glucocorticoid use	369 (56)
Recent renal involvement	299 (45)
Disease duration (years)	14.7±8.7
Disease activity (SLAQ[c])	10.4±6.9
Months from T1 to T2	12.6±2.8

[a] Depression defined as a new onset of Center for Epidemiological Studies – Depression Score at or above 23 at Time 2 compared to Time 1.

[b] MI – Myocardial infarction

[c] SLAQ – Systemic Lupus Activities Questionnaire

Table 2

Predictors of the Development of Depression over One Year [a]

(n = 2224 observations)	Univariate Analyses	Multivariate Analyses		
		Model 1	Model 2	Model 3
	OR (95 %CI)	OR (95 %CI)	OR (95 %CI)	OR (95 %CI)
Sociodemographics				
Age				
Age 20-39	1.3 (0.8,2.1)	1.5 (1.0, 2.5)	**2.1 (1.2, 3.5)**	**2.4 (1.4, 4.2)**
Age 40-59	**1.6 (1.0, 2.4)**	1.4 (1.0, 2.2)	**1.7 (1.1, 2.6)**	**1.7 (1.1, 2.7)**
Age 60+ (*reference*)				
Gender				
Female	1.3 (0.7, 2.1)	1.1 (0.7, 1.9)	1.2 (0.7, 2.1)	1.1 (0.6, 1.9)
Male (reference)				
Education				
High school graduate or less	**1.8 (1.0, 3.3)**	1.3 (0.7, 2.4)	1.1 (0.6, 2.1)	1.1 (0.5, 2.1)
Some college	**2.4 (1.5, 3.9)**	**2.3 (1.4, 3.6)**	**2.0 (1.2, 3.2)**	**1.8 (1.1, 3.0)**
College graduate	1.7 (0.9, 2.8)	1.7 (0.9, 2.8)	1.16 (0.9, 2.7)	1.5 (0.9, 2.6)
Post graduate (*reference*)				
Living below poverty threshold	1.9 (1.3, 2.9)	1.2 (0.7, 2.0)	1.1 (0.7, 1.9)	1.0 (0.6, 1.7)
Race/Ethnicity				
Hispanic/Latino(a)	**1.8 (1.2, 2.8)**	**1.6 (1.0, 2.4)**	**1.7 (1.1, 2.6)**	**1.8 (1.2, 2.8)**
African American	1.5 (0.8, 2.5)	1.1 (0.6, 2.1)	1.0 (0.5, 1.9)	1.0 (0.6, 1.9)
Asian	0.7 (0.4, 1.2)	0.7 (0.4, 1.2)	0.7 (0.4, 1.2)	0.7 (0.4, 1.2)
Other	0.7 (0.4, 1.3)	0.5 (0.3, 0.9)	0.5 (0.3, 1.0)	0.5 (0.3, 0.9)
Caucasian (*reference*)				
Baseline depression (CESD score)	**1.2 (1.1, 1.2)**	**1.2 (1.1, 1.2)**	**1.2 (1.1, 1.2)**	**1.1 (1.1, 1.2)**
Traditional cardiovascular risk and disease				
Heart disease	**1.5 (1.1, 2.1)**		1.3 (0.9, 1.8)	1.1 (0.8, 1.6)
History of MI [b] or stroke	**1.5 (1.0, 2.2)**		1.2 (0.8, 1.8)	1.2 (0.8, 1.8)
Hypertension	1.3 (0.9, 1.7)		1.2 (0.9, 1.7)	1.2 (0.9, 1.7)
Hypercholesterolemia	1.3 (0.9, 1.7)		1.0 (0.7, 1.5)	1.0 (0.7, 1.5)
Diabetes	**2.6 (1.7, 3.9)**		**1.8 (1.1, 2.7)**	**1.7 (1.1, 2.7)**
Family History	1.0 (0.8, 1.3)		0.9 (0.6, 1.2)	0.9 (0.6, 1.2)
Obesity (Body Mass Index >30)	**1.6 (1.2, 2.2)**		1.1 (0.8, 1.7)	1.1 (0.7, 1.6)
History of smoking	1.1 (0.8, 1.5)		1.2 (0.9, 1.7)	1.3 (0.9, 1.8)
Current smoking	1.3 (0.8, 2.2)		1.3 (0.8, 2.2)	1.3 (0.7, 2.1)
SLE-specific disease characteristics				
Glucocorticoid use	**1.5 (1.2, 2.0)**			1.2 (0.8, 1.6)
Recent renal involvement	**1.4 (1.0, 1.8)**			0.9 (0.7, 1.3)
Disease duration (years)	1.0 (0.9, 1.0)			1.0 (1.0, 1.1)
Disease activity (SLAQ[c])	**1.6 (1.4, 1.7)**			**1.2 (1.1, 1.4)**

Note: Bold Font = significant at p<0.05 level

[a]Depression defined as new incidence of Center for Epidemiological Studies – Depression Score (CESD) at or above 23 compared to the previous annual interview

[b]MI – Myocardial infarction

[c]SLAQ – Systemic Lupus Activities Questionnaire per 5 unit increment