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The Association between Depression and Self-Reported Cardiovascular Disease among Individuals with Systemic Lupus Erythematous

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The Association between Depression and Self-Reported Cardiovascular Disease among Individuals with Systemic Lupus Erythematous

By

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B.S.

Florida Gulf Coast University

2011

Thesis Committee Chair: Tené T. Lewis, PhD

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Master of Public Health
in Epidemiology
2016

Abstract

The Association between Depression and Self-Reported Cardiovascular Disease among Individuals with Systemic Lupus Erythematous

By Daniel Bowen

Background: The association between cardiovascular disease (CVD) and depression has been thoroughly examined through numerous studies. However, few studies have examined this association in populations that suffer from autoimmune disorders, who are at higher risk for developing both CVD and depression. This study seeks to address this gap in knowledge by examining the association between CVD and depression in a population based sample of individuals who have confirmed systemic lupus erythematous diagnoses.

Methods: Data for this study was obtained from 630 participants of the Georgians Organized Against Lupus cohort. Depressive symptoms were measured using the PHQ-9. In addition, we calculated a PHQ-6 score subtracting the scores from the somatic items of the PHQ-9. CVD was defined as self-reported diagnosis by a physician of either myocardial infarction, stroke, coronary heart disease. Multivariate analyses were run to estimate the measure of association among the entire cohort using the PHQ-9 and the PHQ-6. We ran similar analyses stratified by race and gender. Finally, a somatic subscale was calculated from the three items removed from the PHQ-9. Correlations between the somatic scale and lupus disease activity, employment status, and CVD status were assessed.

Results: Of the 630 participants, 221 (35.1%) had depressive symptoms, while 409 (64.9%) did not have depressive symptoms using the standard PHQ-9 cutoff score of 10. After adjusting for age, race and education, depressive symptoms were significantly associated with CVD (Odds Ratio (OR): 1.52, 95% CI: 1.01, 2.28). A similar result was discovered when restricting to women in the sample (OR: 1.64, 95% CI 1.08, 2.50). When using the PHQ-6, the fully adjusted model showed a significant protective association among women (OR: 0.49, 95% CI: 0.25, 0.98).

Conclusion: When measuring depressive symptoms, including the somatic items of the PHQ-9 yielded a positive and statistically significant association between depressive symptoms and CVD when adjusting for age, sex, and education level. When using the PHQ-6, the association was no longer seen among the entire cohort and depression appeared to have a protective effect among the women in the study sample.

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Background and Literature Review

Systemic Lupus Erythematous

Systemic lupus erythematous (SLE) is a relapsing-remitting chronic auto-immune disorder characterized by systemic inflammation, fatigue, and joint pain. SLE is idiopathic, but it has been hypothesized that a mixture of genetic, hormonal, and environmental factors contribute to the etiology of SLE (1). The prevalence of SLE is much higher among women. It is estimated there are between 4.3 to 13.6 cases of SLE among women for every case among men (2). African-Americans, especially African-American women, have a much higher prevalence of SLE, with estimated prevalence ratios between 2.7 to 25.8 times higher when compared with Caucasians (2). Although disease activity appears to be more severe in African-Americans, evidence suggests that disparities in socioeconomic status explain these differences (3).

Individuals with auto-immune diseases are at higher risks of developing both depression and CVD. A meta-analysis of 28 studies found that the risk of developing CVD among individuals with SLE is at least two times greater when compared to the general public, with older patients and young women having the greatest risk (4) Inflammation, a near universal clinical manifestation of SLE, is known to increase the rate of atherosclerosis, which subsequently increases the risk of developing CVD (5). While specific prevalence rates for depression among individuals with SLE are difficult to determine due to methodological issues, cross-sectional studies have suggested the prevalence of major depressed disorder among individuals with SLE is between 20% and 47% (6).

Association between Depression and Cardiovascular Disease

Depression and cardiovascular disease (CVD) have become two of the most common and costly morbidities in the United States (7). It has been estimated that the national prevalence of depression is 8.7%, while the prevalence of a lifetime diagnosis of depression is 15.7% (7). Nationally, the prevalence of CVD, which is an umbrella term which typically includes coronary heart disease, myocardial infarction, and cerebrovascular accidents, has been estimated to be 7.2% (8).

Recent epidemiologic research has suggested these two pathologies are associated with one another. Cross sectional studies across various populations have reported depression to increased odds of CHD by one and a half to three times (9-11). Prospective cohort studies have provided evidence for the directionality between depression and the development of CVD. A prospective community based study by Larson et al. found that individuals with depression were at more than two times the risk of having a cerebrovascular accident (RR: 2.67, 95% CI: 1.08, 6.63) (12) . Another prospective community based study found that individuals with major depressive disorder were at close to four times the risk of having a fatal cardiovascular event (RR: 3.9, 95% CI: 1.4, 10.9) (13). Other prospective cohort studies have reported similar results (14-20).

Not all studies support the association between depression and CVD. Several studies have found a significant association in one sex, while finding the association insignificant in the other. A study by Ferketich et al. found that when adjusting for race and clinical covariates the association between depression was significantly associated with CVD among men (OR: 2.34, 95% CI: 1.54, 3.56), while the association was not significant among women (OR: 0.74, 95% CI: 0.40, 1.48) (21). Another study by Pratt et al. produced opposite results, with a marginally significant association found among the

female participants, while an insignificant association among the male participants (17). Pratt et al. suggested this difference is due to how depressive symptoms were measured and how CVD was defined (17).

Plausible Mechanisms

A definitive mechanism as to how depression increases the risk of developing CVD is not yet known. Several authors suggest a relation between depression and increased immune response driven inflammation may link depression to CVD (22, 23). Studies have found that individuals diagnosed with depression present with increased inflammatory markers (e.g. C-reactive protein, Interleukin-6, and Tissue Necrosis Factor) (5) and inflammation is known to increase the rate of atherosclerosis development (5). In addition to the possible biomedical mechanism, the depression – CVD association may be driven by a behavioral component as well. Depression has been associated with adverse health behaviors, such as excessive alcohol use, drug use, insufficient physical activity, and failure to comply with medical regiments, which all may increase the risk of developing CVD (24-26).

Depression and Cardiovascular Disease in Cohorts with Auto-Immune Diseases

Although there have been numerous studies that have examined the association between depression and CVD, relatively few have examined this association in individuals with auto-immune diseases. Studies have examined the association among individuals with rheumatoid arthritis (RA). Although the pathophysiology is different from SLE, those with RA are at a similar increased risk of developing depression and CVD (27). Two studies, a prospective cohort by Ying et al. and a retrospective cohort by Scherrer et al., examined the association of depression and CVD among individuals with

RA. Ying et al. found a significant association between depression and subclinical atherosclerosis among those with RA (28). Scherrer et al. found that among a cohort of 15,634 U.S adults with RA, those who had depression had 1.38 times the hazard of myocardial infarction than those who did not have depression after adjustment (HR: 1.38, 95% CI: 1.09, 1.75) (29).

Only two studies have examined the association between depression and CVD among individuals with SLE. In a cross sectional study of 161 women with SLE, Greco et al. found that depression was independently associated with cardiovascular disease (OR. 3.85, 95% CI: 1.37, 10.87). In another study by Greco et al., this time a one to one matched case-control study consisting of 322 women, found that among women with SLE, depression was associated at more than two time the odds (OR: 2.48, 95% CI: 1.05, 5.87) of having any coronary arterial calcification, a clinical biomarker used to detect atherosclerosis. However, after adjusting for BMI the association was no longer statistically insignificant (OR: 1.72, 95% CI: 0.61, 4.89). This suggests that the depression-CAC pathway among women with SLE is mediated by BMI.

Although the long term health outcomes of patients with SLE has improved, mortality rates related from CVD have not decreased to the same degree (30). Treating depression in patients with autoimmune conditions has been found to be a highly effective and inexpensive method of improving their overall quality of life (31). Determining to what extent an association between depression and CVD exists among individuals with SLE would provide clinicians another treatment path for those suffering from this common and debilitating illness, with the long term goal of reducing CVD related mortality among individuals with SLE.

Manuscript

The Association between Depression and Self-Reported Cardiovascular Disease among Individuals with Systemic Lupus Erythematous

Abstract

Background: The association between cardiovascular disease (CVD) and depression has been thoroughly examined through numerous studies. However, few studies have examined this association in populations that suffer from autoimmune disorders, who are at higher risk for developing both CVD and depression. This study seeks to address this gap in knowledge by examining the association between CVD and depression in a population based sample of individuals who have confirmed systemic lupus erythematous diagnoses.

Methods: Data for this study was obtained from 630 participants of the Georgians Organized Against Lupus cohort. Depressive symptoms were measured using the PHQ-9. In addition, we calculated a PHQ-6 score subtracting the scores from the somatic items of the PHQ-9. CVD was defined as self-reported diagnosis by a physician of either myocardial infarction, stroke, coronary heart disease. Multivariate analyses were run to estimate the measure of association among the entire cohort using the PHQ-9 and the PHQ-6. We ran similar analyses stratified by race and gender. Finally, a somatic subscale was calculated from the three items removed from the PHQ-9. Correlations between the somatic scale and lupus disease activity, employment status, and CVD status were assessed.

Results: Of the 630 participants, 221 (35.1%) had depressive symptoms, while 409 (64.9%) did not have depressive symptoms using the standard PHQ-9 cutoff score of 10. After adjusting for age, race and education, depressive symptoms were significantly associated with CVD (Odds Ratio (OR): 1.52, 95% CI: 1.01, 2.28). A similar result was discovered when restricting to women in the sample (OR: 1.64, 95% CI 1.08, 2.50). When using the PHQ-6, the fully adjusted model showed a significant protective association among women (OR: 0.49, 95% CI: 0.25, 0.98).

Conclusion: When measuring depressive symptoms, including the somatic items of the PHQ-9 yielded a positive and statistically significant association between depressive symptoms and CVD when adjusting for age, sex, and education level. When using the PHQ-6, the association was no longer seen among the entire cohort and depression appeared to have a protective effect among the women in the study sample.

Introduction

Cardiovascular disease (CVD) and depression are two of the most common morbidities in the United States (32). It has been estimated that the national prevalence of depression is 8.7%, while the prevalence of a lifetime diagnosis of depression is 15.7% (7). Nationally, the prevalence of CVD, which is an umbrella term that typically includes coronary heart disease, myocardial infarction, and cerebrovascular accidents, has been estimated to be 7.2% (8).

Multiple studies have shown a positive association between depression and the development of CVD (10, 12, 14-16, 33). Some studies have shown a positive association when restricting to one sex or another (17, 21, 34). In these cases, the association is more often significant in women when compared to men. An exact mechanism has not been determined to explain the association between depression and CVD. Depression has been associated with adverse health behaviors, such as excessive alcohol use, drug use, insufficient physical activity, and failure to comply with medical regiments, which may lead to the development of CVD (24-26). Other studies have found that individuals diagnosed with depression present with increased inflammatory markers (e.g. C-reactive protein, Interleukin-6, and Tissue Necrosis Factor) (5). Inflammation is known to increase the rate of atherosclerosis, which subsequently increases the risk of developing CVD (5).

Systemic lupus erythematous (SLE) is a relapsing-remitting chronic autoimmune disorder characterized by systemic inflammation, fatigue, and joint pain. SLE disproportionally affects women and African-Americans (35). Individuals suffering from

SLE are more susceptible to CVD and depression when compared with the general population (6). While specific prevalence rates for depression among individuals with SLE are difficult to determine due to methodological issues, cross-sectional studies have suggested the prevalence of major depressed disorder among individuals with SLE is between 20% and 47% (6). Individuals with SLE are more than double the risk of developing CVD when compared with those in the general population (36) . In recent years, the long term health outcomes of patients with SLE has improved, however, mortality rates related from CVD have not decreased to the same degree (30). Examining a potential risk for the development of CVD among individuals with SLE carries significant public health implications.

Although there have been extensive studies that examine the association between depression and CVD, relatively few have set out to study this association in individuals with auto-immune disorders (28, 29, 37-39). To address this gap in the literature, this study sets out to investigate the association between depressive symptoms and cardiovascular disease in a population based cohort of individuals who have been diagnosed with SLE.

Methods

Study Sample

Data for the analyses were obtained from the population-based Georgian Organized Against Lupus (GOAL) cohort. The GOAL cohort consists of diagnosed SLE patients from metropolitan Atlanta, Georgia. Over 70% of the individuals in the cohort were recruited through the Georgia Lupus Registry, a registry funded by the Centers for Disease Control and Prevention to accurately assess the incident and prevalence of SLE

in Atlanta, GA (40). The remainder of the cohort was recruited through various rheumatology clinics around metropolitan Atlanta, Emory University Hospital, and the Grady Health System (40). Validation of SLE cases were based upon either the fulfillment of four or more of the American College of Rheumatology (ACR) Classification Criteria for SLE or three ACR criteria with an examination and final SLE diagnosis by a board-certified rheumatologist (40-42).

For this study, data was obtained for 801 individuals who participated in the GOAL cohort during fall of 2011 (Wave 1) and 715 individuals who had participated in the GOAL cohort during fall of 2013 (Wave 3). Multiple waves were needed to gather all necessary covariates. Individuals were excluded if they did not participate in both Wave One and Wave Three of the cohort. The final sample size consisted of 630 GOAL cohort participants.

Cardiovascular Disease Measure

The self-administered version of the Brief Index of Lupus Damage (SA-BILD) was used to collect participant's cardiovascular disease status. The SA-BILD, a modified version of the Brief Index of Lupus Damage measure, was designed to be a cost effective and efficient method of measuring organ damage caused by SLE to a wide range of individuals regardless of socioeconomic status (43). The SA-BILD was developed specifically to collect data among GOAL participants, among whom it has been tested and shown to be valid and highly reliable (43). Specifically, cardiovascular disease was defined as any self-reported diagnoses by a physician of either myocardial infarction, stroke, coronary heart disease, or any combination of these morbidities.

Depressive Symptoms Measure

Depressive symptoms were measured using the 9-item Patient Health Questionnaire (PHQ-9). The PHQ-9 is a brief validated instrument that is widely used to measure depressive symptoms in the general population, populations with auto-immune disorders, and populations with heart disease (44). The PHQ-9 scale can be scored from 0 to 27, with each question scored from 0 (not at all) to 3 (nearly every day) (45). We assessed PHQ-9 as a continuous measure and as a dichotomous measure using the standard cutoff of 10 (45).

In addition, we calculated a PHQ-6 score subtracting the scores from the somatic items of the PHQ-9 ("In the past 2 weeks, how often have you been bothered by: Trouble falling or staying asleep, or sleeping", "In the past 2 weeks, how often have you been bothered by: Feeling tired or having little energy.", and "In the past 2 weeks, how often have you been bothered by: Moving or speaking slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual."). Somatic items were removed due to the fact that individuals who suffer from auto-immune disorders typically experience symptoms similar to these regardless of depression status.

Covariates

We controlled for common socio-demographic covariates associated with CVD including: age, sex, race, highest level of education achieved, and current employment status (10, 11, 14). Continuous years of education were categorized into: Junior High/High School, College/University, and Graduate/Professional. In addition, we controlled for clinical covariates commonly associated with CVD diagnoses in healthy populations (9, 11, 14, 15) and in individuals with SLE (37, 38). Body mass index,

defined as weight in kilograms divided by height in meters squared, was calculated using self-reported height and weight. SLE disease activity score was calculated as the sum of the self-reported Lupus Disease Activity Score measure. Age at SLE diagnosis was calculated by using self-reported month and year of SLE diagnosis. Individuals were categorized as either "smoker" or "non-smoker" based on whether or not the individual had reported smoking over 100 cigarettes over the course of their lives. A similar categorization scheme for smoking status has been done in previous studies (38, 46). Previous diagnosis of diabetes was collected using the SA-BILD.

Statistical Analysis

To begin, we calculated the mean and standard deviations for each of the continuous covariates. We determined counts and percentages for categorical covariates. To compare the covariate distribution among those who had depressive symptoms versus those who did not, we used $\chi 2$ tests to compare the categorical covariates and ran t-tests to compare the continuous covariates.

We ran multivariate logistic regression analyses to examine the association between depression and self-reported CVD. Model 1 included standard demographic characteristics (age, race, sex, and education status). Model 2 added a term for current employment status. Models 2a and 2b tested for significant interactions between depression and gender and between depression and race. Fully adjusted multivariate logistic regression models (Model 3) included demographic characteristics, current employment status, clinical history, and any interaction terms determined to be significant. We ran models 1-3 with the complete PHQ-9 scale using the standard cutoff of 10. We also ran models 1-3 using the PHQ-6 scores with the same cut-off of 10.

We ran stratified logistic regression models by sex due to the relatively small number of men when compared with the number of women in the study sample. We also ran stratified logistic regression models by race due to the relatively small number of non-African-Americans relative to African-Americans in the study sample. The initial stratified models included base demographic characteristics. Fully adjusted models were only constructed if the depression-CVD association was statistically significant in any of the base models. Stratified models were run with the complete PHQ-9 and the PHQ-6 using the standard cutoff of 10.

Finally, a somatic subscale was calculated from the three items removed from the PHQ-9. Correlations between the somatic scale and lupus disease activity, unemployment/disabled status, and CVD status were assessed. All analyses were carried out using SAS version 9.4 (SAS Institute, Cary, N.C.).

Results

Sample Characteristics

Of the 630 GOAL cohort participants used in this study, 590 (93.7%) were female. Overall, 492 (78.1%) of the study participants identified as African-American, 63 (10%) had a previous diagnosis of diabetes, and 348 (55.2%) had a previous diagnosis of hypertension. The mean age of the participants was 49 years (SD 13.15).

Table 1 shows the characteristics of the GOAL cohort participants in the current analysis by depressive symptoms. Individuals with depressive symptoms were more likely to be female (96.8%, 91.9%), more likely to self-report a diagnosis of diabetes (14.7%, 7.6%), more likely to be diagnosed with hypertension (62.1%, 52.4%), and have a higher mean lupus disease activity score (Mean: 12.6, SD: 8.0; Mean: 22.7, SD 7.2). In

addition, depressed individuals were more likely to be unemployed/disabled (51.4%, 29.2%) and less likely to be fully employed (18.8%, 32.4%).

Associations between Depressive Symptoms and CVD

Table 2 shows the results of the multivariate logistic regression conducted on the entire study sample to estimate the association between depressive symptoms and CVD. After adjusting for age, race and education, depressive symptoms were significantly associated with CVD (OR: 1.52, 95% CI: 1.01, 2.28). This association became statistically insignificant in model 2 after adding employment status (OR: 1.24. 95% CI: 0.81, 1.90) and was further attenuated in model 3 after adjusting for the clinical covariates (OR: 1.06, 95% CI: 0.64, 1.77).

Table 3 shows the results of the multivariate logistic regression conducted on only the women in the study sample. The results were comparable to those in the full sample. Model 1 showed a statistically significant association between depressive symptoms and CVD among women with SLE (OR: 1.64, 95% CI: 1.08, 2.50). After adjusting for clinical covariates, the association was no longer statistically significant (OR: 1.25, 95% CI: 0.74, 2.11). The association was further attenuated after the addition of employment status to the model (OR: 1.06, 95% 0.64, 1.77). Among men, depressive symptoms were not significantly associated with CVD in age and education adjusted models (OR: 0.93, 95% CI: 0.11, 7.59).

Table 4 shows the results of the multivariate logistic regression analyses using the calculated PHQ-6 score and the same cutoff value of 10 for exhibiting depressive symptoms by sex. Models 1 and 2 both show a statistically insignificant inverse association between depressive symptoms and CHD diagnosis among women with SLE.

The fully adjusted model 3 showed a statistically significant inverse relationship between depressive symptoms and CVD among women with SLE (OR: 0.49, 95% CI: 0.25, 0.98). Again, depressive symptoms were not significantly associated with CVD among men, when adjusting for age and education (OR: 0.78, 95% CI: 0.05, 13.14).

Somatic Subscale

Finally, there was a significant difference in the mean somatic subscale score between those with self-reported CVD and those without (Mean: 3.87, SD: 2.25 vs Mean: 3.39, SD: 2.44, p – value: 0.0358). Also, there was a significant difference in the mean somatic subscale among the various employment status categories. Those who were employed and working full time had a mean subscale score of 2.83 with a standard deviation of 2.09, while those who were unemployed or disabled had a mean subscale score of 4.38 with a standard deviation of 2.46. The somatic subscale score and lupus disease activity score tended to increase together (r = .63, p-value: <0.0001).

Discussion

In a community-based sample of individuals with SLE, we found a statistically significant association between depression and self-reported CVD after adjusting for standard demographic covariates and when using the complete PHQ-9 at the standard cutoff of 10. The association was no longer significant after adjusting for employment or clinical covariates. Analyses stratified by sex revealed that the findings in the full cohort were primarily driven by the female participants in the sample. Among women in the cohort, the association between depression and self-reported CVD was significant to a similar magnitude after adjusting for demographic covariates and using the complete PHQ-9 at the standard cutoff. In the additional analyses without the somatic items (PHQ-

6), the association between depression and CVD became protective in the fully adjusted model among women in the cohort.

These results suggest that the somatic items of the PHQ-9 drove the initial positive association between depression and CVD among individuals with SLE. Similar results have been presented in other studies that have examined the association between depression and CVD among healthy individuals. In a study by Hawkins et al., it was discovered that the somatic cluster of the Center for Epidemiologic Studies Depression Scale (CES-D), a measure of depressive symptoms similar to the PHQ-9, was the only cluster to significantly be associated with coronary heart disease (47). Two other prospective cohort studies found that only the somatic cluster of the CES-D was predictive of developing CVD among a sample of older but healthy individuals (48, 49). However, other studies have shown that the cognitive symptoms of depression predict developing CVD in middle aged healthy individuals (50, 51). Our sample, although middle aged, is not healthy. This may explain why our results differ somewhat from the literature.

One possible explanation as to why the somatic items drive the association between depression and CVD among individuals with SLE may relate to the pathophysiology of depression. The somatic items of the PHQ-9 might be linked to, and be the cluster of items that best identifies, the adverse effects on the cardiovascular system caused by the increased inflammation and physiological dysregulation associated with depression (5, 52). Another possible explanation is that the somatic items of the PHQ-9 might be a measure of some other medical condition that is also associated with developing CVD, in this instance, SLE.

The protective effect of depression that was seen after removing the somatic items among women with SLE is perplexing. The protective effect may be due to the strong association observed between the covariates and reports of CVD in the full model. For example, employment status was highly associated with self-reported CVD across models. Specifically, those who were retired or unemployed/disabled showed the strongest association with self-reported CVD. A diagnosis of diabetes or hypertension was also found to be associated with self-reported CVD. With that said, after the removal of the somatic items from the PHQ-9, we can only speculate as to the characteristics of the women who still met the criteria for depression. Future investigations into how these women differ from those who show more severe somatic symptoms of depression is necessary to understand this protective effect.

Due to the cross-sectional design of this study, we are unable to determine the directionality of the association between depression and CVD among individuals with SLE. The directionality of the depression-CVD has been disputed, but most authors agree the relationship is bidirectional (37, 38). Another limitation of our study is the reliance of self-reported data for the diagnosis of CVD. Without implementing a clinically obtained biomarker to define CVD, such as the use of coronary arterial calcium or arterial plaque, we are unable to account for subclinical cases of CVD. A final limitation is the lack of information about anti-depressant use among those individuals who had elevated depressive symptoms. Some anti-depressants are known to have adverse effects on cardiovascular health (47). Without this information, we cannot assess whether anti-depressant usage is partially responsible for the associations we reported.

The primary strength of this study is that the study sample was obtained from a population-based cohort. By recruiting from the Georgia Lupus Registry, the GOAL cohort limits the possibility any particular group of individuals is excluded from the cohort, which reduces the chances of selection bias. This study also benefited from the extensive amount of demographic and clinical information collected by the GOAL. This ensured we were able to control for many necessary covariates.

In conclusion, the results presented in this study suggest that depression, specifically somatic depression, is associated with self-reported CVD among individuals with SLE. These results suggest that rheumatologist and general practitioners who have patients with SLE should be mindful of an increased in perceived somatic depression symptoms. Further study is needed to determine if the depression – CVD association is directional or bidirectional in SLE. To that end, longitudinal studies should be conducted. In addition, future studies should consider using a biomarker to define CVD. This will increase sensitivity and enable detection of subclinical CVD.

Tables

Table 1. Demographic and Clinical Characteristics of All GOAL Cohort Participants with and without Symptoms of Depression, defined as a PHQ-9 score above 10, in Atlanta, GA from 2011 and 2013 (n = 630)

Characteristic	*No Depressive Symptoms (n = 409)*	*Depressive Symptoms (n = 221)*	*p-value*
Age Mean [SD]	49.2 [13.6]	48.8 [12.3]	0.7159
Female, n (%)	376 (91.9)	214 (96.8)	**0.0134**
Hispanic, n (%)	19 (4.7)	14 (6.4)	0.3703
Race, n (%)			0.0671
American Indian or AK Native	2 (0.5)	0 (0)	
Asian	7 (1.7)	1 (0.5)	
Black or African American	319 (78.0)	173 (78.3)	
Native Hawaiian/Pacific Islander	2 (0.5)	2 (1.0)	
White	79 (19.3)	45 (20.4)	
Education, n (%)			0.4805
Junior High/High School	120 (29.8)	70 (32.4)	
College/University	187 (46.4)	109 (50.5)	
Graduate/Professional	96 (23.8)	37 (17.1)	
Current Employment Status, n (%)			**<0.0001**
Working - Full Time	129 (32.4)	41 (18.8)	
Working - Part Time	40 (10.1)	11 (5.1)	
Retired	66 (16.6)	30 (17.8)	
Homemaker	32 (8.0)	14 (6.4)	
Student	15 (3.8)	10 (4.6)	
Unemployed/Disabled	116 (29.2)	112 (51.4)	
Marital Status, n (%)			0.9018
Never Married	132 (32.4)	57 (26.0)	
Married	141 (34.6)	70 (32.0)	
Separated	14 (3.4)	21 (9.6)	
Divorced	70 (17.2)	42 (19.2)	
Widowed	26 (6.4)	8 (3.7)	
Living with Partner	24 (5.9)	21 (9.6)	
BMI, Median [IQR]	27.0 [9.0]	29.3 [9.9]	0.6815
Diabetes, n (%)	31 (7.6)	32 (14.7)	**0.0073**
Diagnosis of Hypertension, n (%)	212 (52.4)	136 (62.1)	**0.0195**
Age at SLE Diagnosis, Mean [SD]	32.9 [12.9]	32.8 [11.4]	0.9230
Smoking Status, n (%)	123 (30.4)	75 (33.9)	0.3208
Disease Activity Score Mean [SD]	12.6 [8.0]	22.7 [7.2]	**<0.001**

Table 2. Adjusted Odds Ratio of Depressive Symptoms, defined as a PHQ-9 score above 10, and Cardiovascular Disease Among All Participants of the GOAL Cohort in Atlanta, GA from 2011 and 2013 (n = 630)

	Model 1		**Model 2**		**Model 3**	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
PHQ-9 Score						
No Depressive Symptoms	1.00	-	1.00	-	1.00	-
Depressive Symptoms	**1.52**	**[1.01, 2.28]**	1.24	[0.81, 1.90]	1.06	[0.64, 1.77]
Age (years)	1.05	[1.03, 1.06]	1.03	[1.01, 1.05]	1.04	[1.01, 1.07]
Race						
White	1.00	-	1.00	-	1.00	-
Black/African American	2.17	[1.28, 3.75]	1.95	[1.10, 3.46]	1.64	[0.89, 3.05]
Sex						
Female	1.00	-	1.00	-	1.00	-
Male	2.56	[1.28, 5.15]	2.67	[1.26, 5.66]	2.80	[1.26, 6.23]
Education						
Graduate/Professional	1.00	-	1.00	-	1.00	-
College/University	1.02	[0.60, 1.73]	0.76	[0.43, 1.33]	0.69	[0.38, 1.28]
Jr. High/ High School	1.01	[0.57, 1.78]	0.69	[0.37, 1.27]	0.57	[0.29, 1.10]
Current Employment Status						
Full Time Work (Ref)						
Part Time Work			3.68	[1.40, 9.65]	3.47	[1.24, 9.75]
Retired			6.37	[2.73, 14.85]	5.87	[2.42, 14.27]
Student			4.53	[1.64, 12.52]	3.97	[1.34, 11.74]
Homemaker			3.31	[0.80, 13.75]	3.30	[0.75, 14.54]
Unemployed/Disabled			6.68	[3.19, 13.97]	5.84	[2.64, 12.89]
Age at SLE Diagnosis					0.98	[0.96, 1.01]
BMI					0.99	[0.96,1.02]
Hypertension					1.97	[1.20, 3.24]
Smoking					1.08	[0.68, 1.71]
Diabetes					2.06	[1.08, 3.91]
Disease Activity Score					1.02	[0.99, 1.05]

OR = Odds Ratio, CI = Confidence Interval, SLE = Systemic Lupus Erythematous BMI = Body Mass Index

Table 3. Adjusted Odds Ratio of Depressive Symptoms, defined as a PHQ-9 score above 10, and Cardiovascular Disease Among Female Participants of the GOAL Cohort in Atlanta, GA from 2011 and 2013 (n = 590)

	Model 1		**Model 2**		**Model 3**	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
PHQ 9 Score						
No Depressive Symptoms	1.00	-	1.00	-	1.00	-
Depressive Symptoms	**1.64**	**[1.08, 2.50]**	1.25	[0.74, 2.11]	1.19	[0.70, 2.03]
Age (years)	1.04	[1.03, 1.06]	1.05	[1.02, 1.07]	1.04	[1.01, 1.07]
Race						
White	1.00	-	1.00	-	1.00	-
Black/African American	2.34	[1.31, 4.17]	2.01	[1.07, 3.76]	1.94	[1.01, 3.73]
Education						
Graduate/Professional	1.00	-	1.00	-	1.00	-
College/University	1.02	[0.59, 1.75]	0.88	[0.49, 1.59]	0.73	[0.39, 1.36]
Jr. High/ High School	0.86	[0.47, 1.55]	0.65	[0.34, 1.25]	0.50	[0.25, 0.99]
Age at SLE Diagnosis			0.99	[0.96, 1.01]	0.99	[0.96, 1.01]
BMI			0.98	[0.95, 1.01]	0.98	[0.95, 1.01]
Hypertension						
No			1.00	-	1.00	-
Yes			1.90	[1.19. 3.12]	1.91	[1.14, 3.18]
Smoking						
No			1.00	-	1.00	-
Yes			1.03	[0.64, 1.66]	1.02	[0.63, 1.67]
Diabetes						
No			1.00	-	1.00	-
Yes			2.20	[1.72, 4.11]	2.28	[1.19, 4.38]
Disease Activity Score			1.03	[1.00, 1.06]	1.01	[0.98, 1.05]
Current Employment Status						
Full Time Work (Ref)					1.00	-
Part Time Work					3.29	[1.11, 9.74]
Retired					5.36	[2.11, 13.61]
Student/Homemaker					4.19	[1.52, 11.52]
Unemployed/Disabled					5.90	[2.58, 13.48]

OR = Odds Ratio, CI = Confidence Interval, SLE = Systemic Lupus Erythematous BMI = Body Mass Index

Table 4. Adjusted Odds Ratios of Depressive Symptoms, defined as a PHQ-6 score of 10 or above, and Cardiovascular Disease Among Female Participants of the GOAL cohort in Atlanta, GA from 2011 and 2013 (n = 590)

	Model 1		**Model 2**		**Model 3**	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
PHQ-6 Score						
No Depressive Symptoms	1.00	-	1.00	-	1.00	-
Depressive Symptoms	1.00	[0.56, 1.78]	0.59	[0.30, 1.16]	**0.49**	**[0.25, 0.98]**
Age	1.04	[1.03, 1.06]	1.05	[1.02, 1.07]	1.04	[1.01, 1.07]
Race						
White	1.00	-	1.00	-	1.00	-
Black/African American	2.30	[1.28, 4.01]	2.01	[1.07, 3.76]	2.02	[1.05, 3.90]
Education						
Graduate/Professional	1.00	-				
College/University	1.08	[0.51, 1.65]	0.86	[0.47, 1.56]	0.70	[0.37, 1.31]
Jr. High/ High School	0.92	[0.51, 1.65]	0.63	[0.33, 1.22]	0.46	[0.23, 0.93]
Age at SLE Diagnosis			0.99	[0.96, 1.01]	0.99	[0.96, 1.01]
BMI			0.98	[0.95, 1.01]	0.98	[0.95, 1.01]
Hypertension						
No			1.00	-	1.00	-
Yes			1.90	[1.19. 3.21]	1.92	[1.15, 3.22]
Smoking						
No			1.00	-	1.00	-
Yes			1.03	[0.64, 1.66]	1.04	[0.63, 1.70]
Diabetes						
No			1.00	-	1.00	-
Yes			2.21	[1.18, 4.13]	2.29	[1.19, 4.40]
Disease Activity Score			1.04	[1.02, 1.07]	1.03	[1.00, 1.06]
Current Employment Status						
Full Time Work (Ref)					1.00	-
Part Time Work					3.25	[1.09, 9.66]
Retired					5.51	[2.16, 14.02]
Student/Homemaker					4.51	[1.63, 12.47]
Unemployed/Disabled					6.35	[2.78, 14.54]

OR = Odds Ratio, CI = Confidence Interval, SLE = Systemic Lupus Erythematous BMI = Body Mass Index

References

1. Muñoz LE, Janko C, Schulze C, et al. Autoimmunity and chronic inflammation—two clearance-related steps in the etiopathogenesis of SLE. *Autoimmunity reviews* 2010;10(1):38-42.
2. Petri M. Epidemiology of systemic lupus erythematosus. *Best Practice & Research Clinical Rheumatology* 2002;16(5):847-58.
3. Alarcón GS, McGwin Jr G, Bastian HM, et al. Systemic lupus erythematosus in three ethnic groups. VIII. Predictors of early mortality in the LUMINA cohort. *Arthritis Care & Research* 2001;45(2):191-202.
4. Schoenfeld SR, Kasturi S, Costenbader KH. The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: a systematic review. *Semin Arthritis Rheum* 2013;43(1):77-95.
5. Baune BT, Stuart M, Gilmour A, et al. The relationship between subtypes of depression and cardiovascular disease: a systematic review of biological models. *Transl Psychiatry* 2012;2:e92.
6. Palagini L, Mosca M, Tani C, et al. Depression and systemic lupus erythematosus: a systematic review. *Lupus* 2013;22(5):409-16.
7. Tara W. Strine MPH, Ali H. Mokdad PD, Lina S. Balluz MPH, Sc.D., et al. Depression and Anxiety in the United States: Findings From the 2006 Behavioral Risk Factor Surveillance System. *Psychiatric Services* 2008;59(12):1383-90.
8. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation* 2014;129(3):e28-e292.
9. Baune BT, Adrian I, Arolt V, et al. Associations between major depression, bipolar disorders, dysthymia and cardiovascular diseases in the general adult population. *Psychother Psychosom* 2006;75(5):319-26.
10. Goldstein BI, Fagiolini A, Houck P, et al. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. *Bipolar Disord* 2009;11(6):657-62.
11. Herbst S, Pietrzak RH, Wagner J, et al. Lifetime major depression is associated with coronary heart disease in older adults: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychosom Med* 2007;69(8):729-34.
12. Larson SL, Owens PL, Ford D, et al. Depressive disorder, dysthymia, and risk of stroke: thirteen-year follow-up from the Baltimore epidemiologic catchment area study. *Stroke* 2001;32(9):1979-83.
13. Penninx BW, Beekman AT, Honig A, et al. Depression and cardiac mortality: results from a community-based longitudinal study. *Archives of General Psychiatry* 2001;58(3):221-7.
14. Anda R, Williamson D, Jones D, et al. Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of US adults. *Epidemiology* 1993;4(4):285-94.

15. Aromaa A, Raitasalo R, Reunanen A, et al. Depression and cardiovascular diseases. *Acta Psychiatrica Scandinavica* 1994;89(s377):77-82.

16. Barefoot JC, Schroll M. Symptoms of Depression, Acute Myocardial Infarction, and Total Mortality in a Community Sample. *Circulation* 1996;93(11):1976-80.

17. Pratt LA, Ford DE, Crum RM, et al. Depression, Psychotropic Medication, and Risk of Myocardial Infarction: Prospective Data From the Baltimore ECA Follow-up. *Circulation* 1996;94(12):3123-9.

18. Rowan PJ, Haas D, Campbell JA, et al. Depressive symptoms have an independent, gradient risk for coronary heart disease incidence in a random, population-based sample. *Ann Epidemiol* 2005;15(4):316-20.

19. Schwartz SW, Cornoni-Huntley J, Cole SR, et al. Are sleep complaints an independent risk factor for myocardial infarction? *Annals of epidemiology* 1998;8(6):384-92.

20. Seldenrijk A, Vogelzangs N, Batelaan NM, et al. Depression, anxiety and 6-year risk of cardiovascular disease. *J Psychosom Res* 2015;78(2):123-9.

21. Ferketich AK, Schwartzbaum JA, Frid DJ, et al. Depression as an antecedent to heart disease among women and men in the NHANES I study. *Archives of Internal Medicine* 2000;160(9):1261-8.

22. Goldston K, Baillie AJ. Depression and coronary heart disease: a review of the epidemiological evidence, explanatory mechanisms and management approaches. *Clinical psychology review* 2008;28(2):288-306.

23. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. *Biological psychiatry* 2003;54(3):227-40.

24. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of internal medicine* 2000;160(14):2101-7.

25. Grunberg NE, Baum A. Biological commonalities of stress and substance abuse. *Coping and substance use* 1985:25-62.

26. Cohen S, Rodriguez MS. Pathways linking affective disturbances and physical disorders. *Health Psychology* 1995;14(5):374.

27. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *New England Journal of Medicine* 2011;365(23):2205-19.

28. Liu YL, Szklo M, Davidson KW, et al. Differential Association of Psychosocial Comorbidities With Subclinical Atherosclerosis in Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)* 2015;67(10):1335-44.

29. Scherrer JF, Virgo KS, Zeringue A, et al. Depression increases risk of incident myocardial infarction among Veterans Administration patients with rheumatoid arthritis. *Gen Hosp Psychiatry* 2009;31(4):353-9.

30. Bjornadal L, Yin L, Granath F, et al. Cardiovascular disease a hazard despite improved prognosis in patients with systemic lupus erythematosus: results from a Swedish population based study 1964-95. *Journal of Rheumatology* 2004;31(4):713-9.

31. Blackburn-Munro G, Blackburn-Munro R. Chronic pain, chronic stress and depression: coincidence or consequence? *Journal of neuroendocrinology* 2001;13(12):1009-23.

32. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *Plos med* 2006;3(11):e442.

33. Ford DE, Mead LA, Chang PP, et al. Depression is a risk factor for coronary artery disease in men: the precursors study. *Archives of Internal Medicine* 1998;158(13):1422-6.

34. Mendes de Leon CF, Krumholz HM, Seeman TS, et al. Depression and risk of coronary heart disease in elderly men and women: New Haven EPESE, 1982-1991. *Archives of Internal Medicine* 1998;158(21):2341.

35. Danchenko N, Satia J, Anthony M. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. *Lupus* 2006;15(5):308-18.

36. Schoenfeld SR, Kasturi S, Costenbader KH. The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: a systematic review. Presented at Seminars in arthritis and rheumatism2013.

37. Greco CM, Kao AH, Sattar A, et al. Association between depression and coronary artery calcification in women with systemic lupus erythematosus. *Rheumatology (Oxford)* 2009;48(5):576-81.

38. Greco CM, Li T, Sattar A, et al. Association between depression and vascular disease in systemic lupus erythematosus. *J Rheumatol* 2012;39(2):262-8.

39. Julian LJ, Tonner C, Yelin E, et al. Cardiovascular and disease-related predictors of depression in systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2011;63(4):542-9.

40. Drenkard C, Rask KJ, Easley KA, et al. Primary preventive services in patients with systemic lupus erythematosus: study from a population-based sample in Southeast U.S. *Semin Arthritis Rheum* 2013;43(2):209-16.

41. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis & Rheumatism* 1997;40(9):1725-.

42. Lim SS, Bayakly AR, Helmick CG, et al. The incidence and prevalence of systemic lupus erythematosus, 2002–2004: the Georgia Lupus Registry. *Arthritis & rheumatology* 2014;66(2):357-68.

43. Drenkard C, Yazdany J, Trupin L, et al. Validity of a self-administered version of the brief index of lupus damage in a predominantly African American systemic lupus erythematosus cohort. *Arthritis Care Res (Hoboken)* 2014;66(6):888-96.

44. McManus D, Pipkin Ss Fau - Whooley MA, Whooley MA. Screening for depression in patients with coronary heart disease (data from the Heart and Soul Study). (0002-9149 (Print)).

45. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. *Journal of General Internal Medicine* 2001;16(9):606-13.

46. Peterson JC, Charlson ME, Wells MT, et al. Depression, coronary artery disease, and physical activity: how much exercise is enough? *Clin Ther* 2014;36(11):1518-30.

47. Hawkins MA, Callahan CM, Stump TE, et al. Depressive symptom clusters as predictors of incident coronary artery disease: a 15-year prospective study. *Psychosom Med* 2014;76(1):38-43.

48. Boyle SH, Jackson WG, Suarez EC. Hostility, anger, and depression predict increases in C3 over a 10-year period. *Brain, behavior, and immunity* 2007;21(6):816-23.

49. Stewart JC, Rand KL, Muldoon MF, et al. A prospective evaluation of the directionality of the depression–inflammation relationship. *Brain, behavior, and immunity* 2009;23(7):936-44.

50. Everson SA, Goldberg DE, Kaplan GA, et al. Hopelessness and risk of mortality and incidence of myocardial infarction and cancer. *Psychosomatic Medicine* 1996;58(2):113-21.

51. Matthews KA, Räikkönen K, Sutton-Tyrrell K, et al. Optimistic attitudes protect against progression of carotid atherosclerosis in healthy middle-aged women. *Psychosomatic medicine* 2004;66(5):640-4.

52. Barden N. Implication of the hypothalamic–pituitary–adrenal axis in the physiopathology of depression. *Journal of Psychiatry and Neuroscience* 2004;29(3):185.

Summary, Public Health Implications, Future Studies

This study sought to address a gap in the current literature by examining the association between CVD and depression in a population-based sample of individuals with systemic lupus erythematosus. Through multivariate logistic regression analyses, we found a statistically significant association between depression and self-reported CVD after adjusting for standard demographic covariates and when using the complete PHQ-9 at the standard cutoff of 10. We found the same association with a similar magnitude among women in the cohort. Additional analyses after removing the somatic items from the PHQ-9 depression measure found a significant protective effective among women with SLE after adjusting for demographics, employment status, and health covariates.

These results suggest that rheumatologist and general practitioners who have patients with SLE should be mindful of an increased in perceived somatic depression symptoms, such as increased feelings of lethargy and bouts of insomnia. However, due to our study's cross-sectional design, future longitudinal studies will be needed to determine the directionality of the association between CVD and depression among individuals with SLE. Future studies may also wish to measure CVD using a validated biomarker to detect subclinical CVD. Future studies may also benefit from collecting information about anti-depressant usage among those with depressive symptoms.