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Inflammatory and vascular correlates of mood change over 8 weeks

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Abstract

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This manuscript has been read and approved by all authors and represents their honest work.

Contribution Details

	Birdsall	Schmitz	Abosi	DuBose	Pierce	Fiedorowicz
Concepts	x	x				x
Design	x	x				x
Definition of intellectual content	x	x	x	x	x	x
Literature search	x	x				x
Clinical studies	x	x	x			x
Experimental studies	x	x	x	x		x
Data acquisition	x	x	x	x		x
Data analysis		x		x		
Statistical analysis	x	x				x
Manuscript preparation	x					
Manuscript editing	x	x	x	x	x	x
Manuscript review	x	x	x	x	x	x
Guarantor	x	x				x

Background—Mood disorders have been associated with a variety of cardiovascular disease risk factors, including inflammation and large artery stiffness, particularly while depressed although longitudinal studies have been limited.

Methods—With measurements at baseline and 8 weeks, the researchers prospectively assessed mood, levels of inflammatory markers (hsCRP and TNF- α), serum lipids, and large artery stiffness in a cohort of 26 participants with a diagnosis of a mood disorder, enriched for current depression. Depressive symptoms were measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) at baseline and 8 weeks. Associations between depressive symptoms and other measures were assessed using linear mixed models, unadjusted and adjusted for age and BMI.

Results—The mean age of the participants (n=26) was 41.6 (standard deviation [SD] 12.8) years, and 81% were female. During the study, there was a mean (SD) MADRS score improvement of 9.5 (9.4) from baseline to eight weeks. Reductions in the primary outcome TNF- α with improvement in depression fell short of significance ($P=0.076$). In secondary analyses, there was a statistically significant association between improved cholesterol ratio ($P=0.038$) and triglycerides ($P=0.042$) with depression improvement. There was no statistically significant change in large artery stiffness during the study.

Conclusion—Improved depressive symptoms were associated with improved cholesterol ratios even after adjustment, suggesting possible mechanism by which acute mood states may influence cardiovascular disease risk. Future longitudinal studies with extended and intensive follow-up investigating cardiovascular disease risk related to acute changes and persistence of mood symptoms is warranted.

Keywords

Bipolar Disorder; Major Depressive Disorder; Mood Disorder; Cardiovascular Disease Risk; Inflammation; Lipids; Pulse Wave Velocity; Arterial Stiffness

Introduction

Mood disorders are associated with excess cardiovascular mortality, approximately two-fold greater than expected from general population estimates^[1,2,3] and this risk may be greatest in those with more chronic mood symptoms.^[4,5] In an effort to determine how this risk is mediated, prior studies of vascular function in mood disorders has shown a variety of vascular measurements to be impaired relative to controls, especially in older adults with a longer and more persistent course of illness.^[6,7] In a year-long prospective study of 37 participants in medical internship, those who developed depressive symptoms, as measured with Patient Health Questionnaire (PHQ-9) every three months, also had reduced endothelial function when symptomatic.^[8] Similar findings were seen in a cross-sectional study of adolescent girls, presumably without atherosclerosis, but here their depressive symptoms were measured using the Beck Depression Inventory.^[9] Although these two studies measured depressive symptoms by a different method, endothelial function was measured with the same methodology: using finger plethysmography and subsequent determination of a reactive hyperemia index. Furthermore, it has been shown that the association between large artery stiffness (measured by carotid-femoral pulse wave velocity) and depressive

symptoms is strengthened when those with depressive disorders meet DSM-IV criteria, perhaps suggesting a dose response with severity.^[10]

The autonomic nervous system and hypothalamic-pituitary adrenal (HPA) axis are putative physiological mechanisms that link mood disorders with cardiovascular disease. Alterations in sympathetic activity^[11,12] or HPA axis^[13] can trigger a pro-inflammatory state, and inflammation accelerates atherosclerosis.^[14] Taken together, it seems that these may be mechanisms that mediate cardiovascular disease risk. There have been numerous cross-sectional studies that demonstrated excess pro-inflammatory markers in individuals with mood disorders. One meta-analysis of case-control studies in bipolar disorder found that those with bipolar disorder had higher concentrations of soluble interleukin-2 receptor (sIL-2R), interleukin-6 receptor (sIL-6R), tumor necrosis factor alpha (TNF- α), soluble tumor necrosis factor receptor type 1 (sTNFR1), and interleukin-4 (IL-4).^[15] Another meta-analysis of inflammatory markers showed that C-reactive protein (CRP), IL-1, and IL-6 were all significantly associated with depression.^[16] A separate meta-analysis showed that levels of TNF- α and IL-6 were significantly elevated in depressed subjects when compared to controls.^[17] A cross-sectional analysis of the representative Third National Health and Nutrition Examination Survey (NHANES III) data, suggests that mood related inflammation may persist for one to six months.^[18]

These aforementioned meta-analyses of mood disorders and pro-inflammatory states only included cross-sectional studies, and longitudinal approaches are needed to establish temporal associations between inflammation and mood states. In prior work, greater inflammation during mood states in those with bipolar I disorder has been observed.^[19] Changes in serum lipids related to depressive symptoms have not been observed.^[20] With the opportunity to follow a cohort of individuals being treated for diagnosed mood disorders (major depression, bipolar II disorder, and bipolar I disorder) in the midst of a major depressive episode, the researchers sought to evaluate for potential change in markers of vascular risk. The researchers hypothesized that improvements in depressive symptoms would be correlated with reductions in TNF- α , as well as hsCRP (Aim 1), but not serum lipids (Aim 2). The researchers also explored (Aim 3) whether any changes in depressive symptoms are related to measures of arterial stiffness, as measured by carotid-femoral pulse wave velocity.

Materials and Methods

Subjects

The researchers recruited from an existing sample of individuals diagnosed with bipolar I disorder, bipolar II disorder, or major depressive disorder – all were recruited from those screened for a separate study of proteomics for mood disorders, funded by Myriad Genetics, Inc. Salt Lake City, Utah, USA. All participants provided written informed consent in this institutional review board approved study. During screening, the researchers confirmed diagnoses with the relevant portions of the Structured Clinical Interview for DSM-5 (SCID)^[21] and the Mini International Neuropsychiatric Interview (MINI).^[22] The researchers enrolled those who met diagnostic criteria for mood disorder. Given that in the parent study the researchers recruited those with a current depressive episode, the sample was enriched

for higher levels of depressive symptoms although this was not a formal inclusion criterion for this study and two participants were not in an episode. All participants were being treated for their mood disorder by their providers, and there were no psychotropic medications that were prohibitive for inclusion in the study. The inclusion criteria also required participants to be between 18 and 70 years of age. The researchers excluded those at a high risk for suicide, those with severe substance use disorders, a diagnosis of borderline personality disorder, medical conditions with neurologic sequelae, those with severe chronic pain or with acute unstable medical illness, those on high-potency immune-modulating medications, and pregnant females.

Mood Assessments

There was a baseline assessment and eight-week follow up assessment. Weights were measured without shoes, in light clothing, using a scale that measures to the nearest 0.25 kg. Standing heights were measured without shoes, to the nearest 0.1 cm, using a free-standing stadiometer. These weights and heights were utilized for the computation of body mass index (BMI). A medical history and structured psychiatric history (MINI + SCID portions) were obtained during the first visit with medication use recorded at both visits, including a list of medications taken in the last 12 months. Participants filled out the MacArthur Scale of Subjective Social Status and Beck's Anxiety Inventory during the first visit.

During both visits, participants were assessed with the Young Mania Rating Scale (YMRS)^[23] and the Montgomery-Åsberg Depressive Rating Scale (MADRS)^[24] for clinician assessment of manic and depressive symptoms, respectively. Participants also filled out the Major Depressive Inventory (MDI)^[25,26] to self-assess depressive symptoms.

Inflammatory Markers and Lipid Panel

Venous blood was obtained during each visit to measure hsCRP (turbidimetric method) and TNF- α . Plasma TNF- α was measured by a high sensitivity four-hour solid phase ELISA (R&D Systems, Inc. Minneapolis, Minnesota, USA) in duplicate using a sandwich enzyme immunoassay technique. These data were used to investigate the primary aim of the study: to assess change in inflammatory markers with mood. Non-fasting measures of total cholesterol, high density lipoprotein cholesterol (HDL-c), plasma triglycerides, and glucose were obtained. Low density lipoprotein cholesterol (LDL-c) was calculated from these values so long as triglycerides did not exceed 400 mg/dL. Cholesterol ratio was calculated by dividing total cholesterol by HDL-c. According to the longitudinal analysis of the Framingham Offspring Cohort (N=3,014), this cholesterol ratio is predictive of insulin resistance (measured by Homeostasis Model Assessment of Insulin Resistance) with an area under the curve of 0.71.^[27] Total cholesterol and HDL-c vary little with respect to fasting status, so in order to make follow up less burdensome yet still provide quality measurements of insulin resistance, the participants were not fasting.^[28] The lipid panel data was used to investigate the secondary aim of the study: the relationship between changes in mood and serum lipids.

Carotid-Femoral Pulse Wave Velocity (PWV)

Carotid-femoral PWV is an independent predictor of coronary heart disease and stroke in healthy subjects,^[29] and an independent predictor of mortality in the general population,^[30] in hypertensive subjects,^[31] in older community^[32] and hospitalized^[33] individuals, and in patients with end-stage renal disease.^[34] A standard deviation increase in carotid-femoral PWV has also been associated with a 48% increase in first-onset cardiovascular disease (CVD) event risk, in one community-based observational study of middle-aged and older participants (N=2232).^[35] Carotid-femoral, carotid-brachial, and carotid-radial PWV were measured non-invasively by recording carotid, femoral, brachial and radial artery pressure waveforms sequentially with an applanation tonometer (Non-invasive Hemodynamics Workstation, Cardiovascular Engineering, Inc. Norwood, Massachusetts, USA). Pressure waveforms are gated to the ECG R wave in order to calculate the transit time (t) between the foot of the carotid and the respective peripheral (femoral, brachial, radial) waveforms. The carotid-femoral transit distance (CFTD) is estimated between the two anatomical sites as the difference between the suprasternal notch (SSN) to carotid (SSN-C) and femoral (SSN-F) sites. Thus, the CFTD is calculated as $CFTD = (SSN-F) - (SSN-C)$ and PWV calculated as $CFTD/t$. This approach accounts for parallel transmission of the pulse wave up the brachiocephalic and carotid arteries, and simultaneously along the aortic arch using the SSN as a fiducial point where parallel transmission begins (i.e., bifurcation site of aortic arch and brachiocephalic artery).

Statistical Analyses

R 3.5.2 (R Core Team, Vienna, Austria) and package “lme4” were used to conduct data analysis.^[36,37] To assess the relationship between the MADRS score and the outcome variables (TNF- α , hsCRP, serum lipids, PWV) the researchers used a linear mixed model with a random intercept. A linear mixed model allows for baseline MADRS score responses to vary between individuals, account for repeated observations (baseline and week eight), and adjust for other variables, while still determining whether a shared relationship with the outcome variables exists. The researchers initially performed unadjusted analyses, and subsequently adjusted for age and BMI. A sensitivity analysis of the relationship between self-reported MDI scores and the outcome variables was also done to compare with clinician-administered MADRS analysis. An *a priori* statistical analysis plan was done and set the level of statistical significance to be $P < 0.05$ for the primary outcome (TNF- α). As a cross-sectional analysis, a univariate Spearman’s rank correlation of baseline and week eight MADRS scores with the outcome variables (TNF- α , hsCRP, PWV, serum lipids, vitals) was done.

Results

The mean age of the participants (n=26) was 41.6 (standard deviation [SD] 12.8) years, and 81% were female. Ten participants (38%) had bipolar I disorder, nine (35%) had bipolar II disorder, and seven (27%) had major depressive disorder. Half of participants were employed and had a mean (SD) of 15.3 (2.5) years of education. The racial distribution of the participants was 88% white and 8% black with 4% of the participants reporting a Hispanic ethnicity. With regards to significant past medical history, one (4%) participant had

a heart attack, three (12%) had heart disease, four (15%) had diabetes, and six (23%) had hypertension. Additional sociodemographic information can be found in Table 1,^[38,39] and baseline clinical characteristics can be found in Table 2. Additional clinical characteristics of the sample can be found in Supplemental Table 1.

During the eight-week study period, there was a mean (SD) decrease of 9.5 (9.4) in MADRS scores for those with baseline and follow-up assessments, as anticipated with subjects being treated for depression by their providers. This improvement is also reflected in the self-reported MDI the participants filled out. The means and standard deviations of all variables in the study, at the two time-points, are shown in Table 3. Only two participants reached remission (MADRS<10) at the end of the study. There were no participants in the study that started a new selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI), while 14 were on this class of medication throughout, and four changed their dose: three increased, one decreased. Ten participants had dose changes in non-psychotropic medications between baseline and eight weeks, and four participants started new non-psychotropic medications during the study.

When modeling MADRS on TNF- α levels over an eight-week period, the researchers found reductions in TNF- α corresponding to improvements in MADRS that fell short of statistical significance ($P=0.076$). There were no statistically significant associations between MADRS scores and change in the secondary inflammatory marker, hsCRP, as shown in Table 4. No statistically significant associations were reflected between self-reported MDI and TNF- α or hsCRP.

Contrary to expectations, the secondary analysis showed statistically significant associations between lower cholesterol ratio ($P=0.038$) and lower triglycerides ($P=0.042$) with reductions in MADRS. The statistically significant relationship for cholesterol ratio remained statistically significant ($P=0.034$) after adjusting for age and BMI, while triglycerides no longer crossed the threshold of significance ($P=0.063$). There were no statistically significant associations between MADRS scores over time and any of the other metabolic measurements, including cholesterol, HDL-c, LDL-c, and glucose. These results are shown in Table 4. A similar relationship appears when running an unadjusted sensitivity analysis comparing self-reported MDI with serum lipids, except the researchers no longer see significance for triglycerides ($P=0.269$) or cholesterol ratio ($P=0.066$). A sensitivity analysis of the effect that psychotropic medications might have on these results was also conducted, with separate models adding indicator variables for all psych meds, antidepressants, antipsychotics, and mood stabilizers. This did not substantially alter results or change the statistical significance when also adjusting for age and BMI.

In the exploratory analysis of carotid-femoral PWV using linear mixed models, there were no statistically significant associations between carotid-femoral PWV and MADRS scores over eight weeks ($P=0.892$). When looking at Spearman's rank correlations of baseline and week eight MADRS scores and our outcomes of interest, statistical significance for a positive correlation in baseline TNF- α ($P=0.011$) was shown. These results are in Table 5."

Discussion

In this small prospective eight-week study of individuals with rigorously diagnosed mood disorders, the researchers observed a reduction in the primary outcome (TNF- α) and improvement in depressive symptoms (MADRS) in the expected direction that fell short of statistical significance. The researchers did not expect associations between serum lipids and mood over time, based on previous work done by Persons et al. 2017.^[20] Interestingly, the largest observed effects involved reductions in cholesterol ratio and triglycerides with improvement of depressive symptoms. Persons et al. did not explore cholesterol ratio in their analysis, so this may be a finding that warrants further investigation. Other surrogate measures for insulin resistance have been used to show a significant cross-sectional association between insulin resistance and depression, as detailed in a systematic review and meta-analysis by Kan et al. 2013.^[40]

Total cholesterol / HDL-c ratio has been linked to greater risk of cardiovascular disease^[41] and highly correlated with insulin resistance.^[42] Furthermore, insulin resistance is associated with risk factors for coronary artery disease, such as increased triglyceride concentration.^[43] In the current study, the association between cholesterol ratio and depression is strengthened by the persistence of this statistically significant relationship after adjusting for change in BMI. The pattern observed could be related to an increase in insulin resistance amongst those in a depressive episode, thereby increasing cardiovascular disease risk with more frequent or chronic depressive episodes. This association does not appear to be confounded by BMI. The study did not measure insulin levels, and glucose levels alone would not be sensitive enough to detect changes in insulin resistance. Insulin resistance that improves with depressive symptom resolution, as measured by the clinician-administered Hamilton Rating Scale for Depression (HRSD), has been shown previously in a prospective study of 20 non-diabetic patients.^[44] In the aforementioned study, every HRSD point improvement would see an average increase in 2.34 insulin sensitivity index, a measurement from the intravenous glucose tolerance test. The 20 depressed patients had oral and intravenous glucose tolerance tests when symptomatic at baseline and a mean (SD) of 82 (28) days later following treatment with tricyclic antidepressants, then compared to age-, sex-, and BMI-matched healthy subjects (n=13) who had one measurement with the intravenous glucose tolerance test. The authors opted not to use SSRIs because of possible weight reduction, as has been observed in short term studies of SSRIs, or improvement in insulin sensitivity. A systematic review published years later by different authors describes this finding that serotonergic antidepressants are associated with increased insulin sensitivity.^[45] Perhaps aggressively treating depression with serotonergic medication leads to a better cardiometabolic profile in patients, rather than owing the relationship to depressive symptom resolution.

Finally, the exploratory analysis of changes in arterial stiffness (PWV) with improvements in depressive symptoms did not show statistical significance. The short duration of follow up may not be long enough to see significant changes in arterial stiffness. In a recent prospective study of participants with type two diabetes mellitus with dyslipidemia being treated with diet and low-dose atorvastatin, a 7.5% reduction in carotid-femoral PWV was observed at 12 weeks from baseline with statistical significance ($P<0.001$).^[46] The

previously mentioned Fiedorowicz et al. study on endothelial dysfunction during medical internship investigated changes in reactive hyperemia index at baseline and one year later, another indication that changes in vascular function need to be studied over a longer period of time.^[8] The sample was not aggressively treated with only two participants achieving remission (MADRS<10) and followed for only eight weeks.^[47]

Nonetheless the study sample's depressive symptoms did improve over the course of the study; so, the researchers could appropriately address the question of whether immediate depressive symptom improvement is associated with improved measures of cardiovascular risk, presuming the effects were observable within eight weeks and didn't require remission of symptoms to resolve. MADRS and MDI scores both improved but unlike MADRS, the MDI analyses did not show statistically significant associations with any of the dependent variables. MADRS was more sensitive to changes in the sample. This difference could be due to interviewer (MADRS)- or self (MDI)- reporting ratings, or how each scoring system is weighted. There are two measurements related to mood in MADRS, as opposed to just one item in MDI. MADRS is also framed in the context of the previous week, rather than the previous two weeks in the MDI – perhaps the more precise time frame of MADRS better captures mood symptoms, and their changes, particularly in such a short-term study. It is worth noting that MADRS measures sleep and appetite in a unidirectional fashion: a higher score results from less sleep and appetite, which would not capture those with atypical depression. Interestingly, in a cross-sectional study of 153 adolescents comparing self- vs. interviewer-ratings of the negative impact acute and chronic stressors have on the individual, the interviewer assessments are stronger predictors of adolescent low-grade inflammation than adolescents' own evaluation of the impact of the very same stressful life events.^[48]

The small sample size is a key limitation in the study, leaving the study powered to detect only moderate to large effects. Since most subjects were female, it is worth noting that these findings cannot be generalizable to males and should warrant further research in this area – a larger sample size could better study the distribution of male and female participants that reflects the population. With the primary outcome negative, the secondary findings should be considered hypothesis-generating and require replication, ideally in a larger sample and including better assessments of insulin resistance. The duration of the study is also a limitation in evaluating lasting relationships between cardiovascular health and mood disorders, as these are both chronic health conditions. Observations of arterial stiffness changes due to depressive symptoms and the proposed subsequent inflammation may take longer than 8 weeks. Infrequent remission of the sample size is another limitation and would bias results to the null hypothesis. Strengths of the study include its prospective design with a population whose symptoms improved with treatment, an *a priori* statistical analysis plan to decrease risk of type I error, and a well-characterized cohort.

Conclusion

The cohort had improved cardiovascular disease risk factors with improvement of their depressive symptoms. Long-term prospective studies are lacking in the study of how acute changes in mood may negatively affect cardiovascular health and hence, larger samples that are treated to remission should be explored for a longer term. The results highlight the

potential acute role of lipid changes that perhaps reflect underlying insulin resistance. With marginally significant findings in this small sample, the researchers can neither confirm nor rule out inflammation as another potentially relevant mediator. Longitudinal study in mood disorders with their episodic nature holds some promise for identifying the most relevant mechanisms for this public health disparity in which those with mood disorders face nearly twice the expected risk of cardiovascular disease and mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline Sociodemographic Characteristics (N=26).

Variable	N (%)	Mean (SD)
Age, years		41.6 (12.8)
Female sex	21 (81%)	
Race/Ethnicity		
White, non-Hispanic	23 (88%)	
White, Hispanic	1 (4%)	
Black, non-Hispanic	2 (8%)	
Education, years		15.3 (2.5)
Employment		
Employed, Full-time	9 (35%)	
Employed, Part-time	4 (15%)	
Student	6 (23%)	
Unemployed	12 (46%)	
Subjective Social Status [*]		4.2 (2.4)
Adverse Childhood Experiences [†]		3.9 (2.8)
Smoking status		
Current/past	10 (38%)	
Never	16 (62%)	
Smoking pack*years, (N=10)		12.8 (12.7)

* Goodman et al. 2001.

† Felitti et al. 1998.

Table 2.

Baseline Clinical Characteristics (N=26).

Variable	N (%)	Mean (SD)
Diagnosed Mood Disorder		
Bipolar I disorder	10 (38%)	
Bipolar II disorder	9 (35%)	
Major depressive disorder	7 (27%)	
Age at onset of mood disorder, years		18.8 (5.3)
Duration illness, years		22.8 (11.4)
Lifetime depressive episodes		40.7 (40.7)
Lifetime hypomanic episodes, bipolar disorder (N=17)		25.1 (23.1)
Lifetime manic episodes, bipolar disorder (N=17)		8.4 (13.8)
Number of suicide attempts		1.4 (1.8)
Number of hospitalizations		4.4 (6.6)
Comorbid psychiatric disorders		
Panic disorder (current or lifetime)	9 (36%)	
Agoraphobia (current)	7 (28%)	
Social phobia (current - generalized)	5 (20%)	
Posttraumatic stress disorder	2 (8%)	
Generalized anxiety disorder	6 (24%)	
Psychotropic medications during study		
Selective serotonin reuptake inhibitor	7 (27%)	
Serotonin and norepinephrine reuptake inhibitor	7 (27%)	
Other antidepressant	12 (46%)	
Second generation antipsychotic	11 (42%)	
Lithium	5 (19%)	
Anticonvulsant	13 (50%)	
Benzodiazepines	5 (19%)	
Other sedative/anxiolytics	8 (31%)	
Stimulant	4 (15%)	

Table 3.

Values of Key Variables at Baseline and Follow-Up.

Measure	Baseline		8-Week	
	N	Mean (SD)	N	Mean (SD)
Duration from baseline, weeks	26	-	21	8.8 (1.4)
Mood Ratings				
MADRS	26	26.6 (8.9)	21	18.6 (7.7)
MDI	26	31.1 (9.7)	19	23.6 (10.0)
YMRS	26	4.2 (4.5)	21	3.1 (3.7)
BAI	16	16.8 (9.0)	13	16.0 (11.0)
Inflammation markers				
TNF- α , pg/mL	26	1.4 (0.6)	20	1.3 (0.4)
hsCRP, mg/L	23	6.6 (6.8)	19	6.3 (7.5)
Vascular Assessment				
Carotid-brachial pulse wave velocity, m/s	21	7.3 (1.3)	17	7.6 (1.6)
Carotid-radial pulse wave velocity, m/s	21	8.7 (1.2)	17	8.2 (1.7)
Carotid-femoral pulse wave velocity, m/s	15	6.8 (1.0)	13	7.4 (1.9)
Vitals				
Body Mass Index, kg/m ²	26	35.6 (12.2)	21	36.8 (12.4)
Systolic blood pressure, mmHg	25	125.8 (13.0)	19	123.1 (20.7)
Diastolic blood pressure, mmHg	25	74.7 (9.8)	19	70.9 (10.4)
Heart rate, beats per minute	25	74.7 (12.9)	19	74.5 (13.6)
Labs				
Cholesterol, mg/dl	26	193.5 (36.0)	20	192.5 (36.2)
HDL-c, mg/dl	26	49.2 (18.6)	20	50.2 (18.0)
LDL-c, mg/dl	23	112.1 (32.7)	20	107.2 (30.5)
Cholesterol ratio *	26	4.6 (2.1)	20	4.1 (1.8)
Triglycerides, mg/dl	26	195.4 (113.9)	20	166.4 (68.8)
Glucose, mg/dl	26	112.8 (45.6)	20	124.1 (55.7)

* (Total cholesterol)/(HDL-c)

MADRS = Montgomery-Åsberg Depression Rating Scale; MDI = Major Depression Index; YMRS = Young Mania Rating Scale; BAI = Beck Anxiety Inventory; TNF- α = Tumor necrosis factor alpha; hsCRP = High Sensitivity C-Reactive Protein; LDL-c = low density lipoprotein-cholesterol; HDL-c = high density lipoprotein-cholesterol

Table 4.

Linear mixed model: effects of total MADRS score on outcomes

Measure	Model 1: Unadjusted				Model 2: Adjusted for age and BMI			
	β	SE	DF	P	β	SE	DF	P
Inflammation markers								
TNF- α , pg/mL	0.012	0.007	19	0.076	0.010	0.007	19	0.130
hsCRP, mg/L	-0.014	0.048	16	0.774	-0.030	0.046	16	0.520
Vascular Assessment								
Carotid-brachial pulse wave velocity, m/s	0.001	0.018	13	0.961	-0.001	0.018	13	0.954
Carotid-radial pulse wave velocity, m/s	0.020	0.023	13	0.393	0.026	0.023	13	0.282
Carotid-femoral pulse wave velocity, m/s	-0.003	0.021	8	0.892	-0.006	0.021	8	0.772
Vitals								
Body Mass Index, kg/m ²	0.007	0.021	20	0.728				
Systolic blood pressure, mmHg	0.420	0.223	17	0.077	0.325	0.210	16	0.141
Diastolic blood pressure, mmHg	0.206	0.100	17	0.054	0.171	0.099	16	0.104
Heart rate, beats per minute	0.035	0.124	17	0.784	0.015	0.124	16	0.906
Labs								
Cholesterol, mg/dl	0.549	0.391	19	0.177	0.451	0.389	19	0.261
HDL-c, mg/dl	-0.191	0.125	19	0.143	-0.210	0.127	19	0.117
LDL-c, mg/dl	0.536	0.319	18	0.111	0.480	0.322	18	0.154
Cholesterol ratio	0.029	0.013	19	0.038*	0.030	0.013	19	0.034*
Triglycerides, mg/dl	3.027	1.384	19	0.042*	2.773	1.400	19	0.063
Glucose, mg/dl	-0.135	0.492	19	0.787	-0.208	0.482	19	0.672

* $P < 0.05$;

MADRS = Montgomery-Åsberg Depression Rating Scale; TNF- α = Tumor necrosis factor alpha; hsCRP = High Sensitivity C-Reactive Protein; LDL-c = low density lipoprotein-cholesterol; HDL-c = high density lipoprotein-cholesterol; BMI = body mass index

Table 5.

Spearman's Rank Correlation of MADRS

Measure	Baseline		8-Week	
	rho	P-value	rho	P-value
Inflammation markers				
TNF- α , pg/mL	0.490	0.011 [*]	0.192	0.417
hsCRP, mg/L	0.068	0.757	-0.089	0.717
Vascular Assessment				
Carotid-brachial pulse wave velocity, m/s	0.117	0.614	0.048	0.854
Carotid-radial pulse wave velocity, m/s	0.059	0.798	-0.106	0.685
Carotid-femoral pulse wave velocity, m/s	0.146	0.604	0.055	0.858
Lipids				
Cholesterol, mg/dl	0.256	0.208	-0.027	0.909
HDL-c, mg/dl	-0.176	0.390	-0.423	0.063
LDL-c, mg/dl	0.207	0.342	0.056	0.814
Cholesterol ratio	0.267	0.187	0.366	0.113
Triglycerides, mg/dl	0.346	0.084	0.281	0.230
Glucose, mg/dl	0.206	0.313	0.109	0.647
Vitals				
Systolic blood pressure, mmHg	0.143	0.496	0.338	0.157
Diastolic blood pressure, mmHg	0.215	0.302	0.194	0.427
Heart Rate, BPM	-0.008	0.9685	0.027	0.911

^{*} $P < 0.05$;

MADRS = Montgomery-Åsberg Depression Rating Scale; TNF- α = Tumor necrosis factor alpha; hsCRP = High Sensitivity C-Reactive Protein; LDL-c = low density lipoprotein-cholesterol; HDL-c = high density lipoprotein-cholesterol