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Impact of Mood on Endothelial Function and Arterial Stiffness in Bipolar Disorder

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Abstract

Background: Previous research in bipolar disorder demonstrates greater than expected vascular dysfunction later in the course of illness, proportionate to the cumulative burden of mood symptoms. However, little is known about the effect of acute mood states on vascular function. Here we examine the relation between vascular function and mood state in individuals with bipolar disorder.

Method: This prospective study followed 40 individuals with bipolar disorder for up to 6 months. Participants were assessed for mood state and vascular function at baseline, 2 weeks, and 6 months. Mood state was determined using clinician-administered Montgomery-Åsberg Depression Rating Scale and Young Mania Rating Scale. Vascular function was assessed by flow-mediated dilation (FMD) of the brachial artery, forearm vascular resistance (FVR), and arterial stiffness.

Results: Participants had a mean age of 30.1 years and 75% were male. Primary outcome measures FMD and nitroglycerine-mediated dilation were not found to have statistically significant associations with depressive or manic symptoms. In unadjusted models, higher manic symptoms were significantly associated with increased FVR nitroprusside-mediated dilation and diastolic blood pressure. In adjusted models, higher depressive symptoms were significantly

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associated with increases in augmentation index adjusted for heart rate of 75 bpm, and higher manic symptoms remained associated with increases in diastolic blood pressure.

Conclusion: FMD may have limited sensitivity as a biomarker for measuring short-term effects of mood state. Longer-term prospective studies are needed to clarify the temporal relation between chronic mood symptoms and vascular function in bipolar disorder.

Keywords

Bipolar disorder; endothelial dysfunction; arterial stiffness; cardiovascular risk

Introduction

The risk of cardiovascular death for bipolar disorder is approximately two times greater than expected from the general population.[1] This elevated risk persists even after accounting for the high prevalence of cardiovascular risk factors present in individuals with bipolar disorder.[1-3] Long-term depressive and manic symptom burden has been independently linked to poor endothelial function, which plays a role in the development of atherosclerosis and subsequent cardiovascular morbidity and mortality.[4-6] The precise mechanism that leads to development of endothelial dysfunction in bipolar disorders is unknown; however, the persistence and duration of mood syndromes has been associated with impaired vascular function.[1, 7]

Biomarkers of Endothelial Function

The majority of studies addressing the impact of mood on biomarkers of endothelial function are cross-sectional.[4, 5, 7, 8] Available prospective studies have primarily examine increased mortality in patients with bipolar and other mood disorders due to suicide rates, other cardiovascular risk factors, or the effects of antipsychotic medications prescribed.[9-11] Fiedorowicz et al. demonstrated in a cohort of individuals from the National Institute of Mental Health Collaborative Depression Study that participants with a greater longitudinal burden of manic symptomatology over follow-up exhibited subsequent poorer endothelial function as measured by flow-mediated dilation of the brachial artery.[7] However, there are no prospective studies that establish a temporal relationship between specific mood states in bipolar disorder and changes in endothelial function. Endothelial dysfunction is an important outcome of interest because it plays a role in the development of atherosclerosis, which in turn leads to increased cardiovascular morbidity and mortality.[6] Well-validated measures of endothelial function include flow-mediated dilation, forearm vascular resistance, and aortic stiffness, which are useful indicators for future cardiovascular events and mortality.[8, 12-16]

Purpose of the Research

The purpose of this study was to clarify the temporal relations between acute mood episodes and vascular function; to accomplish this, we utilized flow-mediated dilation, nitroglycerine-mediated dilation, forearm vascular resistance, and aortic stiffness measures in a prospective study to determine if burden of depressive and manic mood symptoms are associated with increased endothelial or other vascular dysfunction over short-term (2 weeks) or

intermediate-term (6 months). We hypothesized that the severity of mood symptoms would be associated with worsened endothelial function, as measured by flow-mediated dilatation, within 6 months.

Material and Methods

A total of 40 participants were identified from a prospective cohort, originally described in Fiedorowicz et al.[17], looking at the role of incident antipsychotic use and blood vessel function in a sample of individuals broadly-defined as having bipolar disorder or related mood disorders (Diagnostic and Statistical Manual of Mental Disorders-IV defined bipolar I; bipolar II; bipolar not otherwise specified; schizoaffective disorder; major depressive disorder with psychotic features)[18] All participants completed an evaluation to sign consent prior to providing written informed consent in this institutional review board approved study. [19] Participants were recruited between 2007 and 2014 from the University of Iowa Hospitals and Clinics using electronic medical records, electronic mail, targeted mailings, clinical referral and advertisements. This sample was recruited from individuals with acute illness most likely to begin antipsychotic medications estimated by a locally-derived propensity score based on age, and presence of mania and/or psychosis, marital status, and lithium use.[20] Exclusion criteria included neoplasm, untreated thyroid disease, pregnancy or planned pregnancy, alcohol abuse in the past month (≥5 drinks on a single occasion in past month and ≥2 on CAGE),[21] any use of illicit drugs in the past month, and alcohol or substance dependence in the past year.

Vascular Outcome Measures

Prior to vascular assessments all participants confirmed with a trained research nurses that they had fasted for at least 12 hours and abstained from smoking tobacco in the preceding 2 hours before measurements were taken. Vitals were measured after the participant rested in a seated position for 5 minutes. Height and weight were measured without shoes in light clothing.

Flow-mediated dilation was assessed non-invasively via ultrasound measurement of brachial artery diameter during changes in brachial artery flow. Images of brachial artery diameter and doppler velocities from the center of the vessel were recorded using a 10-13 MHz linear array transducer ultrasound system (Biosound ESAOTE, Indianapolis, IN). After obtaining baseline diameter and velocity measures, an occluding forearm cuff was placed on the forearm just below the antecubital fossa and inflated 50 mmHg above systolic blood pressure for five minutes.[8] The brachial artery diameter and Doppler velocities were continuously recorded before, during and after cuff deflation. The resulting change in arterial diameter from baseline to one minute measured nitroglycerine-mediated dilation, a measure of endothelium-dependent dilation.[22] Following a return to baseline (10 minutes of rest), 400 mcg of sublingual nitroglycerine was administered. Brachial artery diameter and velocity were measured for an additional 6 minutes. The resulting change in arterial diameter from baseline to four minutes after nitroglycerine administration measured endothelium-independent flow-mediated dilation.

Arterial stiffness was captured using pulse wave velocity – the velocity of the blood pressure pulse waveform is dependent on the stiffness of the artery along which the pulse is traveling; increases in these values reflecting an increase in arterial stiffness.[7, 23] Carotid, radial, and femoral pressure waveforms as well as electrocardiogram waveforms were recorded using SphygmorCor Technology (AtCor Medical, Sydney, Australia). Aortic systolic pressure, augmentation pressure, and augmentation index adjusted for a heart rate of 75 bpm measurements were derived from radial pressure waveforms and brachial blood pressures measurements using pulse wave analysis software. Pulse wave velocity was calculated from the mean R-wave time difference and the arterial path length between the superficial carotid and femoral artery sites.

Forearm vascular resistance was assessed through administration of three vasoactive agents: acetylcholine an endothelial dependent vasodilator, nitroprusside an endothelial independent vasodilator and verapamil an endothelial and nitric oxide–independent vasodilator as previously described.[24, 25] Forearm blood flow was measured by venous occlusion plethysmography using indium/gallium-in-silastic strain gauges. The three vascular agents were administered through brachial artery infusion at three doses: acetylcholine (3,10,30 μg/min), nitroprusside (1,3,10 μg/min), and verapamil (10,30,100 μg/min). Verapamil was administered last in all subjects due to its long half-life. Each drug was administered over the course of 18 minutes, increasing the dose every 6 minutes. The percentage change of flow ratio in response to the drug was utilized as the outcome measure.

Exploratory outcomes were assessed from a venous blood sample and included pre-determined cardiovascular risk factors; low-density cholesterol, triglycerides, high-density cholesterol, C-reactive protein, and insulin resistance (determined using the homeostatic model assessment for insulin resistance (HOMA-IR) calculated from fasting blood glucose and insulin).[26]

Exposure Assessment

Individuals diagnosis, clinical characteristics, and medical history were obtained through direct interviewing with a board-certified psychiatrist (JGF).[27] Mood symptoms were characterized for each visit using the Montgomery-Åsberg Depression Rating scale (MADRS) for depressive symptoms and the Young Mania Rating Scale (YMRS) for manic symptoms.[28, 29] Current psychiatric treatment was not directed by the study and was collected during each study visit. Medication exposures were recorded and pooled into the following broad classes for analyses: first generation antipsychotics, second generation antipsychotics, selective serotonin reuptake inhibitor, lithium, lamotrigine, valproic acid derivatives, carbamazepine, benzodiazepines, and other antidepressants.

Statistical Analyses

Descriptive statistics are reported for all participants who completed at least one visit with mood ratings and vascular measurements. Primary analyses were conducted using linear mixed models with a random intercept term to account for repeated observations within participants. The vascular outcomes were modeled as dependent variables and mood

symptoms were modeled as independent variables. Models were adjusted for age (continuous, linear effect), sex and medication group exposures. Time effects were modeled as a categorical variable, a preferred choice for this analysis with unevenly spaced times designed to distinguish acute from sub-acute effects.[30] All analyses were conducted using R 3.5.2 (R Core Team, Vienna, Austria) and package "nlme."[31, 32]

Results

Baseline clinical and sociodemographic characteristics of the sample are illustrated in Table 1. and Table 2. This sample had a mean age of 30.1 (SD=9.4, range:18-55) years and 75% were male. During the study 45% of participants were being treated with one or more mood stabilizer medications, 63% with antipsychotics, and 50% with antidepressants; of these 20% received combination therapy of both mood stabilizers and antipsychotics. Both depressive and manic symptoms, measured by mean MADRS and YMRS scores, reduced from baseline to 6-months. Mood rating scales, vascular measurements, and cardiovascular risk factors and vitals from each visit (baseline, 2-week, and 6-month) are highlighted in Table 3.

Primary outcome measures FMD and nitroglycerine-mediated dilation were not found to have statistically significant associations with depressive or manic symptoms over time. Of the secondary and exploratory outcome measures, only augmentation index adjusted for heart rate of 75 (AIX@75), had a statistically significant association with depressive symptoms over time (β=0.216, SE=0.101, *P*=0.04) when adjusted for age, sex and medication. In unadjusted models, increases in manic symptoms had a statistically significant association with increases in both FVR nitroprusside-mediated dilation (β=8.840, SE=4.068, *P*=0.04) and diastolic blood pressure (β=0.216, SE=0.096, *P*=0.03). After adjustment, the association of diastolic blood pressure with manic symptomatology remained statistically significant (β=0. 0.271, SE=0.099, *P*=0.01). No other secondary or exploratory vascular outcome measures were associated with manic or depressive symptoms. Results for linear mixed models for depression and manic symptomology on endothelial function are in Tables 4 and Table 5, respectively.

Discussion

In this prospective study of the influence of mood state on vascular function in bipolar disorder, we did not observe any acute or subacute changes in our primary outcome of FMD corresponding to mood state. There were several positive secondary outcomes, including AIX@75, nitroprusside-mediated (endothelium-independent) forearm resistance vessel dilation, and diastolic/mean arterial blood pressure. With regard to depressive symptoms, we observed increases in arterial stiffness (AIX@75) with greater MADRS scores. For manic symptomology, we observed better endothelium-independent resistance vessel function, measured by forearm vascular resistance in response to intraarterial nitroprusside and higher diastolic blood pressure with a higher YMRS score. As secondary outcomes, these findings should be treated as hypothesis-generating. Overall, while predominantly negative, the results are informative for future study of the impact on mood on vascular risk.

In the present study, depression was associated with AIX@75 in an adjusted model and mania was marginally associated. These findings are consistent with that of previous studies. Oulis et al. observed greater arterial stiffness in patents with depression compared to controls, however, after 6 weeks of treatment patients experienced acute reversals of arterial stiffness in association to depression severity.[33] Similary, Kokras et al. found acute improvements in arterial stiffness associated with decreased depression in patients that reached remission after receiving 6-months of treatment.[34] Taken together, these studies suggest that mechanisms that can acutely change arterial stiffness, beyond atherosclerosis which does so more insidiously, may be involved. Some such reported mechanisms include inflammation,[35-37] unhealthy lifestyle habits,[38] medications,[39] autonomic nervous system stress,[40, 41] and blood pressure.[42, 43]

Our findings linking changes in manic symptoms with diastolic blood pressure and mean arterial pressure provide some insight. Cardiovascular mortality is elevated in those with greater mania symptomology.[1, 11] This has generally been assumed to develop over the long-term course of illness in relation to cardiometabolic consequences (e.g., weight gain, dyslipidemia) of illness and treatments thereof and through the development of atherosclerosis. The acuteness of the changes in blood pressure observed, however, suggest relevance for other mechanisms, perhaps involving the autonomic nervous system, which has been surprisingly understudied with mania.

An unexpected finding in our study was mania acutely associated with an apparent protective effect on forearm vascular resistance with nitroprusside in the unadjusted model. This finding suggests that acute physiological changes associated with mania may also improve endothelial independent vasodilation. Nitroprusside acts as a nitic oxide donor and increased dilation might suggest greater responsiveness to the vascular smooth muscle to this stimulus. Both the neuronal and endothelial isoforms of nitric oxide synthase have been associated with bipolar disorder, although these genetic associations are modest and this small sample was not genotyped.[44] While we attempted to adjust for medication use, our study wasn't well designed to do so, and the participants had several changes in medications in response to acute episodes. In an in vitro model, lithium was shown to slightly increase endothelium-dependent vasodilation and had no impact on endothelium-independent vasodilation.[45] Valproic acid has been shown to increase nitric oxide production in vitro.[46] Interestingly, in our model that adjusted for medication use with indicator variables for broad categories, flow-mediated dilation was found to be marginally associated with manic symptoms in the adjusted model. This and our aforementioned finding with nitroprusside-mediated dilation of forearm resistance vessels contrast the previously observed long-term burden of manic symptoms on FMD.[1, 7] It is possible that biomarkers of cardiovascular risk may differ within acute mood episodes from those of acquired risk over the long-term course of illness. While this might seem paradoxical, acute and chronic stress are differentiated by several wide-ranging physiological distinctions.[47]

This is the first prospective study that looks specifically at the vascular function in different mood states in participants with bipolar disorder. A notable strength of the study is its prospective nature, which allows for assessment of the temporal relationships between the vascular function and mood symptoms. The study also utilized well-validated, clinician-

administered mood scales to measure the severity of mood symptoms. There are several important limitations to the study. The study had a small sample size and missing data which increased the potential for type II error. Inclusion of participants with a diagnosis of bipolar disorder was based on clinical diagnosis with a broad definition of bipolar disorder. The ability to detect associations may be limited if mood symptoms influence vascular function only in diagnostic subgroup. Our co-primary outcomes were negative, and the positive results observed were from secondary analyses. The potential for a spurious finding or Type I error must subsequently be considered. The follow-up time may not have been long enough to capture vascular changes related to mood episodes if the effects of mood symptoms on vascular measures are delayed or accumulated over the long-term course of illness. Additional prospective studies of individuals experiencing new episodes may be able to better discern any acute effects of mood, perhaps focusing on other physiological measures.

More sensitive biomarkers are needed to assess the relevant mood-induced physiological changes that influence risk of vascular disease in small samples to elucidate how the physiological changes associated with mood may impact the dramatic elevated risk of vascular disease seen in mood disorders. There is a need for an extended prospective study of larger samples to discern the temporal relationships between mood states and changes in intermediate phenotypes for vascular disease, such as endothelial function.

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Appendix

Contribution Details

	Schmitz	Abosi	Persons	Sinkey	Fiedorowicz
Concepts	x				x
Design				x	x
Definition of intellectual content	x	x	x	x	x
Literature search	x	x			x
Clinical studies				x	x
Experimental studies				x	x
Data acquisition				x	x
Data analysis	x	x	x	x	
Statistical analysis	x	x	x		
Manuscript preparation	x	x			
Manuscript editing	x	x	x	x	x
Manuscript review	x	x	x	x	x

	Schmitz	Abosi	Persons	Sinkey	Fiedorowicz
Guarantor	x	x	x	x	x

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Table 1.

Baseline Sociodemographic Characteristics of Sample (N=40)

	N (%)	Mean (SD)
Age, years		30.1 (9.4)
Sex, Male	30 (75%)	
Race/Ethnicity		
White, non-Hispanic	33 (83%)	
Native American	4 (10%)	
Black, non-Hispanic	3 (8%)	
Education, years		13.8 (2.0)
Employment (N=39)		
Employed	15 (39%)	
Student	12 (31%)	
Unemployed	12 (31%)	
Living Situation (N=38)		
Rent/Dorm	20 (53%)	
Own home	13 (34%)	
Live with family	3 (8%)	
Homeless/shelter	2 (5%)	
Marital Status		
Single	16 (65%)	
Married	7 (18%)	
Divorced/separated	6 (15%)	
Widowed	1 (3%)	
Smoking Status (N=39)		
Current	8 (21%)	
Former	19 (49%)	
Never	12 (31%)	
Smoking pack*years		7.7 (11.0)

Table 2.

Baseline Clinical Characteristics of Sample (N=40)

	N (%)	Mean (SD)
Medical History (N=37)		
Alcohol abuse/dependence *	19 (51%)	
Drug abuse/dependence *	17 (46%)	
Allergies	14 (38%)	
Endocrinopathy	5 (14%)	
Lung disease	4 (11%)	
Hypertension	2 (5%)	
Renal disease	2 (5%)	
Gastrointestinal disease	2 (5%)	
Neoplastic disease	1 (3%)	
Skin disease	1 (3%)	
Hematologic disease	1 (3%)	
Psychiatric History		
History of psychiatric hospitalization	35 (88%)	
Number of hospitalizations		3.2 (3.7)
History of suicide attempt (N=39)	14 (36%)	
Number suicide attempts		1.1 (2.6)
Psychotropic medication during study		
Antidepressants	**20 (50%)**	
Selective serotonin reuptake inhibitors	10 (25%)	
Other antidepressant	16 (40%)	
Mood Stabilizers	**18 (45%)**	
Lithium	13 (33%)	
Lamotrigine	5 (13%)	
Valproic acid derivative	3 (8%)	
Carbamazepine	1 (3%)	
Antipsychotics	**25 (63%)**	
First generation antipsychotic	3 (8%)	
Second generation antipsychotic	24 (60%)	
Benzodiazepine	**15 (38%)**	

* History of abuse/dependence, individuals with active abuse/dependence were excluded.

Table 3.

Primary and secondary outcome measure findings.

Measure	Baseline		2-Week		6-Month	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Duration from baseline, weeks	39	-	28	3.1 (1.5)	27	29.0 (3.1)
Range	-	(1.9-7.0)	(19.7 - 35.1)			
Mood Ratings						
MADRS	39	18.2 (12.4)	28	11.8 (8.3)	27	11.9 (9.5)
YMRS	38	10.1 (9.5)	28	8.5 (9.4)	26	4.2 (4.9)
Vascular Assessment						
Flow-mediated dilation (%)	34	8.0 (3.9)	23	8.4 (5.1)	17	9.1 (4.3)
Nitroglycerine-mediated dilation (%)	34	14.2 (3.7)	23	13.4 (4.3)	17	15.8 (6.5)
Pulse wave velocity (m/s)	33	6.8 (1.2)	26	6.9 (1.4)	24	7.0 (1.0)
Aortic systolic pressure (mmHg)	34	105.5 (11.8)	25	103.1 (9.9)	25	104.2 (10.1)
Augmentation pressure (mmHg)	34	2.4 (6.7)	25	2.0 (5.4)	25	3.3 (4.5)
AIX@75 (mmHg)	34	2.7 (16.7)	25	1.4 (15.8)	25	3.3 (14.1)
FVR acetylcholine 30 μg/min response (%)	25	474.4 (330.3)	16	342.1 (191.3)	15	378.0 (226.4)
FVR nitroprusside 10 μg/min response (%)	25	449.4 (213.8)	15	365.1 (138.8)	15	424.0 (252.2)
FVR verapamil 100 μg/min response (%)	23	410.6 (221.0)	15	312.9 (124.1)	13	262.1 (121.5)
Vital Signs and Labs						
Systolic blood pressure (mmHg)	39	120.6 (11.0)	28	117.8 (10.3)	27	117.8 (10.6)
Diastolic blood pressure (mmHg)	39	75.0 (10.6)	28	71.4 (9.1)	27	72.2 (10.3)
Mean arterial pressure (mmHg)	39	87.8 (17.3)	28	86.8 (8.6)	27	87.4 (9.6)
Pulse pressures (mmHg)	39	44.8 (11.5)	28	46.5 (8.5)	27	45.6 (8.4)
Heart rate (beats per minute)	39	74.4 (11.3)	28	77.2 (12.9)	27	71.8 (12.4)
HOMA-IR *	37	2.1 (1.3)	27	3.2 (3.0)	21	2.9 (2.5)
C-reactive protein (mg/L)	35	2.6 (4.9)	24	4.0 (8.5)	21	2.4 (3.5)
Triglycerides (mg/dl)	36	132.6 (107.0)	26	135.1 (79.3)	25	149.2 (60.7)
LDL-c (mg/dl)	36	97.1 (31.1)	26	103.8 (31.2)	26	107.5 (36.7)
HDL-c (mg/dl)	36	45.7 (14.2)	26	46.7 (13.1)	26	45.2 (13.7)

* HOMA-IR is used to assess β- cell function and insulin resistance using fasting glucose and insulin concentrations.

MADRS = Montgomery-Åsberg Depression Rating scale; YMRS = Young Mania Rating Scale; AIX@75 = augmentation index adjusted for heart rate of 75; FVR = forearm vascular resistance; HOMA-IR = homeostatic model assessment for insulin resistance; LDL-c = low density lipoprotein-cholesterol; HDL-c =high density lipoprotein-cholesterol

Table 4.

Effects of depression symptoms on vascular outcomes: linear mixed model analysis

	Model 1: Unadjusted				Model 2: Adjusted for age, gender, and psychotropic medication			
Measure	**β**	**SE**	**DF**	***P***	**β**	**SE**	**DF**	***P***
Vascular Assessment								
Flow-mediated dilation (%)	−0.027	0.048	34	0.58	−0.035	0.054	34	0.52
Nitroglycerine-mediated dilation (%)	0.015	0.051	34	0.77	0.021	0.056	34	0.71
Pulse wave velocity (m/s)	0.0002	0.012	46	0.99	0.005	0.011	46	0.66
Aortic systolic pressure (mmHg)	0.037	0.093	46	0.69	0.093	0.090	46	0.31
Augmentation pressure (mmHg)	0.013	0.044	46	0.77	0.022	0.041	46	0.59
AIX@75 (mmHg)	0.202	0.110	46	0.07	0.216	0.101	46	0.04 *
FVR acetylcholine 30 μg/min response (%)	1.034	3.269	24	0.75	2.573	3.525	24	0.47
FVR nitroprusside 10 μg/min response (%)	3.145	2.522	24	0.22	4.489	2.765	24	0.12
FVR verapamil 100 μg/min response (%)	−1.587	2.463	22	0.53	0.932	2.798	22	0.74
Vital Signs and Labs								
Systolic blood pressure (mmHg)	0.003	0.099	51	0.98	0.045	0.105	51	0.67
Diastolic blood pressure (mmHg)	0.114	0.091	51	0.22	0.175	0.095	51	0.07
Mean arterial pressure (mmHg)	0.080	0.084	51	0.34	0.132	0.088	51	0.14
Pulse pressures (mmHg)	−0.111	0.087	51	0.21	−0.172	0.090	51	0.06
Heart rate (beats per minute)	0.210	0.106	51	0.054	0.173	0.113	51	0.13
HOMA-IR †	0.043	0.024	43	0.08	0.012	0.026	43	0.65
C-reactive protein (mg/L)	0.010	0.058	41	0.87	0.012	0.062	41	0.84
Triglycerides (mg/dl)	0.697	0.893	45	0.44	0.869	0.912	45	0.35
LDL-c (mg/dl)	−0.236	0.214	46	0.27	−0.204	0.219	46	0.36
HDL-c (mg/dl)	−0.136	0.086	46	0.12	−0.141	0.086	46	0.11

* P-value < 0.05

† HOMA-IR is used to assess β- cell function and insulin resistance using fasting glucose and insulin concentrations.

AIX@75 = augmentation index adjusted for heart rate of 75; FVR = forearm vascular resistance; HOMA-IR = homeostatic model assessment for insulin resistance; LDL-c = low density lipoprotein-cholesterol; HDL-c =high density lipoprotein-cholesterol

Tables 5.

Effects of mania symptoms on vascular outcomes: linear mixed model analysis

	Model 1: Unadjusted				Model 2: Adjusted for age, gender, and psychotropic medication			
Measure	**β**	**SE**	**DF**	***P***	**β**	**SE**	**DF**	***P***
Vascular Assessment								
Flow-mediated dilation (%)	0.096	0.060	33	0.12	0.106	0.066	33	0.12
Nitroglycerine-mediated dilation (%)	0.061	0.062	33	0.34	0.056	0.065	33	0.40
Pulse wave velocity (m/s)	−0.004	0.013	45	0.77	0.006	0.013	45	0.67
Aortic systolic pressure (mmHg)	−0.046	0.102	45	0.66	0.018	0.100	45	0.85
Augmentation pressure (mmHg)	0.024	0.046	45	0.60	0.041	0.044	45	0.35
AIX@75 (mmHg)	0.177	0.115	45	0.13	0.222	0.112	45	0.053
FVR acetylcholine 30 μg/min response (%)	4.481	5.660	23	0.44	3.296	6.336	23	0.61
FVR nitroprusside 10 μg/min response (%)	8.840	4.068	23	0.04*	8.188	4.527	23	0.08
FVR verapamil 100 μg/min response (%)	4.702	3.970	21	0.25	3.321	4.606	21	0.48
Vital Signs and Labs								
Systolic blood pressure (mmHg)	0.033	0.114	50	0.77	0.083	0.119	50	0.49
Diastolic blood pressure (mmHg)	0.216	0.096	50	0.03*	0.271	0.099	50	0.01*
Mean arterial pressure (mmHg)	0.156	0.090	50	0.09	0.205	0.093	50	0.03*
Pulse pressures (mmHg)	−0.114	0.103	50	0.27	−0.142	0.109	50	0.20
Heart rate (beats per minute)	0.103	0.120	50	0.40	0.077	0.125	50	0.54
HOMA-IR †	0.002	0.029	43	0.94	0.029	0.031	43	0.36
C-reactive protein (mg/L)	−0.040	0.067	40	0.55	−0.006	0.070	40	0.94
Triglycerides (mg/dl)	−0.782	1.063	44	0.47	0.514	1.106	44	0.64
LDL-c (mg/dl)	0.094	0.230	45	0.69	0.182	0.234	45	0.44
HDL-c (mg/dl)	−0.133	0.092	45	0.16	−0.087	0.092	45	0.35

* $P < 0.05$

† HOMA-IR is used to assess β- cell function and insulin resistance using fasting glucose and insulin concentrations.

AIX@75 = augmentation index adjusted for heart rate of 75; FVR = forearm vascular resistance; HOMA-IR = homeostatic model assessment for insulin resistance; LDL-c = low density lipoprotein-cholesterol; HDL-c =high density lipoprotein-cholesterol