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Bipolar disorder and related mood states are not associated with endothelial function of small arteries in adults without heart disease

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Abstract

Background—Individuals with bipolar disorder are at increased risk for adverse cardiovascular disease (CVD) events. This study aimed to assess endothelial function and wave reflection, a risk factor for CVD, as measured by finger plethysmography in bipolar disorder to investigate whether CVD risk was higher in bipolar disorder and altered during acute mood episodes. We hypothesized that EndoPAT would detect a lower reactive hyperemia index (RHI) and higher augmentation index (AIX) in individuals with bipolar disorder compared with controls. Second, we predicted lower RHI and higher AIX during acute mood episodes.

Methods—Reactive hyperemia index and augmentation index, measures of microvascular endothelial function and arterial pressure wave reflection respectively, were assessed using the EndoPAT 2000 device in a sample of 56 participants with a DSM-IV diagnosis of bipolar I disorder with 82 measures spanning different mood states (mania, depression, euthymia) and cross-sectionally in 26 healthy controls.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Results—RHI and AIX were not different between adults with and without bipolar disorder (mean age 40.3 vs. 41.2 years; RHI: 2.04 ± 0.67 vs. 2.05 ± 0.51 ; AIX@75 (AIX adjusted for heart rate of 75): 1.4 ± 19.7 vs. 0.8 ± 22.4). When modeled in linear mixed models with a random intercept (to account for repeated observations of persons with bipolar disorder) and adjusting for age and sex, there were no significant differences between those with bipolar disorder and controls ($p=0.89$ for RHI; $p=0.85$ for AIX@75).

Conclusions—Microvascular endothelial function and wave reflection estimated by finger plethysmography were unable to detect differences between adults with and without bipolar disorder or changes with mood states. Future research is necessary to identify more proximal and sensitive, yet relevant, biomarkers of abnormal mood-related influences on CVD risk or must target higher risk samples.

INTRODUCTION

Cardiovascular mortality is known to be one of the leading cause of excess mortality in bipolar disorder [1]. Large, contemporary population-based studies suggest an elevated risk of cardiovascular disease mortality with estimated standardized mortality ratios ranging from 1.6 to 2.7 [2–4]. Traditional risk factors of cardiovascular disease such as smoking, obesity, inflammation, glucose homeostasis, and diabetes mellitus are more prevalent in the population of people with bipolar disorder [5–9]. Overall, adults with bipolar disorder in the US population have a 5-fold increased risk of CVD as well as 14 year earlier onset of CVD compared to adults without mood disorders [10]. In a nationally representative sample, the association between bipolar disorder and vascular disease, at least in women, was found to be independent of age, urbanicity, marital status, race, employment, family history of heart disease, obesity, high blood pressure and diabetes [11].

In its classic form, bipolar disorder is characterized by recurrent episodes of mania and depression [12]. The individual course of illness can vary considerably with regards to the propensity for and persistence of mood episodes [13]. The specific mechanisms by which the risk of cardiovascular disease in bipolar disorder have not been fully elucidated [14], although there is some evidence that those with a greater symptom burden or a more persistent course of illness are at greater relative risk, suggesting that mood symptom burden may contribute to risk in a dose-dependent fashion [15–18]. In a meta-analysis of 27 studies with 2,161 patients with bipolar disorder and 81,932 controls, CRP levels were moderately elevated during episodes of depression and euthymia, and greatly elevated during manic episodes [6], suggesting mechanisms beyond traditional risk factors may be involved.

Through the process of deposition of lipids and smooth muscle cells, inflammatory infiltration, plaque formation, continued remodeling, and eventual destruction of vessel lumen, endothelial dysfunction is a useful marker for poor vascular health [19, 20]. Furthermore, chronic endothelial dysfunction may have a shared inflammatory mechanism between insulin resistance, metabolic syndrome, and severe mental disorders that result in poor vascular health [7]. To investigate mechanisms by which mood states can influence cardiovascular disease events or mortality, intermediate physiological measures reactive hyperemia index (RHI) and augmentation index (AIX) were collected as surrogate outcomes

for CVD. There have been no prospective studies of endothelial function across mood episodes in bipolar disorder. Two prospective studies in those with depressive episodes have demonstrated changes in endothelial function, as measured by finger plethysmography with EndoPAT, corresponding to onset of depressive symptoms. The first demonstrated worsening endothelial function in adolescent and young adult females who developed depressive symptoms, which did not persist when depression resolved [21]. Similarly in a study of medical interns, worsening depressive symptoms over follow-up were inversely associated with endothelial function [22]. EndoPAT, which measures volumetric changes in the fingertip, quantifies microvascular endothelial function with a reactive hyperemia index [23, 24]. A cuff occludes blood flow through the brachial artery, and nitric oxide-mediated vascular dilation results when the cuff is deflated as a result of elevation in blood flow and shear stress [23, 25]. Additionally, augmentation index, a value derived from the timing and amplitude of pressure wave reflection, is a strong independent risk marker for coronary vascular disease in some studies [26]. EndoPAT has several advantages over other methods, which include being non-invasive, correlated to multiple traditional risk factors for cardiac events, and predictive of cardiovascular events [27, 28].

Previous studies utilizing EndoPAT have identified peripheral endothelial dysfunction in patients during depression episodes [21, 22]. This current study is the first to utilize EndoPAT to evaluate endothelial function in clinically diagnosed sample with bipolar disorder and does so across different mood states. In a sample of individuals with diagnosed bipolar disorder and healthy controls, we tested the hypothesis that RHI would be lower and AIX adjusted for heart rate of 75 (AIX@75) would be higher in individuals with bipolar I disorder compared with controls. In addition, we predicted lower RHI and higher AIX@75 during acute mood episodes compared with normal mood state.

METHODS

A total of 82 unique volunteers participated in this study, consisting of a group of 56 participants with a DSM-IV diagnosis of bipolar I disorder and a group of 26 healthy control participants, balanced by age and sex (Table 1). Community diagnosis was confirmed by a semi-structured, one-hour clinical interview by a study psychiatrist (JGF), using a template ensured that DSM-IV criteria for bipolar I disorder was met and also specifically screened for tobacco, alcohol and drug use/abuse/dependence as well as common comorbidities such as psychosis, obsessions, compulsions, and panic attacks. Participants with bipolar I disorder were in either a manic episode (Young Mania Rating Scale (YMRS) ≥ 20), a depressive episode (Montgomery-Åsberg Depression Rating Scale (MADRS) > 20), or a euthymic state (YMRS ≤ 12 and MADRS < 10) during the assessment. Some participants were evaluated repeatedly in different mood states. Healthy control participants had no history of psychiatric illness (DSM-IV Axis I or Axis II), confirmed using a telephone screener and the semi-structured clinical interview administered by a research assistant. Participants were recruited through advertisements, referrals from the University of Iowa Hospitals and Clinics (outpatient and inpatient), and a research registry. Controls were recruited through advertisements in the same media. The sample was primarily recruited for a neuroimaging study in bipolar disorder that prospectively imaged individuals across discrete mood episodes, identified by either participants themselves or intermittent compensated research

assistant follow-up calls [29–32]. Exclusion criteria included history of brain damage, neurological problems such as seizure disorder, syncope, or migraine with aura, cardiac or respiratory diseases, alcohol or drug dependence, amphetamine use, or any contraindication to magnetic resonance imaging (MRI). Participants provided written informed consent for this study, which was approved by the University of Iowa Institutional Review Board.

Trained research nurses confirmed that participants fasted for at least 12 hours and had not smoked for at least 2 hours prior. They then measured vital signs, height (without shoes to nearest 0.1 cm), and weight (without shoes in light clothing to the nearest 0.25 kg). A member of the research team then obtained a health and psychiatric history, and administered psychiatric rating scales, MADRS and YMRS. Basic assessments of clinical and demographic data were acquired. Information regarding cardiovascular risk factors including family history, diabetes, dyslipidemia, and smoking history was collected by trained health professional.

RHI and AIX, which are measures of microvascular endothelial function and pressure wave reflection, respectively were gauged using the EndoPAT 2000 device (Itamar Medical Inc., Caesarea, Israel) on study visits between 5/15/2012 and 5/13/2016, during which 87% of participants from the imaging study completed EndoPAT assessments. Subjects were positioned in a quiet, temperature-regulated room. The subjects were instructed to remain still during the measurement period consisting of 5 minutes of baseline measurement, 5 minutes of occlusion measurement, and 5 minutes of post-occlusion measurement. Endothelial function was measured by the reactive hyperemia-peripheral arterial tonometry index. Finger probes comprising of latex air cuffs connected to the inflating device controlled through a computer algorithm were placed on the index finger of each subject's hand. A blood pressure cuff on the test arm was inflated to 200 mmHg with increases in pressure when necessary to assure occlusion of arterial flow, this confirmed by reduction of PAT tracing to zero for five minutes. After the five-minute occlusion, the cuff was deflated and the PAT tracing was recorded for at least five more minutes. The ratio of the PAT signal after the cuff was released compared to baseline was calculated through computer algorithm that normalized the baseline signal and index to the contralateral arm (RHI value). Higher RHI values indicate greater dilatation in the finger arteries, which reflects greater nitric-oxide-mediated vasodilation of these vessels and, thus, better local endothelial function. AIX was adjusted for a heart rate of 75 beats/min. Higher AIX@75 values correspond to greater pressure wave reflection.

Data analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC). All statistical tests were two-tailed with an $\alpha=0.05$. We hypothesized there would be a lower RHI value in the bipolar disorder group, particularly during abnormal mood states of mania and depression. We secondarily assessed differences in arterial pressure wave reflection as measured by AIX@75. To account for repeated assessments across mood states for some participants, linear mixed models (LMM) included a random intercept for individual participant with fixed effects for age (linear, continuous) and sex (dichotomous). Models for the full sample assessed for the impact of bipolar disorder (vs. controls) and models restricted to those with bipolar disorder assessed mood state, depression or mania with euthymia as the reference category. Based on the assumptions of an independent samples t -

test, with 56 cases (without repeated observations) and 26 controls, this sample would have 80% power to detect an effect size of 0.67 SD at an $\alpha=0.05$ and only greater power with repeated, correlated observations.

RESULTS

The sample included 26 healthy controls and 56 participants with bipolar I disorder with sample characteristics as detailed in Table 1. The 56 participants with bipolar I disorder had a total of 82 EndoPat measurements, 38 during periods of euthymia, 24 during episodes of depression (mean (SD) MADRS 30.6 (5.1)), and 20 during episodes of mania (mean (SD) YMRS 25.4 (4.3)). The 26 repeat assessments occurred a mean (SD) of 32 (22) weeks after the prior assessment. Those with repeat assessments were more likely to be depressed or manic at the first visit ($\chi^2=10.7$, $df=2$, $p=0.005$).

The mean (SD) RHI for assessments of persons diagnosed with bipolar disorder was 2.04 ± 0.67 and for controls was 2.05 ± 0.51 . When modeled in LMM and adjusting for age and sex, there were no differences between those with a diagnosis of bipolar disorder and controls ($p=0.89$), even after adjusting for age ($p=0.78$) and sex ($p=0.45$). In analogous models, restricted to those diagnosed bipolar disorder, there were no significant effects of mood state ($p=0.79$). The values for the primary outcome, RHI, by group are illustrated in Figure 1.

The mean (SD) AIX@75 was 1.4 ± 19.7 for persons diagnosed with bipolar disorder and 0.8 ± 22.4 for controls. When modeled in LMM and adjusting for age and sex, categorical diagnosis of bipolar disorder was not associated with AIX@75 ($p=0.85$). Higher AIX@75 values were seen with increasing age ($p<0.0001$) and in females ($p<0.0001$). In analogous models restricted to those with bipolar disorder, there were no significant effects of mood state ($p=0.83$).

DISCUSSION

Despite the strong associations between bipolar disorder and cardiovascular morbidity and mortality, our sample failed to demonstrate significant differences in both RHI and AIX@75. We also did not observe any effects of mood on RHI-inferred endothelial function by mood state. In contrast, a prior analysis of a sub-sample of this cohort demonstrated robust differences across an array of cytokines between abnormal mood states and normal mood [31]. This suggests that perhaps measures of small vessel endothelial function, as measured by EndoPAT, may not be as sensitive to acute changes in mood.

Per systemic review from Matsuzawa et al. 2015, that pooled six clinical studies including 1602 participants that examined reactive hyperemia peripheral arterial tonometry found that 0.1 increase in Ln_RHI correlated to a relative risk of 0.79 [0.71–0.87], $P<0.001$ [33]. Furthermore, from a prognostic standpoint: 1 SD increase or decrease is associated with approximately half or double the risk of cardiovascular events, respectively [33]. In general, there has been found to be an inverse relationship between endothelial function by RHI and risk factors known to cause cardiovascular disease (BMI, dyslipidemia, diabetes, smoking) [27]. A value of less than 1.67 is suggestive of endothelial dysfunction per studies of

populations at risk for ischemic heart disease [34, 35]. Official reference values are not available, but higher values above 2 are a normal response ((Endo-PAT2000 product information; Itamar Medical Ltd, Caesarea, Israel)). When measured by EndoPAT, the intraindividual variability in AIX (coefficient of variation 37%) was found to be a less stable measure than RHI (coefficient of variation 13%) [36].

The negative results of the current analysis stand in contrast to two prior studies in that demonstrated an inverse relationship between changes in depressive symptoms and endothelial function [21, 22]. While our current study focuses specifically on bipolar disorder, it seems unlikely that measures that can detect the vascular changes associated with unipolar depression would not similarly have the sensitivity to detect changes in bipolar disorder. The duration of follow-up for the other studies was 1 to 2.5 years [21, 22]. In the current analysis, the mean time between repeat assessments across mood states for those with bipolar disorder was 32 weeks. These over-estimates the time from the last mood state, as the transition may have occurred at any point in between the two assessments. If any change in endothelial function related to mood state occurs, it may persist following the episode for an unknown period. There is some cross-sectional evidence that the inflammatory marker C-reactive protein following depression remains elevated for 1–6 months following an episode [37]. There is a need for studies to elucidate the time course for physiological changes associated with mood episodes.

Residual effects of mood state, however, do not explain the lack of differences between those diagnosed with bipolar disorder and controls. A review of prior studies of vascular function in bipolar disorder showed detectable association between vascular measures of endothelial function and CVD risk factors among adolescents diagnosed with BD. However, this study was limited by small sample size, was unable to derive the effects of mood, and lacked a control group [38]. Studies that failed to demonstrate an association between bipolar disorder and endothelial dysfunction have consisted of younger participants with mean age of 32 years and 33 years [39, 40]. Positive studies came from samples of mixed mood disorders with an older mean age of 43 to 72 years [41–43]. The mean age of this current analysis, although older than prior analyses of bipolar disorder, falls between these age ranges. Our sample also excluded those with a history of heart disease and if individuals with bipolar disorder are more likely to have cardiovascular disease in this age range may have introduced a selection bias toward the null hypothesis.

This analysis represents the largest study of vascular function in bipolar disorder conducted to date and one of a few studies of vascular function with a prospective component. However, possible limitations of this study include repeat assessments on a minority of the sample, the data presented herein remains largely cross-sectional. Endothelial function has been primarily studied through flow-mediated dilation of the brachial artery as measured by high resolution ultrasound and this measure has been prospectively associated with vascular outcomes [44]. This technique, however, carries considerable variability within individual measures and is sensitive to acute stimuli that alter autonomic nervous system tone [45]. The use of a semi-structured rather than a structured interview to confirm diagnosis represents another limitation. The availability of other measures of vascular function, such as flow-mediated dilation, would have been useful in clarifying whether the null result reflected the

lack of differences between groups compared or was due to the surrogate outcome selected. Controls were recruited through advertisements, in attempt to overlap as much as possible with the secondary study base for recruitment of cases. The secondary study base was likely broader than that sampled for controls, which may subsequently not have been fully representative of the population from which the cases arose [46].

The EndoPAT evaluates peripheral arterial tone through measurements of plethysmographic pressure changes caused by arterial pulses. The changes in vascular tone after occlusion of the brachial artery reflect the magnitude of an endothelial mediated hyperemic response, which is a measurement of arterial endothelial function [36]. However, this may be unsuitable to detect early vascular changes. Although previous studies have demonstrated alterations in reactive hyperemia to be sensitive to changes with mood [21, 22], those studies were prospective and over a long duration, while the current analysis had a relatively short time frame between prospective assessments, when even available. Reproducibility of this measure in those with known coronary artery disease is moderate and suboptimal reproducibility could also negatively impact sensitivity to change with mood [47]. Future prospective studies investigating changes in vascular function in bipolar disorder should include adequate duration and enroll older adults or those who have had a longer course of affective illness. This sample was recruited from a single academic medical center and may not be generalizable.

Given the substantive risk conveyed mood disorders, such as bipolar disorder, in the development of cardiovascular disease, there is great need to understand the most relevant mechanisms by which risk is mediated [48]. Considering the present findings and the existing literature, the use of measures of endothelial function to distinguish risk related to mood states appear to require longer term follow-up (years). The cumulative effects of symptom burden are more likely to be identified in those later in life and in proportion to lifetime symptom burden. Future studies informed by these design considerations are needed to understand how mood episodes influence cardiovascular risk.

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References

1. Nordentoft M, et al. Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden. *PLoS One*. 2013; 8(1):e55176. [PubMed: 23372832]
2. Weiner M, Warren L, Fiedorowicz JG. Cardiovascular morbidity and mortality in bipolar disorder. *Ann Clin Psychiatry*. 2011; 23(1):40–7. [PubMed: 21318195]

3. Laursen TM, et al. Increased mortality among patients admitted with major psychiatric disorders: a register-based study comparing mortality in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. *J Clin Psychiatry*. 2007; 68(6):899–907. [PubMed: 17592915]
4. Osby U, et al. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry*. 2001; 58(9):844–50. [PubMed: 11545667]
5. Kilbourne AM, et al. Burden of general medical conditions among individuals with bipolar disorder. *Bipolar Disord*. 2004; 6(5):368–73. [PubMed: 15383128]
6. Fernandes BS, et al. C-reactive protein concentrations across the mood spectrum in bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry*. 2016; 3(12):1147–1156. [PubMed: 27838212]
7. Hope S, et al. Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor. *Bipolar Disord*. 2009; 11(7): 726–34. [PubMed: 19839997]
8. Garcia-Rizo C, et al. Abnormal glycemc homeostasis at the onset of serious mental illnesses: A common pathway. *Psychoneuroendocrinology*. 2016; 67:70–5. [PubMed: 26878465]
9. Ning F, et al. Development of coronary heart disease and ischemic stroke in relation to fasting and 2-hour plasma glucose levels in the normal range. *Cardiovasc Diabetol*. 2012; 11:76. [PubMed: 22731255]
10. Goldstein BI, et al. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. *Bipolar Disord*. 2009; 11(6):657–62. [PubMed: 19689508]
11. Fiedorowicz JG, He J, Merikangas KR. The association between mood and anxiety disorders with vascular diseases and risk factors in a nationally representative sample. *J Psychosom Res*. 2011; 70(2):145–54. [PubMed: 21262417]
12. Belmaker RH. Bipolar disorder. *N Engl J Med*. 2004; 351(5):476–86. [PubMed: 15282355]
13. Judd LL, et al. Long-term symptomatic status of bipolar I vs. bipolar II disorders. *Int J Neuropsychopharmacol*. 2003; 6(2):127–37. [PubMed: 12890306]
14. Murray DP, et al. Mania and mortality: why the excess cardiovascular risk in bipolar disorder? *Curr Psychiatry Rep*. 2009; 11(6):475–80. [PubMed: 19909670]
15. Fiedorowicz JG. Depression and cardiovascular disease: an update on how course of illness may influence risk. *Curr Psychiatry Rep*. 2014; 16(10):492. [PubMed: 25163592]
16. Fiedorowicz JG, et al. Vasculopathy related to manic/hypomanic symptom burden and first-generation antipsychotics in a sub-sample from the collaborative depression study. *Psychother Psychosom*. 2012; 81(4):235–43. [PubMed: 22584147]
17. Fiedorowicz JG, et al. Vascular mortality in participants of a bipolar genomics study. *Psychosomatics*. 2014; 55(5):485–90. [PubMed: 24746452]
18. Fiedorowicz JG, et al. Manic/hypomanic symptom burden and cardiovascular mortality in bipolar disorder. *Psychosom Med*. 2009; 71(6):598–606. [PubMed: 19561163]
19. Wong BW, et al. The biological role of inflammation in atherosclerosis. *Can J Cardiol*. 2012; 28(6):631–41. [PubMed: 22985787]
20. Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2012; 32(9):2045–51. [PubMed: 22895665]
21. Tomfohr LM, et al. Multiwave associations between depressive symptoms and endothelial function in adolescent and young adult females. *Psychosom Med*. 2011; 73(6):456–61. [PubMed: 21715299]
22. Fiedorowicz JG, et al. The development of depressive symptoms during medical internship stress predicts worsening vascular function. *J Psychosom Res*. 2015; 79(3):243–5. [PubMed: 26115588]
23. Kuvin JT, et al. Assessment of peripheral vascular endothelial function in the ambulatory setting. *Vasc Med*. 2007; 12(1):13–6. [PubMed: 17451088]
24. Goswami N, et al. Effect of orthostasis on endothelial function: a gender comparative study. *PLoS One*. 2013; 8(8):e71655. [PubMed: 24147147]
25. Rozanski A, et al. Peripheral arterial responses to treadmill exercise among healthy subjects and atherosclerotic patients. *Circulation*. 2001; 103(16):2084–9. [PubMed: 11319199]

26. Weber T, et al. Arterial stiffness, wave reflections, and the risk of coronary artery disease. *Circulation*. 2004; 109(2):184–9. [PubMed: 14662706]
27. Hamburg NM, et al. Cross-sectional relations of digital vascular function to cardiovascular risk factors in the Framingham Heart Study. *Circulation*. 2008; 117(19):2467–74. [PubMed: 18458169]
28. Rubinshtein R, et al. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. *Eur Heart J*. 2010; 31(9):1142–8. [PubMed: 20181680]
29. Johnson CP, et al. Quantitative T1rho mapping links the cerebellum and lithium use in bipolar disorder. *Mol Psychiatry*. 2015; 20(2):149. [PubMed: 25727373]
30. Shaffer JJ Jr. Impaired sensory processing measured by functional MRI in Bipolar disorder manic and depressed mood states. *Brain Imaging Behav*. 2017
31. Fiedorowicz JG, et al. Peripheral inflammation during abnormal mood states in bipolar I disorder. *J Affect Disord*. 2015; 187:172–8. [PubMed: 26339927]
32. Shaffer JJ Jr, et al. Relationship altered between functional T1rho and BOLD signals in bipolar disorder. *Brain Behav*. 2017; 7(10):e00802. [PubMed: 29075562]
33. Matsuzawa Y, et al. Prognostic Value of Flow-Mediated Vasodilation in Brachial Artery and Fingertip Artery for Cardiovascular Events: A Systematic Review and Meta-Analysis. *J Am Heart Assoc*. 2015; 4(11)
34. Yeo TW, et al. Impaired nitric oxide bioavailability and L-arginine reversible endothelial dysfunction in adults with falciparum malaria. *J Exp Med*. 2007; 204(11):2693–704. [PubMed: 17954570]
35. Yinon D, et al. Pre-eclampsia is associated with sleep-disordered breathing and endothelial dysfunction. *Eur Respir J*. 2006; 27(2):328–33. [PubMed: 16452588]
36. Moerland M, et al. Evaluation of the EndoPAT as a Tool to Assess Endothelial Function. *Int J Vasc Med*. 2012; 2012:904141. [PubMed: 22500237]
37. Danner M, et al. Association between depression and elevated C-reactive protein. *Psychosom Med*. 2003; 65(3):347–56. [PubMed: 12764206]
38. Hatch J, et al. Non-invasive vascular imaging is associated with cardiovascular risk factors among adolescents with bipolar disorder. *Pediatr Cardiol*. 2015; 36(1):158–64. [PubMed: 25096903]
39. Murray DP, et al. Vascular function is not impaired early in the course of bipolar disorder. *J Psychosom Res*. 2012; 72(3):195–8. [PubMed: 22325698]
40. Sodhi SK, et al. Evidence for accelerated vascular aging in bipolar disorder. *J Psychosom Res*. 2012; 73(3):175–9. [PubMed: 22850256]
41. Paranthaman R, et al. Vascular function in older adults with depressive disorder. *Biol Psychiatry*. 2010; 68(2):133–9. [PubMed: 20609838]
42. Rybakowski JK, et al. Impairment of endothelial function in unipolar and bipolar depression. *Biol Psychiatry*. 2006; 60(8):889–91. [PubMed: 16730331]
43. Lavoie KL, et al. Association between clinical depression and endothelial function measured by forearm hyperemic reactivity. *Psychosom Med*. 2010; 72(1):20–6. [PubMed: 19875632]
44. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010; 55(13):1318–27. [PubMed: 20338492]
45. Vogel RA, Corretti MC, Plotnick GD. A comparison of brachial artery flow-mediated vasodilation using upper and lower arm arterial occlusion in subjects with and without coronary risk factors. *Clin Cardiol*. 2000; 23(8):571–5. [PubMed: 10941541]
46. Miettinen OS. The “case-control” study: valid selection of subjects. *J Chronic Dis*. 1985; 38(7):543–48. [PubMed: 4008595]
47. Nil M, et al. Reproducibility of peripheral arterial tonometry measurements in male cardiovascular patients. *Eur J Clin Invest*. 2014; 44(11):1065–71. [PubMed: 25252103]
48. Goldstein BI, et al. Major Depressive Disorder and Bipolar Disorder Predispose Youth to Accelerated Atherosclerosis and Early Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2015; 132(10):965–86. [PubMed: 26260736]

Figure 1.

Reactive Hyperemia Index (RHI) by Group. There were no significant differences observed in the primary outcome (RHI) between those with bipolar disorder or controls or by mood state within bipolar disorder.

Table 1

Baseline Participant Sociodemographic Characteristics of Sample (N=82)

	Controls (N=26)	Bipolar disorder (N= 56)	<i>p</i>-value
Sex, N (%)			
Female	9 (35%)	22 (39%)	0.81 *
Male	17(65%)	34 (61%)	
Marital Status			
Single	9 (35%)	22 (39%)	
Married	15 (58%)	21 (38%)	0.14 *
Divorced	2 (8%)	13 (23%)	
Race			
American Indian/ Alaskan Native	0	2 (4%)	
Asian	0	1 (2%)	0.59 *
African American	0	2 (4%)	
White	26 (100%)	51 (91%)	
Ethnicity			
Hispanic	0	1 (2%)	
Not Hispanic	26 (100%)	52 (93%)	0.69 *
Unknown	0	3 (5%)	
Employment			
Unemployed	2 (8%)	20 (36%)	<0.001 *
	Controls (N=26)	Bipolar disorder (n=56)	<i>p</i>-value
	Mean (SD)		
Age (years)	41.2 (13.8)	40.3 (12.8)	0.81
Education years	16.6 (2.1)	14.7 (2.1)	<0.001
Smoking (pack * years)	1.4 (3.5)	7.3 (12.5)	0.002
Body mass index (kg/m2)	26.2 (3.9)	29.7 (8.9)	0.08

* Exact tests used across categorical variables for consistency given low observed cell counts with most variables.