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Evidence for accelerated vascular aging in bipolar disorder

Simrit K. Sodhi^a, Jonathan Linder^a, Catherine A. Chenard^c, Del D. Miller^a, William G. Haynes^{b,c}, and Jess G. Fiedorowicz^{a,b,d,e}

^aDepartment of Psychiatry Roy J. and Lucille A. Carver College of Medicine, The University of Iowa Iowa City, Iowa, 52242

^bDepartment of Internal Medicine Roy J. and Lucille A. Carver College of Medicine, The University of Iowa Iowa City, Iowa, 52242

^cInstitute for Clinical and Translational Science The University of Iowa Iowa City, Iowa, 52242

^dDepartment of Epidemiology College of Public Health, The University of Iowa Iowa City, Iowa, 52242

Abstract

Objective—Persons with bipolar disorder face excess risk of cardiovascular disease, although the biobehavioral mechanisms and time course are unclear. We measured vascular stiffness in a cross-sectional sample of participants with bipolar disorder and compared results to published normative data to assess time-course and relationship to behavioral risk factors.

Methods—62 individuals with bipolar disorder (33±6.7 years; 64% female) underwent non-invasive assessment of arterial stiffness through arterial applanation tonometry. Lifetime tobacco exposure was estimated on clinical interview. Physical activity was assessed using the long-version of the International Physical Activity Questionnaire (IPAQ). A food frequency questionnaire was used to compute Alternate Healthy Eating Index (AHEI), a measure of overall dietary quality. Medication histories were systematically abstracted from pharmacy records.

Results—Participants over the age of 32 (median split) had greater arterial stiffness than expected from age-based population norms for pulse wave velocity (PWV) (7.6 vs. 7.0 m/s, $p=0.02$) and estimated aortic augmentation pressure (AIx) (14.2 vs. 8.2%, $p=0.0002$). The younger portion of the sample did not differ from population norms on these measures (PWV 6.3 vs. 6.4 m/s, $p=0.45$ and AIx 7.6 vs. 7.4%, $p=0.60$). In the older half of the sample, physical activity was inversely associated with AIx and poorer diet marginally associated with PWV. These findings were independent of body mass index (BMI), which was strongly related to arterial stiffness.

Conclusion—Risk for vascular disease may be acquired over the long-term course of affective illness. This risk appears to reflect maladaptive health behaviors, which may be amenable to intervention.

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^eCorresponding author. Address: 200 Hawkins Drive W278GH, Iowa City, IA 52242-1057 Phone: (319) 384-9267, Fax (319) 353-8656, jess-fiedorowicz@uiowa.edu.

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Keywords

Bipolar disorder; cardiovascular disease; physical activity; diet; arterial stiffness; pulse wave analysis

INTRODUCTION

Vascular mortality is a leading cause of excess death in bipolar disorder [1] although the behavioral mechanisms and time course for the development of this excess risk remain unclear [2, 3]. We have previously demonstrated a relationship between manic symptom burden and cardiovascular mortality [4] and endothelial dysfunction [5]. However, in a recent analysis, we found no difference in vascular function between cases with bipolar disorder and matched controls in a young sample [6]. One explanation for these findings is that excess cardiovascular risk is acquired over the long-term course of illness in bipolar disorder.

The atherosclerotic process increases vascular stiffness, which can be reliably measured using pulse tonometry. The gold-standard technique of carotid femoral pulse wave velocity (PWV) measures the speed at which the pulse wave travels through central conduit arteries, and augmentation index (AIx) measures the amount by which central aortic pressure is increased by reflection of the peripheral pulse wave [7, 8]. Normative values from reference samples have recently become available for these arterial stiffness measures [9, 10], enabling comparison to expected values to test the hypothesis that vascular dysfunction appears acquired over the long-term course of illness in bipolar disorder. In a larger sample than the prior report [6], powered to detect differences between groups on a median split, we sought to determine if older individuals with bipolar disorder were more likely to deviate from expected, age-based reference values. We further hypothesized that these differences would reflect retrospectively assessed chronicity of illness and be related to health related behaviors.

METHODS

Sample

We recruited 62 individuals with the diagnosis of bipolar disorder (type I or type II), identified from billing data at the University of Iowa Hospitals and Clinics, and constituting a separate, non-overlapping sample from the aforementioned study [6]. All participants provided informed consent in this study approved by the University of Iowa Institutional Review Board. Participants were included if they were between ages of 20 and 46 and received care from a faculty physician at the hospital. Participants were excluded if they had any history of cancer, untreated thyroid disease, pregnancy or peripheral vascular disease.

A member of the research team confirmed the faculty physician diagnosis using a clinical interview reviewing prior mood syndromes. Clinical characteristics such as age of onset, duration of illness, number of hospitalizations related to the illness, and chronicity of depression and mania over the past decade were ascertained by direct questioning. Current use of medications at the time of interview was recorded and detailed medication histories were obtained through systematic review of all pharmacy records for the previous five years. Exposure to tobacco (pack*years) was also ascertained by direct interview. Participants were screened for potential alcohol misuse using AUDIT-C using established optimal thresholds of ≥ 3 for women and ≥ 4 for men [11]. Participants were also screened for current intermittent or daily use of marijuana or other illicit drugs.

Health Behavior Assessment

Physical Activity was assessed using the long form of International Physical Activity Questionnaire (IPAQ) [12], which estimates physical activity across a comprehensive set of domains to yield a score in MET-minutes. METs are multiples of resting metabolic rate and multiplying the MET score of an activity by the total number of minutes the activity was performed gives a score of MET-minutes. The IPAQ has established validity in the assessment of overall physical activity in healthy adults [12]. To mitigate the impact of over-reporting, activity was truncated in accordance with IPAQ guidelines.

Diet over the past year was assessed with a web-based, self-reported semi-quantitative food frequency questionnaire [13, 14]. From this, the Alternate Healthy Eating Index (AHEI) was calculated. AHEI considers fat quality, white-to-red meat ratio, moderate use of alcohol, duration of multivitamin use, fruit, vegetable, nut and soy, and cereal fiber consumption [15] and has been linked with biomarkers for vascular disease and vascular mortality [16-18]. Points for each category except multivitamin use were assigned proportionately between zero and 10 based on the degree to which the dietary criteria were met; multivitamin use for more than five years was assigned 7.5 points and use less than five years or no use received 2.5 points. Points for each category were then summed and the resulting scores ranged from 2.5 (least healthy) to 87.5 (most healthy).

Vascular Assessment

Our primary outcomes, selected based on the existence of reference norms, were augmentation index (AIx) and pulse wave velocity (PWV), recorded using the SphygmoCor arterial tonometry system (Atcor Medical, West Ryde, Australia). A two hour fast from food, caffeine, and nicotine was verified prior to the procedure. A member of the research team measured vital signs, height and weight. AIx was measured by arterial applanation tonometry of the radial artery through pulse wave analysis with a high fidelity micromanometer. Using the radial pulse waveform, an inbuilt transfer function in the SphygmoCor system estimates Aix, the estimated augmentation of aortic systolic blood pressure, corrected for pulse pressure and expressed as percent of pulse pressure. Higher AIx values indicate greater arterial stiffness, particularly of peripheral vessels. For the measurement of PWV, the pressure pulse waveform over the carotid and femoral arteries is timed to the R-wave of an electrocardiogram signal [8]. Elevated PWV values indicate greater arterial stiffness, particularly of central elastic conduit vessels.

Statistical Analyses

All analyses were conducted using SAS 9.2. Descriptive statistics were compiled on sociodemographic and clinical variables. Participants were stratified into two age groups by median age. Expected values for our two primary outcomes, AIx and PWV, were calculated from published norms using relevant clinical information for each participant [9, 10]. Expected values for AIx were calculated from reference norms based on participant age, sex, height, and heart rate using the following formulas [9]:

$$\text{Men: } 148 * \text{Age}^{0.267} * \text{Height}^{-0.576} * \text{HeartRate}^{-0.215}$$

$$\text{Women: } 121 * \text{Age}^{0.319} * \text{Height}^{-0.594} * \text{HeartRate}^{-0.196}$$

Expected values for PWV were calculated from the following reference norms based on participant age and blood pressure using the following formulas [10]:

$$\text{Optimal Blood Pressure: } 0.000 * \text{age} + 0.00083 * \text{age}^2 + 5.55$$

$$\text{Normal Blood Pressure: } 0.000 * \text{age} + 0.00099 * \text{age}^2 + 5.69$$

$$\text{High Normal Blood Pressure: } 0.000 * \text{age} + 0.00105 * \text{age}^2 + 5.91$$

$$\text{Grade I Hypertension: } 0.000 * \text{age} + 0.00118 * \text{age}^2 + 6.17$$

$$\text{Grade II/III Hypertension: } 0.044 * \text{age} + 0.00085 * \text{age}^2 + 5.73$$

The differences between observed and expected values significantly deviated from normality for PWV and AIx. Observed values were compared to the expected values from the relevant reference normative data using the Wilcoxon signed rank sum test. Impact of behavioral risk factors on arterial stiffness was evaluated in multivariate linear regression models including diet, physical activity, tobacco exposure, age, and gender. Residuals from these models were assessed for any deviation from normality. A *post hoc* analysis separately assessed diet and physical activity, controlling for age and gender, in the older half of the sample.

Power was calculated to detect a clinically significant difference in arterial stiffness. In a meta-analysis of longitudinal studies of PWV and mortality, an effect size of 1SD was associated with a 47% greater likelihood of cardiovascular events, 47% greater cardiovascular mortality, and 42% greater overall mortality [19]. Our study was powered to detect an effect size of 0.60 SD with >90% power at an $\alpha=0.05$ within each subgroup following median split of age based on the assumptions of a paired t-test, which would correspond to a 28% increased risk of cardiovascular events and mortality based on the Vlachopoulos et al. meta-analysis [19]. Age was selected for primary analysis over retrospectively assessed symptom burden as our measure as the latter has not been validated and may be prone to misclassification. Graphs for figures were created using SigmaPlot 12.0.

RESULTS

Individuals in the study had a mean (SD) age of 33 (6.7) and ranged from 20- 46 years. Almost 64% of the participants were female. Sociodemographic and clinical characteristics are outlined in Table 1. The mean body mass index (BMI) was in the obese range (30.3 kg/m²), consistent with chart review data from our institution [20, 21]. Participants retrospectively estimated spending a median of 22% (mean 28%) of time depressed and 7% (mean 12%) of the time manic in the past decade or since onset of illness if within the past decade. Mean (SD) AHEI score was 36.8 (10.2). The mean AHEI score for men was 39.5 (range 18.5 - 60.5) and for women was 35.6 (range 15.5 - 63.5). Only three of our participants (5%) had scores > 55. Among the nine dietary components, the four with the healthiest ratings were *trans* fat, nut and soy protein, cereal fiber, and ratio of

polyunsaturated:saturated fatty acids. The remaining five components (vegetables, white:red meat ratio, fruits, moderate alcohol consumption, and long-term multivitamin use) had mean scores of 3.2 or less. The mean (SD) energy consumption was 2,641 (1,526) kcals with 15.2 (4.1)% of energy from protein, 30.7 (7.8)% from fat, 50.7 (9.9)% from carbohydrate, and 3.4 (9.9)% from alcohol.

The mean (SD) PWV and Aix for our sample were 6.7 (1.2) m/s and 10.5 (10.6) %, respectively. Among the whole group, participants had a greater than expected augmentation index (mean of 10.5 vs. 7.7%, $S=356.5$, $p=0.01$), but not pulse wave velocity (mean of 6.9 vs. 6.7 m/s, $S=158.5$, $p=0.27$). Those older than the median age (32 years) had greater stiffness of elastic arteries (AIX) and the aorta (PWV) than expected based on normative data as highlighted in Figure 1. Participants over the age of 32 (median split) had greater arterial stiffness than expected from age-based population norms for pulse wave velocity (PWV) (7.6 vs. 7.0 m/s, $S=87$, $p=0.03$) and estimated aortic augmentation pressure (AIX) (14.2 vs. 8.2%, $S=134$, $p=0.0004$). The younger portion of the sample, aged 32 years or younger, did not differ from population norms on these measures (PWV 6.3 vs. 6.4 m/s, $S=-47$, $p=0.45$ and AIX 7.6 vs. 7.4%, $S=33$, $p=0.60$). When age is treated as a continuous variable, age is significantly correlated with the difference between the observed and expected AIX ($\rho=0.37$, $p=0.003$) but not the difference between observed and expected PWV ($\rho=0.19$, $p=0.14$). Graphical representation of the relationship between age and the difference between observed and expected AIX do not reveal a clear age threshold as shown in Figure 2.

Participants estimated spending a mean (median; SD) of 28.4 (22.0; 25.2) percent of the time with depressive and 12.2 (7.0; 0.14) with manic symptomatology over their course of illness. When stratified by retrospectively estimated depressive symptom burden (duration of illness * percent of time depressed), the half with greater estimated depressive symptom burden had a significantly greater than expected AIX ($S=122.5$, $p=0.01$) and PWV ($S=95.5$, $p=0.048$). When stratified by retrospectively estimated manic symptom burden (duration of illness * percent of time manic/hypomanic), the half with greater estimated manic symptom burden had a significantly greater than expected AIX ($S=97.5$, $p=0.04$), but not PWV ($S=74.5$, $p=0.13$).

The older half of the sample were not significantly more likely to be obese, defined as a BMI ≥ 30 kg/m², (48% vs. 46%, $\chi^2=0.04$, $df=1$, $p=0.85$) and had a non-significantly higher mean BMI compared with the younger half of the sample (mean (SD) 31.6 (8.0) vs. 29.4 (6.0), $t=-1.22$, $df=60$, $p=0.23$). When the sample is stratified by the presence or absence of obesity only those with obesity were noted to have greater than expected AIX (14.3 vs. 7.8%, $S=148.5$, $p=0.0005$) while those without obesity had AIX values in the expected range (7.1 vs. 7.7%, $S=8.5$, $p=0.88$). Similarly, obese individuals had greater PWV relative to expected (7.3 vs. 6.7 m/s, $S=113.5$, $p=0.01$) and this was not seen in those without obesity (6.5 vs. 6.6 m/s, $S=-45.5$, $p=0.42$). In the full sample, multivariate models including age, gender, BMI and behavioral risk factors (diet (AHEI), physical activity, tobacco exposure), revealed a significant effect of only age and BMI on arterial stiffness measures. When reduced models (including age and gender) were applied to the older half of the sample, greater physical activity was significantly associated with a lower AIX (partial $R^2=0.18$, $p=0.04$), and AHEI score approached significance with slower PWV (partial $R^2=0.15$, $p=0.054$). When additionally controlling for BMI, these effects of physical activity and diet appeared surprisingly independent of BMI, which was also significantly associated with both AIX (partial $R^2=0.26$, $p=0.01$) and PWV (partial $R^2=0.41$, $p=0.0005$) in models controlling for age and gender with the older half of the sample. Significant relationships between BMI and AIX (partial $R^2=0.06$, $p=0.05$) and PWV (partial $R^2=0.16$, $p=0.001$) were also seen in the entire sample, but not the younger half of the sample.

In sensitivity analyses, inclusion of cumulative (5 year) or current antipsychotic or mood stabilizer exposure to models did not substantially alter findings and was not associated with PWV or AIx. Similarly, findings were not altered by inclusion of alcohol misuse or current illicit drug use and there was no evidence of an age*sex interaction.

DISCUSSION

Although it is clear that bipolar disorder is associated with greater risk of cardiovascular morbidity and mortality [22-24], our prior analysis of a young sample found no evidence of vasculopathy relative to age, gender, and smoking matched controls [6], leading to the hypothesis that the negative results were due to either the young age of the sample or a balancing of health behaviors related to smoking. The current cross-sectional study, which compares individuals to age-based reference norms, supports this hypothesis. Greater than expected arterial stiffness was only seen in the older half of the sample, relative to age-based norms. The younger half of the sample aligned well with the reference norms, suggesting it was appropriate to use these normative formulae. While we were unable to assess symptom burden prospectively as in prior analyses, it would appear that chronicity of illness, even based on retrospective estimates, contributes to vascular risk [4, 5].

Multivariate models assessing the role of health behaviors produced significant results in only the older half of the sample. This could be due to the fact that the adverse vascular effects of poor diet and inadequate physical activity were yet to be identified, perhaps due to the insidious onset of vascular disease. A recent report of 3,154 young adults followed for 20 years found that following a healthy lifestyle during early adulthood was associated with a low cardiovascular risk profile in middle age [25]. The quality of diet, as measured by the AHEI, was lower than reported elsewhere. In a sample of over 100,00 participants from the Nurses' Health Study and Health Professionals Follow-up Study, the mean AHEI score for women was 45.0 ± 11.1 (range 8.8 – 86.0) and for men was 38.4 ± 10.3 (range 9.8-83.6) [17], although these samples may be biased toward those with more desirable health related behaviors. In the Whitehall II British occupational cohort, the mean AHEI scores for the lower, intermediate, and upper tertiles were 36.6, 50.6, and 63.3 respectively [18]. Our sample means would fall solidly into this lower tertile, suggesting our participants consume a diet with lower nutritional quality.

Several studies have found vascular risk factors or related co-morbidities to be more prevalent in youth with bipolar disorder [26-29], which might be unexpected given our current findings. Child and adolescent samples with an earlier onset of illness may differ with regard to the time course for the development of excess vascular disease and evidence of elevated vascular risk may be present prior to changes in arterial stiffness are observed. Our conclusion that the excess risk of vascular disease appears to be acquired over the long-term course of bipolar disorder must be tempered by recognition of the nature of our outcome measure and limitations imposed by the study design. Most notably, the cross-sectional design of the study precludes ascertainment of temporality. An ideal study to test this hypothesis would involve assessing arterial stiffness longitudinally in cases with bipolar disorder and controls over long-term follow-up. In the absence of such study, our findings shed some light on the probable time course for the development of excess vasculopathy in bipolar disorder. Temporality also cannot be established for the observed relationship between the behavioral risk factors studied and arterial stiffness in the older half of the sample. These behavioral risk factors, diet and physical activity, are also particularly vulnerable to misclassification. The food frequency questionnaire may be sensitive to under-reporting, particularly with regard to energy intake [30]. Physical activity questionnaires may also encourage over-reporting with regard to time spent in organized exercise [31]. While we used established truncating protocols to address this for physical activity and

automated corrections for potential over- or under-reporting of fruit and vegetable consumption on food frequency questionnaires, there is concern for probable misclassification of diet and physical activity, which presumably, although not invariably, would render it more difficult to detect an association, if present. The Alternate Healthy Eating Index, while having the advantage of being a summary measure for use in linear regression and having been previously shown to predict incident cardiovascular disease [17], may not optimally capture vascular risk secondary to diet. The determination of bipolar disorder was not made by structured interview, which may limit reliability in diagnosis. Our retrospective estimates of depressive symptom burden (mean of 28.4% and median of 22.0% of the time depressed) were strikingly consistent with that observed in a large prospective cohort (mean of 31.7 and median of 22.1 percent of the time depressed) [32]. Based on similar prospective data, however, our retrospective estimates of manic symptom burden appear likely over-estimates with participants reporting a mean of 12.2 and median of 7.0 percent of the time with clinically significant manic symptoms compared to the mean of 11 and median of 4% for bipolar I disorder and mean of 1 and median of 0.4% for bipolar II disorder previously reported in large prospective studies [4]. We did not survey menstrual status in female patients, which has been associated with augmentation index [33] but not pulse wave velocity [33-35]. Our primary analysis focuses on age rather than symptom burden though secondary analyses suggest that these differences may reflect not simply age, but the long-term course of illness.

Our findings suggest that the risk for vascular illness is acquired over the long-term course of the affective illness. The increased arterial stiffness observed represents both a sign of vasculopathy and a risk for future events because greater augmentation of central aortic systolic pressure increases left ventricular afterload and myocardial oxygen consumption, while potentially reducing diastolic perfusion pressure. The greater arterial stiffness observed in our sample would be expected to have a meaningful impact on risk of vascular events. In a study of adults with coronary artery disease, a difference in AIx of 10% was associated with a 28% increase in risk of major adverse cardiovascular events [36]. In a general population adult sample, each SD change in PWV, corresponding to 3.4 m/s, was associated with a 61% increase in cardiovascular mortality [36]. In a meta-analysis of prospective studies, an effect size of 1 SD in PWV was associated with a 47% greater likelihood of cardiovascular events and mortality [19]. BMI was strongly associated with arterial stiffness measures in our sample. Obesity may augment sympathetic activity through selective leptin resistance [37, 38] and such obesity-mediated sympathetic activity may adversely impact AIx [39]. While age is a non-modifiable risk factor, physical activity and a diet can be addressed. Integration of health promoting interventions addressing lifestyle and diet [40] with mental health care provides clinicians working with this at-risk population a unique opportunity to impact risk through weight loss.

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a

b

Figure 1. Arterial Stiffness Relative to Reference Values

The augmentation index (AIx) for participants was greater than expected from age, height, and heart rate based norms. AIx was greater than expected was seen for the older, but not younger half of the sample on median split. Pulse wave velocity (PWV) for participants in the older, but not younger half of the sample was greater than expected from age and blood pressure based norms.

Figure 2. Relationship between Age and Difference from Expected AIx values

The observed AIx for participants with bipolar disorder was more likely to exceed age-based reference values among the older participants in the sample.

Table 1

Sociodemographic and Clinical Characteristics (N = 62)

	Mean (SD)
Age	33 (7)
Age of mood disorder onset	19 (6)
Education (Years)	15.3 (2.0)
Pack years (smoking)	8 (11)
Body mass index (kg/m ²)	30.3 (6.9)
Systolic blood pressure (mmHg)	117 (9)
Diastolic blood pressure (mmHg)	68 (9)
Physical activity (MET*mins/week)	5330 (4933)
Hours sedentary hours per week	43.9 (18.4)
Alternate Healthy Eating Index score ^a	36.8 (10.2)
Vegetable score ^b	2.0 (1.8)
Fruit score ^b	2.8 (2.1)
Nut and soy protein score ^b	6.2 (3.7)
White:Red meat score ^b	2.1 (3.4)
Cereal fiber score ^b	5.5 (2.7)
Trans fat score ^b	6.5 (1.5)
Polyunsaturated:Saturated fat score ^b	5.5 (1.9)
Multivitamin score ^c	3.2 (1.8)
Alcohol score ^b	2.9 (3.4)
	N (%)
Female gender	40 (64%)
White, not Hispanic	18 (67%)
Employed	35 (56%)
Bipolar I diagnosis	36 (58%)
Hypertension	4 (6%)
Diabetes mellitus	2 (3%)
Ever smoked tobacco	37 (60%)
Current alcohol misuse	26 (42%)
Current marijuana use (intermittent)	19 (31%)
Current marijuana use (daily)	3 (5%)
Current other illicit drug use	1 (2%)

^a score range 2.5 (least healthy) to 87.5 (most healthy)^b score range 0 to 10 (met dietary criteria)^c score range 2.5, 7.5 (use 5 years or longer)