Vasculopathy Related to Manic/Hypomanic Symptom Burden and First-Generation Antipsychotics in a Sub-Sample from the Collaborative Depression Study

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Key Words

Adult • Antipsychotics • Major depression • Bipolar disorder • Cardiovascular mortality • Mania

Abstract

Background: Mood disorders substantially increase the risk of cardiovascular disease, though the mechanisms are unclear. We assessed for a dose-dependent relationship between course of illness or treatment with vasculopathy in a well-characterized cohort. **Methods:** Participants with mood disorders were recruited for the National Institute of Mental Health Collaborative Depression Study (CDS) and followed prospectively. A cross-sectional metabolic and vascular function evaluation was performed on a sub-sample near completion after a mean follow-up of 27 years. **Results:** A total of 35 participants from the University of Iowa (33) and Washington University (2) sites of the CDS consented to a metabolic and vascular function assessment at the Iowa site. In multivariate linear regression, controlling for age, gender,

and smoking, manic/hypomanic, but not depressive, symptom burden was associated with lower flow-mediated dilation. Cumulative exposure to antipsychotics and mood stabilizers was associated with elevated augmentation pressure and mean aortic systolic blood pressure. This appeared specifically related to first-generation antipsychotic exposure and mediated by increases in brachial systolic pressure. Although second-generation antipsychotics were associated with dyslipidemia and insulin resistance, they were not associated with vasculopathy. **Conclusions:** These results provide evidence that chronicity of mood symptoms contribute to vasculopathy in a dose-dependent fashion. Patients with more manic/hypomanic symptoms had poorer endothelial function. First-generation antipsychotic exposure was associated with arterial stiffness, evidenced by higher augmentation pressure, perhaps secondary to elevated blood pressure. Vascular phenotyping methods may provide a promising means of elucidating the mechanisms linking mood disorders to vascular disease.

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Introduction

The National Institute of Mental Health Collaborative Depression Study (CDS) investigated the nature, course, and etiology of mood disorders [1, 2]. The five participating centers of the clinical studies component (Massachusetts General Hospital and Harvard University in Boston, Rush Presbyterian – St. Luke's Medical Center in Chicago, University of Iowa in Iowa City, New York State Psychiatric Institute and Columbia University in New York, and Washington University in St. Louis) recruited 955 individuals with mood disorders from 1978 to 1981 and followed them for up to 31 years. Publications from the CDS have contributed greatly to understanding the nosology and prognosis of mood disorders. Recent work has quantified the impact of mood disorders on disability [3, 4], suicide [5], and cardiovascular mortality [6].

The relationship between mood disorders and vascular disease has been seen across specific mood diagnoses in representative samples [7–9] and with vascular outcomes in those with coronary artery disease [10, 11]. Potential mechanisms have been divided into direct pathways involving physiological changes secondary to mood, indirect pathways involving traditional risk factors for vascular disease, or through background factors that contribute to developing both mood disorders and vascular disease [12]. Vascular phenotyping may be a useful tool to identify relevant mechanisms although there has been limited study with available research demonstrating significant impairments in vascular function or stiffness with depression and/or bipolar disorder in most [13–17] but not all studies [18]. These cross-sectional studies have focused on the presence or absence of illness without dosing mood [15–17, 19], apart from assessing duration of illness [13].

The identification of a dose-response supports a causal relationship between mood and vascular outcomes. Lesperance et al. [20] found severity of depressive symptoms at baseline and 1 year following myocardial infarction to be associated with mortality in a dose-dependent fashion. With an episodic course common to mood disorders, reliable methods of dosing mood quantitatively using longitudinal data may better classify symptom burden as an exposure, though the requisite data are seldom available. Prospective studies of symptom burden have found manic [6], but not depressive symptoms [6, 21], associated with subsequent cardiovascular mortality. Treatments for mood disorders may also adversely impact vascular risk factors and thus events [22, 23]. Pharmacoepidemiological studies have associated antipsychotics with sudden cardiac death [24], but otherwise there are limited data di-

rectly linking treatments with adverse vascular outcomes apart from cerebrovascular events in dementia [25].

Vasculopathy, defined as impaired function or structure of blood vessels, can be identified prior to adverse cardiovascular events using validated techniques. Assessment of endothelial function, in particular, provides a useful intermediate phenotype for the study of atherosclerosis and may serve as a clinically relevant, quantitative and sensitive surrogate outcome [26, 27]. Endothelial function is impaired by every known risk factor for atherosclerosis, precedes the development of atherosclerotic lesions, and predicts progression and complications of atherosclerosis [28], even independent of conventional risk factors [29]. Flow-mediated dilation (FMD), a measure of endothelial function, prospectively predicts vascular events in a manner that allows the clinical relevance of findings to be translated. In population-based samples of older adults, an effect size of 2/3 standard deviations (SD) in FMD has been associated with a 25–30% increased risk of cardiovascular events [30, 31].

To ascertain whether lifetime symptom burden or medication exposure are predictive of vascular dysfunction, we assessed vascular function cross-sectionally in a sample of individuals with affective disorders whose phenomenological and treatment histories have been rigorously assessed over roughly one quarter century through participation in the CDS. Based on our prior findings with cardiovascular mortality in this sample [6], we hypothesized that manic, but not depressive, symptom burden would be associated with poorer vascular function. Based on metabolic profile, we further hypothesized that treatment with second-generation antipsychotics and valproic acid derivatives would be associated with poorer vascular function.

Patients and Methods

Sample

The CDS involved a large, prospective cohort of individuals followed for up to 31 years to test hypotheses related to the nosology, phenomenology, and etiology of mood disorders [1]. The sample included Caucasian (genetic hypotheses were proposed), English-speaking individuals who had knowledge of their biological parents and provided written informed consent. We recruited participants from those who completed the CDS study at two of five CDS sites and resided near Iowa City. Participants with a history of diabetes, hyperlipidemia, hypertension, or heart disease at intake into the CDS were excluded. We additionally excluded any participants over 80 years of age. A total of 59 former participants from The University of Iowa in Iowa City, Iowa, and 7 former participants from Washington University in St. Louis, Mo., representing all of those meeting inclusion criteria were contacted, of whom 44 (75%) were female. Two of the male former

participants were deceased. Procedures were approved by the respective Institutional Review Boards.

CDS Assessments

On intake into the CDS, participants underwent interviews for the Schedule for Affective Disorders and Schizophrenia [32] and the Personal History of Depressive Disorders (available upon request). Follow-up assessments categorized severity of affective psychopathology from Psychiatric Status Ratings (PSRs) using the Longitudinal Interval Follow-up Evaluation, administered every 6 months in the first 5 years and annually thereafter [33–35]. The PSRs provided weekly ratings of symptom levels for each Research Diagnostic Criteria syndrome [36], as previously described [33]. The PSRs have demonstrated intraclass correlation coefficients of 0.9 [37]. Intake and follow-up ratings facilitated rigorous ascertainment of mood disorder diagnosis using previously outlined methods [6, 33, 38].

PSRs were used to quantify longitudinal affective morbidity. Using previously published methods [6], a week of clinically significant affective symptoms was defined as a PSR cutoff score of $>2/6$ (required at least obvious evidence of the disorder) on the major depression, schizoaffective depression scale, mania, or schizoaffective mania scales or a score of 3/3 (definite criteria) for minor depression, intermittent depression, or hypomania. Burden of clinically significant depressive or manic/hypomanic morbidity was expressed as the proportion of weeks during follow-up with depressive or manic/hypomanic symptoms, respectively, exceeding these thresholds. These measures have been previously shown to have stability over long-term follow-up for both major depression and bipolar disorder [39, 40]. Treatment exposure was recorded during follow-up and included the following classes of medications: first-generation antipsychotics, second-generation antipsychotics, lithium, valproic acid derivatives, carbamazepine, lamotrigine, tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, other antidepressants, and benzodiazepines [6]. These classes were pooled into two broad medication classes: mood stabilizers/antipsychotics and antidepressants. In this observational CDS study, study investigators observed but did not direct treatment.

Chart Review

Weight or other metabolic assessments were not obtained at baseline through the CDS. We systematically reviewed the medical records within 2 years of CDS intake of all participants to abstract height, weight, total cholesterol, blood pressure and heart rate.

Metabolic and Vascular Assessments

Participants were instructed to fast for 12 h and not to smoke 2 h prior to assessment and this was verified by direct questioning. Upon arrival, a research nurse measured vital signs, height, weight, and waist circumference. A blood sample was drawn. Participants then provided a health history and underwent physical examination.

Vascular function was assessed using pulse wave analysis, pulse wave velocity, and conduit vessel function by individuals blinded to diagnosis, current medications, and any CDS data. Our primary outcomes of interest were FMD (endothelium-dependent) and nitroglycerin (NTG; endothelium-independent) mediated vasodilation of the brachial artery, assessed noninvasively via ultrasound measurement of brachial artery diameter using previ-

ously described methods [41] with a 10-MHz linear array transducer (Biosound Esaote AU5) by a trained sonographer. These measures were selected as the primary outcome because they represent the most extensively studied and validated non-invasive measures of endothelial function though are seldom used clinically because of the cost and need for highly trained operators [42]. A longitudinal section of the brachial artery was imaged above the antecubital fossa where baseline images of diameter and Doppler velocities were recorded. FMD was assessed 1 min after release of a distal occluding forearm cuff that had been inflated to 50 mm Hg above systolic pressure for 5 min. After 10 min of rest and restoration of baseline flow and diameter, nitroglycerin 400 μ g was administered by sublingual spray. NTG-mediated vasodilation was assessed 4 min later.

Vascular damage (such as endothelial dysfunction) leads to increased vascular stiffness, and this translates into accelerated return of peripheral pulse waves to the aortic, leading to increases in augmentation pressure, augmentation index, and overall aortic systolic pressure. Secondary outcomes included pulse wave velocity, aortic augmentation pressure, augmentation index (adjusted for heart rate of 75), and systolic aortic pressure. These were assessed using Sphygmocor arterial tonometry system [43], which measures peripheral arterial pulse wave timing and characteristics. For the measurement of pulse wave velocity, the pressure pulse waveform was recorded simultaneously with an electrocardiogram signal, which provides an R-wave timing reference. Recordings were performed consecutively at the carotid and femoral artery sites to measure the pulse wave velocity in a section of artery that includes the aorta. Information from peripheral pressure pulse waveform in addition to systolic and diastolic pressures were used to derive central aortic pressure waveform and a range of central indices of ventricular-vascular interaction.

Exploratory outcomes included risk factors for vascular disease: body mass index (BMI), waist circumference, fasting cholesterol (high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, Lp(a)), fasting triglycerides (total, LDL, very low density lipoprotein (VLDL)), apolipoprotein B, brachial (clinic) arterial pressure, insulin resistance (calculated from fasting insulin and glucose by homeostatic model assessment for insulin resistance (HOMA-IR) [44]), highly sensitive C-reactive protein, and interleukin-6.

Statistical Analyses

All analyses were conducted using SAS 9.2. Descriptive statistics were compiled on a variety of sociodemographic and clinical variables, which were compared to that of the full CDS sample of those who completed at least 24 years of follow-up ($n = 362$) using *t* tests and chi-square tests for continuous and categorical variables, respectively.

The proportion of weeks with clinically significant manic, hypomanic, minor depressive or major depressive symptoms during follow-up quantified the symptom burden. To minimize risk of type I error on multiple comparisons and given overlapping metabolic adverse effects, treatment exposures were lumped into two broad classes: mood stabilizers/antipsychotics and antidepressants. Analyses of more refined medication classes followed any significant findings. Given the infrequent use of these agents, carbamazepine and lamotrigine were not included in these follow-up analyses for mood stabilizer/antipsychotic exposure though exposure to these agents was included in the broad classification.

Table 1. Sociodemographic and clinical characteristics of the sample as available from CDS (n = 35)

Age, years	61 ± 8
Age of onset for mood disorder, years	25 ± 7
Time with clinically significant symptoms, %	
Depressive	30.0 ± 26.6
Manic/hypomanic (if bipolar)	7.1 ± 19.9
Female sex ¹	29 (83%)
Unipolar major depression	15 (43%)
Bipolar disorder	20 (57%)
Bipolar I	14 (40%)
Bipolar II	6 (17%)
History of tobacco use	22 (63%)
Any history of medication treatment	
First-generation antipsychotics	25 (71%)
Second-generation antipsychotics	11 (31%)
Valproic acid derivatives	13 (37%)
Lithium	22 (63%)
Carbamazepine	7 (20%)
Lamotrigine	3 (9%)
Antidepressants	31 (89%)

Figures are means ± SD or numbers with percentages.

¹ Significantly higher than expected from the CDS participants with at least 24 years of follow-up ($\chi^2 = 5.04$; d.f. = 1; $p = 0.025$).

Table 2. Clinical characteristics of the sample from cross-sectional metabolic and vascular assessment

BMI, kg/m ²	29.8 ± 6.2
Waist circumference, cm	100.2 ± 15.4
FMD diameter, % change	4.6 ± 4.3
NTG-mediated diameter, % change	11.0 ± 5.4
Augmentation pressure, mm Hg	14.9 ± 8.0
Augmentation index adjusted for HR = 75	25.6 ± 9.2
Systolic aortic pressure, mm Hg	122 ± 17
Pulse wave velocity, m/s	10.8 ± 3.8
Triglycerides, mg/dl	
Total	122.2 ± 91.6
LDL	41.8 ± 12.9
VLDL	65.5 ± 54.9
Cholesterol, mg/dl	
Total	204.0 ± 31.9
LDL	121.6 ± 27.9
HDL	55.1 ± 12.5
VLDL	21.6 ± 12.0
Apolipoprotein B, mg/dl	92.3 ± 20.8
Glucose, mg/dl	100.5 ± 16.6
Total insulin, µU/ml	10.9 ± 9.0
Leptin, ng/ml	22.3 ± 20.1
Highly sensitive C-reactive protein, mg/l	4.0 ± 4.8
Interleukin-6, pg/ml	2.4 ± 1.8
Cumulative tobacco exposure, pack years	13.0 ± 20.0

Figures are means ± SD. HR = Heart rate.

Individuals on combinations of medications were considered exposed if any one of those medications belonged to an exposure group of interest. To minimize the impact of outliers and to maximize the likelihood that residuals were normally distributed in this small sample, exposures of interest were modeled as the logit transformation of the proportion of time exposed. Linear regression models determined the effect of symptom burden and treatment exposure on vascular function, controlling for age, gender, and tobacco exposure in pack years. Because symptom burden and respective treatments were highly correlated in this small sample, symptom burden and treatment exposure were modeled separately to mitigate multicollinearity and overfitting. Linear regression models followed the following format:

$$Y = \beta_0 + \beta_1\chi_1 + \beta_2\chi_2 + \beta_3\chi_3 + \beta_4\chi_4 + \beta_5\chi_5 + \varepsilon,$$

where Y represents our dependent outcome variable, χ_1 is age (linear effect), χ_2 is gender, and χ_3 is tobacco exposure in pack years. In symptom burden models, χ_4 is proportion of follow-up with clinically significant depressive symptoms and χ_5 is the proportion of follow-up with clinically significant manic or hypomanic symptoms. In the treatment models, χ_4 is the proportion of follow-up treated with antidepressants and χ_5 is the proportion of follow-up treated with antipsychotics or mood stabilizers. To explore for any potential overfitting, sensitivity analyses using reduced models, including only age with symptom burden or treatment exposure variables, were created for any models producing significant results.

Exploratory analyses investigated the relationship between symptom burden and treatment exposure and potential physiological mediators: body fat percentage, body mass index, waist circumference, brachial systolic blood pressure, laboratory measures, and HOMA-IR. Any potential mediators found to have a significant association with exposures of interest (symptom burden and treatment exposure) were added to regression models in which these exposures were associated with primary or secondary outcomes. The reduction in R^2 for the exposure of interest after inclusion of the potential physiological mediator was used to estimate possible impact. Mediation was further explored in a sub-sample of participants with available data from chart abstraction for changes in relevant mediators over the course of CDS follow-up.

Results

Baseline Demographic and Clinical Characteristics

Thirty-five participants from the University of Iowa (33) and Washington University (2) sites of the CDS consented for cross-sectional vascular and metabolic assessment at the University of Iowa. The enrolled participants had been followed for a mean (SD) of 26.8 (1.2), median of 27, at least 24 and up to 30 years. Sociodemographic

Table 3. Results of multivariate linear regression models for exposures of interest on primary outcomes

	χ^2	SE	t	p
<i>Dependent variable = FMD (n = 34)</i>				
Symptom burden model				
Depressive symptom burden	-0.576	0.385	-1.50	0.15
Manic/hypomanic symptom burden	-0.993	0.449	-2.21	0.035*
Treatment model				
Antidepressant exposure	-0.221	0.276	-0.80	0.43
Mood stabilizer/antipsychotic exposure	-0.225	0.173	-1.31	0.20
<i>Dependent variable = NTG-mediated dilation (n = 35)</i>				
Symptom burden model				
Depressive symptom burden	0.808	0.465	1.74	0.09
Manic/hypomanic symptom burden	0.308	0.536	0.57	0.57
Treatment model				
Antidepressant exposure	0.411	0.320	1.29	0.21
Mood stabilizer/antipsychotic exposure	-0.111	0.204	-0.54	0.59

* $p < 0.05$. Coded such that greater manic/hypomanic symptoms were associated with poorer endothelial function. All models controlled for age, gender, and tobacco exposure (pack years).

characteristics of the sample are outlined in table 1. The mean (SD) age of participants was 61 (8) (range 50–76), 83% were female, and 57% had a diagnosis of bipolar disorder. The mean (SD) body mass index was 30 (6) and 63% smoked tobacco. Participants significantly differed from others in the full CDS sample that completed 24 years of follow-up only regarding gender ($\chi^2 = 5.04$, d.f. = 1, $p = 0.03$) though did not significantly differ from those recruited based on our inclusion criteria.

Clinical characteristics of the sample as assessed are detailed in table 2. FMD data for one participant could not be interpreted due to motion. Pulse wave velocity could not be reliably obtained on four participants. Augmentation index could not be calculated to a heart rate of 75 for two participants due to unusually low resting heart rates. The total number of participants included in the analyses varies accordingly for models on these outcomes described below.

Depressive symptom burden was highly correlated with cumulative exposure to antidepressants ($r = 0.86$, $p < 0.0001$) as was manic symptom burden with cumulative exposure to mood stabilizers and antipsychotics ($r = 0.72$, $p < 0.0001$). For this reason, symptom burden and treatment variables were modeled separately. There was a negative correlation between manic and depressive symptom burden ($r = -0.47$, $p < 0.004$).

Symptom Burden and Vascular Function

Table 3 presents results of symptom burden and treatment exposure models on primary outcome measures. In multivariable linear regression, controlling for age, gender, and tobacco exposure, manic symptom burden was associated with lower FMD ($t = -2.21$, partial $R^2 = 0.15$, $p = 0.035$). This would represent an absolute reduction of 2.2% (0.52 SD) in FMD (baseline = 4.6%) across the inter-quartile range of those with bipolar disorder (0.6–5.6% manic/hypomanic symptom burden). Using data from the entire CDS sample, this would represent an absolute difference of 2.3% dilation (0.54 SD) on FMD (or about a 50% relative change in FMD) between those with 0.4% and 4% manic/hypomanic symptom burden, the previously reported median for bipolar II and bipolar I, respectively [6]. Manic symptom burden was not associated with NTG-mediated vasodilation. Depressive symptom burden was not associated with any of the tested measures as reported. Symptom burden measures were not associated with any of the secondary outcomes. Exploratory analyses associated manic symptom burden with hypertriglyceridemia ($t = 2.12$, partial $R^2 = 0.13$, $p = 0.043$), but not specifically with LDL triglycerides or VLDL triglycerides. Manic symptom burden was also associated with higher BMI ($t = 2.55$, partial $R^2 = 0.18$, $p = 0.016$), waist circumference ($t = 2.79$, partial $R^2 = 0.21$, $p = 0.009$), and HOMA-IR ($t = 2.94$, partial $R^2 = 0.23$, $p = 0.006$). Depressive symptom burden was associated

Table 4. Results of multivariate linear regression models for treatment exposure on augmentation pressure and systolic aortic pressure (n = 35)

	χ^2	SE	t	p
<i>Dependent variable = augmentation pressure</i>				
Treatment model				
Antidepressant exposure	-0.364	0.452	-0.80	0.43
Mood stabilizer/antipsychotic exposure	0.769	0.290	2.66	0.013*
Individual mood stabilizer/antipsychotic classes (modeled separately)				
First-generation antipsychotics	1.137	0.457	2.49	0.019*
Second-generation antipsychotics	0.522	0.684	0.76	0.45
Lithium	0.613	0.353	1.74	0.09
Valproic acid derivatives	0.267	0.597	0.45	0.66
<i>Dependent variable = systolic aortic pressure</i>				
Treatment model				
Antidepressant exposure	-0.846	1.016	-0.83	0.41
Mood stabilizer/antipsychotic exposure	1.539	0.650	2.37	0.025*
Individual mood stabilizer/antipsychotic classes (modeled separately)				
First-generation antipsychotics	3.275	0.930	3.52	0.001*
Second-generation antipsychotics	1.776	1.486	1.20	0.24
Lithium	0.745	0.803	0.93	0.36
Valproic acid derivatives	0.331	1.319	0.25	0.80

* p < 0.05. Coded such that greater manic/hypomanic symptoms were associated with poorer endothelial function. All models included age, gender, and tobacco exposure (pack years).

with a higher heart rate ($t = 2.11$, partial $R^2 = 0.13$, $p = 0.044$). However, in the 28 participants with available data, manic symptom burden was not correlated with change in BMI nor was depressive symptom burden with change in heart rate.

Medication Exposure and Vascular Function

Antipsychotic/mood stabilizer and antidepressant exposure were not associated with FMD or NTG-mediated vasodilation. Cumulative exposure to antipsychotics and mood stabilizers was associated with vascular stiffness as evidenced by elevated aortic systolic augmentation pressure ($t = 2.66$, partial $R^2 = 0.20$, $p = 0.013$) and total aortic systolic blood pressure ($t = 2.37$, partial $R^2 = 0.16$, $p = 0.025$). Treatment exposure models for these measures are reported in table 4. As evidenced in table 4, first-generation antipsychotics were the only medication class significantly associated with these findings. An increase of 5.8 mm Hg (0.73 SD) in augmentation pressure and 16.8 mm Hg (1.00 SD) in aortic systolic blood pressure was observed across the interquartile range of those exposed to first-generation antipsychotics (3–44% exposure). In exploratory analyses, first-generation antipsychotics were associated with elevated peripheral brachial

systolic arterial pressure ($t = 3.41$, partial $R^2 = 0.28$, $p = 0.002$). Second-generation antipsychotics were associated with hypertriglyceridemia ($t = 3.11$, partial $R^2 = 0.24$, $p = 0.004$) and insulin resistance ($t = 2.16$, partial $R^2 = 0.13$, $p = 0.039$). Valproic acid derivative exposure was associated with hypertriglyceridemia ($t = 2.96$, partial $R^2 = 0.23$, $p = 0.006$), insulin resistance ($t = 2.28$, partial $R^2 = 0.15$, $p = 0.030$), and low HDL-cholesterol ($t = -4.33$, partial $R^2 = 0.38$, $p = 0.0002$). For second-generation antipsychotics and valproic acid derivatives, similar results were observed for VLDL triglycerides as total triglycerides, but LDL triglycerides were not related to exposure. In the subset of 28 individuals with available data, exposure to first-generation antipsychotics was significantly associated with change in systolic blood pressure, even after controlling for age, gender, and tobacco exposure.

The 25 individuals who received first-generation antipsychotics were taking them for 23% of the observed follow-up period and were more likely to have bipolar I disorder ($\chi^2 = 5.25$, d.f. = 1, $p = 0.02$) though otherwise did not differ from the remainder of the sample. Controlling for diagnosis did not substantially alter the aforementioned findings. In an exploratory follow-up analysis, there was no relationship between lithium exposure

and our primary and secondary vascular function outcomes.

Reduced Models

Very similar results were obtained for significant findings in the primary and secondary analyses above in the sensitivity analysis using reduced models that included only age as a covariate. In these models, manic symptom burden no longer crossed the threshold for statistical significance on FMD ($p = 0.06$).

Exploratory Mediation Analyses

When manic symptom burden was modeled individually with its physiological correlates, BMI produced the greatest reduction in the partial R^2 for manic symptom burden on FMD (52%). Mediation of manic symptoms on FMD by BMI, however, was not supported by the lack of an association between manic symptom burden and change in BMI in the sub-sample with available data with baseline ($n = 28$). Further, those with a higher manic symptom burden tended to have a higher BMI at baseline though this correlation was not significant. Adding peripheral brachial systolic pressure dramatically reduced the partial R^2 between first-generation antipsychotic exposure and central aortic augmentation pressure (by 82%). In the sub-sample with available baseline data ($n = 28$), change in systolic blood pressure reduced the partial R^2 between first-generation antipsychotic exposure and central aortic augmentation pressure as well (by 33%), rendering the initial association no longer significant. Models with peripheral brachial systolic blood pressure on aortic systolic blood pressure were not produced as the latter is derived from the former. In the sub-sample, inclusion of change in systolic blood pressure reduced the partial R^2 for first-generation antipsychotic exposure on aortic systolic blood pressure by 42% while first-generation antipsychotic exposure remained significantly associated.

Discussion

Measures of mania chronicity were inversely proportional to endothelial function (FMD). With data linking an effect size of 0.66 SD in FMD to a 25–30% increased risk of cardiovascular events [30, 31], our finding of 0.54 SD FMD from the manic symptom burden of 0.4% for a typical bipolar II to the manic symptom burden of 4% for a typical bipolar I [6] would be expected to translate to roughly a 20–25% increased risk of such events. First-

generation antipsychotic exposure was associated with greater arterial stiffness, evidenced by higher augmentation pressure and aortic systolic pressure. In exploratory mediation models, this appears to be mainly due to elevation of peripheral systolic arterial pressure with first-generation antipsychotics. Long-term exposure to second-generation antipsychotics and valproic acid derivatives were associated with several vascular risk factors of the metabolic syndrome.

The demonstration of an association between first-generation antipsychotics and arterial stiffness is of particular interest and was not anticipated by our hypotheses or previously studied. The alpha-1 adrenergic antagonism of many first-generation antipsychotics would be expected, if anything, to reduce total peripheral resistance and subsequently blood pressure. Through this mechanism, antipsychotics can induce orthostatic hypotension [45]. Unlike most clinical trials, our analysis assesses medication exposure over several decades. Chronic administration of haloperidol induces vasoconstriction in animal models [46]. D_2 receptors are involved in the inhibition of sympathetic nerve activity [47] and D_2 antagonism, which is characteristic of first-generation antipsychotics, could perhaps increase sympathetic tone and subsequently blood pressure. Hypertension is arguably the most robust cause of increased vascular stiffness [48]. The potential mediation of the induction of arterial stiffness with antipsychotics by systolic blood pressure appears biologically plausible and amenable to confirmatory study.

Methodological strengths of our approach include application of the concept of symptom burden, which overcomes mere evaluation of the presence/absence of a disorder and the inherent selection bias therein. Symptom burden also overcomes the limitations of dosing severity at a single time point, which fails to capture the burden of affective symptomatology over the long-term course of an often episodic illness that fluctuates in its severity. Interview-based ratings of symptoms were obtained, which may be more sensitive in detecting cognitive symptoms of depression [49]. We also utilized vascular function as a primary outcome, facilitating mechanistic investigation. There are, nonetheless, several limitations to our study. Participants were not randomized to treatment. Our relatively high acuity clinical sample may have underrepresented those with milder forms of depressive illness, restricting our range of exposure and subsequently decreasing our ability to detect an effect of depressive symptom burden. The relatively small sample size similarly increases risk of type II error and limits generaliz-

ability. Risk of type I error was mitigated by defining primary outcomes a priori and grouping exposures classes. Our primary finding is further consistent with our previous report of a link between manic/hypomanic symptom burden and cardiovascular mortality in the CDS [6]. Exploration of mediation was limited by sample size and design. Temporal relationships between the potential mediators and vascular outcomes cannot be established with a single cross-sectional metabolic and vascular assessment so we acquired baseline data in a sub-sample from chart review. The design focused on potential physiological mediators relevant to vasculopathy, assuming that behavioral and psychological factors mediate their effects through physiological measures. Subsequent study of potential behavioral and psychological mediators would add value. Several of these factors could be related to symptom burden and have been linked with vascular outcomes, including but not limited to hostility [50], anxiety [51, 52], and social isolation [53].

The use of existing data from the CDS allowed us to rigorously classify symptom burden and treatment exposures to assess their impact on vascular function, adding considerably to the developing literature on vasculopathy in mood disorders. Our cross-sectional vascular phenotyping methods were similarly rigorous and allowed us to identify associations between manic symptom burden and endothelial dysfunction and first-generation antipsychotics with arterial stiffness. In exploratory analyses, we were able to delve into potential mechanisms, such as elevated blood pressure on the relationship between first-

generation antipsychotics and arterial stiffness. Future studies may target other mediators within a causal pathway, such as behavioral or psychological variables that may link manic symptom burden with FMD and first-generation antipsychotics with autonomic dysregulation. Due to their quantitative nature and sensitivity to vascular risk factors, vascular phenotyping methods provide a promising means of elucidating the mechanisms linking mood disorders to vascular disease.

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References

- 1 Katz MM, Klerman GL: Introduction: overview of the clinical studies program. *Am J Psychiatry* 1979;136:49–51.
- 2 Katz MM, Secunda SK, Hirschfeld RM, Koslow SH: NIMH clinical research branch collaborative program on the psychobiology of depression. *Arch Gen Psychiatry* 1979;36:765–771.
- 3 Judd LL, Akiskal HS, Zeller PJ, Paulus M, Leon AC, Maser JD, Endicott J, Coryell W, Kunovac JL, Mueller TI, Rice JP, Keller MB: Psychosocial disability during the long-term course of unipolar major depressive disorder. *Arch Gen Psychiatry* 2000;57:375–380.
- 4 Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, Coryell W, Maser JD, Keller MB: Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. *Arch Gen Psychiatry* 2005;62:1322–1330.
- 5 Coryell W, Haley J, Endicott J, Solomon D, Leon AC, Keller M, Turvey C, Maser JD, Mueller T: The prospectively observed course of illness among depressed patients who commit suicide. *Acta Psychiatr Scand* 2002;105:218–223.
- 6 Fiedorowicz JG, Solomon DA, Endicott J, Leon AC, Li C, Rice JP, Coryell WH: Manic/hypomanic symptom burden and cardiovascular mortality in bipolar disorder. *Psychosom Med* 2009;71:598–606.
- 7 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;70:145–154.
- 8 Baune BT, Adrian I, Arolt V, Berger K: Associations between major depression, bipolar disorders, dysthymia and cardiovascular diseases in the general adult population. *Psychother Psychosom* 2006;75:319–326.
- 9 Osby U, Brandt L, Correia N, Ekblom A, Sparen P: Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry* 2001;58:844–850.
- 10 Ormel J, de Jonge P: Unipolar depression and the progression of coronary artery disease: toward an integrative model. *Psychother Psychosom* 2011;80:264–274.
- 11 Zuidersma M, Thombs BD, de Jonge P: Onset and recurrence of depression as predictors of cardiovascular prognosis in depressed acute coronary syndrome patients: a systematic review. *Psychother Psychosom* 2011;80:227–237.
- 12 Barth J, Schumacher M, Herrmann-Lingen C: Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med* 2004;66:802–813.

- 13 Rybakowski JK, Wykretowicz A, Heymann-Szlachcinska A, Wysocki H: Impairment of endothelial function in unipolar and bipolar depression. *Biol Psychiatry* 2006;60:889–891.
- 14 Broadley AJ, Korszun A, Jones CJ, Frenneaux MP: Arterial endothelial function is impaired in treated depression. *Heart* 2002;88:521–523.
- 15 Lavoie KL, Pelletier R, Arsenault A, Dupuis J, Bacon SL: Association between clinical depression and endothelial function measured by forearm hyperemic reactivity. *Psychosom Med* 2010;72:20–26.
- 16 Rajagopalan S, Brook R, Rubenfire M, Pitt E, Young E, Pitt B: Abnormal brachial artery flow-mediated vasodilation in young adults with major depression. *Am J Cardiol* 2001;88:196–198.
- 17 Pizzi C, Manzoli L, Mancini S, Costa GM: Analysis of potential predictors of depression among coronary heart disease risk factors including heart rate variability, markers of inflammation, and endothelial function. *Eur Heart J* 2008;29:1110–1117.
- 18 Paranthaman R, Greenstein AS, Burns AS, Cruickshank JK, Heagerty AM, Jackson A, Malik RA, Scott ML, Baldwin RC: Vascular function in older adults with depressive disorder. *Biol Psychiatry* 2010;68:133–139.
- 19 Broadley AJ, Korszun A, Abdelaal E, Moskvina V, Deanfield J, Jones CJ, Frenneaux MP: Metirapone improves endothelial dysfunction in patients with treated depression. *J Am Coll Cardiol* 2006;48:170–175.
- 20 Lesperance F, Frasure-Smith N, Talajic M, Bourassa MG: Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation* 2002;105:1049–1053.
- 21 Coryell W, Turvey C, Leon A, Maser JD, Solomon D, Endicott J, Mueller T, Keller M: Persistence of depressive symptoms and cardiovascular death among patients with affective disorder. *Psychosom Med* 1999;61:755–761.
- 22 Murray DP, Weiner M, Prabhakar M, Fiedorowicz JG: Mania and mortality: why the excess cardiovascular risk in bipolar disorder? *Curr Psychiatry Rep* 2009;11:475–480.
- 23 Weiner M, Warren L, Fiedorowicz JG: Cardiovascular morbidity and mortality in bipolar disorder. *Ann Clin Psychiatry* 2011;23:40–47.
- 24 Ray WA, Chung CP, Murray KT, Hall K, Stein CM: Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med* 2009;360:225–235.
- 25 Jeste DV, Blazer D, Casey D, Meeks T, Salzman C, Schneider L, Tariot P, Yaffe K: ACNP White Paper: update on use of antipsychotic drugs in elderly persons with dementia. *Neuropsychopharmacology* 2008;33:957–970.
- 26 Haynes WG: Triglyceride-rich lipoproteins and vascular function. *Arterioscler Thromb Vasc Biol* 2003;23:153–155.
- 27 Anderson TJ, Uehata A, Gerhard MD, Meredith IT, Knab S, Delagrang D, Lieberman EH, Ganz P, Creager MA, Yeung AC, Selwyn AP: Close relation of endothelial function in the human coronary and peripheral circulations. *J Am Coll Cardiol* 1995;26:1235–1241.
- 28 Ross R: The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993;362:801–809.
- 29 Heitzer T, Schlinzig T, Krohn K, Meinertz T, Munzel T: Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. *Circulation* 2001;104:2673–2678.
- 30 Shimbo D, Grahame-Clarke C, Miyake Y, Rodriguez C, Sciacca R, Di Tullio M, Boden-Albala B, Sacco R, Homma S: The association between endothelial dysfunction and cardiovascular outcomes in a population-based multi-ethnic cohort. *Atherosclerosis* 2007;192:197–203.
- 31 Yeboah J, Folsom AR, Burke GL, Johnson C, Polak JF, Post W, Lima JA, Crouse JR, Herrington DM: Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. *Circulation* 2009;120:502–509.
- 32 Endicott J, Spitzer RL: A diagnostic interview: the schedule for affective disorders and schizophrenia. *Arch Gen Psychiatry* 1978;35:837–844.
- 33 Keller MB, Lavori PW, Friedman B, Nielsen E, Endicott J, McDonald-Scott P, Andreasen NC: The Longitudinal Interval Follow-up Evaluation: a comprehensive method for assessing outcome in prospective longitudinal studies. *Arch Gen Psychiatry* 1987;44:540–548.
- 34 Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, Solomon DA, Leon AC, Keller MB: A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry* 2003;60:261–269.
- 35 Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB: The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 2002;59:530–537.
- 36 Spitzer RL, Endicott J, Robins E: Research diagnostic criteria: rationale and reliability. *Arch Gen Psychiatry* 1978;35:773–782.
- 37 Fiedorowicz JG, Leon AC, Keller MB, Solomon DA, Rice JP, Coryell WH: Do risk factors for suicidal behavior differ by affective disorder polarity? *Psychol Med* 2009;39:763–771.
- 38 Fiedorowicz JG, Endicott J, Leon AC, Solomon DA, Keller MB, Coryell WH: Sub-threshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. *Am J Psychiatry* 2011;168:40–48.
- 39 Coryell W, Fiedorowicz J, Solomon D, Endicott J: Age transitions in the course of bipolar I disorder. *Psychol Med* 2009;39:1247–1252.
- 40 Coryell W, Solomon D, Leon A, Fiedorowicz JG, Schettler P, Judd L, Keller M: Does major depressive disorder change with age? *Psychol Med* 2009;39:1689–1695.
- 41 Guthikonda S, Sinkey CA, Haynes WG: What is the most appropriate methodology for detection of conduit artery endothelial dysfunction? *Arterioscler Thromb Vasc Biol* 2007;27:1172–1176.
- 42 Ghiadoni L, Versari D, Giannarelli C, Fatta F, Taddei S: Non-invasive diagnostic tools for investigating endothelial dysfunction. *Curr Pharm Des* 2008;14:3715–3722.
- 43 O'Rourke MF, Pauca AL: Augmentation of the aortic and central arterial pressure waveform. *Blood Press Monit* 2004;9:179–185.
- 44 Sarafidis PA, Lasaridis AN, Nilsson PM, Pikiilidou MI, Stafilas PC, Kanaki A, Kazakos K, Yovos J, Bakris GL: Validity and reproducibility of HOMA-IR, 1/HOMA-IR, QUICKI and McAuley's indices in patients with hypertension and type II diabetes. *J Hum Hypertens* 2007;21:709–716.
- 45 Verhaeverbeke I, Mets T: Drug-induced orthostatic hypotension in the elderly: avoiding its onset. *Drug Saf* 1997;17:105–118.
- 46 Gepdiremen A, Aydin N, Halici Z, Sahin O, Unal B, Aydin MD, Bakuridze K: Chronic treatment of haloperidol causes vasoconstriction on basilar arteries of rats, dose dependently. *Pharmacol Res* 2004;50:569–574.
- 47 Mannelli M, Lazzeri C, Ianni L, La Villa G, Pupilli C, Bellini F, Serio M, Franchi F: Dopamine and sympathoadrenal activity in man. *Clin Exp Hypertens* 1997;19:163–179.
- 48 McEniery CM, Spratt M, Munnery M, Yarnell J, Lowe GD, Rumley A, Gallacher J, Ben-Shlomo Y, Cockcroft JR, Wilkinson IB: An analysis of prospective risk factors for aortic stiffness in men: 20-year follow-up from the Caerphilly prospective study. *Hypertension* 2010;56:36–43.
- 49 Hoen PW, Conradi HJ, Denollet J, Martens EJ, de Jonge P: Interview-based ratings of somatic and cognitive symptoms of depression and their impact on cardiovascular prognosis. *Psychother Psychosom* 2010;79:319–320.
- 50 Lemogne C, Nabi H, Zins M, Cordier S, Ducimetiere P, Goldberg M, Consoi SM: Hostility may explain the association between depressive mood and mortality: evidence from the French GAZEL cohort study. *Psychother Psychosom* 2010;79:164–171.
- 51 Benninghoven D, Kaduk A, Wiegand U, Specht T, Kunzendorf S, Jantschek G: Influence of anxiety on the course of heart disease after acute myocardial infarction – risk factor or protective function? *Psychother Psychosom* 2006;75:56–61.
- 52 Grace SL, Abbey SE, Irvine J, Shnek ZM, Stewart DE: Prospective examination of anxiety persistence and its relationship to cardiac symptoms and recurrent cardiac events. *Psychother Psychosom* 2004;73:344–352.
- 53 Wang HX, Mittleman MA, Leineweber C, Orth-Gomer K: Depressive symptoms, social isolation, and progression of coronary artery atherosclerosis: the Stockholm Female Coronary Angiography Study. *Psychother Psychosom* 2006;75:96–102.

Erratum

In the article by Fiedorowicz 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;81:235–243 (DOI:10.1159/000334779), the first entries in the table headings of tables 3 and 4 are wrong, they inappropriately report χ^2 in the place of the β parameters.
The correct table headings of tables 3 and 4 should read:

β	SE	t	p
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