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Original Article

Association between history of psychosis and cardiovascular disease in bipolar disorder

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Objectives: To determine whether clinical features of bipolar disorder, such as history of psychosis, and cardiovascular disease (CVD) risk factors contribute to a higher risk of CVD among patients with bipolar disorder.

Methods: This cross-sectional study included a sample of 988 patients with bipolar I or bipolar II disorder or schizoaffective bipolar type confirmed by the Structured Clinical Interview for DSM-IV-TR disorders (SCID). Medical comorbidity burden was quantified utilizing the Cumulative Illness Severity Rating Scale (CIRS). This 13-item organ-based scale includes cardiac disease severity quantification. Confirmed by medical record review, patients who scored 1 (*current mild or past significant problem*) or higher in the cardiac item were compared by logistic regression to patients who scored 0 (*no impairment*), adjusting for CVD risk factors that were selected using a backwards stepwise approach or were obtained from the literature.

Results: In a multivariate model, age [odds ratio (OR) = 3.03, 95% confidence interval (CI): 1.66–5.54, $p < 0.0001$], hypertension (OR = 2.43, 95% CI: 1.69–3.55, $p < 0.0001$), and history of psychosis (OR = 1.48, 95% CI: 1.03–2.13, $p = 0.03$) were associated with CVD. When CVD risk factors from the literature were added to the analysis, age (OR = 3.19, 95% CI: 1.67–6.10, $p = 0.0005$) and hypertension (OR = 2.46, 95% CI: 1.61–3.76, $p < 0.01$) remained significant, with psychosis being at the trend level (OR = 1.43, 95% CI: 0.96–2.13, $p = 0.08$).

Conclusions: The phenotype of psychotic bipolar disorder may reflect higher illness severity with associated cardiac comorbidity. Further studies are encouraged to clarify the effect of the disease burden (i.e., depression), lifestyle, and treatment interventions (i.e., atypical antipsychotics) on this risk association.

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Compared to the general population, life expectancy is reduced by up to 20 years in patients with bipolar disorder (1). Outside of suicide and accidental death, cardiovascular (CVD) and cerebrovascular diseases are the most important contributors to mortality, with standardized mortality ratio estimates from 1.6 to 2.5 (1, 2). In general, patients with severe forms of illness (i.e., early onset illness, frequent episodes, and psychiatric comorbidity) have a higher medical illness burden (3). Psychosis is also considered a marker of illness severity and is associated with greater severity of cognitive impairment and use of antipsychotic treatment (4, 5).

As pointed out by the American Heart Association (6), there are several risk factors for CVD that have been consistently shown across different populations: smoking, high blood cholesterol, physical inactivity, overweight and obesity, diabetes, and hypertension. There is an increased prevalence of several CVD risk factors among patients with bipolar disorder compared to people without bipolar disorder: smoking (7), diabetes (8), hypertension (9), obesity (10), and low physical activity (11). Several potential explanations of this have been proposed. Atypical antipsychotics are frequently used in patients with bipolar disorder and have been associated with weight gain (10), diabetes (12), and dyslipidemia (13). In addition, acute exposure to these medications was associated with myocardial infarction in a recent case–crossover study that included patients with bipolar disorder (14). Furthermore, since these patients present with depression more frequently than mania (15, 16), they are more likely to have low physical activity and poor health habits (11). Moreover, since atherosclerosis development as well as bipolar disorder itself is associated with inflammatory processes (17–19), it has been suggested that patients with bipolar disorder may have higher degrees of atherosclerotic burden due to inflammation (20, 21). It is still not fully understood whether the higher prevalence of CVD and CVD risk factors in patients with bipolar disorder is a consequence of psychotropic medication, the illness pathophysiology, or both. The relative contribution of CVD risk factors versus factors specifically associated with bipolar disorder pathophysiology to CVD and cerebrovascular disease remains obscure and needs further investigation.

While cross-sectional studies have reported an increased risk of CVD in patients with bipolar disorder (9, 22–26), other similar studies have reported no association (27). Further evidence supporting the association comes from longitudinal studies that have used large population-based administrative databases (21). The latter studies, however, lack detailed assessment of diagnosis, clinical characteristics of bipolar disorder, and potential important CVD risk factors, such as smoking, obesity, or psychotropic medication utilization. Other longitudinal studies using multiple surveys over time (28, 29) have captured these variables; however, large proportions of the study cohort lost to follow up limit definitive conclusions. No studies have investigated whether subgroups of patients with bipolar disorder have differential risk for developing cardiovascular disease.

There is substantial public health value in identifying differential contributions of CVD risk factors (30, 31) and bipolar disorder-related risk factors for CVD in patients with bipolar disorder. This would allow the design of preventive interventions that would target CVD risk factors and also other risk factors related to the bipolar illness and may eventually decrease the mortality due to CVD in these patients. In addition, it may aid in the identification of subgroups of patients with bipolar disorder that may be at a particularly high risk of CVD and therefore may benefit greatly from treatment and/or prevention of CVD. The aim of this study, therefore, was to determine whether specific clinical characteristics of bipolar disorder, with focus on illness severity markers such as psychosis, and risk factors for CVD are associated with CVD among patients with bipolar disorder.

Participants and methods

The Mayo Clinic Bipolar Disorder Biobank was established in 2009 to collect clinical data and biospecimens from participants with bipolar disorder to enable future biomarker studies of disease risk and treatment response. Enrollment sites, each with site-specific Institutional Review Board approval in accordance with the Helsinki Declaration of 1975, included: Mayo Clinic Rochester, Lindner Center of HOPE/University of Cincinnati

Medical Center, and University of Minnesota. All participants provided written informed consent.

Participants

The sample was drawn from a larger sample of 1,150 consecutive participants age 18 through age 80 years with bipolar I or bipolar II disorder or schizoaffective disorder bipolar type who attended any of the mood clinics or inpatient units at any of the four academic study sites between 14 July 2009 and 16 September 2013 and had complete data on the outcome measure, which yielded 988 participants. Participants were excluded if were actively psychotic or suicidal.

Study measures

Bipolar disorder diagnosis assessment. We confirmed the bipolar disorder diagnosis using the Structured Clinical Interview for Diagnostic and Statistical Manual for Mental Disorders 4th version–Text Revised (SCID) administered by a clinician or a trained study coordinator and this was further confirmed by review of the electronic medical record when available.

Outcome measure

Cardiovascular disease assessment. We used a modified version of the Cumulative Illness Rating Scale (CIRS) (32) to assess the presence of current or past medical illness and illness severity. The CIRS is a valid measure of medical illness severity obtained by clinical interview or medical record review, with high inter-rater reliability (33). It has been utilized to measure medical illness burden in geriatric (34), psychiatric (35), and bipolar disorder (36) populations. In the latter study, participants with bipolar disorder and high medical illness burden were more likely to present with major depressive episodes, obsessive compulsive disorder, a greater number of mood episodes, and be prescribed a greater number of psychotropic medications. However, this study did not report clinical correlates of participants with high scores in the cardiac item specifically.

The original CIRS has 14 items that encompass 13 organ systems. We modified the scale by removing the *psychiatric illness* item, resulting in 13 items. The scale records illness severity on an ordinal scale of: 0, none: no impairment from or problem with that system; 1, mild: current mild or past significant problem; 2, moderate: impairment interferes with normal activity; 3, severe: severe problems and/or disabling impairment and/or hard to control chronic problems; and 4, extremely severe: life threatening. We defined CVD as having a score on the *cardiac* item of the CIRS of 1 or higher. Because there is no standard cutoff score available for specific CIRS items, we utilized *mild* as the cutoff since *mild* cardiac disease is most of the time clinically relevant.

Assessment of clinical variables

Lifetime (current or past) comorbid psychiatric disorders and current medications were clinically determined by a clinician or study coordinator using a structured Clinical Questionnaire (CQ) and further confirmed by medical record review when available. We analyzed medication exposure in two ways: by grouping medications (i) by their psychopharmacological class and (ii) by their weight gain liability (a list of drugs is available upon request) (37, 38). Additional psychiatric illness severity measures in this analysis included: history of psychosis, rapid cycling, number of prior suicide attempts, and composite measures of anxiety disorders and mood instability utilized in a prior study by our group (39). Briefly, the anxiety composite was a continuous variable (range 0–6), and represented the number of the following lifetime comorbid anxiety disorders: post-traumatic stress disorder, generalized anxiety disorder, social anxiety disorder, obsessive compulsive disorder, phobia, and panic disorder. Similarly, the composite measure of mood instability (range 0–5) was determined as the sum of the lifetime presence of any of the following mood instability features: rapid cycling, ultra-rapid cycling/ultradian cycling, cycle acceleration over time, increased episode severity over time, and mixed episodes.

Assessment of cardiovascular disease risk factors

Body mass index (BMI) was calculated using the standard formula [weight in kilograms/(height in meters)^2]. Obesity was defined as a BMI $\geq$ 30 kg/m^2 and morbid obesity as a BMI $\geq$ 40 kg/m^2. Smoking history was assessed in detail with a self-administered questionnaire. Hypertension was defined as CIRS scale *hypertension* item of 1 or higher.

Statistical analysis

Descriptive statistics were determined by comparing participants with bipolar disorder with CVD (BD + CVD) and without CVD (BD – CVD). Means and standard deviations are reported for

continuous variables and proportions for categorical variables. Univariate logistic regression models were used to examine the association of the demographics and clinical and psychiatric measures with CVD, and odds ratios (ORs) and p-values were calculated for all variables.

We developed multivariate logistic regression models using two methods. First, we included all significant variables and their pairwise interactions with univariate p-value < 0.10 using a backwards stepwise approach. All models also considered pairwise interactions between known CVD risk factors, age, BMI, and gender. As a sensitivity analysis, we developed additional multivariate models that included all bipolar disorder clinical variables and CVD risk factors obtained from the literature, regardless of their association with CVD in our sample. These variables included age (in quartiles to address non-normal distribution), gender, hypertension (assessed by the CIRS), BMI, and current smoking.

Results

Among the 1,101 participants who provided consent, we obtained complete CIRS scores for 988, and these participants were included in the statistical analyses (Table 1). Illness severity was high: 51.1% of participants had a history of rapid cycling, 42.6% had a history of psychosis, and 32.9% had a serious suicide attempt that required medical care. These participants had high rates of current or lifetime psychiatric comorbidity, especially anxiety disorders (65.1%), alcohol use disorder (39.5%), and drug use disorder (26.8%). Regarding CVD risk factors, the mean BMI was 30.1 ± 7.0 kg/m^2 (29.5 ± 5.4 kg/m^2 for men and 30.5 ± 7.9 kg/m^2 for women), the prevalence of obesity was 42.7% (40.5% for men and 45.8% for women), and 27% of the participants (26.2% for men and 27.5% for women) were current smokers. CVD assessed by the CIRS scale was present in 14.1% of study population (15.6% for men and 12.9% for women).

Bipolar disorder + CVD phenotype

Among the risk factors for CVD in the general population, age [OR = 1.04, 95% confidence interval (CI): 1.03–1.06] and hypertension (OR = 3.27, 95% CI: 2.30–4.66) were associated with an increased risk of CVD among participants with bipolar disorder (Table 2). There was no significant association between obesity and CVD (OR = 1.14, 95% CI: 0.80–1.64) or male gender and CVD (OR = 1.27, 95% CI: 0.90–1.79). Prior history of psychosis (OR = 1.47, 95% CI: 1.04–2.08) and the use of antidepressants that do not cause weight gain (OR = 1.41, 95% CI: 1.00–1.98) were associated with a higher risk of CVD. However, the use of any atypical antipsychotics or mood stabilizers, even when grouped by their weight gain liability, was not associated with CVD.

Multivariate regression models were developed, adjusting for all the variables significantly associated with CVD. Only age 42–53 years (OR = 2.02, 95% CI: 1.08–3.76), age $\geq$ 54 years (OR = 3.03, 95% CI: 1.66–5.54), hypertension (OR = 2.43, 95% CI: 1.69–3.55), and history of psychosis (OR = 1.48, 95% CI: 1.03–2.13) remained significantly associated with CVD among participants with bipolar disorder (Table 3). Interactions of these variables with age, gender and BMI were not statistically significant (data not shown).

We further explored whether additional CVD risk factors that are also associated with bipolar disorder affected our results. In a multivariate model that included age, gender, current smoking, BMI, and CIRS hypertension ≥ 1 as covariates, history of psychosis remained only as a trend (OR = 1.43, 95% CI: 0.96–2.13).

Discussion

Our data have suggested that psychosis may be associated with an increased risk of CVD among patients with bipolar disorder, after adjusting for age and hypertension. There was insufficient evidence to confirm an association between gender, obesity, smoking, or the use of psychotropic medication and CVD. However, when we included additional CVD risk factors from the literature, psychosis was associated with CVD only at the trend level. While a limitation of our findings, interestingly our group has found an increased risk of myocardial infarction and stroke among patients with bipolar disorder and a history of psychosis in a retrospective cohort study after adjusting for the same covariates (M. L. Prieto, personal communication). Moreover, there is a well-established increased risk of CVD in patients with other psychotic illnesses [i.e., schizophrenia (40)] Therefore, this potential association needs further study and replication.

There are a number of potential explanations for this possible association. Psychosis is generally considered a marker of illness severity in bipolar disorder (4) associated with higher cognitive impairment (5) and use of antipsychotic treatment. These patients may be less prone to engage in exercise and adhere to a healthy life-

Table 1. Clinical characteristics of the full sample (n = 1,101)

	n (%) or mean ± SD
Demographics	
Age, years	42.4 ± 15.1
Gender, female	609 (60.0)
Race/ethnicity	
Caucasian	992 (89.8)
Black	24 (2.2)
Other/mixed/unknown	82 (7.4)
Hispanic	7 (0.6)
Marital status	
Married/widowed/life partner	369 (49.6)
Single/separated/divorced	375 (50.4)
Education	
≤ High school	165 (16.1)
Some college	469 (45.7)
Partial or four-year college	688 (67.0)
Clinical features	
Bipolar I disorder	791 (71.6)
Anxiety disorder	704 (65.1)
PTSD	281 (26.5)
Alcohol abuse/dependence	421 (39.5)
Drug abuse/dependence	276 (26.8)
Binge eating disorder	98 (9.4)
Any eating disorder	164 (15.8)
Illness severity markers	
History of psychosis	462 (42.6)
Rapid cycling	559 (51.1)
≥1 suicide attempt	359 (32.9)
Anxiety sum[a]	1.6 ± 1.4
PTSD	281 (26.5)
GAD	540 (50.8)
SAD	266 (25.3)
OCD	164 (15.5)
Phobia	112 (10.6)
Panic disorder	338 (32.0)
Mood instability sum[b]	1.5 ± 1.4
Rapid cycling	559 (51.1)
Ultrarapid/ultradian	296 (27.2)
Cycle acceleration	271 (25.0)
Increased severity	350 (32.2)
Mixed	130 (15.5)
Cardiovascular risk factors	
Current smoker	271 (27.0)
Nicotine abuse/dependence	410 (38.6)
BMI	30.1 ± 7.0
Obesity (BMI ≥ 30)	434 (42.7)
Morbid obesity (BMI ≥ 40)	102 (10.0)
Medications at baseline	
Antidepressants	512 (46.3)
Mood stabilizers	784 (71.0)
Atypical antipsychotics	512 (46.5)
Lithium	347 (48.7)
Total no. of medication classes	1.6 ± 0.9
Total no. of medications	2.0 ± 1.1
CIRS	
CIRS total score	4.1 ± 3.6
Cardiac item ≥ 1	152 (14.1)
Hypertension item ≥ 1	300 (27.8)

All psychiatric comorbidities refer to lifetime diagnosis unless otherwise specified. Anxiety disorders include generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), social anxiety disorder (SAD), specific phobia, and panic disorder.

BMI = body mass index; CIRS = Cumulative Illness Rating Scale; SD = standard deviation.

[a]Anxiety sum is the sum (range 0–5) of the following lifetime comorbid anxiety disorders: posttraumatic stress disorder (PTSD), GAD, SAD, OCD, phobia, and panic disorder.

[b]Mood instability sum is the sum (range 0–6) of the lifetime presence of rapid cycling, ultrarapid/ultradian cycling, cycle acceleration over time, increased episode severity over time, and mixed episodes.

style, with subsequent increased BMI and higher CVD risk. Furthermore, a number of clinical factors may explain this association between psychotic bipolar disorder and CVD as well as between schizophrenia and CVD. First, high rates of smoking have been consistently observed in patients with psychotic illness (41), and also in patients with bipolar disorder and psychosis (42). Secondly, patients with bipolar disorder with psychosis are very likely to be treated with first-line atypical antipsychotic medications, treatments associated with weight gain, diabetes, and myocardial infarction (14, 43, 44). However, our study, after adjusting for CVD risk factors, did not find an association between atypical antipsychotic medication and CVD. Finally, patients with bipolar disorder with a history of psychosis may have similar genetic risk factors to patients with schizophrenia-spectrum disorders.

In genome-wide association studies (GWASs) combining patients with schizophrenia and bipolar disorder, genetic variants in the voltage-dependent calcium channel (CACNA1C), ankyrin-G (ANK3), inter-alpha-trypsin inhibitor heavy chain H3-H4 (ITIH3-ITIH4), Interferon-induced protein 44-like (IFI44L), major histocompatability complex (MHC) regions, tetra-tricopeptide-repeat and ankyrin repeat containing 1 (TRANK1), MAD1 mitotic arrest deficient-like 1 yeast (MAD1L1), phosphatidyl-4-phosphate 3-kinase catalytic subunit 2 alpha (PIK3C2A) genes were shared between the two disorders (45, 46). Of note, the gene ITIH3 encodes an inter-alpha-trypsin inhibitor that belongs to the family of plasma serine protease inhibitors, which are associated with proinflammatory states (47). Bipolar disorder (18, 19), schizophrenia (48), and cardiovascular disease (17) have all been associated with increased inflammation and a functional variant of the ITIH3 gene specifically has been associated with myocardial infarction (49). These shared genetic variants in the

Table 2. Comparison of clinical characteristics between participants with bipolar disorder (BD) with and without cardiovascular disease (CVD)

	BD + CVD	BD − CVD		
Variables	n (%) or mean ± SD	n (%) or mean ± SD	OR (95% CI)	p-value
Demographics				
Age, years	50.8 ± 15.9	41.1 ± 14.5	1.04 (1.03–1.06)	<0.0001
Gender, male	68 (44.7)	361 (38.9)	1.27 (0.90–1.79)	0.18
Clinical features				
Bipolar I disorder	107 (70.4)	665 (71.7)	0.94 (0.64–1.37)	0.73
Anxiety disorder	105 (70.0)	588 (64.3)	1.29 (0.89–1.37)	0.18
PTSD	43 (28.9)	232 (26.0)	1.16 (0.79–1.70)	0.46
Alcohol abuse/dependence	58 (38.9)	355 (39.4)	0.98 (0.69–1.40)	0.91
Drug abuse/dependence	40 (27.6)	230 (26.7)	1.05 (0.71–1.56)	0.81
Binge eating disorder	13 (8.8)	83 (9.4)	0.94 (0.51–1.73)	0.83
Anorexia/bulimia	12 (8.1)	86 (9.8)	0.82 (0.43–1.53)	0.53
Illness severity markers				
History of psychosis	76 (50.7)	377 (42.2)	1.47 (1.04–2.08)	0.03
Rapid cycling	86 (57.0)	464 (50.5)	1.30 (0.92–1.84)	0.14
≥1 suicide attempt	43 (28.5)	306 (33.3)	0.80 (0.55–1.17)	0.24
Anxiety sum[a]	1.7 ± 1.4	1.6 ± 1.4	1.06 (0.94–1.19)	0.38
Mood instability sum[b]	1.5 ± 1.4	1.5 ± 1.4	1.01 (0.88–1.16)	0.94
CVD risk factors				
Nicotine abuse/dependence	63 (42.9)	338 (37.7)	1.24 (0.87–1.77)	0.23
Current smoker	31 (22.1)	236 (28.1)	0.73 (0.48–1.12)	0.14
BMI	30.3 ± 6.8	30.0 ± 7.1	1.01 (0.98–1.03)	0.62
Obesity (BMI ≥ 30)	64 (46.4)	370 (43.1)	1.14 (0.80–1.64)	0.48
Morbid obesity (BMI ≥ 40)	14 (10.1)	86 (10.0)	1.01 (0.56–1.84)	0.96
CIRS hypertension ≥ 1	76 (50.7)	221 (23.9)	3.27 (2.30–4.66)	<0.0001
Medications at enrollment				
Lithium	44 (43.1)	294 (49.6)	0.77 (0.51–1.18)	0.23
Atypical antipsychotic: no WG	24 (15.8)	155 (16.7)	0.93 (0.58–1.49)	0.77
Atypical antipsychotic: WG	46 (30.3)	306 (33.0)	0.88 (0.61–1.28)	0.50
Mood stabilizer: no WG	49 (32.2)	308 (33.2)	0.96 (0.66–1.38)	0.81
Mood stabilizer: WG	69 (45.4)	433 (46.7)	0.95 (0.67–1.34)	0.76
Antidepressant: no WG	78 (51.3)	397 (42.8)	1.41 (1.00–1.98)	0.05
Antidepressant: WG	5 (3.3)	33 (3.6)	0.92 (0.35–2.40)	0.87
Any atypical antipsychotic	68 (44.7)	436 (47.0)	0.91 (0.65–1.29)	0.60
Any mood stabilizer	105 (69.1)	662 (71.4)	0.99 (0.62–1.30)	0.56
Any antidepressant	81 (53.3)	421 (45.4)	1.37 (0.97–1.93)	0.07
Any of the above: WG	89 (58.6)	549 (59.2)	0.97 (0.69–1.38)	0.88
Sum of medication classes	2.0 ± 1.2	1.6 ± 0.9	1.05 (0.86–1.28)	0.66
Total no. of medications	2.0 ± 1.2	1.9 ± 1.1	1.08 (0.92–1.28)	0.34

The odds ratio (OR) for age refers to the odds of cardiac disease per one-year increase in age. All psychiatric comorbidities refer to lifetime diagnosis unless otherwise specified. Anxiety disorders include generalized anxiety disorder, obsessive compulsive disorder, social anxiety disorder, specific phobia, and panic disorder.

BD + CVD = bipolar disorder with cardiovascular disease (CVD); BD − CVD = bipolar disorder without CVD; BMI = body mass index; CI = confidence interval; CIRS = Cumulative Illness Rating Scale; no WG = no weight gain liability; SD = standard deviation; WG = weight gain liability.

[a]Anxiety sum is the sum (range 0–5) of the following lifetime comorbid anxiety disorders: posttraumatic stress disorder (PTSD), generalized anxiety disorder, social anxiety disorder, obsessive compulsive disorder, phobia, and panic disorder.

[b]Mood instability sum is the sum (range 0–6) of the lifetime presence of mixed episodes, rapid cycling, ultrarapid/ultradian cycling, cycle acceleration over time, and increased episode severity over time.

ITIH3 gene, associated with the risk of both bipolar disorder and schizophrenia, may potentially have a pleiotropic effect and also provide a risk for CVD in these populations.

Different pathophysiological mechanisms may underlie CVD in patients with bipolar disorder as compared to CVD in people without bipolar disorder. Patients with bipolar disorder show abnormal levels of circulating pro- and anti-inflammatory cytokines (18, 19). Since atherosclerosis is mediated by inflammatory processes (17), these cytokine alterations seen in bipolar disorder may increase the risk of atherosclerosis and subsequent CVD over time (20), eventually making CVD a marker of cumulative inflammation in patients with bipolar disorder. However, the lack of

Table 3. Variables associated with cardiovascular disease among participants with bipolar disorder using two multivariate logistic regression models

Variables	OR	95% CI	p-value
Model 1			
Age, years			
Q1 (<29)	Ref.		
Q2 (29–41)	1.33	0.69–2.56	0.39
Q3 (42–53)	2.02	1.08–3.76	0.03
Q4 (>54)	3.03	1.66–5.54	0.0003
CIRS hypertension ≥ 1	2.43	1.69–3.55	<0.0001
Psychosis	1.48	1.03–2.13	0.03
Model 2			
Age, years			
Q1 (<29)	Ref.		
Q2 (29–41)	1.24	0.60–2.56	0.56
Q3 (42–53)	1.98	1.00–3.90	0.05
Q4 (>54)	3.19	1.67–6.10	0.0005
Gender, male	1.24	0.83–1.85	0.30
Current smoker	0.85	0.53–1.38	0.51
BMI	1.00	0.97–1.03	0.75
CIRS hypertension ≥ 1	2.46	1.61–3.76	<0.0001
Psychosis	1.43	0.96–2.13	0.08

Model 1 refers to a backward stepwise method for covariate selection, which adjusted for age, Cumulative Illness Rating Scale (CIRS) hypertension ≥1, and history of psychosis. Model 2 refers to a multivariate model that included all risk factors for cardiovascular disease (CVD) obtained from the literature, regardless of their associations with CVD in our sample. It adjusted for age, gender, current smoking, body mass index (BMI), CIRS hypertension ≥ 1, and history of psychosis. CI = confidence interval; OR = odds ratio.

association of some of the risk factors for CVD may have been driven by a relatively small sample of patients with bipolar disorder and CVD with low statistical power, in the context of a population already enriched for CVD risk factors (50). Conversely, the evidence of vascular dysfunction (a proxy of atherosclerotic disease) in these patients has been conflicting. One study that investigated vascular function (assessed by flow-mediated dilation, a measure of endothelial function) in 35 patients with mood disorders (57% bipolar disorder) found that manic symptom burden was associated with lower flow-mediated dilation (a marker of endothelial dysfunction), after adjusting for gender, age, and smoking (51). A second study conducted in adolescents with bipolar disorder found an association between CVD risk factors and
non-invasive markers of endothelial dysfunction (carotid intima media thickness and flow-mediated dilation) (52). In contrast, another study conducted in 27 young patients with bipolar disorder and 27 age- and gender-matched controls (mean age 32 years; 41% women) did not find a significantly lower flow-mediated dilation in patients compared to controls (53). This evidence, limited by small sample sizes and lack of adequate controls, warrants further study of endothelial and vascular health in patients with bipolar disorder (54).

We observed a higher prevalence of CVD in this sample (14.1%) as compared to prior studies (9, 26) that reported a CVD prevalence of roughly 10%. This difference may be explained by the assessment method, which did not include verification of the CVD diagnosis by a cardiologist or laboratory testing in all the participants. Thus, there may be false positives among the participants who reported a CVD diagnosis, with a subsequent overestimation of the prevalence.

We did not find evidence of a gender difference in the risk of CVD in subjects with bipolar disorder, which replicates the findings of some (2, 55) but not all previous studies (56). Overall, women experience lower prevalence rates of ischemic heart disease and myocardial infarction, but higher mortality rates due to these conditions (6). The lack of a lower prevalence of CVD morbidity in our female cohort with bipolar disorder (versus men with bipolar disorder) may be due to a greater prevalence and effect of depressive symptoms on the risk of CVD in women compared to men (57, 58). Woman compared to men may have greater risk for CVD mortality by both increased prevalence rates of depression and factors related to primary cardiac disease, it's recognition and access/utilization of interventional therapies particularly in women under age 60 years (59). However, this relationship in bipolar women versus depressed women in general, is virtually unstudied. We still lack sufficient studies focused on the effect of gender on the risk of CVD in patients with bipolar disorder.

Strengths and limitations

This study has a number of strengths. First, the detailed assessment of the bipolar disorder phenotype allowed the investigation of bipolar disorder-specific subphenotypes within patients with bipolar disorder and CVD, such as a history of psychosis or rapid cycling. Second, two models of multivariate logistic regression were utilized based on our data and CVD risk factors obtained from the literature.

These findings are limited by the cross-sectional design, which does not allow the direction of the association between the clinical features and the BD + CVD phenotype to be determined. We lacked a comparison group without bipolar disorder. In addition, while the assessment of CVD was conducted using a medical illness severity scale, it

did not provide detailed information on specific CVDs nor allow for validation of the CVD diagnoses using diagnostic criteria or laboratory testing. Furthermore, comorbid psychiatric disorders and clinical characteristics were not ascertained using validated measures. We were not able to assess all potential risk factors for CVD, such as lack of physical activity, dyslipidemia or diabetes. Therefore, there may still be residual confounding in our multivariate analyses. The relatively small sample size for patients with bipolar disorder and CVD may not have provided adequate statistical power to fully demonstrate a lack of association between several CVD risk factors and CVD among patients with bipolar disorder. In addition, the relatively small sample size and the use of additional covariates may have explained why the association between psychosis and CVD in our first analysis did not remain significant after adding several covariates. Finally, medication use was self-reported, did not include dosage or compliance, and was limited to current use.

This study provided evidence to suggest that CVD phenotypes in bipolar disorder may be specifically associated with a history of psychosis. From the public health standpoint, this study may provide preliminary evidence of a subgroup of patients with psychotic bipolar disorder who are at a higher risk of CVD and may specifically benefit from interventions to decrease CVD risk factors. More importantly, CVD preventive measures may be established at the first psychotic episode in patients with bipolar disorder and thus may decrease CVD comorbidity and mortality. This preliminary association should be confirmed in future clinical studies and also in investigations on cardiovascular function and cardiovascular blood biomarkers in patients with psychotic bipolar disorder.

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References

1. Laursen TM, Wahlbeck K, Hällgren J et al. Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic Countries. PLoS ONE 2013; 8: e67133.
2. Westman J, Hallgren J, Wahlbeck K, Erlinge D, Alfredsson L, Osby U. Cardiovascular mortality in bipolar disorder: a population-based cohort study in Sweden. BMJ Open 2013; 3: e002373.
3. Magalhaes PV, Kapczinski F, Nierenberg AA et al. Illness burden and medical comorbidity in the Systematic Treatment Enhancement Program for Bipolar Disorder. Acta Psychiatr Scand 2012; 125: 303–308.
4. Tohen M, Zarate CA Jr, Hennen J et al. The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. Am J Psychiatry 2003; 160: 2099–2107.
5. Martinez-Aran A, Torrent C, Tabares-Seisdedos R et al. Neurocognitive impairment in bipolar patients with and without history of psychosis. J Clin Psychiatry 2008; 69: 233–239.
6. Lloyd-Jones D, Adams RJ, Brown TM et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation 2010; 121: e46–e215.
7. Waxmonsky JA, Thomas MR, Miklowitz DJ et al. Prevalence and correlates of tobacco use in bipolar disorder: data from the first 2000 participants in the Systematic Treatment Enhancement Program. Gen Hosp Psychiatry 2005; 27: 321–328.
8. Regenold WT, Thapar RK, Marano C, Gavirneni S, Kondapavuluru PV. Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with bipolar I affective and schizoaffective disorders independent of psychotropic drug use. J Affect Disord 2002; 70: 19–26.
9. Goldstein BI, Fagiolini A, Houck P, Kupfer DJ. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. Bipolar Disord 2009; 11: 657–662.
10. McElroy SL, Frye MA, Suppes T et al. Correlates of overweight and obesity in 644 patients with bipolar disorder. J Clin Psychiatry 2002; 63: 207–213.
11. Kilbourne AM, Rofey DL, McCarthy JF, Post EP, Welsh D, Blow FC. Nutrition and exercise behavior among

patients with bipolar disorder. Bipolar Disord 2007; 9: 443–452.
12. Guo JJ, Keck PE Jr, Corey-Lisle PK et al. Risk of diabetes mellitus associated with atypical antipsychotic use among Medicaid patients with bipolar disorder: a nested case–control study. Pharmacotherapy 2007; 27: 27–35.
13. Olfson M, Marcus SC, Corey-Lisle P, Tuomari AV, Hines P, L'Italien GJ. Hyperlipidemia following treatment with antipsychotic medications. Am J Psychiatry 2006; 163: 1821–1825.
14. Lin ST, Chen CC, Tsang HY et al. Association between antipsychotic use and risk of acute myocardial infarction: a nationwide case-crossover study. Circulation 2014; 130: 235–243.
15. Judd LL, Akiskal HS, Schettler PJ et al. 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.
16. Judd LL, Akiskal HS, Schettler PJ et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002; 59: 530–537.
17. Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol 2009; 54: 2129–2138.
18. Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. J Clin Psychiatry 2009; 70: 1078–1090.
19. Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. Biol Psychiatry 2013; 74: 15–25.
20. Leboyer M, Soreca I, Scott J et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? J Affect Disord 2012; 141: 1–10.
21. Prieto ML, Cuéllar-Barboza AB, Bobo WV et al. Risk of myocardial infarction and stroke in bipolar disorder: a systematic review and exploratory meta-analysis. Acta Psychiatr Scand 2014; 130: 342–353.
22. Kilbourne AM, Brar JS, Drayer RA, Xu X, Post EP. Cardiovascular disease and metabolic risk factors in male patients with schizophrenia, schizoaffective disorder, and bipolar disorder. Psychosomatics 2007; 48: 412–417.
23. 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.
24. Garcia-Portilla MP, Saiz PA, Bascaran MT et al. Cardiovascular risk in patients with bipolar disorder. J Affect Disord 2009; 115: 302–308.
25. Ghadirian AM, Engelsmann F. Somatic illness in manic-depressive and schizophrenic patients. J Psychosom Res 1985; 29: 281–286.
26. Kilbourne AM, Cornelius JR, Han X et al. Burden of general medical conditions among individuals with bipolar disorder. Bipolar Disord 2004; 6: 368–373.
27. Smith DJ, Martin D, McLean G, Langan J, Guthrie B, Mercer SW. Multimorbidity in bipolar disorder and undertreatment of cardiovascular disease: a cross sectional study. BMC Med 2013; 11: 263.
28. Ramsey CM, Leoutsakos JM, Mayer LS, Eaton WW, Lee HB. History of manic and hypomanic episodes and risk of incident cardiovascular disease: 11.5 year follow-up from the Baltimore Epidemiologic Catchment Area Study. J Affect Disord 2010; 125: 35–41.
29. Ramsey CM, Spira AP, Mojtabai R, Eaton WW, Roth K, Lee HB. Lifetime manic spectrum episodes and all-cause mortality: 26-year follow-up of the NIMH epidemiologic catchment area study. J Affect Disord 2013; 151: 337–342.
30. Greenland P, Knoll MD, Stamler J et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA 2003; 290: 891–897.
31. Yusuf S, Hawken S, Ôunpuu S et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. Lancet 2004; 364: 937–952.
32. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc 1968; 16: 622–626.
33. Hudon C, Fortin M, Vanasse A. Cumulative Illness Rating Scale was a reliable and valid index in a family practice context. J Clin Epidemiol 2005; 58: 603–608.
34. Parmelee PA, Thuras PD, Katz IR, Lawton MP. Validation of the Cumulative Illness Rating Scale in a geriatric residential population. J Am Geriatr Soc 1995; 43: 130–137.
35. Miller MD, Paradis CF, Houck PR et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. Psychiatry Res 1992; 41: 237–248.
36. Kemp DE, Sylvia LG, Calabrese JR et al. General medical burden in bipolar disorder: findings from the LiTMUS comparative effectiveness trial. Acta Psychiatr Scand 2014; 129: 24–34.
37. Roerig JL, Steffen KJ, Mitchell JE. Atypical antipsychotic-induced weight gain: insights into mechanisms of action. CNS Drugs 2011; 25: 1035–1059.
38. Fagiolini A, Chengappa KN. Weight gain and metabolic issues of medicines used for bipolar disorder. Curr Psychiatry Rep 2007; 9: 521–528.
39. McElroy SL, Crow S, Biernacka JM et al. Clinical phenotype of bipolar disorder with comorbid binge eating disorder. J Affect Disord 2013; 150: 981–986.
40. Fan Z, Wu Y, Shen J, Ji T, Zhan R. Schizophrenia and the risk of cardiovascular diseases: a meta-analysis of thirteen cohort studies. J Psychiatr Res 2013; 47: 1549–1556.
41. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr Res 2005; 76: 135–157.
42. Hartz SM, Pato CN, Medeiros H et al. Comorbidity of severe psychotic disorders with measures of substance use. JAMA Psychiatry 2014; 71: 248–254.
43. Kessing LV, Thomsen AF, Mogensen UB, Andersen PK. Treatment with antipsychotics and the risk of diabetes in clinical practice. Br J Psychiatry 2010; 197: 266–271.
44. Bobo WV, Cooper WO, Stein C et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. JAMA Psychiatry 2013; 70: 1067–1075.
45. Schizophrenia Psychiatric Genome-Wide Assocaition Study (GWAS) Consortium. Genome-wide association study identifies five new schizophrenia loci. Nat Genet 2011; 43: 969–976.
46. Ruderfer DM, Fanous AH, Ripke S et al. Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia. Mol Psychiatry 2014; 19: 1017–1024.
47. Zhuo L, Hascall VC, Kimata K. Inter-alpha-trypsin inhibitor, a covalent protein-glycosaminoglycan-protein complex. J Biol Chem 2004; 279: 38079–38082.
48. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry 2008; 63: 801–808.

49. Ebana Y, Ozaki K, Inoue K et al. A functional SNP in ITIH3 is associated with susceptibility to myocardial infarction. J Hum Genet 2007; 52: 220–229.
50. Vancampfort D, Vansteelandt K, Correll CU et al. Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. Am J Psychiatry 2013; 170: 265–274.
51. Fiedorowicz JG, Coryell WH, Rice JP, Warren LL, Haynes WG. 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.
52. Hatch J, Collinger K, Moody A, Olowoyeye O, Zhan JQ, Goldstein BI. Non-invasive vascular imaging is associated with cardiovascular risk factors among adolescents with bipolar disorder. Pediatr Cardiol 2015; 36: 158–164.
53. Murray DP, Metz NS, Haynes WG, Fiedorowicz JG. Vascular function is not impaired early in the course of bipolar disorder. J Psychosom Res 2012; 72: 195–198.
54. Fiedorowicz JG, Solomon DA, Endicott J et al. Manic/hypomanic symptom burden and cardiovascular mortality in bipolar disorder. Psychosom Med 2009; 71: 598–606.
55. Huang KL, Su TP, Chen TJ, Chou YH, Bai YM. Comorbidity of cardiovascular diseases with mood and anxiety disorder: a population based 4-year study. Psychiatry Clin Neurosci 2009; 63: 401–409.
56. Callaghan RC, Khizar A. The incidence of cardiovascular morbidity among patients with bipolar disorder: a population-based longitudinal study in Ontario, Canada. J Affect Disord 2010; 122: 118–123.
57. Haukkala A, Konttinen H, Uutela A, Kawachi I, Laatikainen T. Gender differences in the associations between depressive symptoms, cardiovascular diseases, and all-cause mortality. Ann Epidemiol 2009; 19: 623–629.
58. Hayes SN. Broken-hearted women: the complex relationship between depression and cardiovascular disease. Womens Health 2009; 5: 709–725.
59. Mallik S, Spertus JA, Reid KJ et al. Depressive symptoms after acute myocardial infarction: evidence for highest rates in younger women. Arch Intern Med 2006; 166: 876–883.