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Original Article

Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States

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Objective: Despite ample evidence of excess cardiovascular mortality in bipolar disorder (BD), few studies have demonstrated increased prevalence of cardiovascular disease (CVD) and/or hypertension (HTN) in BD. We therefore examined this topic in a representative epidemiologic sample.

Method: The 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions was used to determine whether prevalence of physician-diagnosed CVD and HTN is elevated among subjects with lifetime bipolar I disorder (BD-I), and whether CVD and HTN are prevalent at earlier ages among subjects with BD-I.

Results: The age-, race-, and sex-adjusted prevalence of CVD was significantly greater among subjects with BD-I versus controls [odds ratio (OR) = 4.95, 95% confidence interval (CI): 4.27–5.75] and versus subjects with major depressive disorder [(MDD); OR = 1.80, 95% CI: 1.52–2.14], as was the prevalence of HTN (OR = 2.38, 95% CI: 2.16–2.62 versus controls, OR = 1.44, 95% CI: 1.30–1.61 versus MDD; $p < 0.0001$ for all). Controlling additionally for marital status, education, income, obesity, smoking, anxiety disorders, and substance use disorders did not substantially alter these findings. The mean age of BD-I subjects with CVD and HTN was 14 and 13 years younger, respectively, than controls with CVD and HTN.

Conclusions: Adults with BD-I are at increased risk of CVD and HTN, prevalent over a decade earlier than non-BD adults. Strategies are needed to prevent excessive and premature cardiovascular burden in BD-I.

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> *Not at all infrequently and in comparative youth arteriosclerosis is present.*
>
> Emil Kraepelin, 1921 (1, p. 50)

Bipolar disorder (BD) is associated with increased and premature mortality due to medical causes, most notably cardiovascular disease (CVD) (2). Excess cardiovascular mortality in BD has been documented for over 70 years, and existed prior to the advent of atypical antipsychotics, and also prior to the use of tricyclic antidepressants and lithium (3, 4). Overall, there appears to be a 1.5- to 2.5-fold increased cardiovascular mortality in BD (2, 3).

Precursors of cardiovascular mortality, such as CVD and hypertension (HTN), are among the most common medical conditions in BD (5), and

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are major contributors to increased treatment costs in BD (6). Increased prevalence of HTN in BD has been found in inpatient (7), outpatient (8–11), and administrative database (12, 13) treatment-seeking samples. Other than HTN, there is evidence for multiple sources of CVD risk among patients with BD, including hyperlipidemia (5), diabetes (14), obesity (15), smoking (16), substance use disorders (SUD) (17), sedentary lifestyle (18), endothelial dysfunction (19), and inflammation (20).

Somewhat surprisingly given these CVD risk factors and the clearly elevated risk of cardiovascular mortality in BD, there is limited evidence regarding the association between BD and CVD. Previous studies of treatment-seeking samples have been constrained by focusing solely on myocardial infarction (13), and by including primarily males (5, 21). Given the known biases of treatment-seeking samples (22), epidemiologic data are needed to determine the scope of the problem of CVD and HTN in a representative sample of subjects with BD. Previous epidemiologic studies have been constrained by modest numbers of subjects with BD (23), and by limiting analyses to subjects aged ≥ 60 years (24). The latter is problematic in light of evidence that CVD may be common among subjects < 60 years of age (25), and that the risk of CVD and cardiovascular mortality conferred by BD may be strongest in younger age groups (2).

Therefore, we examined CVD and HTN in the full age range of subjects with bipolar I disorder (BD-I) and tested the following hypotheses: (i) after controlling for demographic variables, subjects with BD-I will have significantly higher risk of CVD and HTN compared to subjects without BD-I; and (ii) among subjects with CVD and HTN, those with BD-I will be significantly younger than those without BD-I. We also set out to compare the prevalence of CVD and HTN among subjects with BD-I versus those with major depressive disorder (MDD).

Methods

Sample

Subjects were identified from among the respondents of the cross-sectional 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (17). The NESARC is a representative sample of the United States conducted by the National Institute on Alcoholism and Alcohol Abuse (NIAAA). A detailed description of the NESARC can be found elsewhere (17). Briefly, 43,093 non-institutionalized civilian respondents, ≥18 years, completed face-to-face computer-assisted personal interviews. The overall survey response rate was 81% (17). For this analysis, respondents were divided into two groups based on the lifetime presence versus absence of BD-I.

Assessment

Medical diagnoses. NESARC respondents were asked about the presence of 10 medical conditions in the past year. Of these, the current study examined hypertension, arteriosclerosis, angina, and myocardial infarction. If the condition was endorsed, respondents were asked whether a physician or other health professional made the diagnosis. Only diagnoses made by physicians or health professionals were considered present for the purpose of this study. CVD was considered present if past-year diagnosed arteriosclerosis, angina, or myocardial infarction were endorsed. In addition, obesity was defined as having a body mass index [(BMI); weight in kilograms divided by square of height in meters] of ≥ 30 kg/m^2.

Psychiatric diagnoses. The NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV) was used to generate the diagnoses presented in this report. Subjects were considered to have BD-I if they had a lifetime manic or mixed episode that was not secondary to substance use or a medical condition. The AUDADIS-IV explicitly addresses the temporal contiguity of manic and depressive episodes with substance use, when present. BD-I was classified as independent of substance use in the following circumstances: (i) the respondent abstained from alcohol and drug use in the 12 months preceding the assessment; (ii) the episode(s) did not occur in the context of alcohol or drug intoxication or withdrawal; (iii) the episode(s) occurred before alcohol or drug intoxication or withdrawal; (iv) the episode(s) began after alcohol or drug intoxication or withdrawal, but persisted for more than one month after the cessation of alcohol or drug intoxication or withdrawal. Only cases in which mania occurred independently of substance use were included in the BD-I group analyses. The same definition was employed for MDD and anxiety disorders. All mood and anxiety disorders due to general medical conditions, defined as occurring solely when the respondent was physically ill or recovering from being physically ill and a physician or other health professional indicated that the episode was related to the illness or medical condition, were also ruled out.

The anxiety disorders included in the present study were social phobia, panic disorder (with and without agoraphobia), and generalized anxiety disorder. The NESARC provides information regarding nicotine use and regarding abuse and dependence of alcohol and illicit drugs. For the purpose of this report, a category of SUD was computed. Subjects with a lifetime prevalence of abuse or dependence of alcohol or any substance other than nicotine or caffeine were considered to have a SUD. The AUDADIS-IV diagnoses of SUD and of mood and anxiety disorders have demonstrated adequate reliability and validity (17, 26, 27). For analyses, subjects were divided into three groups: (i) subjects with lifetime BD-I (n = 1,411), (ii) subjects with lifetime MDD (n = 6,831), and (iii) controls with neither of these conditions (n = 34,851; controls could have non-MDD, non-BD-I diagnoses including anxiety disorders and SUD). We included all subjects with a lifetime diagnosis of BD-I because each of the putative links between BD-I and CVD/HTN (including medications, obesity, smoking, sedentary lifestyle, inflammation) would be hypothesized to cumulatively assert their influence through the entire course of BD-I, irrespective of whether the individual experienced a manic or mixed episode in the past year. We did not include in the BD-I group subjects with bipolar II disorder due to the fact that evidence for the reliability of this diagnosis in the NESARC is lacking.

Statistical analyses

Standard parametric analyses were conducted to examine between-group differences in demographic variables. Chi-square tests for contingency tables were computed to compare the distribution of the proportions across groups, and regression analyses were used to compare these groups on dimensional measures. Chi-square analysis was used to address our first hypothesis, that physician-diagnosed CVD and HTN are significantly more prevalent among subjects with, versus without, lifetime BD-I. Demographic variables with significant between-group differences were included in a logistic regression analysis to examine the independent contribution of BD-I to the variance in CVD and HTN. Given the large sample size, significance was set at $\alpha < 0.01$. Regression analysis was computed in order to test our second hypothesis, that among subjects with CVD and HTN, those with BD-I will be significantly younger than those without BD-I. In order to provide nationally representative estimates and account for the complex survey design, we used the SURVEY procedures in the SAS statistical package (SAS Institute, Inc., Cary, NC, USA) for all analyses, with appropriate weighting. Standard errors and 95% confidence intervals (CI) were estimated using Taylor series linearization to adjust for the design effects of complex sample surveys such as the NESARC.

Results

Hypothesis 1: Physician-diagnosed CVD and HTN are more common in BD-I

Table 1 contains information regarding between-group differences in demographic and clinical variables among subjects with BD-I, subjects with MDD, and controls. The prevalence of CVD was significantly greater among subjects with BD-I as compared to subjects with MDD, which was in turn significantly greater as compared to controls (10.1% versus 8.0% versus 4.9%, respectively; $\chi^2 = 238.04$, df = 2, $p < 0.0001$). The prevalence of HTN was significantly greater among subjects with BD-I (22.1%) and MDD (21.6%) as compared to controls (18.4%; $\chi^2 = 8.98$, $p < 0.0001$); however, the difference between BD-I and MDD subjects was not significant. Table 2 contains the adjusted odds ratios (OR) and 95% CI for CVD and HTN. Controlling for between-group differences in age, race, and sex, the prevalence of CVD was significantly greater among subjects with BD-I versus subjects with MDD and versus controls, and the prevalence among subjects with MDD was significantly greater than among controls. The same pattern was observed for HTN. Sensitivity analyses examined whether the excessive prevalence of CVD and HTN among subjects with BD-I could be explained by additional demographic variables (education, income, and marital status) or clinical variables (obesity, anxiety, smoking, and SUD). Findings (not presented) remained significant after controlling for these additional covariates. Finally, the association between BD-I and CVD or HTN did not vary significantly by sex (sex × BD-I interaction) for CVD or HTN.

Hypothesis 2: CVD subjects with BD-I will be significantly younger than CVD subjects without BD-I, and HTN subjects with BD-I will be significantly younger than HTN subjects without BD-I

The mean age of BD-I subjects with CVD (50.4 ± 0.7 years) was approximately 14 years younger than that of control subjects with CVD (64.1 ± 0.3 years) and approximately 6 years younger than that of MDD subjects with CVD (56.6 ± 0.4 years; omnibus $F = 56.04$, df =

Table 1. Cardiovascular illness, hypertension and other characteristics among subjects with and without bipolar I disorder (BD-I) and major depressive disorder (MDD)[a]

	BD-I (n = 1,411)	MDD (n = 6,831)	Non BD-I (n = 34,851)	χ^2 or F	df	p
Cardiovascular disease[b,c]	10.1	8.0	4.3	238.04	2	<0.0001
Hypertension[d]	22.1	21.6	18.4	46.57	2	<0.0001
Age in years, mean (±SE)	38.1 (0.2)	43.8 (0.1)	45.8 (0.1)	134.79	2,369	<0.0001
Female	54.1	66.4	49.2	675.81	2	<0.0001
Caucasian race	83.3	88.3	82.3	147.44	2	<0.0001
< High school education	19.1	13.9	15.9	29.32	2	<0.0001
Married	50.4	56.1	63.2	200.93	2	<0.0001
Household income in US$, mean (±SE)	41,077 (483)	53,003 (690)	54,827 (195)	52.77	2,369	<0.0001
Obese[e,f]	29.8	28.2	21.0	210.20	2	<0.0001
Any anxiety[g]	48.2	31.4	5.9	5750.15	2	<0.0001
Daily nicotine use	44.4	31.2	14.0	1875.20	2	<0.0001
Any substance use disorder[h]	70.3	55.2	34.1	1698.46	2	<0.0001

Values reported as percent except where indicated otherwise.
[a]N based on unweighted data; means and percentages based on weighted data.
[b]Angina, arteriosclerosis, or myocardial infarction.
[c]N= 1,403 for BD-I; 6,781 for MDD; and 33,892 for Non BD-I.
[d]N = 1,398 for BD-I; 6,755 for MDD; and 33,805 for Non BD-I.
[e]Body mass index ≥ 30.
[f]N = 1,384 for BD-I; 6,704 for MDD; and 33,564 for Non BD-I.
[g]Generalized anxiety disorder, panic disorder, or social phobia.
[h]Any drug or alcohol abuse or dependence.

Table 2. Adjusted[a] odds ratios (OR) and 95% confidence intervals (CI) for cardiovascular disease and hypertension

	BD-I versus controls OR (95% CI)	BD-I versus MDD OR (95% CI)	MDD versus controls OR (95% CI)
Any cardiovascular disease[b]	4.95 (4.27–5.75)	1.80 (1.52–2.14)	2.70 (2.53–2.88)
Hypertension	2.38 (2.16–2.62)	1.44 (1.30–1.61)	1.63 (1.55–1.72)

[a]Analyses controlled for age, race, and sex; p = 0.001 for all.
[b]Angina, arteriosclerosis, or myocardial infarction.
BD-I = bipolar I disorder; MDD = major depressive disorder.

2,336, $p < 0.001$; all post-hoc t-test comparisons significant). Independent of the main effects of mood status (BD-I, MDD, controls) and CVD, there was a significant mood × CVD interaction ($F = 16.47$, df = 2,369, $p < 0.001$). Similarly, the mean age of BD-I subjects with HTN (48.1 ± 0.6 years) was approximately 13 years younger than that of controls with HTN (61.1 ± 0.1 years) and approximately 6.5 years younger than that of MDD subjects with HTN (54.6 ± 0.3 years; omnibus $F = 129.99$, df = 2,365, $p < 0.0001$; all post-hoc comparisons significant). Independent of the main effects of mood status (BD-I, MDD, controls) and HTN, there was a significant mood × HTN interaction ($F = 50.53$, df = 2,369, $p < 0.001$).

Discussion

This study found a nearly five-fold age-, race-, and sex-adjusted increased risk of CVD and a greater than two-fold increased risk of HTN among adults with BD-I versus controls. Even compared to subjects with MDD, those with BD-I have significantly greater prevalence of CVD and HTN. Moreover, controlling for obesity, smoking, anxiety disorders, and SUD did not substantially alter these findings. The mean age of BD-I subjects with CVD was approximately 14 years younger than that of controls and 6 years younger than that of MDD subjects with CVD. Similarly, the mean age of BD-I subjects with HTN was approximately 13 years younger than that of controls and 6.5 years younger than that of MDD subjects with HTN. These findings, from a representative population sample, suggest that the excessive cardiovascular mortality in BD-I cannot be explained solely by disparities in medical care (28), but rather that there is markedly elevated prevalence of cardiovascular illnesses in BD-I.

These findings must be considered in the context of the methodologic limitations of this study. First, CVD and HTN were ascertained by asking NESARC respondents whether they had ever been diagnosed with these conditions. Medical examination was not undertaken to corroborate these

reports, nor was examination of health records. Using this methodology would not detect undiagnosed CVD and HTN. Second, this study employed a cross-sectional retrospective methodology. As such, the direction of the associations between the variables cannot be determined. Third, the NESARC study did not include information regarding specific medications. Such data would have allowed us to examine the logical question of whether commonly used medications in BD-I, such as lithium and second-generation antipsychotics, are differentially associated with CVD and HTN. Previous findings suggest the possibility that lithium mitigates the impact of BD on excess cardiovascular mortality (29), whereas second-generation antipsychotics are known to exacerbate cardiovascular risk (30). Fourth, this study cannot address specific putative pathophysiological or behavioral underpinnings of these associations, because information regarding physical activity, dietary intake, glucose, lipids, and other biological factors was not collected in the NESARC. Fifth, this study examined BD-I specifically and not bipolar II disorder because evidence of the reliability of this diagnosis in NESARC is lacking. Therefore, present findings may not generalize to bipolar II disorder, cyclothymia, or bipolar disorder not otherwise specified. Finally, as with any large-scale epidemiologic study, this study is limited by its reliance on lay interviewer-administered structured interviews to determine psychiatric diagnoses.

In the present study, 22.1% of BD-I subjects reported being diagnosed with HTN. Previous estimates for HTN prevalence are generally 25–45%, although higher (8) and lower (31) rates have been reported as well. Most previous studies have found increased prevalence of HTN in BD compared to healthy or psychiatric controls (7–9, 11–13), although others have reported no significant differences (32). In the present study, 10.1% of BD-I subjects reported being diagnosed with CVD, which is similar to previous estimates (5, 21). Previous findings regarding the association between CVD and BD have yielded heterogeneous findings (5, 13, 21, 23, 24). One study found lower prevalence of CVD among BD subjects versus controls, but the analyses did not control for age (5). An underpowered population-based study that included 42 subjects with BD found a trend toward an association of BD with CVD (23). Similarly, a prospective administrative database study found greater incidence of myocardial infarction (MI) among BD subjects (2.24%) compared to appendectomy subjects (1.72%); however, this difference did not achieve statistical significance (13). To our knowledge, previous studies have not compared the prevalence of CVD among subjects with BD and MDD; however, a Veterans Affairs (VA) study found that males with BD were 44% more likely to have CVD compared to those with schizophrenia (21).

The mean age of BD-I subjects with CVD and HTN was approximately 14 and 13 years younger, respectively, than controls with CVD and HTN. These discrepancies are in the same direction and of larger magnitude than previously reported. For example, Kilbourne and colleagues (5) found that BD subjects with HTN were 7 years younger and those with CVD were 4 years younger compared to non-BD subjects. Similarly, Lin and colleagues (13) found that BD subjects with MI were 5 years younger than appendectomy subjects with MI.

Despite its limitations, this study confirms and extends previous findings on this subject. CVD and HTN are highly prevalent among adults with BD-I at comparatively young ages. Given the complexity of BD-I itself, compounded by the high rates of psychiatric comorbidity, integration of medical care with psychiatric care is need in order to optimize medical and psychiatric outcomes and minimize costs. Preliminary evidence indicates that such integration may yield improvements in both psychiatric and medical health as well as reduce both forms of service utilization (33, 34). Longitudinal studies are needed to parse the contribution of various genetic, physiologic, pharmacologic, behavioral, and psychiatric factors to CVD and HTN risk in BD-I. These studies should be conducted at the earliest possible stage, and examination of this topic among youth may provide an excellent opportunity. Perhaps most importantly, preventive strategies are needed to reduce the excessive cardiovascular burden among people with BD-I.

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