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Manic/hypomanic Symptom Burden Predicts Cardiovascular Mortality with Bipolar Disorder in the Collaborative Depression Study

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Abstract

Objectives—Bipolar disorder conveys an increased risk of cardiovascular mortality. We compared the risk for cardiovascular mortality between bipolar I and bipolar II subtypes and determined correlates of cardiovascular mortality.

Methods—Participants with major affective disorders were recruited for the National Institute of Mental Health Collaborative Depression Study and followed prospectively for up to twenty-five years. A total of 435 participants met diagnostic criteria for bipolar I (N=288) or bipolar II (N=147) disorder based on Research Diagnostic Criteria at intake and measures of psychiatric symptoms during follow-up. Diagnostic subtypes were contrasted by cardiovascular mortality risk using Cox proportional-hazards regression. Affective symptom burden (the proportion of time with clinically significant manic/hypomanic or depressive symptoms) and treatment exposure were additionally included in the models.

Results—Thirty-three participants died from cardiovascular causes. Participants with bipolar I disorder had more than double the cardiovascular mortality risk of those with bipolar II disorder, after controlling for age and gender (HR=2.35, 95% C.I. 1.04–5.33, $p=0.04$). The observed difference in cardiovascular mortality between these subtypes was at least partially confounded by the burden of clinically significant manic/hypomanic symptoms which predicted cardiovascular mortality independent of diagnosis, treatment exposure, age, gender, and cardiovascular risk factors at intake. Selective serotonin uptake inhibitors appeared protective though were introduced late in follow-up. Depressive symptom burden was not related to cardiovascular mortality.

Conclusions—Participants with bipolar I disorder may face greater risk of cardiovascular mortality than those with bipolar II disorder. This difference in cardiovascular mortality risk may reflect manic/hypomanic symptom burden.

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Keywords

adult; bipolar disorder; cardiovascular mortality; mania; prospective cohort study; risk factors

INTRODUCTION

Mortality data from state hospitals in the early twentieth century suggested an association between manic-depressive psychoses or bipolar disorder and cardiovascular death (1,2). Contemporary clinical and community-based studies continue to demonstrate that individuals with bipolar illness are at increased risk for cardiovascular mortality (3–10). Some of these studies have suggested greater risk of cardiovascular mortality for those with bipolar disorder than other mental illnesses, including unipolar depression and schizophrenia (1–3,6,7,9). Apart from the study of Angst et al., these studies did not differentiate between the bipolar I and bipolar II subtypes.

Several studies have further found a higher prevalence of cardiovascular risk factors such as diabetes mellitus (11,12), hypertension (13–15), and obesity (14,16–20) among those with bipolar disorder compared to general population estimates. Even contrasted to patients with schizophrenia, another at-risk population, those with bipolar disorder have increased risk for hypertension, obesity, coronary artery disease, and dyslipidemia (13,21). Many of these cardiovascular risk factors are incorporated in the construct of the metabolic syndrome, which has been strongly associated with cardiovascular mortality (22,23). The prevalence of metabolic syndrome is elevated in bipolar disorder (24–29). Despite being younger, inpatients with bipolar disorder were more likely to have hypertension and hyperlipidemia than controls hospitalized for appendectomy though statistically significant differences in subsequent myocardial infarction were not observed (30).

Individuals with bipolar II experience a greater burden of depressive symptoms than those with bipolar I (31) and in community samples, depressive symptoms have been associated with subsequent cardiovascular morbidity and mortality (8,32). In turn, depressive symptoms have also been associated with increased mortality among individuals with hypertension (33), coronary artery disease (34), and status post myocardial infarction (35,36) though a previous analysis of our high-surveillance National Institute of Mental Health Collaborative Depression Study (CDS) data set did not reveal any relationship between cardiovascular mortality and chronicity of depressive symptoms (37).

Individuals with bipolar I experience a greater burden of manic/hypomanic symptoms than those with bipolar II (31). While conditions such as “Bell’s mania” or “manic-depression exhaustive deaths” have historically suggested a connection between acute mania and sudden, often cardiac, death (38–41), we are aware of no recent studies systematically exploring the relationship between manic/hypomanic symptoms and cardiovascular mortality. In these historical case reports, a variety of associated symptoms were described suggesting agitated delirium, including confusion, disorientation, visual hallucinations, and high fever (38–40). In Derby’s classic 1933 review of 386 deaths at Brooklyn State Hospital, “a high death rate in the manic-depressive group” was reported with one-third of deaths attributed to cardiac causes and another 40% simply to “exhaustion” (40).

Patients may be more likely to receive medication treatment for bipolar I than for bipolar II disorder (42) and many of these medications used to treat bipolar disorder have been demonstrated to elevate risk for a variety of cardiovascular risk factors. Lithium is associated with significant weight gain (43,44). It has not been clearly associated with diabetes mellitus or insulin resistance in clinical samples (45), however, it has insulin-like physiological effects

(46,47) and may increase plasma glucose in animal models (48). Valproic acid derivatives have long-been associated with insulin resistance and weight gain (49,50) while carbamazepine has been associated with hyperlipidemia (51). Antipsychotics, particularly second generation antipsychotics, may induce hyperlipidemia (52–56), insulin resistance/diabetes mellitus (53, 57–63), and obesity (53,64–66).

Despite the cardiovascular risk posed by medications used for bipolar disorder, treatment has not been directly associated with cardiovascular mortality. Angst et al. (2002) assessed the mortality of 220 bipolar depressive or manic patients followed for over 30 years, beginning in 1959, and observed a total of 59 cardiovascular deaths (5). They also found greater risk for cardiovascular death among untreated patients (SMR=2.23) than among treated patients with bipolar disorder (SMR=1.68), where treatment was defined as a least six months or an entire intra-episode period on a medication (5). Patients with bipolar I had a greater risk of mortality from vascular diseases, including cardiovascular disease, compared to their bipolar II counterparts (5).

No subsequent study has compared cardiovascular mortality rates by bipolar subtype. We utilized our CDS cohort to determine whether participants with bipolar I experience excess cardiovascular mortality relative to their bipolar II counterparts. An additional objective of the study was to examine the influence of symptom burden and medication exposure on cardiovascular mortality in bipolar disorder. Our null hypothesis was that medication exposure and affective symptom burden would not be associated with cardiovascular mortality.

RESEARCH DESIGN AND METHODS

Sample

A total of 435 participants with bipolar I and II disorder were identified from a prospective cohort of Caucasian, English-speaking individuals knowledgeable about their biological parents, and were recruited between 1978 and 1981 for participation in the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression from five academic centers: Massachusetts General Hospital and Harvard University in Boston, Rush Presbyterian – St. Luke’s Medical Center in Chicago, the University of Iowa in Iowa City, New York State Psychiatric Institute and Columbia University in New York, and Washington University School of Medicine in St. Louis. All participants provided informed consent.

Baseline Assessments

Baseline sociodemographic and clinical information was obtained from intake data recorded on the Schedule for Affective Disorders and Schizophrenia (67) and the Personal History of Depressive Disorders (available upon request). Follow-up assessments categorized severity of affective psychopathology from Psychiatric Status Ratings (PSRs) using various forms of the Longitudinal Interval Follow-up Evaluation (LIFE), which was administered semiannually in the first five years and annually thereafter (68–70). The PSRs provided weekly ratings of symptom levels for each Research Diagnostic Criteria (RDC) syndrome (71) and registered onsets and offsets of mania or hypomania among all participants, including those with an intake diagnosis of unipolar depression (72). The PSRs provide data during follow-up and have demonstrated intraclass correlation coefficients of 0.9 (73). For use in the analyses reported here, an initial diagnosis of bipolar I was determined from intake RDC diagnoses of either bipolar I, schizoaffective manic (mainly affective), or schizoaffective depressed (mainly affective) with a history of mania (72). The latter categories are indistinguishable from mania as defined by the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as the RDC defined schizo-affective manic type as “an episode of illness that fulfills the criteria for a manic syndrome” with psychotic symptoms “concurrent with the manic

episode.” An initial diagnosis of bipolar II was drawn from the intake RDC (72). While the DSM-IV and RDC identify similar symptoms for a diagnosis of hypomania, the DSM-IV requires a four day duration for diagnosis while the RDC requires two days for a probable and one week for a definite diagnosis. A definite diagnosis of hypomania was required for our purposes. An initial diagnosis of unipolar major depression was based on intake RDC diagnosis of major depressive disorder or schizoaffective-disorder, depressed, mainly affective subtype and no prior mania. The latter category is analogous to DSM-IV-defined major depression.

Follow-up Assessments

Follow-up ratings from the LIFE Psychiatric Status Rating (PSR) were used to reclassify participants diagnostically (Table 1). Participants with unipolar depression on intake who developed mania or hypomania during follow-up were thus reclassified as bipolar I or bipolar II, respectively. Participants initially diagnosed with bipolar II who developed mania during follow-up were classified as bipolar I. For consistency and to utilize the most accurate diagnoses, these prospective diagnoses were utilized for all analyses on the assumption that initial syndromes were a manifestation of the same illness. For example, if an individual with bipolar I first presents with a depressive syndrome only to later to manifest mania, recognition of the initial depression as a bipolar depression presents a more parsimonious explanation than assuming a new condition arose. PSR ratings also were utilized to determine the affective morbidity experienced by each individual. A week of clinically significant affective symptoms was operationalized utilizing 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 depressive morbidity was expressed as the proportion of weeks during follow-up with clinically significant depressive symptoms. Burden of manic/hypomanic morbidity was expressed as the proportion of weeks followed up with any clinically significant hypomanic or manic symptoms.

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 (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors, other antidepressants, and benzodiazepines. To limit selection bias related to duration of follow-up, exposure was quantified as the proportion of weeks treated at any dose during follow-up. Proportions were utilized to best estimate cumulative exposure with the available data, assuming the proportions were similar during periods not in follow-up. In this observational study, treatment was provided in the community and study investigators observed all treatment but did not direct it.

Main Outcome

When a death was noted to occur during the prospective follow-up, information was obtained from family informants and death certificates. The participant's social security number was utilized to access government vital statistics records through the National Death Index (NDI) or the Social Security Death Index (SSDI) and to subsequently obtain a copy of the death certificate from which cause of death was abstracted. As a supplement to this process, mortality of participants lost to follow-up was assessed through the NDI or SSDI.

Statistical Analyses

Bipolar I and II disorder were compared with regard to baseline demographics and available cardiovascular risk factors recorded at intake. Chi-square tests and t-tests were used for categorical and continuous variables, respectively. Differences in symptom burden by bipolar subtype were compared using the Wilcoxon Rank Sum Test. Time to cardiovascular death was

illustrated using Kaplan-Meier analysis. Survival time reflected the number of weeks from intake into the CDS until cardiovascular death. For the initial analyses of mortality risk by bipolar subtype, participants were censored at the latter of the most recent vital statistics survey or when lost to follow-up. Censoring and mortality were assumed to be independent.

Proportions for exposure were multiplied by a factor of 10. Thus, the variables for manic/hypomanic and depressive morbidity were coded such that hazard ratios would reflect the influence of a 10% difference in affective symptom burden. Variables for treatment exposure were similarly coded such that hazard ratios would reflect the influence of a 10% difference in exposure. Symptom morbidity and treatment exposure were not imputed when data was missing, which occurred with 8 participants (1.8%). The low exposure for some medications limited their utility as a covariate in survival analysis. An exposure threshold was therefore operationalized to include only those medications with adequate distributions of exposure. Medications for which at least 10% of participants were exposed to greater than one-quarter of the time were included in the analysis. This cut-off was selected *a priori* to include only medications for which stable hazard estimates could be likely obtained. The analysis focused hazards for cumulative exposure to medications and affective symptoms, assuming proportional hazards.

Cox proportional hazards regression was used to compare survival by bipolar subtype while adjusting for gender and age at intake as a continuous variable. Cox proportional hazards were also used to assess potentially relevant confounders such as affective morbidity and treatment exposure. Cardiovascular risk factors were evaluated as potential mediators of cardiovascular mortality and subsequently were not included in the primary analysis. Data were not available for cardiovascular risk factors prior to onset of affective disorder. Age was modeled as a time-dependent covariate to assess any non-linear age effects. Other variables were modeled as fixed, assuming the proportional hazards assumption was not violated for that variable.

Sensitivity analysis tested several assumptions of the initial, primary analyses. Because medication exposure and affective symptom burden could only be assessed during follow-up, these estimates may have been less stable for those with shorter durations of follow-up. For the sensitivity analysis, participants lost to follow-up were censored with the earlier of the most recent vital statistics survey or three years after follow-up. This timeline was based on review of outliers for duration lost to follow-up prior to cardiovascular mortality and resulted in the additional censoring of three individuals prior to cardiovascular death. Thirty cardiovascular deaths were therefore included in these analyses. Available cardiovascular risk factors from study intake also were included into this model: hypertension, history of myocardial infarction, heart valve abnormality, diabetes mellitus, and prior medical or surgical hospitalization. Data on smoking and dyslipidemia were not collected on intake. Given the cardiovascular risk associated with smoking, which was not assessed at intake, we compared groups by smoking status as assessed by the Charlson comorbidity index, administered in 2003 (sub-sample N=108). To expand our initial phenomenological focus, we created an additional Cox regression model to include the burden of clinically significant psychotic symptoms (defined as PSR > 2/3 on scales of unspecified psychosis or delusions). Selective attrition was further assessed.

RESULTS

Baseline Demographic and Clinical Characteristics

Participants in this sample were followed for a mean of 16.3 (median: 20; SD: 8.6) years and for up to twenty-five years. The demographic and clinical characteristics of bipolar I and bipolar II participants are summarized in Table 2. Compared to bipolar II participants at intake, those with bipolar I were significantly less likely to be female, to have had a heart valve abnormality,

or to have a previous medical or surgical hospitalization. Participants with bipolar I were further more likely to have been inpatients when recruited and had a slightly lower Global Assessment Scale at intake, suggesting greater psychopathological morbidity at intake. Psychopathological morbidity, expressed as affective symptom burden, was included as a covariate in the primary analyses reported. Age at intake and age of affective illness onset were not significantly different by bipolar subtype.

Cardiovascular Mortality by Bipolar Subtype

Thirty-three cardiovascular deaths were included in this analysis. Of those who died of cardiovascular causes, 24 were bipolar I and 9 were bipolar II (8.3% versus 6.1%, $\chi^2=0.7$, $df=1$, $p=0.4$). The differences in time to cardiovascular death by bipolar subtype are illustrated in Figure 1. Bipolar I was significantly associated with cardiovascular mortality (HR=2.35, 95% C.I. 1.04–5.33, $p=0.04$) when modeled in Cox Regression adjusting for gender and age.

Medication Exposure and Affective Morbidity

Exposure was limited for some identified medication classes, particularly for those introduced late in the prospective cohort study. As expected, participants with bipolar I had greater medication exposure. Four medication classes, first-generation antipsychotics, lithium, TCAs, and SSRIs met our operationalized threshold for inclusion in the Cox regression analysis (10% of participants exposed for at least one-quarter of follow-up). Exposures to second-generation antipsychotics, valproic acid derivatives, carbamazepine, lamotrigine, monoamine oxidase inhibitors, other antidepressants, and benzodiazepines were less common and/or circumscribed to a limited time period. Figure 2 illustrates medication exposure by bipolar subtype for the four medication groupings with the greatest exposure: first-generation antipsychotics, lithium, TCAs, and SSRIs. As is evident in this figure, participants with bipolar I were more likely to be exposed to first generation antipsychotics and lithium while those with bipolar II were more likely to be exposed to antidepressants. Exposure to SSRIs occurred later in follow-up with a median first exposure between years 12 and 13 of follow-up, at which point 12 cardiovascular deaths had already been recorded.

Participants with bipolar I spent a median of 16% (mean: 27; SD: 28) of follow-up weeks with clinically significant depressive symptomatology and a median of 4% (11;17) of follow-up weeks with clinically significant manic/hypomanic symptomatology as previously defined. The bipolar II group spent a median of 31% (mean: 37; SD: 28) and 0.4% (1;3) with depressive and manic/hypomanic symptomatology, respectively. Participants with bipolar I had significantly greater manic ($p<0.001$) and fewer depressive symptoms ($p<0.001$).

When modeled in Cox regression with age, gender, bipolar subtype, the proportion of weeks exposed to each of the four selected medication classes (first-generation antipsychotics, lithium, TCAs, and SSRIs), and the proportion of weeks with clinically significant depressive symptoms; the proportion of follow-up with clinically significant manic/hypomanic symptomatology was predictive (HR=1.30, 1.09–1.55, $p<0.01$) although bipolar subtype no longer predicted cardiovascular mortality (HR=1.85, 0.74–4.65, $p=0.19$). Exposure to first generation antipsychotics, lithium, and TCAs did not predict cardiovascular mortality. SSRI exposure appeared protective though was confined to the latter portion of follow-up. Depressive morbidity further did not predict cardiovascular mortality. The hazards ratio estimates from this primary model are detailed in Table 3.

Sensitivity Analyses

Psychotic symptom burden failed to predict cardiovascular mortality and did not alter the association observed between manic/hypomanic symptomatology and subsequent cardiovascular mortality. Those lost to follow-up at one year or earlier had a trend for a greater

percentage of follow-up with clinically significant manic/hypomanic symptoms (median of 2.5% versus 1.6%) though none died from cardiovascular causes. When those lost to follow-up in the first year are removed from the analysis, our results do not differ and are only strengthened. Manic/hypomanic symptomatology continued to significantly predict cardiovascular mortality in a reduced model including only age, gender, bipolar subtype, and depressive morbidity. In this reduced model, bipolar subtype also did not predict cardiovascular mortality. Among those followed prospectively through 2003, smoking was not cross-sectionally associated with manic/hypomanic symptom burden ($t=-1.1$, $df=106$, $p=0.3$) or bipolar subtype ($\chi^2=0.8$, $df=1$, $p=0.3$).

Because assessment of medication exposure and affective morbidity was limited to the period of prospective follow-up, participants in the sensitivity analysis were censored if mortality was not assessed within three years of loss to follow-up. We additionally included available cardiovascular risk factors from intake in this expanded model. With a dependent variable of time-to-cardiovascular mortality, the sensitivity analysis model included independent variables for a linear effect of age, gender, bipolar subtype, the proportion of weeks on selected medications (first-generation antipsychotics, lithium, TCAs, and SSRIs), the proportion of weeks with clinically significant depressive symptoms, the proportion of weeks with clinically significant manic/hypomanic symptoms, hypertension, history of myocardial infarction, heart valve abnormality, diabetes mellitus, and any prior medical or surgical hospitalization. When modeled as such in Cox regression, manic/hypomanic symptomatology ($HR=1.48$, 95% C.I. 1.16–1.89, $p=0.002$) but not bipolar subtype again predicted cardiovascular mortality. SSRI exposure continued to appear protective.

DISCUSSION

In this prospective cohort study, manic/hypomanic symptom burden independently predicted cardiovascular mortality and largely explained the apparent increased risk for cardiovascular mortality with the bipolar I versus bipolar II subtype. While a number of studies have established an elevated risk for cardiovascular mortality with bipolar disorder (3–10), only one prior study has assessed risk by bipolar subtype, and this study did not assess the influence of exposure to specific medications or affective symptom burden (5). Consistent with previous findings from Angst et al. (5), we found a greater risk of cardiovascular mortality in participants with bipolar I than bipolar II. Apart from SSRI exposure, medication exposure did not appear to be related to cardiovascular mortality. While SSRI exposure appeared protective, the late exposure window and the magnitude of the estimated effect are suspicious for survivor bias. Surprisingly, manic/hypomanic but not depressive symptoms were associated with subsequent cardiovascular mortality and appeared to at least partially confound the observed differences between the bipolar subtypes.

This analysis has several important limitations. Some participants were lost to follow-up prior to the assessment of the primary outcome, cardiovascular mortality. This loss to follow-up limits our ability to assess exposure to medications and burden of clinically significant affective symptomatology. To mitigate this risk while maintaining a clinical focus on cumulative exposure, we utilized proportions of weeks exposed during follow-up for these variables. We further censored participants after being lost to follow-up for more than three years prior to mortality assessment in a sensitivity analysis. Our measures of medication exposure and affective symptom burden, however, can only infer cumulative lifetime exposure and assume the proportions observed during follow-up are representative of periods where participants were not followed prospectively. A repeat assessment of mortality among those lost to follow-up would only worsen any bias secondary to this assumption. With many participants recruited during acute episodes, this limitation may further overestimate the burden of affective symptoms and perhaps medication exposure for those lost to follow-up early. A differential

misclassification of exposure may subsequently exist. Less than 3% of our sample was lost by one year and exclusion of this portion of our sample did not alter our results. Limited observed exposure to several medication classes impeded the pursuit of a more refined medication exposure assessment. This prevented the analysis of more recently marketed or less commonly prescribed medications. Our analysis of treatment exposure was therefore limited to first-generation antipsychotics, lithium, TCAs, and SSRIs, yet participants were also taking other agents, the influence of which could not be fully assessed. Furthermore, in this observational study, treatment exposure is not controlled and may therefore be confounded by a variety of factors, including severity of illness and general health-seeking behaviors. Our assessment of baseline cardiovascular risk was limited by available data, with dyslipidemia, body mass index, and smoking history notably absent. Prior studies of cardiovascular mortality in bipolar disorder also did not assess dyslipidemia or smoking (3–5,7,9,10,74,75). Our primary outcome variable, cardiovascular mortality was observed in 33 participants (30 after censoring with the sensitivity analysis), limiting statistical power. Nonetheless, we were able to detect a statistically significant association between manic/hypomanic symptoms and subsequent cardiovascular mortality, a robust finding which persisted after several assumptions of our initial model were tested in a sensitivity analysis. With 30 observed outcomes and twelve predictor variables, the expanded model in the sensitivity analysis may risk over-fitting the data, however, the findings generally reflected those of both our primary analysis and reduced model sensitivity analysis. The results from our entirely Caucasian sample may further not generalize to other populations.

Despite these limitations, our prospective cohort provided an exceptionally rigorous assessment of diagnosis, affective morbidity, and treatment exposure during follow-up. Prior studies of cardiovascular mortality in bipolar disorder have largely used diagnostic data from medical records or registries, which may be less reliable than structured interviews at intake with ongoing diagnostic re-assessment (3,4,9,10,74,75). This use of prospective diagnoses substantially reduced the risk of diagnostic misclassification and enhanced the credibility of our primary finding. Further, our detailed assessment of affective morbidity revealed that differences in mortality by diagnostic subtype reflected the burden of manic/hypomanic rather than depressive symptomatology. Our estimates of affective morbidity were comparable to prior analyses (69,70) with the somewhat lower estimates reflecting our exclusion of subsyndromal symptoms. The observed relationship between manic/hypomanic symptoms and cardiovascular mortality could be mediated by physiological mechanisms intrinsic to the disease process or reflect propensity to engage in maladaptive health-related behaviors. Unfortunately, our inability to further refine medication exposure because of observed frequencies for unique medication classes, limits our ability to draw any firm conclusions about medication exposure and cardiovascular mortality in bipolar disorder. Given these limitations, it is quite possible that the association with mania is further confounded by other variables, including treatments or unmeasured exposures.

SSRI exposure appeared to have a protective effect on cardiovascular mortality in this cohort. Fluoxetine was first introduced to the U.S. market in 1988. Of those exposed to SSRIs, first exposure occurred at a median of just under 13 years of follow-up. Thus, the apparent protective effect of SSRIs may be exaggerated by or even entirely reflect a survivor bias. Nonetheless, several properties of SSRIs, including inherent anti-platelet effects (76), have been proposed to potentially reduce cardiovascular risk (77). Given the limitations reported herein, however, definitive conclusions cannot be drawn regarding any protective benefit of SSRIs.

Bipolar disorder represents a serious, potentially treatable medical condition with considerable morbidity (70,78–87) and mortality (88–90). Our study supports a prior finding of greater cardiovascular mortality with the bipolar I subtype and reveals a previously unreported association between manic/hypomanic symptoms and cardiovascular mortality. These findings

should encourage further study to confirm these initial findings and to assess pathophysiological links between manic/hypomanic syndromes and cardiovascular morbidity.

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This study was conducted with the current participation of the following investigators: M.B. Keller, M.D. (Chairperson, Providence, RI); W. Coryell, M.D. (Co-Chairperson, Iowa City, IA); D.A. Solomon, M.D. (Providence, RI); W. Scheftner, M.D. (Chicago, IL); J. Endicott, Ph.D., A.C. Leon, Ph.D., and J. Loth, M.S.W. (New York, NY); and J. Rice, Ph.D., (St. Louis, MO).

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Glossary

CDS	Collaborative Depression Study
DSM-IV	4 th edition of the Diagnostic and Statistical Manual of Mental Disorders
LIFE	Longitudinal Interval Follow-up Evaluation
NDI	National Death Index
RDC	Research Diagnostic Criteria
PSR	Psychiatric Status Rating
SSDI	Social Security Death Index

* deceased

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Cardiovascular Mortality by Bipolar Subtype

Figure 1. Cardiovascular mortality by subtype of bipolar disorder

Participants with bipolar I had significantly greater cardiovascular mortality during prospective follow-up. The mortality curves were derived from a Kaplan-Meier analysis. When modeled in Cox Regression adjusting for gender and age of intake, these differences were statistically significant (HR=2.35, 95% C.I. 1.04–5.33, $p=0.04$).

Figure 2. Exposure frequencies for selected medications by subtype of bipolar disorder
 The distribution of exposure for first-generation antipsychotics, lithium, tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs) met our operational criteria for inclusion in the analysis. Participants with bipolar I had greater exposure to first generation antipsychotics (upper left) and lithium (lower left) whereas those with bipolar II tended to have greater exposure for antidepressants (right).

TABLE 1

Psychiatric Status Rating (PSR) Scales

Code	Status	Definition
Six-point weekly PSR scale for major syndromes (i.e. mania, major depression)		
1	Asymptomatic: Usual self	Return to "usual self" without any residual symptoms of the disorder
2	Residual: Mild symptoms or impairment	One or more symptoms of disorder in no more than mild degree
3	Partial Remission: Moderate symptoms or impairment	Less psychopathology than full criteria yet obvious evidence of the disorder with no more than moderate impairment
		Major symptoms or impairment but does not meet definite RDC criteria
4	Marked: Major symptoms or impairment	Meets RDC criteria but is without prominent psychotic symptoms or extreme impairment
5	Definite Criteria: Without	
6	Definite Criteria -- Severe: Prominent psychotic symptoms or extreme impairment	Meets RDC criteria with prominent psychotic symptoms or extreme functional impairment
Three-point weekly PSR scale for minor syndromes (i.e. hypomania, minor depression)		
1	Asymptomatic	No evidence of previously met RDC criteria
2	Probable Criteria -- Mild	Minor manifestations of disorder that do not meet full criteria
3	Definite Criteria -- Severe	Meets definite RDC criteria for disorder

TABLE 2

Baseline Demographic and Clinical Characteristics of Participants by Diagnosis

	Bipolar I N=288 # (%)	Bipolar II N=147 # (%)
Demographic/Clinical Characteristics		
Age, mean (median; SD)	36.7 (34; 13.1)	35.7 (31; 13.4)
Age of onset (median; SD)	23.1 (21; 9.2)	22.1 (20; 9.6)
Female ^a	154 (53%)	96 (65%)
Inpatient ^b	261 (91%)	98 (67%)
Lowest Global Assessment Scale ^{c,f}	31 (31; 11)	36 (35; 10)
Marital Status ^f		
Married	92 (32%)	56 (38%)
Divorced/separated	61 (21%)	38 (26%)
Single	127 (44%)	51 (35%)
Widowed	8 (3%)	2 (1%)
Educational Level ^f		
Without Diploma	30 (10%)	23 (16%)
High School Graduate	73 (25%)	42 (29%)
Some College	105 (36%)	42 (29%)
College Graduate	80 (28%)	40 (27%)
Income ^f		
Unknown	12 (4%)	6 (4%)
Less than \$10,000	103 (36%)	45 (31%)
\$10,000 to less than \$22,000	97 (34%)	55 (37%)
\$22,000 to less than \$34,000	45 (15%)	20 (14%)
\$34,000 or greater	31 (11%)	21 (14%)
Medical History ^f		
Diabetes Mellitus	14 (5%)	3 (2%)
Hypertension	37 (13%)	20 (14%)
Heart valve abnormality ^d	13 (5%)	14 (10%)
Myocardial Infarction	8 (3%)	3 (2%)
Medical/Surgical Hospitalization ^e	211 (76%)	129 (88%)
Co-occurring Psychiatric Diagnoses ^f		
Alcohol abuse	90 (28%)	40 (27%)
Drug abuse	22 (8%)	18 (12%)
Generalized anxiety disorder	13 (5%)	7 (5%)
Obsessive-compulsive disorder	6 (2%)	4 (3%)
Panic disorder	9 (3%)	6 (4%)
Phobic disorder	11 (4%)	12 (8%)

^a $\chi^2=5.6$, $df=1$, $p<0.02$;^b $\chi^2=38.7$, $df=1$, $p<0.001$;^c $t=4.4$, $df=433$, $p<0.001$ ^d $\chi^2=12.0$, $df=1$, $p<0.001$;^e $\chi^2=3.9$, $df=1$, $p<0.05$;^fAssessed at intake

TABLE 3

Cox proportional hazards ratio (HR) estimates for cardiovascular mortality in bipolar disorder

Variable	HR	95% C.I. HR
Age ^a	1.13	1.09 – 1.16
Male gender ^b	3.23	1.54 – 6.78
Bipolar I subtype	1.85	0.74 – 4.65
First-generation antipsychotics exposure	0.99	0.88 – 1.10
Lithium exposure	1.06	0.96 – 1.18
TCA exposure	0.87	0.74 – 1.03
SSRI exposure ^b	0.31	0.14 – 0.72
Manic symptom burden ^b	1.3	1.09 – 1.55
Depressive symptom burden	1.14	0.98 – 1.33

^a
 $p < 0.001$ ^b
 $p < 0.01$