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Vascular Mortality in Participants of the Bipolar Genomics Study

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Abstract

Objective—In prior work, we have identified a relationship between symptom burden and vascular outcomes in bipolar disorder. We sought to replicate these findings using a readily accessible measure of mood disorder chronicity and vascular mortality.

Methods—We conducted a mortality assessment using the National Death Index for 1,716 participants with bipolar I disorder from the National Institute of Mental Health Genetics Initiative Bipolar Disorder Consortium. We assessed the relationship between the duration of the most severe depressive and manic episodes and time to vascular mortality (cardiovascular or cerebrovascular) using Cox Proportional Hazards Models, adjusting for potentially confounding variables.

Results—Mortality was assessed a mean of 7 years following study intake at which time 58 participants died, 18 from vascular causes. These participants were depressed much longer than their counterparts (Wilcoxon Rank Sum $Z=2.30$, $p=0.02$) and the duration of the longest depressive episode in years was significantly associated with time to vascular mortality in models ($HR=1.16$, 95% C.I. 1.02–1.33, $p=0.02$), which controlled for age, gender, vascular disease equivalents, and vascular disease risk factors. The duration of longest mania was not related to vascular mortality.

Conclusion—The duration of the most severe depression is independently predictive of vascular mortality, lending further support to the idea that mood disorders hasten vascular mortality in a dose-dependent fashion. Further study of relevant mechanisms by which mood disorders may

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DISCLOSURES

All authors have no potential conflicts of interest to disclose.

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hasten vascular disease and of integrated treatments for mood and cardiovascular risk factors is warranted.

Keywords

bipolar disorder; cardiovascular disease; cerebrovascular disease; epidemiology mortality

INTRODUCTION

Vascular disease is a leading cause of excess death in individuals with bipolar disorder,^{1–3} for whom life expectancy has been reliably estimated to be between 8.5 and 13.6 years less than the general population^{4, 5}. Our group has demonstrated relationships between manic symptom burden and both cardiovascular mortality⁶ and endothelial dysfunction⁷ as well as between depressive symptom burden and measures of arterial stiffness,⁸ which are not seen early in the course of illness.⁹ Considered in aggregate, these findings demonstrate a “dose-response” between the persistence of clinically significant mood symptoms and vascular disease, which provides evidence of causality, creates potential opportunities for mechanistic investigations, and identifies potential targets for treatment.

Several hypotheses related to the link between bipolar disorder and cardiovascular mortality posit that physiological changes induced by chronic mood states may mediate adverse vascular effects. Dysfunction of the autonomic nervous system and hypothalamic-pituitary adrenal axis are two such physiological mechanisms that may be invoked over the long-term course of bipolar disorder.^{10, 11} If such mechanisms are indeed relevant, then abnormal mood states could be conceptualized as an exposure, the duration of which would be associated with vascular disease as an outcome. Thus, a relationship between symptom burden and vascular disease in mood disorders could motivate study of physiological mediators and could even be exploited in the study of such mediators.

We sought further evidence of such a relationship between affective symptom burden and vascular outcomes in participants of the National Institute of Mental Health (NIMH) Genetics Initiative Bipolar Disorder Consortium study using a continuous measure of symptom burden or persistence that may be readily accessible to clinicians. We hypothesized that the duration of the most severe depressive episode and the duration of the most severe manic episode would be related to vascular mortality independent of potential confounding variables.

METHODS

Sample

Several waves of the NIMH Genetics Initiative Bipolar Disorder Consortium have identified individuals with bipolar disorder through clinical referrals, confirmed by structured interviews using the Diagnostic Interview for Genetics Studies (DIGS, NIMH, Molecular Genetics Initiative, 1992). Investigators identified probands from multiplex families with bipolar disorder through screening at treatment facilities, advertisement (advocacy groups, websites), and professional organizations. These methods for recruitment have been

described in greater detail elsewhere.^{12–14} Information from the DIGS, medical records, and other family informants were used to determine a final best estimate diagnosis. Our sample included those with a final best estimate diagnosis of bipolar I disorder from centers that due to the wording of the original informed consents were able to provide personal identifiers to facilitate searching of the National Death Index (NDI). These centers included the University of Iowa, University of Pennsylvania, Indiana University, and Washington University in Saint Louis. Our exposures of interest were the best estimates of affective symptom burden from the DIGS: duration of the most severe episodes of mania and of depression. These measures were obtained from structured interview using the DIGS which asked for the duration of “the most severe period in your life” when in a major depressive episode or manic episode, respectively. The DIGS also assessed for current and prior psychotropic medication exposures and provided a complete list of current medications. For 1,231 (72%) of participants, questions systematically screened for whether a doctor had diagnosed them with high blood pressure, diabetes mellitus, heart attack, congestive heart failure or stroke in questions analogous to that used in the National Co-morbidity Survey – Replication.¹⁵ For the entire sample, medical histories were assessed in an open-ended, rather than systematic fashion for individual medical conditions. Conditions were identified through computer code written for text mining that was cross-checked across all participants to ensure complete capture of relevant information, including for discernible misspellings. The validity of this method was also assessed in comparison to systematic screening in the 1,231 participants with available data. While sensitivity could not be assessed as data reported on screening for individual conditions may not be reported in free text medical history, the specificity of the text mining approach in comparison to the systematic assessment was 75% for hypertension, 86% for diabetes mellitus, and 84% for the presence of a cardiovascular disease risk equivalent.

Outcome Assessment

We systematically assessed mortality by matching personal identifiers, without social security number, with NDI records in 1,716 participants with available age, gender, and index date a mean of 7.3 years after their initial evaluation for the genetics study. The NDI is a national file of identifying death record information and was searched using an algorithm developed by the National Program of Cancer Registries for use in other studies, to determine which potential NDI matches were most likely true matches.^{16, 17} Vascular disease was *a priori* defined as death due to cardiovascular or cerebrovascular causes. The primary outcome of vascular disease was determined based on independent clinician review of the death record data by two investigators (JGF, WHC), which was adjudicated in the case of any disagreement. All-cause mortality was assessed in a secondary analysis. Exploratory analyses pursued measures that might capture illness severity in ways beyond the concept of “symptom burden,” which is the basis for the primary exposure measures. Illness severity was alternatively assessed through indicator variables for prior psychiatric hospitalization, multiple prior psychiatric hospitalizations, suicide attempts, and multiple prior suicide attempts.

Statistical Analyses

All analyses were conducted in SAS 9.3 (SAS Institute, Cary, N.C.). We modeled the probability of vascular mortality (cerebrovascular or cardiovascular) and all-cause mortality with semi-parametric Cox Proportional Hazards Models. To facilitate interpretation across measures, each exposure variable (duration of major depression and mania/hypomania) was converted to years. Cardiovascular disease or equivalents were drawn from Adult Treatment Panel III guidelines¹⁸ and were therefore based on the presence of coronary heart disease, cerebrovascular disease, history of cardiovascular or cerebrovascular events, peripheral vascular disease, or diabetes mellitus (diagnosis or treatment). Cardiovascular risk factors included hypertension (diagnosis or treatment), hyperlipidemia (diagnosis or treatment), obstructive sleep apnea, smoking, borderline diabetes (impaired fasting glucose or impaired glucose tolerance), or the presence of a murmur or arrhythmia. To control for confounding while assessing potential for over-fitting, the relationship between exposure and outcome was examined in both expanded and reduced models. The expanded proportional hazards model was represented by:

$$h_i(t, x_{1i}, \dots, x_{5i}) = h_0(t) * \exp(\beta_1 x_{1i} + \beta_2 x_{2i} + \beta_3 x_{3i} + \beta_4 x_{4i} + \beta_5 x_{5i})$$

where x_{1i} represents the age at evaluation for i^{th} subject (continuous, linear effect), x_{2i} represents an indicator variable for male sex, x_{3i} indicates the presence of vascular disease or equivalent, x_{4i} indicates the presence of a risk factor for vascular disease, x_{5i} is the exposure of interest (years). Reduced models assessed the exposure of interest with only age and sex as covariates. To address for other confounds without over-parameterization, the effect of adding other variables on parameter estimates for the exposures of interest was examined by adding the following variables individually to reduced models: panic disorder, alcohol use disorder, other substance abuse, thyroid disorder, diabetes diagnosis and/or treatment, borderline diabetes, hypertension diagnosis and/or treatment, hyperlipidemia diagnosis and/or treatment, obstructive sleep apnea, smoking status, other cardiac issues (e.g., murmur or arrhythmia), first and/or second generation antipsychotic use, mood stabilizer use (combined and individually, carbamazepine, lithium, valproic acid derivatives), antidepressant use (combined and individually, monoamine oxidase inhibitors, tricyclic antidepressants, serotonin reuptake inhibitors, other antidepressants), stimulant use, and benzodiazepine use. Sex was assessed as a potential moderator. All models assumed proportional hazards and the assumption of proportional hazards was tested via interactions with time in the reduced models.

RESULTS

Participants were a mean (SD) of 42.3 (13.0) years old on study intake and approximately 2/3 of the sample was female. Demographic and clinical characteristics of the sample are outlined in Table 1. As evident in the table, assignment of diabetes, hypertension, and hyperlipidemia status was largely driven by treatment for the relevant risk factors. Participants spent a mean (median; SD) of 29.1 (12.0; 68.6) weeks with depression in the most severe episode and 10.5 (4.0; 25.5) weeks with mania in the most severe episode.

A total of 58 participants died at the time of NDI assessment, 18 of which represented adjudicated deaths from vascular disease. The most severe major depressive episodes of these 18 participants were much longer than those of their counterparts with average durations of 71 (SD 99) and 29 (SD 69) weeks, respectively (Wilcoxon Rank Sum $Z=2.30$, $p=0.02$). The relationship between the exposures of interest (duration of mania and depression) and time to vascular mortality in the multivariate Cox regression models is illustrated in Table 2. The duration of the most severe depression was related to time to vascular mortality in reduced (HR 1.17, 95% C.I. 1.02–1.33, $p=0.02$) and expanded (HR 1.16, 95% C.I. 1.02 – 1.33, $p=0.02$) models. The duration of the most severe mania was not, however, related to time to vascular mortality in reduced (HR 0.95, 95% C.I. 0.39–2.33, $p=0.92$) or expanded (HR 0.97, 95% C.I. 0.41–2.35, $p=0.98$) models. Parameter estimates for each covariate of interest did not substantively differ between the reduced and expanded models. The presence of a cardiovascular risk factor, which primarily served as an indicator for treatment of that risk factor, had a marginally protective effect in the expanded model where duration of depression was the exposure of interest. In an expanded model with the exposure of interest omitted (controlling for age, male sex, and cardiovascular disease equivalent), the diagnosis or treatment of a vascular risk factor was marginally associated with reduced vascular mortality (HR 0.35, 95% C.I. 0.11 – 1.14, $p=0.08$). Models which individually assessed the impact of other confounds did not substantively alter the parameter estimates. There was no evidence of moderation by sex. All-cause mortality was not associated with the duration of the most severe depression (reduced model HR 1.04, 95% C.I. 0.88 – 1.24, $p=0.63$; expanded model HR 1.04, 95% C.I. 0.88 – 1.24, $p=0.63$) or the duration of the most severe mania (reduced model HR 0.67, 95% C.I. 0.22 – 2.00, $p=0.47$; expanded model HR 0.68, 95% C.I. 0.22 – 2.05, $p=0.49$). Other indices of illness severity (prior suicide attempt, multiple suicide attempts, prior hospitalization, multiple prior hospitalizations) were not significantly related to vascular or all-cause mortality in full or reduced models (all $p>0.20$).

DISCUSSION

In our follow-up analysis of mortality among participants in a bipolar disorder genetics study, we found evidence that the duration of the most severe depression was independently predictive of vascular mortality in a dose-dependent fashion. Our exposures of interest to assess duration were retrospectively assessed and could be readily accessed in clinical interview. Each year that the most severe depressive episode persisted was associated with a 16% increased risk of vascular mortality. Thus, clinicians may have at their fingertips readily accessible data to assess risk of vascular illness related to depression in bipolar I disorder. Unlike a prior analysis using symptom burden⁶ and an analysis of manic symptom count,¹⁹ we failed to show an association between manic symptom burden and vascular mortality. With broad confidence intervals, this may represent Type II error. It may also reflect misclassification of exposure given prior findings suggestive that manic symptom burden may be over-estimated retrospectively.⁸ While two prior analyses did not find any relationship between depressive symptom burden and cardiovascular mortality⁶ and endothelial dysfunction,⁷ these prior analyses were conducted in a sample with a relatively high severity of illness. Although the presence of bipolar disorder itself has been strongly

linked with increased all-cause mortality,^{20, 21} we found no relationship between symptom burden measures and all-cause mortality in this population, suggesting some specificity in the association of these symptom burden measures with vascular mortality. In some multivariate Cox models, the presence of cardiovascular risk factors appeared only marginally, but paradoxically protective. This is most likely due to these risk factors being largely inferred from treatment. Thus, the indicator variable primarily represents those treated for a given risk factor while failing to capture those with an unidentified/untreated risk factor. This result parallels findings from a national cohort study in which the association between bipolar disorder and mortality was significantly less among those with a prior diagnosis of the chronic medical condition.⁴ This underscores the potential importance of more timely diagnosis and appropriate treatment of risk factors, although the current study does not directly test the benefit of such intervention.

This study has several important limitations that must be considered. The infrequency of the outcome of interest limited the number of covariates that could be included in models without over-parameterization. Furthermore, vascular risk factors, especially smoking, were under-ascertained in this sample. Treatment variables could be included only individually in models exploring for other potential confounds. Taken together, this leaves potential for residual confounding. We attempted to address this through individual inclusion of broader and more refined covariates, though methodologically this inherent limitation cannot be overcome. Our measure of affective symptom burden was measured retrospectively and thus is vulnerable to misclassification. While presumably any such misclassification is non-differential, this can only be assumed and not tested. The ease with which our exposure variable could be obtained in a routine clinical interview is another notable strength. The analysis also involves a large sample with systematic psychiatric phenotyping. Our sample was 66% female, somewhat more than the near 60% estimated from prevalence studies of bipolar I disorder,²² though not unexpected since females are more likely to participate in such research.²³ While this slight over-representation of females might decrease the number of outcomes observed, it seems unlikely to substantively impact the relationship between exposure and outcome, and there was no evidence of moderation by gender.

The finding of a relationship between depressive symptom burden and vascular mortality supports the notion that the persistence of mood symptoms in bipolar disorder hastens vascular mortality in a dose-dependent fashion. The independence of this relationship from established risk factors suggests mediation by novel mechanisms. Future studies should attempt to identify relevant mediators for further study. Treatment of traditional risk factors may nonetheless mitigate this risk and integration of medical and psychiatric care for this at-risk population, simultaneously targeting the burden of mood symptoms and vascular risk factors, is needed to address the excess burden of vascular disease.

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TABLE 1

Demographic and Clinical Characteristics of Bipolar Genomics Study Sample (N=1,716)

Variable	Mean (SD)
Age	42.3 (13.0)
Years of followup	7.3 (4.4)
Most severe depression years (N=1,589)	0.56 (1.32)
Most severe mania years (N=1,647)	0.20 (0.50)
	N (%)
Female gender	1139 (66.4%)
Prior psychiatric hospitalization (N=1,708)	1464 (85.7%)
Prior suicide attempt (N=1,683)	796 (47.3%)
Panic disorder	348 (20.3%)
Alcohol use disorder (N=1,715)	632 (36.9%)
Other substance abuse (N=1,404)	233 (16.6%)
Thyroid disorder (N=1,702)	340 (20.0%)
Cardiovascular Equivalent	236 (13.8%)
Diabetes diagnosis or treatment	174 (10.1%)
Diabetes diagnosis	163 (9.5%)
Diabetes treatment	75 (4.4%)
Vascular disease	83 (4.8%)
Cardiovascular Risk Factor	556 (32.4%)
Hypertension diagnosis or treatment	422 (24.6%)
Hypertension diagnosis	328 (19.1%)
Hypertension treatment	272 (15.9%)
Hyperlipidemia diagnosis or treatment	165 (9.6%)
Hyperlipidemia diagnosis	82 (4.8%)
Hyperlipidemia treatment	122 (7.1%)
Obstructive sleep apnea	33 (1.9%)
Smoker	2 (0.1%)
Borderline diabetes	3 (0.2%)
Other (e.g. murmur, arrhythmia)	48 (2.8%)

TABLE 2

Cox proportional hazards ratio (HR) estimates for duration of illness and time to vascular mortality.

Variable	HR	95% C.I. HR	<i>p</i> -value
Model 1: Mania (Reduced)			
Age (years)	1.08	1.03 – 1.13	0.0005
Male sex	2.38	0.83 – 6.88	0.11
Duration of most severe mania (years)	0.95	0.39 – 2.33	0.92
Model 2: Mania (Expanded)			
Age (years)	1.07	1.03 – 1.12	0.002
Male sex	2.35	0.81 – 6.79	0.12
Cardiovascular disease equivalent	4.04	1.12 – 14.56	0.03
Cardiovascular risk factor	0.70	0.19 – 2.55	0.59
Duration of most severe mania (years)	0.97	0.41 – 2.35	0.98
Model 3: Depression (Reduced)			
Age (years)	1.09	1.04 – 1.13	0.0001
Male sex	3.60	1.18 – 11.0	0.02
Duration of most severe depression (years)	1.17	1.02 – 1.33	0.02
Model 4: Depression (Expanded)			
Age (years)	1.09	1.04 – 1.14	0.0001
Male sex	3.25	1.06 – 9.93	0.04
Cardiovascular disease equivalent	4.59	1.37 – 15.45	0.01
Cardiovascular risk factor	0.25	0.06 – 1.01	0.051
Duration of most severe depression (years)	1.16	1.02 – 1.33	0.02