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Subthreshold Hypomanic Symptoms in Progression From Unipolar Major Depression to Bipolar Disorder

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Abstract

Objective—We determined if subthreshold hypomanic symptoms predicted new onset mania or hypomania.

Method—We identified 550 individuals followed for at least one year in the National Institute of Mental Health Collaborative Depression Study with a diagnosis of major depression at intake. All participants were screened at baseline for a total of five manic symptoms: elevated mood, decreased need for sleep, high energy, increased goal-directed activity, and grandiosity. Participants were followed prospectively for a mean of 17.5 and up to 31 years. Longitudinal Interval Follow-up Examinations monitored course of illness and identified any hypomania or mania. The association of subthreshold hypomanic symptoms at baseline with subsequent hypomania or mania was determined in survival analyses using Cox Proportional-Hazards Regression.

Results—With a cumulative probability of one-in-four on survival analysis, 19.6% (N=108) of the sample experienced hypomania or mania, resulting in revision of diagnoses for 12.2% to bipolar II and 7.5% to bipolar I disorder. The number of subthreshold hypomanic symptoms, psychosis, and age of onset predicted progression to bipolar disorder. Less need for sleep, unusual energy, and increased goal-directed activities were specifically implicated.

Conclusions—Symptoms of hypomania, even when of low intensity, were very frequently associated with subsequent progression to bipolar disorder, although the majority of patients who converted did not have any symptoms of hypomania at baseline. Therefore, continued monitoring for the possibility of progression to bipolar disorder over the long-term course of major depressive disorder is necessary.

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Keywords

Age of Onset; Bipolar disorder; Depressive disorder; Delusions; Prospective studies

INTRODUCTION

Bipolar disorder is characterized by recurrent episodes of hypomania or mania and major depression. Because bipolar disorder may present with depression, individuals who present with major depression may have a major depressive disorder (MDD) or a bipolar disorder, which would not be recognized until the occurrence of a defining mania or hypomania. Subthreshold hypomanic symptoms have been posited to be of nosological relevance (1–3) though the predictive validity of such symptoms toward the development of a frank bipolar disorder is not established.

Prospective cohort studies with structured diagnostic interviews of individuals with MDD at baseline have reported varied rates of diagnostic conversion to bipolar disorder as detailed in Table 1 (4–12). The rate reported by a representative community sample of adolescents and young adults in Germany (4) appears lower than that from clinical samples. Higher rates of conversion are seen in the child and adolescent samples (7–12). In a sample of seriously ill inpatients from Switzerland, the rate of conversion was greatest in the first four years after onset of first episode and thereafter was linear at a change rate of about 1.25% per year (13). On analysis of the National Institute of Mental Health Collaborative Depression Study (CDS) at 10 years of follow-up, approximately 10% of those with MDD developed bipolar disorder (5). The current manuscript extends these findings from the CDS after up to 31 years of follow-up.

Several variables have been prospectively associated with the development of mania or hypomania in MDD. The most robust predictors, based on replication in several studies of separate samples include early age of onset (4,13,14), psychosis (5,6,10,11,14), and a family history of mania (5,10,12–14). The presence of a pedigree loaded with affective illness has further been associated (14), especially in child and adolescent samples (10,12,15). The higher conversion rates reported from child and adolescent samples (7–12) may at least in part be explained by the high rates of familial aggregation seen in child probands with bipolar disorder (16,17) or a possible secular trend for early age of onset in more recently born cohorts (18). Other clinical predictors of progression to bipolar disorder reported by more than one study include acute onset of mood syndrome (10,19), multiple prior depressive episodes (4,13), and hypersomnia or psychomotor retardation (10,14). There exists a surprising paucity of study regarding whether subthreshold hypomanic symptoms may predict progression to bipolar disorder with one recent study supporting this hypothesis (20).

We sought to determine the diagnostic conversion rate from MDD to bipolar disorder. We also assessed whether subthreshold hypomanic symptoms predicted subsequent diagnostic conversion, alone and in relation to established risk factors. The CDS data are ideally suited to accurately estimate the conversion of MDD to bipolar disorder among those with MDD at intake because of its long and relatively high intensity follow-up. As part of the CDS, all participants were screened for a history of manic symptomatology in five domains during the intake episode: elevated mood, decreased need for sleep, high energy, increased goal-directed activity, and grandiosity. To our knowledge, this is the first analysis to systematically assess the impact of subthreshold manic symptoms on subsequent diagnostic conversion to bipolar disorder.

METHODS

Participants

Patients with mood disorders were recruited for the CDS from five academic centers: Massachusetts General Hospital and Harvard University, Rush Presbyterian–St. Luke’s Medical Center in Chicago, the University of Iowa, New York State Psychiatric Institute and Columbia University, and Washington University School of Medicine in St. Louis. The study was approved by the institutional review boards at each site. All participants were Caucasian (genetic hypotheses examined), spoke English, had knowledge of their biological parents, and provided written consent. Treatment was not assigned or required in this observational study. Participants met Research Diagnostic Criteria (RDC) for MDD, schizoaffective disorder, or manic disorder at study intake based upon medical records and use of the Schedule for Affective Disorders and Schizophrenia (SADS) (21,22).

Intake diagnosis was used to identify participants with MDD, based on an intake RDC diagnosis of MDD or schizoaffective disorder, depressed, mainly affective. DSM-IV-TR criteria for MDD is very similar to these conditions from the RDC. Age of onset and co-occurring conditions were identified at study intake. Restricting the sample to those with at least one year of follow-up to ensure a minimum of two follow-up assessments yielded 550 participants with MDD and at risk of subsequent progression to bipolar disorder.

Procedures

The SADS was used to identify the presence of delusions, hallucinations, hypersomnia, or psychomotor retardation. The presence of delusions or hallucinations defined psychosis. To determine family history, we analyzed data for consensus diagnoses from 2,467 first-degree biological relatives, who were interviewed in person or by telephone as part of a family study that 331 individuals from this sample participated in. Raters blind to proband diagnosis used the lifetime version of the SADS to interview all adult, first-degree relatives willing to participate. Investigators formulated a consensus diagnosis from the SADS and all available sources of information to derive RDC diagnoses. Consensus diagnoses for 1,519 first-degree relatives of another 214 individuals who did not participate in the family study were based on the Family History Research Diagnostic Criteria, which uses an interview with one or more family members to estimate diagnoses on relatives not interviewed. Diagnoses from family history data were not available for only five participants (0.9%), for whom this data was imputed as negative. The CDS sample and family study have been well-described elsewhere (23–25).

The SADS screened all participants at baseline for five manic symptoms. Raters were well-trained on the SADS (26) and, for these manic symptoms, demonstrated reliability with intraclass correlation coefficients of 0.98 for elevated mood, 0.96 for less need or sleep, 0.93 for unusually energetic, 0.86 for increased goal-directed activity, and 0.73 grandiosity (27). Participants were not uniformly screened for other symptoms of mania. Each item was rated on a six point scale. The sleep item focused on the amount of sleep needed to “feel rested” compared to usual need. The scale for the relevant SADS items are available in online Appendix A. Any score of greater than 1 was used to signify the presence of these symptoms, because of the low frequencies for higher scores in this sample and desire to target subthreshold symptoms. The low threshold allowed the identification of symptoms that would not warrant diagnosis of bipolar disorder. The total number of items present with a score greater than 1 (range 0–5) was tested as a predictor for subsequent manic symptom development. In a secondary analysis, the sum of scores on these five items (range 5–30) was calculated, herein referred to as the total score from manic screening questions.

Follow-up assessments were completed using the Longitudinal Interval Follow-up Evaluation (28) or a revised version, which was administered semiannually in the first five years and annually thereafter, tracking the severity of each RDC syndrome weekly to identify the weeks of onset for any hypomania or mania that developed during follow-up.

Data Analyses

Those who converted to bipolar I and bipolar II disorder were compared to those who did not using analysis of variance for continuous measures and chi-square for categorical measures. Survival was examined using Kaplan-Meier product limit estimate with survival time reflecting the primary outcome of time to onset of either hypomania or mania. An additional analysis modeled time to hypomania in those that did not later develop mania (progression to bipolar II) and time to mania (progression to bipolar I). Participants were censored upon loss to follow-up, death, drop-out, or end of the study. Survival analysis was also performed using Cox proportional hazards regression. Primary analyses were unadjusted. Later analyses included covariates for the most robust predictors from prior studies: age of onset, psychosis (hallucinations or delusions), and family history of bipolar disorder. Also included in models were any sociodemographic variables found to be associated with both affirmative responses to manic screening questions and outcome. Age of intake and age of onset were each modeled as continuous, assuming a linear effect. Censuring and diagnostic conversion were assumed to be independent. Proportional hazards were assumed for all variables modeled in Cox regression. Analyses were performed using SAS 9.2 software with exception of ROC analysis (29). Kaplan-Meier survival curves were calculated using SPSS Statistics 17.0.

RESULTS

Participants were followed for a mean (median; SD) of 17.5 (19.9; 9.9) years with 390 (70.9%) completing at least 10 years of follow-up. Diagnostic change to bipolar disorder was noted in 108/550 (19.6%) participants. The majority of these diagnostic conversions, 67/550 (12.2%) involved the development of hypomania without mania. Another 41/550 (7.5%) developed mania, of which 24/41 (59%) had a preceding hypomania. Table 2 outlines the demographic characteristics for this sub-sample of the CDS. At intake, the participants who experienced a prospectively observed mania or hypomania were significantly younger, less likely to be married, had an earlier age of onset of illness, and were more likely to have delusions. Those who eventually developed mania or hypomania were more likely to have had a family history of bipolar disorder, which was generally consistent with the specific bipolar subtype of ultimate diagnosis. Of those re-diagnosed as bipolar I, 10% had a family history of bipolar I versus 1% for bipolar II. Of those re-diagnosed as bipolar II, 19% had a family history of bipolar II versus 15% for bipolar I. There were no differences with regard to gender or inpatient status at intake.

The majority of participants (N=431, 78%) did not endorse any manic symptoms on screening, 52 individuals (9.5%) endorsed one symptom, 26 (4.7%) endorsed two symptoms, 14 (2.5%) endorsed three symptoms, 18 (3.3%) endorsed four symptoms, and 9 (1.6%) endorsed all five symptoms. Subthreshold manic symptoms reported included elevated or expansive mood (N=60, 11%), less need for sleep (N=36, 7%), unusually energetic (N=64, 12%), increase in goal-directed activity (N=65, 12%), and grandiosity (N=38, 7%). Gender and married status were not associated with total number of manic symptoms screened positive. Total number of manic symptoms screened positive was negatively correlated with intake age (Kruskal-Wallis $\chi^2=23.4$, $df=5$, $p=0.0003$) and was not related to subsequent antidepressant exposure (Kruskal-Wallis $\chi^2=5.2$, $df=5$, $p=0.40$).

Kaplan-Meier survival curves illustrate the time to development of any (hypo)manic syndrome (Figure 1a), mania (Figure 1b), and hypomania without subsequent mania (Figure 1c). As illustrated in the figure, the cumulative probability of developing mania or hypomania was approximately one in four (26.3%). In the primary Cox regression analyses, the total number of manic symptoms present at intake predicted the onset of hypomania or mania with each additional symptom conveying an increased risk of 29% (HR 1.29, 95% C.I. 1.13–1.47, $p=0.0001$). This measure was also associated with time to mania (HR 1.41, 95% C.I. 1.17–1.69, $p=0.0003$), though was not significantly associated with time to hypomania (HR 1.14, 95% C.I. 0.94–1.37, $p=0.17$).

The total score from manic screening questions further predicted development of hypomania or mania (HR 1.34, 95% C.I. 1.17–1.54, $p<0.0001$), suggesting a 34% increased risk of developing (hypo)mania for every standard deviation (2.5 points) increase on this metric. These results proved similarly significant for hypomania (HR 1.23, 95% C.I. 1.02–1.17, $p=0.03$) and mania (HR 1.28, 95% C.I. 1.09–1.52, $p=0.003$).

Multivariate models determined the magnitude of these associations compared to the most robust predictors in the literature. With age at intake, age of onset, psychosis, and family history of bipolar disorder as covariates, the total number of manic symptoms was similarly associated with subsequent mania or hypomania (HR 1.24, 95% C.I. 1.09–1.41, $p=0.001$). Table 3 details the hazard ratio estimates for these multivariate models. Psychosis at study intake was associated with the development of mania and an earlier age of onset with the subsequent development of hypomania without mania. Further, family history of bipolar disorder was associated with time to mania or hypomania. In a *post hoc* analysis, a family history of bipolar I appeared related to time to mania (HR 3.85, 95% C.I. 1.23–12.00, $p=0.02$), and a family history of bipolar II was associated with time to hypomania without subsequent mania (HR 2.07, 95% C.I. 1.12–3.82, $p=0.02$).

Secondary analyses sought to determine which individual items from the SADS appeared most relevant. Individual items were entered separately into models as they were highly correlated. In univariate analyses, the following manic symptoms individually predicted onset of hypomania or mania: decreased need for sleep, unusually energetic, and increased goal-directed activity. Decreased need for sleep, unusually energetic, increased goal-directed activity, and grandiosity were predictive specifically of mania. Decreased need for sleep and unusually energetic predicted hypomania without mania. These results of these individual univariate analyses are highlighted in Table 4.

To estimate the clinical utility of the above findings, receiver operator characteristic curves (ROC) were performed on the total number of manic symptoms present at intake (0–5). A fitted ROC yielded an area of 0.61. An optimal cut off of ≥ 3 manic symptoms was identified which yielded a low sensitivity of 16% and specificity of 95%. The positive predictive value for this cut-off was 42%, and the negative predictive value was 82%. With 73/431 (16.9%) of individuals without any subclinical hypomanic symptoms at baseline subsequently developing hypomania or mania, lowering the threshold only improved sensitivity to a maximum of 32%.

CONCLUSIONS

At the close of this prospective cohort study, approximately one-quarter of those with a diagnosis of MDD progressed to bipolar disorder. The number of subthreshold hypomanic symptoms present was associated with the subsequent onset of threshold mania or hypomania, independent of established risk factors. Of the individual symptoms, elevated or expansive mood was not associated with later progression to bipolar disorder, which is

noteworthy given its nosological position as a stem criterion for (hypo)mania. Many individuals that did not endorse a history of subthreshold hypomanic symptoms went on to develop (hypo)mania. The presence of the symptoms was therefore not very sensitive for the detection of subsequent mania. However, when present in sufficient quantities (with 3/5 as the optimal cutoff), these symptoms proved to be quite specific though the positive predictive value of 41.5% should lend caution to the prudent clinician.

Akin to previously reported data showing higher rates of diagnostic conversion or progression early in follow-up, our analysis shows more rapid progression in the first five years of follow-up, followed by a slower linear decline thereafter. The slower decline corresponded to the time at which surveillance decreased from semiannually to annually. Angst et al. reported a similar pattern when intensity of surveillance decreased from approximately every two to every five years (13). The lower frequency of surveillance in the Angst et al. study nonetheless did not yield lower rates of progression. It is difficult to discern whether this change in progression rates at year five reflects a greater likelihood for progression earlier in the course of illness or an artifact of surveillance bias. Presumably, any such surveillance bias would disproportionately influence milder, more subtle episodes of mood elevation symptoms, yet our finding is evident for the development of both mania and hypomania without mania. This finding was present only in the younger half of the sample, further arguing against this representing an artifact of surveillance bias. The overall rate of progression observed was lower than other prospective studies. A variety of variables may influence this rate of progression, including acuity and age of the sample, accuracy of intake diagnosis, and rigor of prospective monitoring. Our sample was older at intake than others. If progressing to bipolar disorder is more likely to happen at younger ages, our sample may have had fewer at risk of converting.

The family history of those with major depression who developed mania or hypomania was more likely to include first degree relatives with bipolar disorder. Those with a family history of bipolar I were more likely to develop mania and those with a family history of bipolar II were more likely to develop hypomania without mania. These findings strengthen prior analyses from the CDS showing a preponderance of bipolar II relatives in the families of bipolar II probands (30). In this case, our findings extend to some who were initially “misclassified” as having a unipolar MDD prior to the onset of the defining features of bipolar disorder. This lends further support to the validity of bipolar II and highlights just some of the challenges inherent to genetic studies in mood disorders.

Our study generally replicated the most robust predictors identified from prior studies. However, contrary to the findings of Angst et al. (13), our analysis found that an early age of onset was associated with a change in diagnosis to bipolar II but not bipolar I. Akiskal et al. previously identified an associations of energy-activity with conversion to bipolar II and psychotic symptoms with conversion to bipolar I with CDS data at up to 11 years of follow-up (19) and the current report extends this to 31 years of follow-up. Another prior CDS analysis found delusions in the setting of major depression and a family history of bipolar disorder to be associated with bipolar as opposed to unipolar depression (31). Our analysis similarly found these features, when present in MDD, were associated with subsequent progression. Our results uniquely contribute to the literature in associating subthreshold hypomanic symptoms with progression from MDD to bipolar disorder in a prospective sample followed for several decades.

There are several limitations of this observational study. Our relatively high acuity sample may not generalize to lower acuity populations. Subthreshold hypomanic symptoms were assessed at study intake, posing some risk for misclassification of exposure over the course of follow-up. Limitations in rating assessments and the potential for lack of insight into

manic symptoms may have also contributed to misclassification. These assessments were, however, systematically collected on all participants at intake for the current episode prior to the time of evaluation. Treatment was not controlled for in this cohort and patients received a variety (or lack) of treatments during follow-up. Those with a history of subthreshold hypomanic symptoms were not differentially prescribed antidepressants. Treatments could have influenced the development of mania or hypomania, although evidence does not generally support that assumption that antidepressants induce mania (32–37). In prospective studies, all who developed antidepressant-associated mania went on to later have episodes of spontaneous mania though these studies included a limited number of cases with pharmacologically-induced hypomania (10,14). The family histories of those with antidepressant-associated mania further resemble those of individuals with spontaneous mania. For these reasons, opinion leaders do not currently distinguish antidepressant-induced manias from those that arise spontaneously (38) and this assumption underlies our analyses (39,40). The proposed revisions for DSM-V now also include the caveat “A full manic or hypomanic episode emerging during antidepressant treatment (medication, ECT etc) and persisting beyond the physiological effect of that treatment is sufficient evidence for a manic or a hypomanic episode diagnosis.”

Our participants were interviewed semiannually for the first 5 years of follow-up and annually thereafter. Although the interval histories were reconstructed in a systematic and reliable manner, there exists potential for recall bias. Some hypomanias could have been missed and our estimate of diagnostic conversion may therefore be underestimated. Although differential surveillance for the first five years compared with subsequent years could influence reported rates of progression, there was certainly no differential surveillance by exposure (presence of subthreshold hypomanic symptoms) to influence the associations observed. As aforementioned, such bias would be expected to impact hypomania more than mania and change in rates of diagnostic conversion after five years is observed for both hypomania and mania. Further, it is biologically plausible that individuals with bipolar disorder would be likely to first manifest the defining features of illness (hypomania and mania) earlier in the course of illness, particularly given a mean (SD) age of onset of 18.2 (11.6) for bipolar I disorder and 20.3 (9.7) for bipolar II disorder (1).

Notable strengths of the current study include the rigor of phenomenological assessments and the long duration of relatively intense follow-up, which increased our ability to capture eventual mood elevation syndromes. Further, the baseline assessments included a comprehensive structured interview and medical record review, decreasing the risk for false negatives at intake (i.e. misdiagnosis of bipolar disorder as MDD) that could inflate estimates of subsequent diagnostic conversion. Our data demonstrate that a substantial portion of individuals treated clinically for MDD will ultimately be recognized as having a bipolar disorder.

Our findings further suggest that the presence of even low-grade hypomanic symptoms may be as strongly associated with progression to bipolar disorder as the most robustly established predictors to date. Although survival analyses are most appropriate for these time to event data, the secondary ROC analyses demonstrate a modest area under the curve and positive predictive value, such that these subclinical hypomanic symptoms would certainly not warrant a change in diagnosis. This suggests that our ability to recognize those individuals with major depression, who will go on to develop (hypo)mania, remains limited and underscores the importance of rigorously evaluating and closely monitoring those in treatment for mood disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix

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Figure 1. Kaplan-Meier Survival Curves for Time to Change in Diagnosis for Patients with Major Depressive Disorder (N=550)

As shown in the upper panel, in the first five years, the rate of change in diagnosis approximates 2.5% per year and thereafter declines in a near linear fashion at a rate of roughly 0.5% per year. The survival curve in the lower panel contrasts the change in diagnosis between those with (N=41) and without (N=509) three or more subthreshold hypomanic symptoms at intake.

TABLE 1
Studies of Diagnostic Conversion from Unipolar Depression to Bipolar Disorder

First Author (Year)	N	Mean (SD) [†] Age at Intake	Sample Acuity	Mean (SD) [†] Follow-up in Years	Number of Prospective Assessments	Bipolar II (%)	Bipolar I (%)	Total Conversion (%)
Beesdo (2009)	649	14–24 [‡]	Representative community sample	~ 7 [‡]	3	1.7%	2.3%	4.0%
Coryell (1995)	381	36.8 (13.6)	3/4 Inpatient	10	15	5.0%	5.2%	10.2%
Geller (2001)	72	10.3 (1.5) prepubertal	Outpatient	9.9 (1.5)	Not reported	15.3%	33.3%	48.6%
Goldberg (2001)	74	23.0 (3.8)	Inpatient	14.7	5	25.7%	14.9%	40.5%
Kovacs (1994)	60	11.1	Outpatient	6.3	Not reported			15.0%
McCauley (1993)	65	12.3 (2.6)	Inpatient and outpatient	3	4	6.2%	1.5%	7.7%
Rao (1995)	26	15.4 (1.3)	<1/2 Inpatient	7.0 (0.5)	1			19.2%
Strober (1982)	60	~15	Inpatient	3–4	6–8	0.0%	20.0%	20.0%
Strober (1993)	58	~15	Inpatient	2	4			8.6%

This table outlines the results of prospective cohort studies assessing the rate of onset of hypomania or mania in samples with unipolar major depression. Sample size is based on number of individuals with major depression at intake. Only studies with structured diagnostic interviews at baseline assessment were included. In cases wherein a single sample was published repeatedly, the most complete or recent publication was recorded. Retrospective cohorts are not included.

[†] Standard deviations reported only when available.

[‡] Signifies data provided for entire sample, but not specifically reported for sub-sample with major depressive disorder.

TABLE 2

Baseline Characteristics of Patients with a Diagnosis of Major Depression at Study Entry, by Subsequent Diagnosis

Demographic/Clinical Characteristics	Prospective Diagnosis			Entire Sample
	MDD	Bipolar I	Bipolar II	
	N=442 # (%)	N=41 # (%)	N=67 # (%)	
Age at intake, mean (median; SD) [‡]	39 (36; 15)	36 (33; 13)	33 (30; 13)	38 (35; 14)
Age of onset (median; SD) [‡]	31 (28; 14)	27 (22; 13)	24 (23; 9)	30 (27; 14)
Female	267 (60%)	27 (66%)	47 (70%)	341 (62%)
Inpatient	335 (76%)	34 (83%)	51 (76%)	420 (76%)
Delusions [‡]	39 (9%)	13 (32%)	9 (13%)	61 (11%)
Hallucinations	27 (6%)	6 (15%)	6 (9%)	39 (2%)
Prior episodes (number of)				
None	157 (36%)	12 (29%)	17 (25%)	186 (34%)
One	115 (26%)	6 (15%)	17 (25%)	138 (25%)
Two	63 (14%)	5 (12%)	10 (15%)	78 (14%)
Three	37 (8%)	8 (20%)	7 (10%)	52 (9%)
Three or more	70 (16%)	10 (24%)	16 (23%)	96 (17%)
Family history of major depression	224 (51%)	17 (41%)	36 (54%)	277 (51%)
Family history of bipolar disorder [‡]	40 (9%)	8 (20%)	13 (19%)	61 (11%)
Family history of bipolar I [†]	11 (2%)	4 (10%)	1 (1%)	16 (3%)
Family history of bipolar II [‡]	30 (7%)	6 (15%)	13 (19%)	49 (9%)
Psychomotor retardation	180 (33%)	18 (44%)	31 (46%)	229 (42%)
Hypersomnia	151 (34%)	18 (44%)	27 (40%)	196 (36%)
Marital Status [†]				
Married	216 (49%)	14 (34%)	20 (30%)	250 (45%)
Divorced/separated	72 (16%)	9 (22%)	16 (24%)	97 (18%)
Single	133 (30%)	15 (37%)	30 (45%)	178 (32%)
Widowed	21 (5%)	2 (7%)	1 (1%)	25 (5%)
Educational Level				
Without Diploma	86 (19%)	0	11 (16%)	97 (18%)
High School Graduate	119 (27%)	13 (32%)	17 (25%)	149 (27%)
Some College	130 (29%)	15 (37%)	19 (28%)	164 (30%)
College Graduate	107 (24%)	13 (32%)	20 (30%)	140 (25%)
Co-occurring Psychiatric Diagnoses				
Alcohol abuse	113 (26%)	13 (32%)	19 (28%)	145 (26%)
Drug abuse	26 (6%)	4 (10%)	7 (10%)	37 (7%)
Generalized anxiety disorder	30 (7%)	5 (12%)	4 (6%)	39 (7%)
Obsessive-compulsive disorder	7 (2%)	0	2 (5%)	9 (2%)

Demographic/Clinical Characteristics	Prospective Diagnosis			Entire Sample
	MDD	Bipolar I	Bipolar II	
	N=442 # (%)	N=41 # (%)	N=67 # (%)	
Panic disorder	18 (4%)	0	6 (9%)	24 (4%)
Phobic disorder	33 (7%)	3 (7%)	4 (6%)	40 (7%)

[†]
 $p < 0.05$,

[‡]
 $p < 0.01$

TABLE 3

Cox proportional hazards ratio (HR) estimates for onset of (hypo)mania in major depression

Variable	HR	95% C.I. HR	p-value
Model 1: Time to either hypomania or mania			
Number of Positive Manic Screens	1.24	1.09 – 1.41	0.001
Age of Onset	0.97	0.95–0.995	0.02
Family History of Bipolar Disorder	1.91	1.18–3.08	0.008
Psychosis	1.97	1.25–3.10	0.004
Age at Intake	1.00	0.98 – 1.03	0.67
Model 2: Time to mania			
Number of Positive Manic Screens	1.40	1.16 – 1.68	0.0004
Age of Onset	0.98	0.95 – 1.02	0.34
Family History of Bipolar Disorder [†]	1.93	0.88–4.21	0.10
Psychosis	3.54	1.85–6.77	0.0001
Age at Intake	1.01	0.98 – 1.05	0.41
Model 3: Time to hypomania without ever mania			
Number of Positive Manic Screens	1.07	0.89 – 1.29	0.48
Age of Onset	0.97	0.94 – 0.996	0.03
Family History of Bipolar Disorder [†]	1.71	0.93 – 3.15	0.08
Psychosis	1.11	0.56–2.17	0.77
Age at Intake	1.00	0.97 – 1.03	0.95

This table illustrates the relationship between the total number of manic items present at any level on screening and subsequent onset of (hypo)mania in survival analysis.

[†] Significant when modeled *post hoc* as family history of bipolar I ($p=0.02$) and bipolar II ($p=0.02$), respectively.

TABLE 4

Cox proportional hazards ratio (HR) estimates for onset of (hypo)mania in major depression

Variable	HR	95% C.I. HR	<i>p</i> -value
Time to either hypomania or mania			
Elevated or Expansive Mood	1.35	0.78 – 2.33	0.28
Less Need For Sleep	3.07	1.78 – 5.31	<0.0001
Unusually Energetic	2.71	1.72 – 4.26	<0.0001
Increase in Goal-directed Activity	2.29	1.43 – 3.66	0.0005
Grandiosity	1.73	0.92 – 3.22	0.09
Time to mania			
Elevated or Expansive Mood	1.64	0.73 – 3.71	0.23
Less Need For Sleep	3.37	1.49 – 7.61	0.003
Unusually Energetic	3.49	1.78 – 6.83	0.003
Increase in Goal-directed Activity	2.91	1.46 – 5.80	0.003
Grandiosity	3.68	1.70 – 7.97	0.001
Time to hypomania without ever mania			
Elevated or Expansive Mood	1.11	0.53 – 2.32	0.79
Less Need For Sleep	2.30	1.10 – 4.81	0.03
Unusually Energetic	1.87	1.001 – 3.49	0.05
Increase in Goal-directed Activity	1.60	0.84 – 3.06	0.15
Grandiosity	0.63	0.20 – 2.02	0.44

This table illustrates the relationship between the individual manic items present at any level on screening and subsequent onset of (hypo)mania in univariate survival analysis.