Risks for the Transition From Major Depressive Disorder to Bipolar Disorder in the National Epidemiologic Survey on Alcohol and Related Conditions

Stephen E. Gilman, ScD; Jamie M. Dupuy, MD; and Roy H. Perlis, MD

ABSTRACT

Objective: It is currently not possible to determine which individuals with unipolar depression are at highest risk for a manic episode. This study investigates clinical and psychosocial risk factors for mania among individuals with major depressive disorder (MDD), indicating diagnostic conversion from MDD to bipolar I disorder.

Method: We fitted logistic regression models to predict the first onset of a manic episode among 6,214 cases of lifetime MDD according to *DSM-IV* criteria in the National Epidemiologic Survey on Alcohol and Related Conditions. Participants in this survey were interviewed twice over a period of 3 years, in 2000–2001 and in 2004–2005, and survey data were gathered using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV.

Results: Approximately 1 in 25 individuals with MDD transitioned to bipolar disorder during the study's 3-year follow-up period. Demographic risk factors for the transition from MDD to bipolar disorder included younger age, black race/ethnicity, and less than high school education. Clinical characteristics of depression (eg, age at first onset, presence of atypical features) were not associated with diagnostic conversion. However, prior psychopathology was associated with the transition to bipolar disorder: history of social phobia (odds ratio [OR] = 2.20; 95% confidence interval [CI], 1.47–3.30) and generalized anxiety disorder (OR = 1.58; 95% CI, 1.06–2.35). Lastly, we identified environmental stressors over the life course that predicted the transition to bipolar disorder: these include a history of child abuse (OR = 1.26; 95% CI, 1.12–1.42) and past-year problems with one's social support group (OR = 1.79; 95% CI, 1.19–2.68). The overall predictive power of these risk factors based on a receiver operating curve analysis is modest.

Conclusions: A wide range of demographic, clinical, and environmental risk factors were identified that indicate a heightened risk for the transition to bipolar disorder. Additional work is needed to further enhance the prediction of bipolar disorder among cases of MDD and to determine whether interventions targeting these factors could reduce the risk of bipolar disorder.

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Corresponding author: *Stephen E. Gilman, ScD, Harvard School of Public Health, 677 Huntington Ave, Boston, MA 02115 (sgilman@hsph.harvard.edu).*

A majority of individuals with bipolar disorder experience 1 or more major depressive episodes prior to an initial manic episode.[1] The ability to identify those individuals with unipolar depression who are at greatest risk for a manic episode, and therefore subsequent transition to bipolar depression, could allow for more targeted interventions, for symptom surveillance, and potentially for studies aimed at prevention.

What distinguishes individuals with major depressive episodes who will go on to develop mania from those who will not? This question is difficult to answer because, as Mitchell et al concluded, "there are no pathognomonic characteristics of bipolar depression compared to unipolar depression (major depressive disorder)."[2(p149)] Many attempts have been made to compare unipolar depressed to bipolar depressed patients cross-sectionally and, based on these comparisons, develop criteria that could be used to indicate probable bipolar disorder.[2] Features commonly associated with greater risk for bipolar disorder in such studies include more depressive episodes and earlier onset of illness,[2–6] as well as greater depressive severity,[4] atypical depressive symptoms,[7,8] psychotic symptoms,[5,9] and family history of bipolar disorder.[5,6] While such cross-sectional studies are informative, this approach does not necessarily distinguish features that are present *prior* to the first manic episode, for example in terms of psychiatric comorbidity.[3] Moreover, symptoms of bipolar depression are not necessarily stable across episodes.[10] We therefore investigated the clinical and social determinants of the transition from major depressive disorder (MDD) to bipolar disorder in a large 2-wave national sample of individuals meeting *DSM-IV* criteria for MDD. We used data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and attempted to identify risk factors for a manic episode occurring during the study's 3-year follow-up period.

METHOD

Study Sample

The NESARC is a nationally representative household survey conducted by the National Institute on Alcohol Abuse and Alcoholism.[11,12] The response rate for wave 1, conducted in 2000–2001, was 81.2%, resulting in a sample size of 43,093 participants aged ≥ 18 years. The wave 2 survey, conducted approximately 3 years later in 2004–2005, included 34,653 of the wave 1 participants, representing 86.7% of the 39,959 subjects who were eligible for reinterview. The combined response rate for both waves was 70.2%.[13] The analytic sample for the current study included all participants with a diagnosis of MDD at wave 1. This is operationalized in the NESARC as a lifetime history of major depressive episode at wave 1, without a lifetime history of a manic or hypomanic episode (the exclusions in *DSM-IV* major depressive disorder for schizophrenia or psychosis are not implemented in the NESARC).

Clinical Points

- Individuals with major depressive disorder (MDD) are at elevated risk for a manic episode and thus diagnostic conversion from MDD to bipolar I disorder.
- Lower educational attainment, a history of anxiety disorders, and both past-year and childhood psychosocial stressors predicted the development of mania in a population-based sample of individuals with MDD.
- The ability of all of these factors combined to predict diagnostic conversion to bipolar I disorder is modest.

Measures

The assessment instrument used in the NESARC was the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS).[14] The AUDADIS is a fully structured diagnostic interview administered by trained nonclinician interviewers that assessed disorders according to *DSM-IV* criteria.[15–18] The test-retest reliability of depression diagnoses in the NESARC sample was good ($\kappa = 0.65$ for a lifetime diagnosis of major depression, $\kappa = 0.59$ for a past-year diagnosis).[16] The following clinical characteristics of participants' depression were also assessed: age at onset, the presence with atypical features (weight gain, hyperphagia, or hypersomnia),[19] number of lifetime depressive episodes, and a high family history loading of depression, defined as a high proportion (top decile in the entire NESARC sample) of first- and second-degree relatives with depression, weighted by their degree of genetic relatedness to the respondent (0.5 for first-degree and 0.25 for second-degree).[20]

In the sample of individuals with MDD, we investigated the first onset of a manic episode during the NESARC's 3-year follow-up period and therefore the transition to a *DSM-IV* diagnosis of bipolar I disorder. This was assessed at the wave 2 interview through questions probing about symptoms of mania that occurred since the time of the wave 1 interview. Grant et al[21] reported that the test-retest reliability of bipolar diagnoses in the NESARC was good ($\kappa = 0.59$). Although there have been no clinical reappraisal studies of bipolar diagnoses based on the AUDADIS, the validity of bipolar diagnoses obtained from the Composite International Diagnostic Interview (CIDI), a structured diagnostic interview similar to the AUDADIS, was excellent. Kessler et al[22] reported almost perfect sensitivity and specificity of CIDI bipolar diagnoses compared against the Structured Clinical Interview for *DSM-IV*.

We included in our analyses participant demographic characteristics (age, sex, race/ethnicity, and educational attainment), lifetime psychiatric disorders assessed at wave 1, and lifetime stressors. Psychiatric disorders included *DSM-IV* diagnoses of panic disorder, social phobia, generalized anxiety disorder, alcohol dependence, nicotine dependence, cannabis abuse or dependence, and other substance dependence.[23–26] Lifetime stressors included a history of childhood adversities (retrospectively reported at the wave 2 interview) and past-year stressors (reported at the wave 1 interview). The childhood adversities included childhood abuse (neglect, verbal abuse, and physical abuse), sexual maltreatment, and economic deprivation. Abuse and maltreatment during childhood were assessed via a series of items asking participants about their frequency of exposure to different types of adversities, which they rated on a 5-point scale anchored by "never" and "very often." Abuse and maltreatment items were summed and then standardized to a mean of 0 and standard deviation of 1. Childhood economic deprivation was defined as receiving government financial assistance before 18 years of age. Four types of past-year stressors included social support group problems (loss or injury of a close friend or family member, or separation or divorce), social environmental problems (residential changes or serious problems with a neighbor, friend, or relative), occupational problems (fired or laid off, unemployed, trouble with a boss or coworker, or job changes), and economic problems (household below the US federal poverty threshold or received welfare). The test-retest reliabilities of these childhood and past-year stressors in the NESARC are excellent.[27]

Statistical Analyses

The study design involved fitting prediction models for a manic episode occurring between the wave 1 and wave 2 interviews; restricted to cases of major depression at wave 1, these models identify risks for the transition from MDD to bipolar disorder. Logistic regression was used, in which the dependent variable was the presence or absence of a manic episode. We conducted 2 sets of analyses: (1) analyses of clinical characteristics of the participants' depression and lifetime histories of psychiatric disorders and (2) analyses of childhood and past-year adversities. The primary analytic sample included participants with a lifetime history of MDD, as described above; however, in supplemental analyses, we repeated the sequence of logistic regression models among participants with a *past-year* diagnosis of MDD at wave 1 and again among participants with lifetime MDD who sought treatment for their depression. These are groups that could arguably resemble patients enrolled into clinical samples more closely than cases identified in the NESARC overall—in terms of having active disorders in the first instance, and in terms of having sought treatment in the second instance. We sought to determine from these analyses whether there were different patterns of clinical and psychosocial predictors of the transition to bipolar I disorder among individuals with presumably more severe depression.

To determine the extent to which the covariates studied at baseline predict the transition from MDD to bipolar disorder during the 3-year follow-up period, we conducted a receiver operating characteristic (ROC) analysis.[28] We did this by fitting a logistic regression model in the primary analytic sample (ie, lifetime cases of MDD) that included all of the participant demographic factors, clinical characteristics of depression, lifetime psychiatric disorders, and childhood and past-year adversities. The predicted probabilities

Table 1. Descriptive Characteristics of Participants With Lifetime Major Depressive Disorder (MDD), Past-Year MDD, and Lifetime MDD in the National Epidemiologic Survey on Alcohol and Related Conditions

	Lifetime MDD (n = 6,214)		Past-Year MDD (n = 2,585)		Lifetime Treated MDD (n = 3,798)	
Characteristic	n	%	n	%	n	%
Demographic factors						
Age						
18–29 y	1,114	18.9	619	25.0	561	15.7
30–39 y	1,339	20.3	563	20.0	800	19.6
40–49 y	1,454	25.2	585	24.8	969	27.5
50–59 y	1,153	19.5	412	16.5	784	21.2
≥ 60 y	1,154	16.2	406	13.7	684	16.1
Sex						
Male	1,827	32.7	751	32.7	946	27.7
Female	4,387	67.3	1,834	67.3	2,853	72.3
Race/ethnicity						
White	4,088	78.5	1,582	74.6	2,650	82.2
Black	856	7.4	412	9.2	418	5.5
Hispanic	1,004	8.5	463	9.5	584	7.6
Other	266	5.7	128	6.7	146	4.7
Education						
Less than high school	950	13.4	478	16.7	473	10.6
High school or GED	1,683	27.3	733	28.3	975	26.3
Some college or greater	3,581	59.3	1,374	55.0	2,350	63.1
Clinical characteristics of depression						
Depression onset ≤ 12 y	315	4.9	155	5.7	234	5.9
First depression onset in the past year	728	11.0	695	26.1	333	7.7
Presence of atypical features	3,778	60.7	1,653	64.8	2,438	63.4
> 1 Lifetime depressive episode	3,099	50.1	1,649	64.7	2,090	55.5
High family history loading of depression	1,572	27.2	717	30.1	1,070	30.0
Lifetime psychiatric disorders						
Panic disorder	881	14.7	458	18.2	682	18.2
Social phobia	730	12.6	353	15.0	510	14.1
Generalized anxiety disorder	949	16.0	519	20.7	709	19.5
Alcohol dependence	1,223	20.7	541	22.2	739	20.0
Nicotine dependence	1,733	29.8	785	33.0	1,105	30.1
Cannabis abuse or dependence	775	13.2	336	14.2	477	12.7
Other substance dependence	238	3.9	118	4.8	156	4.1
Childhood adversities						
Child abuse[a]	0.28	0.0	0.30	0.0	0.3	0.0
Sexual maltreatment[a]	4.8	0.0	4.8	0.1	5.0	0.1
Economic deprivation	1,075	15.0	500	16.7	626	14.6
Past-year stressors						
Social support group problems	3,879	62.0	1,739	66.4	2,406	62.7
Social environmental problems	1,786	30.7	907	37.0	1,120	31.2
Occupational problems	3,034	48.9	1,440	55.4	1,936	50.5
Economic problems	1,885	25.6	959	32.1	1,084	23.1

[a]Ratings for child abuse and sexual maltreatment are expressed as mean and standard error.
Abbreviation: GED = general equivalency diploma.

from this model were then used to plot the ROC curve, and the area under the curve (AUC) was computed. An AUC value of 50% indicates the model is no better than chance at predicting transition to bipolar, whereas an AUC of 100% indicates perfect prediction.

We conducted the analyses in SUDAAN,[29] which adjusts variances and point estimates for the multistage sampling design and differential selection probabilities used to ascertain the NESARC sample. Missing data on wave 1 covariates (approximately 1% of the sample) and on psychiatric disorders and childhood adversities among wave 2 nonparticipants (approximately 20% of the sample) were imputed using the method of multiple imputation as implemented in IVEware,[30] with adjustments made for the complex sampling design of the NESARC.[31] Results were averaged across 20 multiply-imputed datasets.

RESULTS

The lifetime prevalence of MDD in the NESARC is 14.5% (n = 6,214). Of these MDD cases, 4.0% (n = 245) transitioned to bipolar disorder during the 3-year follow-up period. Among past-year cases of MDD at wave 1 (40.6% of lifetime cases), 5.6% (n = 142) transitioned to bipolar depression during the follow-up period. Further, among lifetime cases of MDD who sought treatment (61.8% of lifetime cases), 4.1% (n = 163) transitioned to bipolar disorder.

The demographic and clinical characteristics of participants in the NESARC included in the analyses of risk for transition to bipolar depression are presented in Table 1. These are shown separately for participants with lifetime MDD, participants with past-year MDD, and participants with lifetime MDD who sought treatment. The samples were majority female (approximately two-thirds) and white (approximately four-fifths). Most participants (approximately two-thirds) had attained some college education. Thus, there were no notable differences between the 3 samples (all MDD cases, past-year cases, and lifetime cases who sought treatment) in the demographic, clinical, and psychosocial factors examined.

We first investigated the phenomenological aspects of MDD that are associated with the transition to bipolar disorder, as well as the influence of lifetime psychiatric disorders on the development of bipolar disorder. Two logistic regression models were fitted, one for the clinical characteristics of depression and a second that added lifetime disorders (Table 2). Odds ratios greater than 1 indicate an increased risk for the transition to bipolar depression. In terms of participant demographic factors, younger age at interview and black race/ethnicity (compared to white) were associated with higher risks for transition to bipolar depression. In addition, failure to complete high school was associated with a 2-fold increased risk for subsequent mania (odds ratio [OR] = 1.95; 95% confidence interval [CI], 1.18–3.22). None of the clinical characteristics of participants' MDD were associated with bipolar transition (eg, younger age at onset, presence of atypical features); however, a history of other psychiatric disorders was—notably, anxiety disorders. Panic disorder (OR = 1.53), social phobia (OR = 2.20), and generalized anxiety disorder (OR = 1.58)

were independently associated with the transition to bipolar disorder among participants with a lifetime history of MDD.

The next set of analyses concerned the role of lifetime and past-year stressors in the transition to bipolar disorder (Table 3). Again, results from 2 logistic regression models are shown: one for childhood adversities and a second model adding past-year stressors. The first finding from these analyses that is notable is that the demographic correlates of transitioning to bipolar disorder observed in Table 2 (higher risks associated with black race/ethnicity and lower educational attainment) are substantially reduced in models that include childhood and past-year stressors. Second, a history of childhood abuse and, to a lesser degree, sexual maltreatment were associated with increased risks for transitioning to bipolar depression (OR for childhood abuse = 1.26; 95% CI, 1.12–1.42). Third, past-year stressors were significantly associated with bipolar disorder (social support group problems, OR = 1.79; economic problems, OR = 1.45).

We then conducted an ROC analysis to determine how accurately the group of covariates studied, in the aggregate, predicts the transition to bipolar disorder. The ROC curve is presented in Figure 1—this plots the sensitivity (y-axis) against (1 minus) the specificity (x-axis) of cutpoints arranged along the distribution of the predicted probabilities of bipolar disorder. The optimal cutpoint (indicated by the triangle in Figure 1) has a sensitivity of 65.8% and a specificity of 67.9% for predicting bipolar disorder and correctly classifies the transition status of 67.9% of the sample. The AUC is 72.4% (95% CI, 69.1%–75.8%), indicating better-than-chance prediction, but not sufficiently high for use as a clinical screening tool for the future development of bipolar disorder among lifetime cases of MDD.

We conducted 2 sets of supplementary analyses, in which we repeated the sequence of logistic regression models described above in 2 subsets of the primary analysis sample: participants with past-year MDD (n = 2,585) and participants with lifetime MDD who sought treatment (n = 3,798) (Table 4). Similar to the results in Table 2, clinical features of participants' depression were not associated with the risk of bipolar disorder in the supplementary analyses. The pattern of associations between lifetime and recent stressors and subsequent bipolar disorder was also the same in the supplementary analyses. However, subtle differences from the primary sample emerged in the analyses of past-year cases of MDD. Panic disorder was no longer significantly associated with risk for transition to bipolar disorder, whereas cannabis abuse or dependence was associated with it (OR = 2.12; 95% CI, 1.10–4.08).

Table 2. Clinical and Sociodemographic Features Associated With the Risk for Transition From Major Depressive Disorder (MDD) to Bipolar Disorder Among Participants With Lifetime MDD (N = 6,214) in the National Epidemiologic Survey on Alcohol and Related Conditions

	Model 1: Clinical Characteristics of Depression		Model 2: Clinical Characteristics of Depression and Lifetime Psychiatric Disorders	
Characteristic	OR	CI	OR	CI
Demographic factors				
Age				
18–29 y	5.58*	2.71–11.49	5.32*	2.58–10.99
30–39 y	5.02*	2.40–10.49	4.62*	2.20–9.71
40–49 y	2.74*	1.31–5.73	2.33*	1.09–4.95
50–59 y	2.85*	1.27–6.41	2.61*	1.16–5.88
≥ 60 y	1		1	
Sex				
Male	1.07	0.75–1.52	1.08	0.74–1.58
Female	1		1	
Race/ethnicity				
White	1		1	
Black	1.59	0.96–2.62	1.72*	1.04–2.84
Hispanic	0.89	0.53–1.50	0.94	0.55–1.62
Other	0.72	0.30–1.73	0.73	0.31–1.73
Education				
Less than high school	2.00*	1.22–3.27	1.95*	1.18–3.22
High school or GED	1.14	0.76–1.70	1.12	0.75–1.68
Some college or greater	1		1	
Clinical characteristics of depression				
Depression onset ≤ 12 y	1.37	0.79–2.37	1.26	0.73–2.16
First depression onset in the past year	0.69	0.39–1.22	0.69	0.39–1.22
Presence of atypical features	1.07	0.77–1.48	1.03	0.74–1.45
No. of lifetime depressive episodes	1.00*	1.00–1.01	1.00	0.99–1.01
High family history loading of depression	1.04	0.74–1.47	0.93	0.66–1.31
Lifetime psychiatric disorders				
Panic disorder			1.53	0.99–2.39
Social phobia			2.20*	1.47–3.30
Generalized anxiety disorder			1.58*	1.06–2.35
Alcohol dependence			1.07	0.68–1.68
Nicotine dependence			1.11	0.75–1.63
Cannabis abuse or dependence			1.27	0.77–2.11
Other substance dependence			0.80	0.35–1.81

*$P < .05$.
Abbreviation: GED = general equivalency diploma.

DISCUSSION

Using data from a large national study with 3 years of follow-up, we found that approximately 1 in 25 (4.0%) individuals with a lifetime diagnosis of MDD transitioned to bipolar disorder; the transition rate was similar for individuals with a past-year diagnosis of MDD (5.6%) and for individuals who sought treatment for their depression (4.1%). These transition rates are comparable to rates observed previously in follow-up studies of clinical samples, which have ranged from 4% to 9% across varying time periods,[2] and the 1% annual conversion rate reported by Angst et al.[32]

This study also provides evidence of sociodemographic, clinical, and psychosocial factors that predict the transition from MDD to bipolar disorder. Younger age is one of the strongest demographic correlates of the transition to bipolar depression, which is consistent with a broad literature indicating that the risk for manic episodes peaks between ages 15–20 years and declines thereafter.[33] In addition, black race/ethnicity was associated with a higher risk for bipolar depression, which to our knowledge has not been previously

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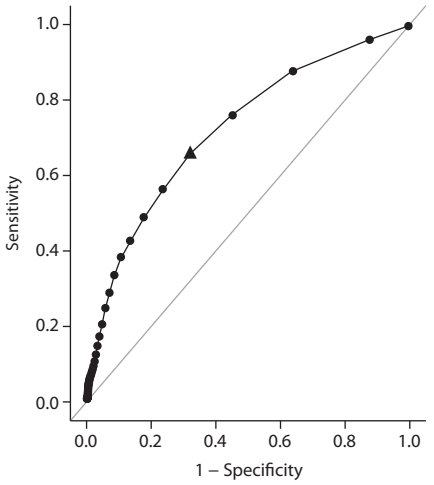
Table 3. Lifetime and Recent Stressors Associated With the Risk for Transition From Major Depressive Disorder (MDD) to Bipolar Disorder Among Participants With Lifetime MDD (N = 6,214) in the National Epidemiologic Survey on Alcohol and Related Conditions

	Model 1: Childhood Adversities		Model 2: Childhood Adversities and Past-Year Stressors	
Characteristic	OR	CI	OR	CI
Demographic factors				
Age				
18–29 y	5.32*	2.59–10.91	4.59*	2.14–9.81
30–39 y	4.50*	2.15–9.44	4.21*	1.98–8.94
40–49 y	2.54*	1.21–5.31	2.40*	1.14–5.07
50–59 y	2.59*	1.16–5.77	2.49*	1.11–5.60
≥ 60 y	1		1	
Sex				
Male	1.18	0.82–1.69	1.24	0.87–1.77
Female	1		1	
Race/ethnicity				
White	1		1	
Black	1.56	0.96–2.54	1.44	0.88–2.36
Hispanic	0.87	0.51–1.47	0.82	0.48–1.39
Other	0.68	0.28–1.62	0.65	0.27–1.56
Education				
Less than high school	1.71*	1.03–2.84	1.45	0.90–2.32
High school or GED	1.06	0.70–1.59	1.02	0.68–1.54
Some college or greater	1		1	
Childhood adversities				
Child abuse	1.27*	1.13–1.42	1.26*	1.12–1.42
Sexual maltreatment	1.05*	1.00–1.11	1.05*	1.00–1.11
Economic deprivation	1.02	0.70–1.49	0.98	0.67–1.43
Past-year stressors				
Social support group problems			1.79*	1.19–2.68
Social environmental problems			1.10	0.75–1.60
Occupational problems			1.18	0.80–1.72
Economic problems			1.45*	1.03–2.06

*$P < .05$.
Abbreviation: GED = general equivalency diploma.

Figure 1. Receiver Operating Characteristic (ROC) Curve for Predicting Transition to Bipolar Disorder During the 3 Years of Follow-Up Among Lifetime Cases of Major Depressive Disorder (N = 6,214) in the National Epidemiologic Survey on Alcohol and Related Conditions[a]



[a]ROC curve estimated from a logistic regression model including all of the covariates listed in Tables 2 and 3. The diagonal line indicates chance prediction, corresponding to an area under the curve (AUC) of 0.50. The model AUC is 0.724. The ▲ symbol indicates the optimal cutpoint, balancing sensitivity and specificity equally.

reported and can be distinguished from the absence of race/ethnicity differences in the risk of bipolar I disorder in the NESARC sample overall.[21] Notably, the magnitude of black-white difference in the transition to bipolar disorder was reduced once past-year stressors were accounted for.

Lower education was also associated with an increased risk of transitioning to bipolar disorder. There is strong evidence that educational attainment is protective against MDD, and in this context, education may also be protective against the transition to bipolar disorder among individuals with MDD.[34] Glahn et al[35] reported that patients with bipolar disorder had lower levels of educational attainment than demographically matched controls, despite having similar IQ scores; in part, their findings were due to the lower likelihood of bipolar patients to complete college. This finding illustrates a set of noncausal explanations for our finding that individuals with less than high school educations were twice as likely to transition from MDD to bipolar disorder than individuals with some college education. Consistent with Glahn and colleagues' study, our finding may reflect the presence of prodromal symptoms of mania that interfere with the completion of education. This explanation would also be consistent with studies suggesting "trait" cognitive deficits in bipolar disorder,[36] as well as evidence that up to one-third of bipolar individuals recall symptoms at or before age 13.[33] Therefore, while our definition of MDD excluded diagnoses of hypomania, this does not fully eliminate the confounding effects of prodromal or subthreshold symptoms of mania. Additionally, education differences in the risk for mania may reflect the consequences on educational attainment of parental bipolar disorder. Individuals with bipolar disorder are more likely to have parents with bipolar disorder (or other serious mental illness),[37,38] which itself may interfere with completion of education even in the absence of symptoms in the individual. On the other hand, we note that the association with mania persists even after adjustment for measures of childhood adversity and that a family history of depression was not predictive of mania.

Among comorbidities, the most robust associations were identified for panic, social phobia, and generalized anxiety. Importantly, these symptoms preceded a first manic episode (though not necessarily depressive symptoms), suggesting their potential utility as risk marker for a bipolar course. Previous studies have also linked anxiety to bipolar liability, most notably the findings by Simon et al, which demonstrated a higher prevalence of comorbid panic disorder and generalized anxiety disorder among patients with bipolar disorder.[4,39] In supplementary analyses (those of past-year cases of MDD), cannabis use disorders were also associated with elevated risk; this finding in particular bears consideration in individuals presenting with a major depressive episode.[40,41] It is consistent with a previous report associating use of cannabis with risk for subsequent manic symptoms[40] and other work associating it with earlier onset age in bipolar or other psychotic disorders.[42,43]

Table 4. Clinical and Psychosocial Predictors of the Transition to Bipolar Disorder Among Participants With Past-Year Major Depressive Disorder (MDD) and With Lifetime Treated MDD in the National Epidemiologic Survey on Alcohol and Related Conditions

	Analysis Sample: Past-Year Cases of Depression at Wave 1 (n = 2,585)				Analysis Sample: Lifetime Cases of Depression Who Sought Treatment (n = 3,798)			
	Model 1: Clinical Characteristics of Depression and Lifetime Psychiatric Disorders		Model 2: Childhood Adversities and Past-Year Stressors		Model 3: Clinical Characteristics of Depression and Lifetime Psychiatric Disorders		Model 4: Childhood Adversities and Past-Year Stressors	
Characteristic	OR	CI	OR	CI	OR	CI	OR	CI
Demographic factors								
Age								
18–29 y	3.14*	1.16–8.52	2.84*	1.03–7.78	5.56*	2.11–14.62	4.75*	1.78–12.70
30–39 y	4.19*	1.51–11.61	4.00*	1.44–11.12	4.51*	1.74–11.69	4.41*	1.67–11.61
40–49 y	1.50	0.54–4.21	1.54	0.55–4.33	1.89	0.72–4.94	2.06	0.78–5.46
50–59 y	2.41	0.84–6.94	2.05	0.72–5.86	2.95*	1.04–8.39	2.86*	1.02–8.03
≥ 60 y	1		1		1		1	
Sex								
Male	0.78	0.45–1.36	0.94	0.55–1.61	0.98	0.61–1.57	1.23	0.76–2.00
Female	1		1		1		1	
Race/ethnicity								
White	1		1		1		1	
Black	1.55	0.81–2.95	1.41	0.74–2.69	1.39	0.67–2.87	1.16	0.57–2.35
Hispanic	0.83	0.40–1.71	0.63	0.30–1.33	1.00	0.51–1.95	0.96	0.51–1.83
Other	0.49	0.15–1.63	0.40	0.11–1.38	1.27	0.54–2.98	1.06	0.45–2.49
Education								
Less than high school	1.98*	1.06–3.68	1.40	0.73–2.68	1.49	0.79–2.83	1.14	0.58–2.24
High school or GED	1.51	0.85–2.67	1.30	0.73–2.33	1.11	0.64–1.93	1.02	0.61–1.73
Some college or greater	1		1		1		1	
Clinical characteristics of depression								
Depression onset ≤ 12 y	1.85	0.95–3.60			1.33	0.71–2.49		
First depression onset in the past year	0.57	0.32–1.03			0.81	0.40–1.62		
Presence of atypical features	1.36	0.87–2.14			0.94	0.65–1.37		
No. of lifetime depressive episodes	1.00	0.98–1.01			1.00	0.99–1.01		
High family history loading of depression	0.93	0.55–1.57			0.91	0.59–1.39		
Lifetime psychiatric disorders								
Panic disorder	1.04	0.60–1.78			1.62*	1.04–2.52		
Social phobia	2.08*	1.19–3.65			2.12*	1.31–3.44		
Generalized anxiety disorder	1.35	0.76–2.41			1.60*	1.00–2.57		
Alcohol dependence	0.73	0.40–1.31			1.22	0.73–2.02		
Nicotine dependence	0.91	0.53–1.58			1.15	0.72–1.82		
Cannabis abuse or dependence	2.12*	1.10–4.08			1.44	0.85–2.43		
Other substance dependence	1.08	0.42–2.80			0.75	0.33–1.70		
Childhood adversities								
Child abuse			1.32*	1.13–1.54			1.26*	1.06–1.49
Sexual maltreatment			1.03	0.96–1.11			1.05	0.98–1.12
Economic deprivation			0.91	0.54–1.51			1.00	0.63–1.57
Past-year stressors								
Social support group problems			1.55	0.92–2.60			1.76*	1.10–2.83
Social environmental problems			1.26	0.77–2.06			1.11	0.71–1.74
Occupational problems			1.15	0.71–1.86			1.20	0.76–1.91
Economic problems			1.62*	1.02–2.58			1.46	0.96–2.21

*$P < .05$.
Abbreviation: GED = general equivalency diploma.

Our examination of lifetime stressors indicates that childhood adversity was significantly associated with the risk of mania, with an approximately 30% increase in the odds of mania with increasing levels of childhood abuse. These results are consistent with and extend numerous investigations of cohorts of individuals with bipolar disorder that report elevated rates of childhood trauma.[44–47] Socioeconomic conditions during childhood and other types of childhood adversities have also been linked with the long-term risk of bipolar disorder.[48–51]

Among stressors in the year prior to initial screen, the most robust risk was associated with social support group problems. This is consistent with a prior study in which the suicide of a family member, in addition to other life events, was associated with risk for first manic hospitalization.[52] As with our education findings, these may be indicators of more severe illness in general, or emergence of subthreshold manic/hypomanic symptoms, which contribute to conflict with social supports. Alternatively, the social supports may protect against transition to mania, perhaps by buffering the life stresses shown to be associated with mania.[52–54] This model would provide further support for interventions that seek to improve the social functioning of individuals with mood disorder.[55]

The risk factors discussed above could serve as potential risk markers for the transition to bipolar disorder among individuals with MDD. However, in the aggregate, their predictive

ability is modest at best, and quite likely overstates the level of prediction that would be expected in a replication sample. In the NESARC, a clinical prediction rule based on all of the covariates studied would fail to detect 35% of individuals who transition to bipolar disorder and falsely identify 32% of individuals as future bipolar cases.

This study focused on the diagnostic conversion from MDD to bipolar I disorder. By not considering hypomania (ie, bipolar II disorder), our results may not reflect the total impact of the predictors studied on the conversion to bipolar (I and II) disorder. The omission of hypomania is notable because evidence suggests that symptoms of mania are common in individuals with MDD and does not suggest the existence of marked discontinuities between diagnoses of MDD, bipolar II, and bipolar I.[56–58]

As a population-based cohort that relies on structured diagnostic interview administered by nonclinician interviewers, the present study has the following limitations. The assessments of mania in the NESARC have modest psychometric properties and have not been validated against diagnoses made by clinicians. The lack of assessments of psychosis in the NESARC interview, and small number of individuals with such symptoms, preclude analysis of one of the most frequently identified predictors of bipolar transition. In addition, the NESARC did not assess participants' family history of mania, which is higher among individuals with bipolar disorder than among individuals with MDD.[4,57] Finally, our analyses of lifetime disorders rely on lifetime reports of disorders, the use of which requires that additional assumptions be made in mixed-aged samples.[59,60]

The current study is one of the first population-based, longitudinal studies to investigate the transition from MDD to bipolar disorder and thus extends the existing evidence, which is based on hospitalized or otherwise selectively ascertained populations. In the aggregate, we find some potential predictors of risk for transition to mania that extend those previously reported. None of these is sufficient to identify with confidence those individuals at greatest risk. A key question for future investigation, however, is whether some of these risks might be modifiable: for example, whether strategies to improve resilience or minimize life stresses might reduce the hazard of, or at least delay, onset of mania.

Author affiliations: Department of Society, Human Development and Health, and Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts (Dr Gilman); and Department of Psychiatry, Massachusetts General Hospital, Boston, and the Bipolar Clinic and Research Program, Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston (Drs Dupuy and Perlis).
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