Molecular Psychiatry (2015) 20, 329–336

www.nature.com/mp

ORIGINAL ARTICLE

Contributions of the social environment to first-onset and recurrent mania

SE Gilman[1,2,3], MY Ni[4], EC Dunn[5,6,7], J Breslau[8], KA McLaughlin[9], JW Smoller[5,6,7] and RH Perlis[7,10]

In treated cohorts, individuals with bipolar disorder are more likely to report childhood adversities and recent stressors than individuals without bipolar disorder; similarly, in registry-based studies, childhood adversities are more common among individuals who later become hospitalized for bipolar disorder. Because these types of studies rely on treatment-seeking samples or hospital diagnoses, they leave unresolved the question of whether or not social experiences are involved in the etiology of bipolar disorder. We investigated the role of childhood adversities and adulthood stressors in liability for bipolar disorder using data from the National Epidemiologic Survey on Alcohol and Related Conditions ($n = 33\,375$). We analyzed risk for initial-onset and recurrent DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) manic episodes during the study's 3-year follow-up period. Childhood physical abuse and sexual maltreatment were associated with significantly higher risks of both first-onset mania (odds ratio (OR) for abuse: 2.23; 95% confidence interval (CI) = 1.71, 2.91; OR for maltreatment: 2.10; CI = 1.55, 2.83) and recurrent mania (OR for abuse: 1.55; CI = 1.00, 2.40; OR for maltreatment: 1.60; CI = 1.00, 2.55). In addition, past-year stressors in the domains of interpersonal instability and financial hardship were associated with a significantly higher risk of incident and recurrent mania. Exposure to childhood adversity potentiated the effects of recent stressors on adult mania. Our findings demonstrate a role of social experiences in the initial onset of bipolar disorder, as well as in its prospective course, and are consistent with etiologic models of bipolar disorder that implicate deficits in developmentally established stress-response pathways.

Molecular Psychiatry (2015) **20,** 329–336; doi:10.1038/mp.2014.36; published online 22 April 2014

INTRODUCTION

There has been a long-standing suspicion that social stressors contribute to the risk of bipolar disorder, but what limited evidence exists is not strong enough to support causation, despite evidence from twin studies indicating that environmental factors account for approximately one-quarter to one-third of the population variance in bipolar disorder.[1] Patients with bipolar disorder report high levels of adverse life events, particularly childhood maltreatment.[2,3] When compared with individuals without bipolar disorder, those with bipolar disorder report significantly greater past exposure to a range of stressful life events.[4–7] Bipolar disorder has also been associated with demographic characteristics such as lower income and education, unemployment and not being married.[8–10] Although the results of these studies are consistent with a social causation model of mania, they could also be explained by the disabling social consequences of living with bipolar disorder.

The strongest evidence to date that adverse experiences increase the risk of developing bipolar disorder comes from the Danish psychiatric registries, demonstrating that the early loss of a parental or sibling more than doubles the risk of hospitalization for bipolar disorder, and that a recent divorce or unemployment also increases the risk of subsequent mania.[11–13] Furthermore, social experiences may exacerbate the course of bipolar disorder, by precipitating recurrent manic episodes among individuals who have already experienced onset of mania; this evidence is based on studies that retrospectively assessed the presence of stressors among patients in treatment for bipolar disorder,[14–17] studies that related stressors to the prospective recurrence of manic episodes[18–23] and from studies that tracked episode recovery as a function of stressful life events.[24,25] However, these studies were based on very small samples selected for treatment seeking, and could not rule out the influences of illness chronicity on the reporting of stressors.

Experiences over the life course have also been suggested to interact in various ways to enhance vulnerability to chronic bipolar disorder. According to a stress sensitization model, the influences of adult stressors on the course of bipolar illness are magnified among individuals with a history of childhood adversities;[26,27] this has been shown, for example, in a major depression.[28] Alternatively, the experience of multiple prior manic episodes may also act to moderate the recurrence risk of manic episodes (i.e., episode sensitization).

The evidence for sensitization effects in bipolar disorder is quite limited. Dienes *et al.*[29] reported an interaction between early

[1]Department of Social and Behavioral Sciences, Harvard School of Public Health, Boston, MA, USA; [2]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA; [3]Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA; [4]School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China; [5]Psychiatric and Neurodevelopmental Genetics Unit, Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA; [6]Department of Psychiatry, Harvard Medical School, Boston, MA, USA; [7]Stanley Center for Psychiatric Research, The Broad Institute of Harvard and MIT, Cambridge, MA, USA; [8]RAND Corporation, Pittsburgh, PA, USA; [9]Department of Psychology, University of Washington, Seattle, WA, USA and [10]Center for Experimental Drugs and Diagnostics, Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA. Correspondence: Dr SE Gilman, Department of Social and Behavioral Sciences, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA.
E-mail: sgilman@hsph.harvard.edu
Received 30 August 2013; revised 27 January 2014; accepted 10 March 2014; published online 22 April 2014

adversity and stressful life events in predicting recurrent manic episodes among 58 adults with bipolar I disorder; individuals exposed to early adversity were more likely to have a manic episode after experiencing an adult stressor than individuals who were not exposed to early adversity. We are unaware of studies evaluating sensitization effects in first-onset mania. Tests of the episode sensitization hypothesis conducted in small clinical samples have largely failed to support it.[16,29–31]

Accordingly, the current study addresses three unresolved questions regarding the social origins of mania: (1) does stress exposure over the life course increase risk for first-onset manic episodes; (2) does stress exposure predict recurrent manic episodes; and (3) do adult stressors associate with recurrence risk differently depending on individuals' history of exposure to childhood stressors (consistent with stress sensitization), or individuals' history of manic episodes (consistent with episode sensitization).

PARTICIPANTS AND METHODS

Study sample

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) is a nationally representative household survey conducted by the National Institute on Alcohol Abuse and Alcoholism.[32,33] The Wave 1 response rate was 81.2%, resulting in a sample size of 43 093 participants aged $\geqslant 18$. The Wave 2 survey, conducted approximately 3 years later, 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%.[34] The analytic sample for the current study included all participants at Wave 2, with complete data on the measures described below.

Measures

The NESARC used the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS),[35] a fully structured diagnostic interview administered by trained non-clinician interviewers, to assess disorders according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) criteria.[36–39] The primary outcome of this study is the presence of a manic episode during 3-year follow-up period. Grant *et al.*[9] reported that the test–retest reliability of diagnoses of bipolar disorder in the NESARC was good ($\kappa = 0.59$).

We investigated stressors that occurred in the past year as well as adversities that occurred in childhood. Past-year stressors were assessed at the baseline interview using a checklist of life events. The test–retest reliability of the NESARC's assessment of stressful life events over a 6-week period was excellent (intraclass correlation = 0.94).[40] We analyzed groupings of past-year stressors using two approaches: a theoretically based approach informed by DSM-IV's Axis IV framework for reporting psychosocial and environmental problems, and an empirically based approach using latent class analysis.[41] The theoretically based approach focuses on the presence or absence of specific types of stressors within individuals, whereas in the empirically based approach, participants are categorized into distinct groups based on the patterns of stressors experienced.

In the theoretically based approach, we categorized past-year stressors into the following groups: problems with primary support group (including death of a close friend or family member; serious illness or injury of a close friend or family member; and separation, divorce or end of a serious relationship); problems related to the social environment (defined as a serious problem with a neighbor, friend or relative); occupational problems (including being fired or laid off; currently unemployed or unemployed for >1 month during the past year; trouble with boss or co-worker; and change of jobs, responsibilities or work hours); economic problems (including having experienced a major financial crisis, declared bankruptcy or more than once been unable to pay bills on time; household income $< 150\%$ of the federal poverty threshold; or received public assistance); problems with access to health-care services (defined as lack of health insurance); and finally, problems related to interaction with the legal system/crime (including trouble with the police, arrested or sent to jail; and victim of a crime).

The empirically based approach entailed using latent class analysis to identify mutually exclusive groups of individuals with distinct patterns of exposure to the above 14 stressors, as described previously.[41] A five-class model provided the best fit to the data, characterized by the following patterns of recent stressors: (1) low-stress exposure; (2) personal loss (death or serious injury of a close friend or family member); (3) financial, interpersonal instability (changed jobs and experienced a major financial crisis, as well as trouble with the police and being the victim of a crime); (4) economic difficulty (poverty and receipt of public assistance); and (5) occupational instability (fired or laid off, unemployed for more than a month, and changed jobs).

The childhood adversities, assessed retrospectively at the Wave 2 interview,[42–44] included childhood abuse (including neglect, verbal abuse and physical abuse), sexual maltreatment and childhood economic deprivation; these were analyzed separately based on prior evidence that physical abuse and sexual abuse confer independent risk for bipolar disorder.[3,17,45] Abuse and sexual maltreatment before the age of 18 years were assessed using 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'. The test–retest reliabilities of these childhood adversities in the NESARC are excellent, with intraclass correlations ranging from 0.80 to 0.94.[40] Abuse and sexual maltreatment scores were summed, and binary indicators of the top decile were created and used for analyses. Childhood economic deprivation was defined as receiving government financial assistance before the age of 18 years.

Statistical analyses

We conducted separate analyses of incident (initial-onset) and recurrent mania. Incident mania was analyzed among individuals without any history of a manic episode when they were enrolled in the study, whereas recurrent mania was analyzed among individuals who upon enrollment had experienced at least one manic episode in their lifetime. We fitted logistic regression models for incident and recurrent manic episodes, with childhood adversities and then past-year stressors entered as predictors, controlling for demographic characteristics (sex, age, educational attainment) and lifetime comorbidities assessed at baseline (alcohol or substance dependence, major depressive disorder).

We then fitted extended models to evaluate sensitization effects by adding interaction terms between childhood adversities and past-year stressors (assessing stress sensitization) and between the number of lifetime manic episodes and past-year stressors (assessing episode sensitization). We conducted all analyses in SUDAAN,[46] which adjusts variances and point estimates for the multistage sampling design, differential selection probabilities used to ascertain the NESARC sample and response probabilities at the follow-up interview.

RESULTS

The analytic sample includes 33 375 of the 34 653 (96.3%) NESARC respondents who participated in the 3-year follow-up interview and provided complete data on all study covariates. Eight hundred and eleven participants (2.3%) met the DSM-IV criteria for a manic episode during the follow-up period. Six hundred and thirty-one of these participants had a first-onset manic episode during the follow-up period, whereas 180 of these participants had a prior history of mania upon enrollment and had recurrent episodes during the follow-up period. The demographic characteristics of participants in the study, as well as exposure to past-year stressors and childhood adversities, are given in Table 1. Guided by the Axis IV approach to categorizing psychosocial stressors, we determined the proportion of participants who endorsed each type of stressor in the year before enrollment, for example, half of the sample reported a problem in their social support group (50.7%), whereas one-tenth reported a legal problem in the past year (10.4%). In contrast, the groupings derived from a latent class analysis (LCA) categorized each participant into a single class according to their overall pattern of stress exposure. Approximately half of the sample was in the 'low-stress' category, 30.1% of the sample experienced a personal loss and smaller proportions were placed in the financial/interpersonal, economic and occupational stress categories. Further details of the LCA solution are provided in Supplementary Table 1, which indicates the prevalence of the 14 stressors among participants in each of the five latent classes, as well as the

Table 1. Characteristics of participants in the NESARC reinterviewed at Wave 2 and included in the analysis sample ($n = 33\,375$)

	Percent (N)
Age at enrollment (years)	
18–29	21.9 (6514)
30–39	20.1 (7022)
40–49	20.9 (6910)
50–59	15.7 (5269)
60+	21.5 (7660)
Sex	
Male	48.0 (14 039)
Female	52.1 (19 336)
Race/ethnicity	
White	71.1 (19 484)
Black	11.0 (6303)
Hispanic	11.5 (6129)
Other	6.4 (1459)
Educational attainment at enrollment	
Less than high school	14.4 (5422)
High school or GED	29.0 (9573)
Some college or more	56.7 (18 380)
History of mania at enrollment	3.5 (1219)
Mania during the 3-year follow-up period	
First onset of mania	1.9 (631)
Recurrent manic episode among participants with a history of mania at enrollment	14.4 (180)
Lifetime alcohol or substance dependence at enrollment	13.2 (4097)
Lifetime major depressive disorder at enrollment	18.2 (6338)
Past-year stressors at enrollment based on Axis IV of DSM-IV	
Social support group problems	50.7 (17 282)
Social environment problems	5.6 (1909)
Occupational problems	33.2 (11 172)
Economic problems	30.4 (11 332)
Lack of health insurance	17.9 (5987)
Legal problems	10.4 (3563)
Empirically based taxonomy of past-year psychosocial stressors at enrollment	
1. Low stress	48.9 (15 936)
2. Personal loss	30.1 (9576)
3. Financial, interpersonal instability	8.0 (2892)
4. Economic difficulty	7.0 (3056)
5. Occupational instability	6.0 (1915)
Childhood adversities	
Childhood abuse	9.8 (3531)
Sexual maltreatment	7.2 (2663)
Economic disadvantage	13.1 (4976)

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; GED, General Education Development; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions.

number of stressors experienced in each category. Participants in the 'low-stress' and 'personal loss' categories experienced relatively few stressors, whereas those in the other three categories experienced on average 3.5 to 5.5 stressors in year preceding enrollment into the study.

First-onset (incident) mania

The relation of childhood adversities and past-year stressors to first-onset manic episodes is shown in Table 2. Model 1 analyzes childhood adversities alone; Model 2 incorporates the Axis IV groupings of past-year stressors, whereas Model 3 incorporates the LCA groupings. Abuse, sexual maltreatment and economic disadvantage during childhood were independently associated with an elevated risk of bipolar disorder, with odds ratios in the range of 1.51–2.74. Past-year stressor assessed at enrollment also predicted first-onset manic episodes during the study's 3-year follow-up period. The most pronounced risks were for the LCA groupings in Model 2. Relative to individuals in the low-stress category, those who experienced a personal loss (odds ratio (OR) = 1.41; confidence interval (CI) = 1.02, 1.94), financial and interpersonal instability (OR = 2.62; CI = 1.95, 3.52) and economic difficulty (OR = 1.93; CI = 1.36, 2.73) were significantly more likely to have a first-onset manic episode. In addition, a history of childhood abuse (OR = 2.23; CI = 1.71, 2.91), sexual maltreatment (OR = 2.10; CI = 1.55, 2.83) and economic disadvantage (OR = 1.27; CI = 0.99, 1.62) remained associated with the risk of a first-onset manic episode.

Although the analysis sample excluded participants who, upon their enrollment into the NESARC, had a lifetime history of mania, subthreshold manic symptoms could have contributed to the likelihood of experiencing stressors before the baseline interview (leading to a 'reverse causation' situation, wherein manic symptoms contributed to the development of the stressors). To address this potential problem, we repeated the analyses in Table 2, further restricting the sample to the 31 301 participants without any history of a manic *or hypomanic* episode upon enrollment, but the results were unchanged (Supplementary Table 2).

We then extended the models that included the LCA-based grouping of past-year stressors to investigate the stress sensitizing effects of childhood adversities by adding interaction terms between childhood and adult stressors. All three interactions were statistically significant (Table 3, last row). To interpret them, we calculated from the logistic regression models risk differences for each category of past-year stressors relative to the 'Low Stress' category, and did so separately for those with and without childhood adversities. The *differences* in these risk differences between participants with and without each childhood adversity, labeled 'Differential effects' in Table 3, quantify the childhood–adult stressor interactions. Differential effects >0 provide support for stress sensitization, in that they reveal a more substantial increase in the probability of mania following a recent stressor among those with a history of childhood adversity than among those without such a history. The most notable evidence for stress sensitization pertained to childhood abuse. Experiencing a personal loss in the past year increased the probability of a first-onset manic episode to a greater degree among adults who were physically abused or neglected as children than among adults without a history of childhood abuse (differential effect = 2.2%).

Estimates of differential effects involving sexual maltreatment were < 0. This result is easily understood given large differences in the risk of mania in the Low Stress category following sexual maltreatment: the probability of a manic episode during the 3-year follow-up period among adults sexually maltreated as children was 4.1%, as compared with only 1.0% among adults not sexually maltreated. Sexual maltreatment was a strong risk factor for mania, and stressors in adulthood did not add further risk; in contrast, in the absence of sexual maltreatment, past-year stressors were associated significant increases in the risk of manic episodes.

Recurrent mania

Childhood adversities and past-year stressors were also strong predictors of recurrent manic episodes during the follow-up period among the 1219 individuals who entered the study with a history of mania (Table 4). Compared with individuals in the

Table 2. Associations between past-year stressors and childhood adversities and the first onset of mania during the 3-year follow-up period of the NESARC[a]

	Model 1[b] *OR (CI)*	*Model 2*[c] *OR (CI)*	*Model 3*[c] *OR (CI)*
Past-year stressors at enrollment according to Axis IV of DSM-IV			
Social support group problems		1.32 (1.06, 1.65)	
Social environment problems		1.27 (0.90, 1.79)	
Occupational problems		1.29 (1.04, 1.62)	
Economic problems		1.48 (1.14, 1.91)	
Lack of health insurance		1.07 (0.82, 1.40)	
Legal problems		1.36 (1.01, 1.83)	
Empirically based taxonomy of past-year psychosocial stressors at enrollment			
1. Low stress			1
2. Personal loss			1.41 (1.02, 1.94)
3. Financial, interpersonal instability			2.62 (1.95, 3.52)
4. Economic difficulty			1.93 (1.36, 2.73)
5. Occupational instability			1.55 (1.00, 2.41)
Childhood adversities			
Childhood abuse	2.74 (2.08, 3.61)	2.22 (1.70, 2.89)	2.23 (1.71, 2.91)
Sexual maltreatment	2.68 (1.98, 3.63)	2.08 (1.55, 2.79)	2.10 (1.55, 2.83)
Economic disadvantage	1.51 (1.18, 1.92)	1.27 (0.99, 1.62)	1.27 (0.99, 1.62)

Abbreviations: CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; NESARC, NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; OR, odds ratio. [a]Results from logistic regression models of incident mania fitted in the sample of NESARC participants without any history of mania upon enrollment ($n = 32\,156$). ORs and corresponding 95% CIs indicate the association of past-year stressors and childhood adversities with the risk of a first-onset manic episode. [b]Model 1 controls for participant sex, age at interview and race/ethnicity. [c]Models 2 and 3 also control for educational attainment, lifetime history of alcohol orsubstance dependence and major depressive disorder.

low-stress group, participants experiencing a recent personal loss, financial or interpersonal problem or economic difficulties were significantly more likely to have a recurrent manic episode (ORs = 2.23, 2.47 and 2.90, respectively). Independent of these increased risks, abuse and maltreatment during childhood were also associated with recurrent episodes (ORs = 1.55 and 1.60, respectively).

There was no support for sensitization effects in recurrent mania, as indicated by the interaction terms between past-year stressors and childhood adversities ($P = 0.347$ for economic deprivation; $P = 0.907$ for childhood abuse; $P = 0.316$ for sexual maltreatment), and by nonsignificant interactions between adult stressors and the number of prior manic episodes in logistic regression models for recurrent mania (evaluated either using a categorical variable for the number of manic episodes (1, 2–3 or $\geqslant 4$), $P = 0.243$; or a dichotomous indicator of 1 vs $\geqslant 2$ prior episodes, $P = 0.932$).

Finally, we conducted analyses to examine whether, in the context of bipolar illness, stressors also predict an increased risk of depressive episodes, and are thus associated with recurrences of any polarity. These analyses were conducted in the same sample used in the analyses of recurrent mania (*the* $n = 1219$ participants with a lifetime diagnosis of bipolar disorder upon their enrollment into the NESARC). As shown in Supplementary Table 3, the financial/interpersonal instability and economic difficulty categories of past-year stressors were associated with depressive episodes during the follow-up period; sexual maltreatment during childhood was also associated with depressive episodes during the follow-up period, although its association was attenuated after controlling for recent stressors.

DISCUSSION

We sought to determine whether experiences in the social environment are associated with risk of first-onset and recurrent mania, and whether such experiences interact over the life course to further increase risk of manic episodes. In a large, representative sample of adults in the United States, stressors characterized as personal losses, financial and interpersonal problems and economic difficulties were associated with 1.5- to 3-fold increases in the risk of both first-onset and recurrent manic episodes during a 3-year follow-up period. Moreover, a history of childhood abuse and sexual maltreatment were associated with the risk of both first-onset and recurrent manic episodes independent of adulthood stressors.

This study advances our understanding of the social determinants of bipolar disorder because of several methodological improvements over previous studies. It overcomes the limitation of prior studies that were cross-sectional, and therefore could not determine whether differences in the prevalence of stressors between individuals with and without bipolar disorder were owing to the role of stressors in precipitating manic episodes, or owing to the disabling social consequences of bipolar disorder. It improves upon studies that relied on samples selected for seeking treatment, as treatment seeking itself may be associated with many of the social determinants we studied.[47]

Limitations

Our results should be interpreted in the context of the following limitations. First, childhood adversities were assessed retrospectively at the time of the 3-year follow-up interview. Although the NESARC's assessment of childhood adversities was shown to be highly reliable,[40] we cannot rule out the possibility that such reports were distorted by current psychopathology. A previous reappraisal of retrospective reports suggested that current psychopathology does not reduce the reliability or validity of recalled childhood adversities.[48] However, biased reporting of childhood adversities cannot be ruled out.[49] Second, past-year stressful life events were ascertained by a checklist, the limitations of which include the lack of information on the frequency and severity of stressors, and personal significance attached to each stressor.[50,51] The checklist also did not allow us to make distinctions between events previously shown to be relevant in bipolar disorders, such as events that impact goal attainment, or events that disrupt sleep/wake rhythms.[21,52] Our use of an

Table 3. Sensitizing effects of childhood stressors following the exposure to past-year stressors in the risk of first-onset mania[a]

	Childhood abuse			*Sexual maltreatment*			*Economic disadvantage*		
	No	*Yes*		*No*	*Yes*		*No*	*Yes*	
	Risk difference (s.e.)	*Risk difference (s.e.)*	*Differential effect (s.e.)*	*Risk difference (s.e.)*	*Risk difference (s.e.)*	*Differential effect (s.e.)*	*Risk difference (s.e.)*	*Risk difference (s.e.)*	*Differential effect (s.e.)*
1. Low stress	Reference	Reference		Reference	Reference		Reference	Reference	
2. Personal loss	0.2% (0.2%)	2.4% (0.9%)*	2.2% (0.8%)*	0.7% (0.3%)*	− 1.5% (1.0%)	− 2.2% (1.0%)*	0.5% (0.2%)	0.7% (0.7%)	0.2% (0.7%)
3. Financial, interpersonal instability	1.7% (0.4%)*	3.7% (1.1%)*	2.0% (1.2%)	2.3% (0.4%)*	0.6% (0.5%)	− 1.7% (1.2%)	2.6% (0.4%)*	0.5% (0.6%)	− 2.0% (0.7%)*
4. Economic difficulty	1.1% (0.4%)*	1.7% (0.9%)	0.6% (0.9%)	1.2% (0.4%)*	0.2% (1.3%)	− 1.0% (1.4%)	1.1% (0.4%)*	1.0% (0.8%)	− 0.1% (0.9%)
5, Occupational instability	1.0% (0.4%)*	− 0.7% (0.8%)	− 1.7% (0.9%)	0.6% (3.7%)	0.7% (2.1%)	0.1% (2.1%)	1.0% (0.5%)*	− 0.4% (0.7%)	− 1.4% (0.9%)
χ^2, d.f. = 4 (P)[b]		12.9 (0.012)			13.7 (0.009)			13.7 (0.009)	

*$P < 0.05$. [a]Percentages in the 'No' and 'Yes' columns are risk differences: they indicate the difference in the risk of a first-onset manic episode between participants in the Personal Loss through Occupational Instability categories (categories 2–5) of past-year life events exposure relative to participants in the Low Stress category. The 'Differential effect' estimate indicates whether the Risk Difference associated with recent stressors varies between individuals with and without each childhood stressor. Estimates generated from logistic regression analyses of incident mania also adjusting for demographic factors (age, sex, educational attainment, race/ethnicity) and a lifetime history of alcohol or substance dependence upon enrollment. [b]χ^2 Test statistics (with 4 d.f.) and P-values correspond to the null hypothesis of no interaction between childhood stressors and adult life events.

empirically derived taxonomy, using latent class analysis, does not overcome this limitation, but it does advance our understanding of the mental health impact of experiencing multiple types of stressors over the past year. The clustering of stressors within an individual may be as relevant for psychopathology as the severity of any individual stressor.[53,54] This same taxonomy was shown to predict anxiety and substance use disorders.[41] Third, the NESARC did not assess family history of bipolar disorder. Offspring of parents with bipolar disorder are at elevated risk for bipolar disorders,[55] and may be more likely to experience childhood and adult adversities.[56] Thus, our results could be due in part to pathways of intergenerational transmission (of both bipolar disorder and social adversity), rather than independent social causation. Finally, while we excluded participants with a history of bipolar disorder from all analyses of incidence, and conducted sensitivity analyses excluding participants with a history of hypomania, we cannot exclude the possibility that subthreshold symptoms of mania existing before enrollment into the NESARC study contributed to the development of the adult stressors analyzed, consistent with a stress generation model.[57]

Social determinants of first-onset and recurrent mania

Our study highlights the potential role of social experiences in the etiology of bipolar disorder, as has been suggested by results of smaller studies.[58] Consistent with our findings, the social experiences that are relevant for predicting bipolar illness include both childhood adversities[59,60] and stressful life events in adulthood.[61,62] These findings add to our understanding of the non-genetic component of the etiology of bipolar disorder, which according to family studies account for approximately 20% of population variance.[1,63]

For the most part, prior studies have investigated the role of social experiences in first-onset bipolar disorder separately from their role in the course of bipolar disorder.[52,64–67] In terms of independent associations of childhood and adult stressors with manic episodes, we observed no meaningful differences in the predictors of incident vs recurrent mania. We interpret this finding to suggest that social context over the life course is associated with heightened vulnerability to mania, and that this vulnerability is not attenuated after remission of an individual's first manic episode. The associations of adversities with incident and recurrent mania are both potentially relevant in terms of public health and clinical practice. To the extent that childhood adversities or adult stressors may be targeted for intervention, or may be used to identify a group at elevated risk for bipolar disorder, the associations involving incident manic episodes as well as depressive episodes occurring in the context of bipolar disorder are significant.[68] Further work remains to determine how information on psychosocial stressors can be incorporated into clinical practice to mitigate the elevated recurrence risk associated with such stressors.[69,70]

These same clinical implications regarding the importance of stressors in the onset and recurrent bipolar disorder also extend to other types of psychopathology. Childhood and past-year stressors predicted recurrences of anxiety and substance use disorders in the general NESARC sample.[41] More broadly, a recent review of life stressors and mental illness suggests substantially more evidence for generalized effects of stressors on multiple psychiatric conditions rather that unique associations between stressors and specific diagnoses.[71]

Sensitization

Sensitization refers to processes wherein the tendency of stressors to precipitate a manic episode depends on past exposure to stressors or on past history of manic episodes. Results from our analyses indicate support for sensitization effects in first-onset mania, but that these effects were contingent on the type of

Table 4. Associations between past-year stressors and childhood adversities and the recurrence of mania during the 3-year follow-up period of the NESARC[a]

	Model 1[b] *OR (CI)*	*Model 2*[c] *OR (CI)*	*Model 3*[c] *OR (CI)*
Past-year stressors at enrollment according to Axis IV of DSM-IV			
Social support group problems		1.31 (0.85, 2.02)	
Social environment problems		1.54 (0.97, 2.45)	
Occupational problems		1.62 (0.99, 2.64)	
Economic problems		0.85 (0.55, 1.32)	
Lack of health insurance		1.33 (0.82, 2.15)	
Legal problems		1.04 (0.63, 1.72)	
Empirically based taxonomy of past-year psychosocial stressors at enrollment			
1. Low stress			1
2. Personal loss			2.23 (1.06, 4.72)
3. Financial, interpersonal instability			2.47 (1.27, 4.81)
4. Economic difficulty			2.90 (1.22, 6.89)
5. Occupational instability			1.54 (0.52, 4.57)
Childhood adversities			
Childhood abuse	1.54 (0.99, 2.38)	1.49 (0.96, 2.30)	1.55 (1.00, 2.40)
Sexual maltreatment	1.84 (1.14, 2.96)	1.67 (1.06, 2.64)	1.60 (1.00, 2.55)
Economic disadvantage	1.44 (0.92, 2.25)	1.33 (0.85, 2.06)	1.31 (0.83, 2.07)

Abbreviations: CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; NESARC, NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; OR, odds ratio. [a]Results from logistic regression models of recurrent mania fitted in the sample of NESARC participants with a lifetime history of mania upon enrollment ($n = 1219$). ORs and corresponding 95% CIs indicate the association of past-year stressors and childhood adversities with the risk of a recurrent manic episode during the follow-up period. [b]Model 1 controls for participant sex, age at interview and race/ethnicity. [c]Models 2 and 3 also control for educational attainment, lifetime history of alcohol or substance dependence and major depressive disorder.

childhood adversity. Adulthood stressors were more likely to precipitate first-onset mania among individuals with a history of childhood physical abuse or neglect. Sexual maltreatment, in contrast, was such a powerful predictor of bipolar disorder that stressful life events in adulthood did not further increase the risk of mania among adults who experienced this type of adversity.[17,45] We found no support for sensitization effects in recurrent mania, despite theoretical arguments that such effects exist.[26,27,66,72,73] However, identifying sensitization typically requires larger samples because such effects imply statistical interactions; even the NESARC might have been underpowered in this regard.

Further research is needed to clarify the mechanisms by which early adversity may have a sensitizing effect on liability to mood disorder. In an example of how such a sensitizing effect could operate, Klengel *et al.*[74] recently reported that exposure to early adversity is associated with enhanced expression of FKBP5 in ways that set the stage for hypothalamic-pituitary axis dysregulation following stressful life events experienced in adulthood. In this case, the sensitizing effect of early life adversity appears to be mediated by epigenetic programming that increases the risk for later stress-related disorders in response to a 'second hit' of adult stressful life events. Whether such epigenetic effects contribute to the sensitizing effect of adversity on risk of mania remains to be determined.

CONCLUSIONS

Our findings provide evidence that adversities experienced during childhood, particularly physical and sexual abuse, and life events experienced in adulthood are associated with a significantly elevated risk of incident and recurrent mania. This evidence is consistent with emerging theoretical models of bipolar disorder that implicate stress-related pathways in the etiology of mania, and propose that these pathways have developmental origins.[27] Results of this study pinpoint specific aspects of the social environment that are associated with the vulnerability to bipolar illness, and should be studied further alongside emerging evidence on genetic variants associated with bipolar disorder[1,59,75] to generate more comprehensive models of bipolar etiology.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We sincerely appreciate the contributions of Ms Kathleen McGaffigan to data management and statistical programming. This work was supported in part by National Institutes of Health Grants RO1MH087544 (to SEG) and K24MH094614 (to JWS).

REFERENCES

1 Barnett JH, Smoller JW. The genetics of bipolar disorder. *Neuroscience* 2009; **164**: 331–343.
2 Marchand WR, Wirth L, Simon C. Adverse life events and pediatric bipolar disorder in a community mental health setting. *Community Ment Health J* 2005; **41**: 67–75.
3 Romero S, Birmaher B, Axelson D, Goldstein T, Goldstein BI, Gill MK, *et al.* Prevalence and correlates of physical and sexual abuse in children and adolescents with bipolar disorder. *J Affect Disord* 2009; **112**: 144–150.
4 Kennedy S, Thompson R, Stancer HC, Roy A, Persad E. Life events precipitating mania. *Br J Psychiatry* 1983; **142**: 398–403.
5 Ambelas A. Life events and mania. A special relationship? *Br J Psychiatry* 1987; **150**: 235–240.
6 Tillman R, Geller B, Nickelsburg MJ, Bolhofner K, Craney JL, DelBello MP, *et al.* Life events in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. *J Child Adolesc Psychopharmacol* 2003; **13**: 243–251.
7 Horesh N, Apter A, Zalsman G. Timing quantity and quality of stressful life events in childhood and preceding the first episode of bipolar disorder. *J Affect Disord* 2011; **134**: 434–437.
8 Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. *Psychol Med* 1997; **27**: 1079–1089.
9 Grant BF, Stinson FS, Hasin DS, Dawson DA, Chou SP, Ruan WJ, *et al.* Prevalence, correlates, and comorbidity of bipolar I disorder and Axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry* 2005; **66**: 1205–1215.

10 Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, *et al*. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 2007; **64**: 543–552.
11 Mortensen PB, Pedersen CB, Melbye M, Mors O, Ewald H. Individual and familial risk factors for bipolar affective disorders in Denmark. *Arch Gen Psychiatry* 2003; **60**: 1209–1215.
12 Kessing LV, Agerbo E, Mortensen PB. Major stressful life events and other risk factors for first admission with mania. *Bipolar Disord* 2004; **6**: 122–129.
13 Tsuchiya KJ, Agerbo E, Mortensen PB. Parental death and bipolar disorder: a robust association was found in early maternal suicide. *J Affect Disord* 2005; **86**: 151–159.
14 Brown GR, McBride L, Bauer MS, Williford WO. Cooperative Studies Program 430 Study T. Impact of childhood abuse on the course of bipolar disorder: a replication study in U.S. veterans. *J Affect Disord* 2005; **89**: 57–67.
15 Garno JL, Goldberg JF, Ramirez PM, Ritzler BA. Impact of childhood abuse on the clinical course of bipolar disorder. *Br J Psychiatry* 2005; **186**: 121–125.
16 Hlastala SA, Frank E, Kowalski J, Sherrill JT, Tu XM, Anderson B, *et al.* Stressful life events, bipolar disorder, and the 'kindling model'. *J Abnorm Psychol* 2000; **109**: 777–786.
17 Leverich GS, McElroy SL, Suppes T, Keck PEJr., Denicoff KD, Nolen WA, *et al.* Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biol Psychiatry* 2002; **51**: 288–297.
18 Christensen EM, Gjerris A, Larsen JK, Bendtsen BB, Larsen BH, Rolff H, *et al.* Life events and onset of a new phase in bipolar affective disorder. *Bipolar Disord* 2003; **5**: 356–361.
19 Ellicott A, Hammen C, Gitlin M, Brown G, Jamison K. Life events and the course of bipolar disorder. *Am J Psychiatry* 1990; **147**: 1194–1198.
20 Hunt N, Bruce-Jones W, Silverstone T. Life events and relapse in bipolar affective disorder. *J Affect Disord* 1992; **25**: 13–20.
21 Johnson SL, Cueller AK, Ruggero C, Winett-Perlman C, Goodnick P, White R, *et al.* Life events as predictors of mania and depression in bipolar I disorder. *J Abnorm Psychol* 2008; **117**: 268–277.
22 Kim EY, Miklowitz DJ, Biuckians A, Mullen K. Life stress and the course of early-onset bipolar disorder. *J Affect Disord* 2007; **99**: 37–44.
23 McPherson H, Herbison P, Romans S. Life events and relapse in established bipolar affective disorder. *Br J Psychiatry* 1993; **163**: 381–385.
24 Johnson SL, Miller I. Negative life events and time to recovery from episodes of bipolar disorder. *J Abnorm Psychol* 1997; **106**: 449–457.
25 Yan-Meier L, Eberhart NK, Hammen CL, Gitlin M, Sokolski K, Altshuler L. Stressful life events predict delayed functional recovery following treatment for mania in bipolar disorder. *Psychiatry Res* 2011; **186**: 267–271.
26 Alloy LB, Abramson LY, Walshaw PD, Keyser J, Gerstein RK. A cognitive vulnerability-stress perspective on bipolar spectrum disorders in a normative adolescent brain, cognitive, and emotional development context. *Dev Psychopathol* 2006; **18**: 1055–1103.
27 Brietzke E, Mansur RB, Soczynska J, Powell AM, McIntyre RS. A theoretical framework informing research about the role of stress in the pathophysiology of bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2012; **39**: 1–8.
28 McLaughlin KA, Conron KJ, Koenen KC, Gilman SE. Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: a test of the stress sensitization hypothesis in a population-based sample of adults. *Psychol Med* 2010; **40**: 1647–1658.
29 Dienes KA, Hammen C, Henry RM, Cohen AN, Daley SE. The stress sensitization hypothesis: Understanding the course of bipolar disorder. *J Affect Disord* 2006; **95**: 43–49.
30 Hammen C, Gitlin M. Stress reactivity in bipolar patients and its relation to prior history of disorder. *Am J Psychiatry* 1997; **154**: 856–857.
31 Swendsen J, Hammen C, Heller T, Gitlin M. Correlates of stress reactivity in patients with bipolar disorder. *Am J Psychiatry* 1995; **152**: 795–797.
32 Grant BF, Kaplan K, Shepard J, Moore T. *Source and accuracy statement for Wave 1 of the 2001-2002 National Epidemiology Survey on Alcohol and Related Conditions*. National Institute on Alcohol Abuse and Alcoholism: Bethesda, MD, 2003.
33 Grant BF, Kaplan K, Moore T, Kimball J. *Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions: Source and Accuracy Statement*. National Institute on Alcohol Abuse and Alcoholism: Bethesda, MD, USA, 2007.
34 Dawson DA, Goldstein RB, Grant BF. Rates and correlates of relapse among individuals in remission from DSM-IV alcohol dependence: a 3-year follow-up. *Alcohol Clin Exp Res* 2007; **31**: 2036–2045.
35 Grant BF, Dawson D. *The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV)*. National Institute on Alcohol Abuse and Alcoholism: Rockville, MD, USA, 2001.
36 Grant BG, Towle LH. Standardized diagnostic interviews for alcohol research. *Alcohol Health & Research World* 1990; **14**: 340–348.
37 Grant BF, Dawson DA, Stinson FS, Chou PS, Kay W, Pickering R. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV): reliability of alcohol consumption, tobacco use, family history of depression and psychiatric diagnostic modules in a general population sample. *Drug Alcohol Depend* 2003; **71**: 7–16.
38 Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, *et al.* Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry* 2004; **61**: 807–816.
39 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. 4th edn. American Psychiatric Association: Washington, DC, USA, 1994.
40 Ruan WJ, Goldstein RB, Chou SP, Smith SM, Saha TD, Pickering RP, *et al.* The alcohol use disorder and associated disabilities interview schedule-IV (AUDADIS-IV): reliability of new psychiatric diagnostic modules and risk factors in a general population sample. *Drug Alcohol Depend* 2008; **92**: 27–36.
41 Gilman SE, Trinh NH, Smoller JW, Fava M, Murphy JM, Breslau J. Psychosocial stressors and the prognosis of major depression: a test of Axis IV. *Psychol Med* 2013; **43**: 303–316.
42 Salum GA, Polanczyk GV, Miguel EC, Rohde LA Effects of childhood development on late-life mental disorders. *Curr Opin Psychiatry* 2010; **23**: 498–503.
43 Clark C, Caldwell T, Power C, Stansfeld SA. Does the influence of childhood adversity on psychopathology persist across the lifecourse? A 45-year prospective epidemiologic study. *Ann Epidemiol* 2010; **20**: 385–394.
44 Benjet C, Borges G, Medina-Mora ME. Chronic childhood adversity and onset of psychopathology during three life stages: childhood, adolescence and adulthood. *J Psychiatr Res* 2010; **44**: 732–740.
45 Hyun M, Friedman SD, Dunner DL. Relationship of childhood physical and sexual abuse to adult bipolar disorder. *Bipolar Disord* 2000; **2**: 131–135.
46 Research Triangle Institute. *SUDAAN Language Manual, Release 9.0*. Research Triangle Institute: Research Triangle Park: NC, USA, 2004.
47 Alegria M, Canino G, Rios R, Vera M, Calderon J, Rusch D, *et al.* Inequalities in use of specialty mental health services among Latinos, African Americans, and non-Latino whites. *Psychiatr Serv* 2002; **53**: 1547–1555.
48 Brewin CR, Andrews B, Gotlib IH. Psychopathology and early experience: a reappraisal of retrospective reports. *Psychol Bull* 1993; **113**: 82–98.
49 Hardt J, Rutter M. Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *J Child Psychol Psychiatry* 2004; **45**: 260–273.
50 Dohrenwend BP. Inventorying stressful life events as risk factors for psychopathology: toward resolution of the problem of intracategory variability. *Psychol Bull* 2006; **132**: 477–495.
51 Dohrenwend BS, Dohrenwend BP, Dodson M, Shrout PE. Symptoms, hassles, social supports, and life events: problem of confounded measures. *J Abnorm Psychol* 1984; **93**: 222–230.
52 Proudfoot J, Doran J, Manicavasagar V, Parker G. The precipitants of manic/hypomanic episodes in the context of bipolar disorder: a review. *J Affect Disord* 2011; **133**: 381–387.
53 Slopen N, Fitzmaurice GM, Williams DR, Gilman SE. Common patterns of violence experiences and depression and anxiety among adolescents. *Soc Psychiatry Psychiatr Epidemiol* 2012; **47**: 1591–1605.
54 Slopen N, Williams DR, Seedat S, Moomal H, Herman A, Stein DJ. Adversities in childhood and adult psychopathology in the South Africa Stress and Health Study: associations with first-onset DSM-IV disorders. *Soc Sci Med* 2010; **71**: 1847–1854.
55 Birmaher B, Axelson D, Monk K, Kalas C, Goldstein B, Hickey MB, *et al.* Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring study. *Arch Gen Psychiatry* 2009; **66**: 287–296.
56 Alloy LB, Abramson LY, Smith JM, Gibb BE, Neeren AM. Role of parenting and maltreatment histories in unipolar and bipolar mood disorders: mediation by cognitive vulnerability to depression. *Clin Child Fam Psychol Rev* 2006; **9**: 23–64.
57 Bender RE, Alloy LB, Sylvia LG, Urosevic S, Abramson LY. Generation of life events in bipolar spectrum disorders: a re-examination and extension of the stress generation theory. *J Clin Psychol* 2010; **66**: 907–926.
58 Alloy LB, Abramson LY, Urosevic S, Walshaw PD, Nusslock R, Neeren AM. The psychosocial context of bipolar disorder: environmental, cognitive, and developmental risk factors. *Clin Psychol Rev* 2005; **25**: 1043–1075.
59 Etain B, Henry C, Bellivier F, Mathieu F, Leboyer M. Beyond genetics: childhood affective trauma in bipolar disorder. *Bipolar Disord* 2008; **10**: 867–876.
60 Gilman SE, Dupuy JM, Perlis RH. Risks for the transition from major depressive disorder to bipolar disorder in the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry* 2012; **73**: 829–836.
61 Johnson SL.. Life events in bipolar disorder: towards more specific models. *Clin Psychol Rev* 2005; **25**: 1008–1027.
62 Johnson SL, McMurrich S. Life events and juvenile bipolar disorder: conceptual issues and early findings. *Dev Psychopathol* 2006; **18**: 1169–1179.
63 Craddock N, Sklar P. Genetics of bipolar disorder. *Lancet* 2013; **381**: 1654–1662.

64 Aronson TA, Shukla S. Life events and relapse in bipolar disorder: the impact of a catastrophic event. *Acta Psychiatr Scand* 1987; **75**: 571–576.
65 Daruy-Filho L, Brietzke E, Lafer B, Grassi-Oliveira R. Childhood maltreatment and clinical outcomes of bipolar disorder. *Acta Psychiatr Scand* 2011; **124**: 427–434.
66 Hlastala SA. Stress, social rhythms, and behavioral activation: psychosocial factors and the bipolar illness course. *Curr Psychiatry Rep* 2003; **5**: 477–483.
67 Miklowitz DJ, Johnson SL. Social and familial factors in the course of bipolar disorder: basic processes and relevant interventions. *Clin Psychol* 2009; **16**: 281–296.
68 McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication II: associations with persistence of DSM-IV disorders. *Arch Gen Psychiatry* 2010; **67**: 124–132.
69 Skodol AE, Shrout PE. Use of DSM-III axis IV in clinical practice: rating etiologically significant stressors. *Am J Psychiatry* 1989; **146**: 61–66.
70 Schrader G, Gordon M, Harcourt R. The usefulness of DSM-III axis IV and axis V assessments. *Am J Psychiatry* 1986; **143**: 904–907.
71 Gilman SE, Daniel J. The role of the social environment over the life course in the etiology of psychiatric disorders. In: Koenen KC, Rudenstine S, Susser E, Galea S (eds). *A Life Course Approach to Mental Disorders*. Oxford University Press: New York, NY, USA, 2013, pp 215–226.
72 Bender RE, Alloy LB. Life stress and kindling in bipolar disorder: review of the evidence and integration with emerging biopsychosocial theories. *Clin Psychol Rev* 2011; **31**: 383–398.
73 Post RM, Rubinow DR, Ballenger JC. Conditioning and sensitisation in the longitudinal course of affective illness. *Br J Psychiatry* 1986; **149**: 191–201.
74 Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM, *et al*. Allele-specific FKBP5 DNA demethylation mediates gene–childhood trauma interactions. *Nat Neurosci* 2013; **16**: 33–41.
75 Ferreira MA, O'Donovan MC, Meng YA, Jones IR, Ruderfer DM, Jones L, *et al*. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat Genet* 2008; **40**: 1056–1058.

Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)