CHAPTER 3

Stressful life events in bipolar I and II disorder: cause or consequence of mood symptoms?

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Abstract

Life events are assumed to be triggers for new mood episodes in bipolar disorder (BD). However whether life events may also be a result of previous mood episodes is rather unclear. In the current study 173 bipolar outpatients (BD I and II) were assessed every three months for two years. Life events were assessed by Paykel's self-report questionnaire. Both monthly functional impairment due to manic or depressive symptomatology and mood symptoms were assessed.

The results show that negative life events were significantly associated with both subsequent severity of mania and depressive symptoms and functional impairment, whereas positive life events only preceded functional impairment due to manic symptoms and mania severity. These associations were significantly stronger in BD I patients compared to BD II patients. For the opposite temporal direction (life events as a result of mood/functional impairment), we found that mania symptoms preceded the occurrence of positive life events and depressive symptoms preceded negative life events.

The use of a self-report questionnaire for the assessment of life events makes it difficult to determine whether life events are cause or consequence of mood symptoms. Second, the results can only be generalized to relatively stable bipolar outpatients, as the number of severely depressed as well as severely manic patients was low.

Life events appear to precede the occurrence of mood symptoms and functional impairment, and this association is stronger in BD I patients. Mood symptoms also precede the occurrence of life event, but no differences were found between BD I and II patients.

3.1 Introduction

The course of bipolar disorder (BD) is assumed to be the result of a complex interaction between genetic and biological vulnerability and environmental factors (92-94). The severity and frequency of the occurrence of (hypo-) manic and depressed episodes is highly variable and unpredictable among BD patients. In order to improve treatment effect and disease outcome, more insight is needed in factors predicting and contributing to relapse into mood episodes. Stressful life events play an important role in the course of BD. The occurrence of major events in the life of BD patients has been associated with an increased risk of relapse into mood episodes (95, 96) and increased time until recovery (97). Especially negative life events seem to be more common in the months prior to both depressive (31, 32, 98-101) and manic episodes (102-107). One of the more recent studies, and the largest follow up study on life events in BD to date, shows that negative life events especially precede depressive symptoms and life events involving goal attainment precede manic symptoms (108). However both for depression (107, 109) and mania (31, 32, 98, 109) findings are inconsistent, and the exact nature, strength and direction of the associations are still unclear.

Further, it has been suggested that life events may also occur as a consequence of the disorder. The so-called 'stress generation theory' in unipolar depression (110) states that individuals with depressive symptomatology may generate stressful events, (for example, marital problems, or loss of a job) due to their depressive symptoms. There is a substantial amount of evidence that supports this relationship in unipolar depression (49), and hence, whether this also holds for BD patients remains unclear, since only one prospective study (50) to date examined this association and found that hypomanic symptoms predicted increases in both negative and positive life events and depressive symptoms appeared to be less stronger predictors of subsequent life events.

There are several factors that complicate examining the association between life events and mood, which may have contributed to inconsistent results. One of the factors that may explain part of the inconsistencies may relate to the BD subtypes that have been studied, as previous studies strongly differ

in terms of the specific BD diagnosis. Some studies examined samples including all BD subtypes (32), others only included cyclothymic and BD II patients (111) or only BD I patients (e.g. 31). This might contribute to inconsistent findings, since growing evidence indicate that BD I and II differ on both clinical (112), genetic (25, 113) and neurocognitive characteristics (114, 115). For instance, compared to BD I, BD II is associated with more comorbidity of psychiatric illnesses (116, 117). Further, BD II is associated with a more chronic course with more frequent episodes (25-27) which may lead to the process of 'kindling' (93), meaning that in time mood episodes may appear more easily without being triggered by any environmental stressor. It is however unclear to what extend kindling is involved in BD in general and in patients with BD II in particular.

A second factor that may have contributed to inconsistent findings, is the fact that most prospective studies rely on rather small sample sizes, ranging from N=41 to N=56 (32, 98, 109, 118) and short follow-up periods. They therefore may have lacked statistical power to detect a consistent association between life events and mood symptoms. To date, only Johnson et al. (31) studied the effect of life events on bipolar mood in a prospective study with both a large sample size (N=125) and a relatively long follow-up period (27 months).

Third, it remains difficult to determine whether life events are a cause or a consequence of bipolar mood episodes. Several studies tried to control for this by excluding those life events that were rated by the researchers as dependent of mood symptoms (e.g. losing a job due to a current depression), and only including life events rated as independent of mood symptoms (e.g. illness or death of a relative) (e.g. 31, 32, 95, 100). However, even though dependent life events may strictly speaking be consequences of the disorder, this does not mean that these events cannot have an adverse effect on the course of the disease as well, illustrating the difficulty in determining the temporal direction of the association.

In the current two-year prospective follow-up study among 173 BD patients we aimed to examine both temporal directions of the association between negative and positive life events and depressive and mania symptomatology and functional impact of mood disturbances. Additionally, to control for possible differences between BD I and II, we examined BD subtype as a pos-

sible moderator of the association between life events and mood symptoms and functional impact.

3.2 Materials and methods

3.2.1 Method

Participants

This is a 2-year prospective follow-up study among 173 bipolar outpatients with a diagnosis of BD I (N=121) or BD II (N=52) (also including BD not otherwise specified (N=2) and cyclothymia (N=1)) according DSM-IV-TR diagnostic criteria. All patients treated for BD by the Outpatient Clinic for Mood Disorders in The Hague (The Netherlands) were invited to participate in the study, either by letter or directly by their treating physician. After written informed consent was obtained, 173 patients were willing to participate and enrolled into the follow-up study. Participants were older than 18 years. Exclusion criteria in this study were schizo-affective disorder, neurological disease and substance abuse disorders.

Diagnoses of BD and psychiatric Axis I co-morbidities were based on DSM-IV criteria and were assessed with a standardized diagnostic interview developed by Sheenan et al. (119) using the Dutch version of the MINI International Neuropsychiatric Interview Plus (version 5.00-R; MINI-PLUS), with good interrater (kappa >.75) and retest reliability (kappa > .75) (119, 120) DSM-IV axis II comorbidity was not assessed. The Questionnaire for Bipolar Illness, Dutch translation (23, 121) was used to specify subtypes of BD, its course over time and detailed information about age of onset of first symptoms regarding hypomanic, manic, and depressive episodes.

Of the total sample, 90.2% of the patients (N=156) completed at least 1 year follow-up, eventually a cumulative number of 44 (25.4%) patients dropped out before the end of the study. The most common reasons for patients to quit prematurely were: being too unstable, being hospitalized, deeming the research too burdensome, discontinuing treatment at our outpatient clinic, and not showing up at an appointment more than 2 times. Figure 3.1 shows the flow-chart with the number of patients who dropped out at the different

time points.

Procedure

All patients signed informed consent before entering the study. After completing the baseline measurement with a psychiatric interview, assessment of current and past mood, and patient and disease characteristics, patients had face-to-face contacts with the research assistant at 3-, 6-, 9-, 12-, 15-, 18-, 21-, and 24- months follow-up. During these contacts manic and/or depressed mood, medication use and stressful life events during the past three months were assessed (see Figure 3.1). In order to increase accuracy of recall of mood severity in the past three months and the occurrence of life events, information from diaries, calendars, patient files or other anchor points were used.

3.2.2 Materials

Life events

The occurrence of life events was assessed every 3 months by Paykel's (122) self-report questionnaire consisting of 61 life events, which was independently completed by the patients. This instrument categorizes possible life events into 10 groups (i.e., employment, education, financial status, somatic health, loss, living place, relationship, criminality, family and social problems, and other events). Patients rated whether the events on the list occurred within the preceding 3 months, and if so they rated on a 5-point scale how upsetting the event has been to them.

The 61 single life event items were summarized into 2 main categories: the number of negative life events, and the number of positive life events. This led to a total of 39 negative life events, such as increasing arguments with the spouse, the end of a romantic relationship, business failure, serious illness of a family member, failure to an important exam, demotion at work, and unemployment for one month. A total of eleven positive life events consisted of events such as promotion at work, engagement, marriage , and a wanted pregnancy. A total of eleven life events, that could not be categorized as either positive or negative, were rated as neutral or ambiguous events (change of work field, change of work hours, moving) and were not included in the

current analyses. The categorization into negative and positive life events was determined a priori by the researchers regardless of patients ratings of the event. This method was chosen since patients ratings may be highly influenced by current mood state and in many previous studies categorization of life events (i.e. positive versus negative life events, dependent versus independent life events) was also based on a priori categorization by the researchers (i.e. 31, 32, 105).

For additional analyses of the effects of specific types of life events , life events were categorized into the above mentioned 10 life event categories.

Illness severity

Illness severity was assessed both in terms of symptoms severity and the functional impact of the mood disturbances. In order to assess mood severity based on number and severity of symptoms the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) (123), and the observer based Young Mania Rating Scale (YMRS)(60) was administered every 6 months. Both the QIDS (123) and the YMRS (60) have good (inter-) reliability and validity. The functional impact of mood disturbance was assessed by the NIMH monthly retrospective life chart method (LCM-r) (21, 124). This tool was used every up to eight assessment sessions, to measure medication use and monthly functional impairment arising from manic or depressed symptomatology of the previous 3 months. The advantage of this monthly tool over its daily counterpart could be the lowering of dropout rate as it demands fewer resources on the part of the clinicians and the patients. However, disadvantages are the fact that patients might not remember every minor episode, especially not when subdepressive or hypomanic symptoms are involved.

The retrospective life chart distinguishes four levels of severity for both mania and depression: mild, moderately low, moderately high, and severe. LCM rating is not based on number or severity of symptoms, but on the level of functional impairment arising from these mood symptoms. With 'mild' manic or depressive symptoms representing a distinct difference from normal mood, but with minimal or no functional incapacity, 'Moderately low'

manic or depressive symptoms reflecting some difficulty in usual roles and functioning, 'moderately high' reflecting much difficulty in usual roles and functioning, and 'severe' manic or depressive symptoms reflecting symptoms that essentially incapacitated the patient or resulted in hospitalization (85). Based on the life chart data, mean severity of functional impairment of depression and mania of every three-month period was calculated by averaging the monthly severity scores. A similar method has been used in previous research (62, 67). Medication use assessed with the life chart was categorized into a dichotomous variable. The psychotropic medication classes that were used most frequently, were coded according to the Anatomical Therapeutic Chemical Classification System (http://www.whocc.no/) and included Lithium (ATC code: N05AN01), anti-epileptics (ATC code: N03AF01, N03AG01, N03AX09, N03AX11), antipsychotic medication (ATC code: N05Ax with exclusion of N05AN01), benzodiazepines (ATC codes: N05BA, N05CD, N03AE01, N05CF), and antidepressants (N06A).

At the different time points during follow-up correlations between QIDS score and life chart depression score of the corresponding month varied between r=.52 and r=.65 (all significant at p<.001). Correlation between YMRS scores and life chart mania scores of the corresponding month varied between r=.40 and r=.65 (all significant at p<.001). This means that QIDS scores account for 28% to 43% of the variance of life chart depression, and YMRS scores account for 16% to 43% of the variance in life chart mania.

3.2.3 Statistical analyses

Sociodemographic and baseline characteristics were summarized as means (standard deviation [SD]) for continuous variable and as numbers (proportions) for categorical variables. Differences between subgroups were analyzed with independent sample t-tests, or chi-square analyses if appropriate.

Because data of this prospective study are nested (repeated measurements within an individual) and missings occurred because of dropouts, multilevel regression analyses (linear mixed-models) were used to analyze the associations between total number of positive and negative life events and mood states. A compound symmetry covariance structure was used consisting of

the time points (i.e. lower level) and the patients (i.e. higher level).

Life chart scores and QIDS and YMRS scores were analyzed separately, since life chart mood was assessed for up to 8 waves (every 3 months), and QIDS and YMRS for up to 4 waves (every 6 months) (see Figure 3.1). Throughout the analyses, we examined both life chart and QIDS and YMRS severity scores as continuous variables, instead of a dichotomous variable (i.e. presence/absence of mood episodes).

In the first set of models we explored to what extent positive/negative life events precede mood/functional impairment. For the first set of models we used the number of positive and negative life events of the last three months as the predictor variable and mood assessed at the subsequent time point (life chart, QIDS, and YMRS) as outcome variable. The direction of the association is shown by the arrows [1] in Figure 3.1. Associations were first assessed in a crude model, only adjusting for time and mood. Subsequently, we repeated multilevel regression analyses additionally adjusting for age, sex, level of education, medication use (adding 5 dichotomous variables).

In the second set of models we explored the reversed temporal relationship, that is to what extent mood /functional impairment precede life events. In these models mood severity (life chart, QIDS and YMRS) was used as predictor variable and positive and negative life events in the subsequent 3 months as outcome variables. This is indicated by the arrows [2] in Figure 3.1. Again, associations were first assessed in a crude model and subsequently in a model adjusting for age, sex, level of education, medication use, and total number of life events at time of assessed mood.

In an additional set of analyses we examined the interaction of BD subtype × (positive and negative) stressful life events for both temporal relationship, in order to determine whether effect of life events on mood/functional impairment and mood/functional impairment on life events were different for the two BD subgroups. All analyses were completed using SPSS for Windows (version 19.0; SPSS, Inc. Chicago, IL). All tests were two-tailed with $p<0.05$ denoting statistically significance.

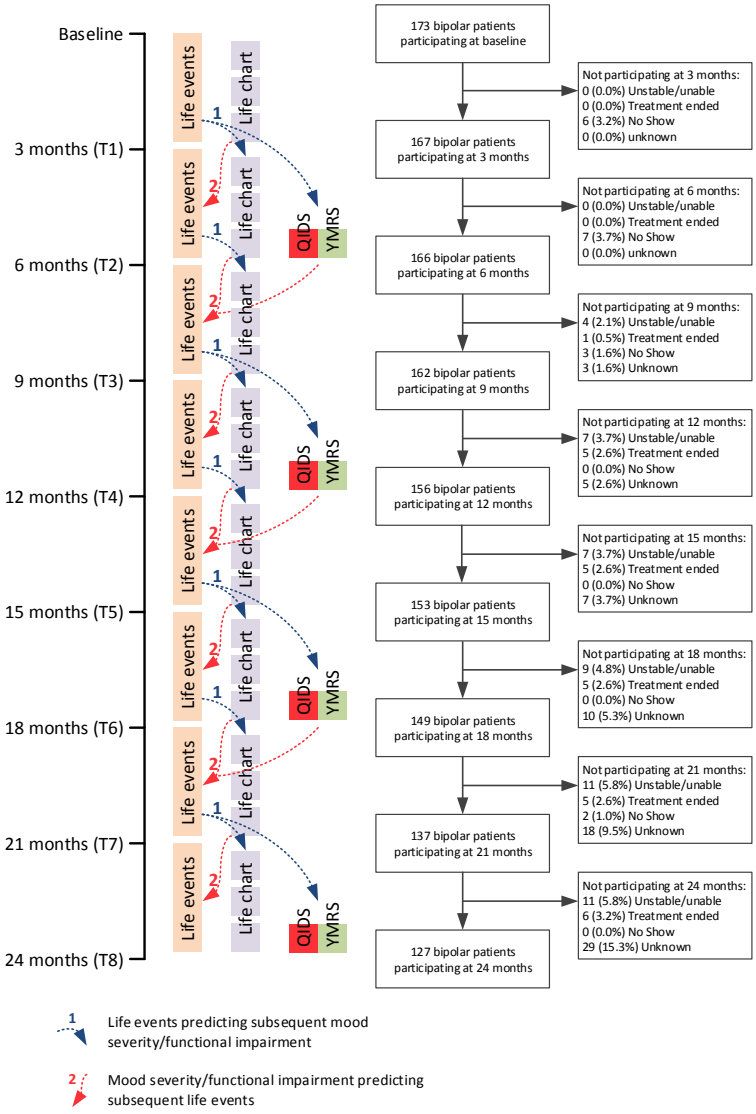

Figure 3.1 | Flow chart of follow-up measurements, direction of associations and drop-out rates.

3.3 Results

3.3.1 Demographics and clinical characteristics

Basic demographic and clinical characteristics of all patients who participated in at least one follow-up measurement (N=173) are summarized in Table 3.1. In total there were 1180 data points with complete data during 24 months of follow-up. The included subjects had a mean age of 49.9 years and were predominantly female (57.8%). Overall, mean score on the QIDS at study entry was 7.5, indicating mild depressive symptoms. Mean YMRS score was 1.7, indicating overall absent or low mania symptoms at study entry. During the duration of the study QIDS scores varied from 0 to 24, with mean scores of the total sample varying from 6.5 (SD=4.8) to 7.4 (SD =4.7). Individual YMRS scores varied between 0 to 39, with overall YMRS mean scores during follow-up varying from 1.5 (SD=3.7) to 2.1 (SD=4.8). During the two year follow-up, patients reported on the life chart functional impaired due to depressed mood 32.7% of the times, manic mood 12.2% of the times and stable mood 57.1% of the total follow up time.

A total of 8 (4.6%) patients reported no life events during the period of the study and individual number of total reported life events (positive and negative) during 3 months periods ranged from 0 to 14. Percentage of patients reporting life events over the eight follow up measurements were as follows: including the data of all timepoints (in total 1180 valid data points); in 76% (N=904) no positive life events were reported, in 16.3% (n=192) 1 positive life event was reported, in 4.8% (N=57) 2 positive life events were reported, and in 2.2% (N=26) 3 or more positive life events were reported. With respect to negative life events during 24-months follow-up, 28.9% (N=342) reported no negative life events, 22.8% (N=269) reported 1 negative event, 19.6% (N=231) reported 2 negative events, 11.7% (N=138) reported 3 negative life events, and 16.9% (N=200) reported 4 or more negative life events.

Between the group who participated until the end of the study (n=127) and the group that dropped out during the study (N=44) no significant differences in baseline demographic and clinical characteristics were found and during the study no differences in mood severity on the QIDS, YMRS and life chart were found. Moreover, number of admissions was the same in both

completers and dropouts, during the study as well as the first 3 months after dropping out.

	Total	BD I	BD II	P-value
Total N	173	121	52	
Male sex; n(%)	73 (42.2)	54 (44.6)	19 (36.5)	.323
Mean age; mean (SD)	49.9 (11.4)	50.6 (11.9)	48.3 (10.2)	.230
Level of education; N (%):				
- primary	39 (22.5)	30 (25.0)	9 (17.6)	.294
- secondary	50 (28.9)	32 (26.7)	18 (35.3)	.257
- higher	82 (47.4)	58 (48.3)	24 (47.1)	-
Clinical characteristics:				
Diagnostic information; N(%)				
BD1	121 (69.9)	-		-
Comorbidity	67 (38.7)	43 (35.6)	24 (46.2)	.169
Age of onset; mean (SD)				
Age of onset first (hypo-) mania	30.8 (10.1)	30.3 (9.9)	31.9 (12.1)	.419
Age of onset first depression	27.6 (10.1)	27.4 (9.9)	27.9 (10.4)	.767
Age of onset disease	27.0 (9.8)	26.9 (9.7)	27.2 (10.1)	.875
Number of episodes; median (IQR)				
No. of manic episodes	5 (8)	4 (8)	5 (18)	.028*
No. of depressive episodes	6 (16)	6 (7)	13 (45)	.001**
QIDS baseline; mean(SD)	7.5 (4.9)	6.4 (4.4)	10.1 (5.3)	<.001**
YMRS baseline; mean (SD)	1.7 (3.1)	1.4 (2.9)	1.9 (2.9)	.385
Medication use baseline; N(%)				
Lithium	119 (68.8)	89 (76.1)	30 (58.8)	.024*
Anti-epileptics	36 (20.8)	24 (20.5)	12 (23.5)	.661
Anti-psychotics	42 (24.3)	39 (33.6)	3 (5.9)	<.001**
Benzodiazepines	42 (24.3)	29 (25.4)	13 (25.5)	.994
Antidepressants	56 (32.4)	35 (30.2)	21 (41.2)	.165

* p-value < .05

** p-value <.001

Table 3.1 | Sociodemographic and clinical characteristics in 173 participants with bipolar disorder.

3.3.2 Stressful life events preceding mood symptom/functional impairment

Table 3.2 shows the results of the multilevel analyses considering the association between total number of negative and positive life events and sub-

sequent functional impairment and severity of mania and depression. Negative life events were strongly and consistently associated with increases in subsequent depression severity/functional impact on the life chart and QIDS and increases in mania severity/functional impact on the life chart and on the YMRS. These results remained unchanged in the multivariate adjusted model. In Figure 3.2 the association between the number of negative life events and life chart functional impairment, and YMRS and QIDS scores is depicted. There appears to be a threshold effect, since severity of both life chart functional impairment and depressive and manic symptoms strongly increases after the occurrence of 4 or more negative life events, whereas scores of one to three negative life events have minimal effects on life chart functional impairment and mood severity.

Positive life events were significantly associated with subsequent life chart and YMRS mania severity, also after multivariate adjustment, but no association was found with life chart and QIDS depression severity in the subsequent months.

Additional analyses showed that there were no differences in the effects of single life events items, suggesting all life events contributed rather equally to the results (data not shown). Also no specific effects were found of groups of life events occurring in certain life domains (e.g. interpersonal problems, work problems, financial problems) (data not shown).

3.3.3 Mood symptoms/functional impairment preceding stressful life events

Next, the opposite temporal direction, mood severity and functional impairment preceding life events, was investigated. The results of both the crude and multivariate adjusted analyses are summarized in Table 3.3. In the multivariate adjusted analyses a significant association was found for YMRS mania severity preceding number of positive life events (β=.124, p=.010), but not negative life events, and QIDS depression severity preceded number of negative life events (β=.151, p=.002). However life chart functional impairment was not significantly associated with subsequent negative or positive life events.

	No. of data points Life Chart	No. of data points QIDS/ YMRS	Mania symptoms				Depressive symptoms			
			Life chart data		YMRS		Life chart data		QIDS	
			Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
Total no. of negative events:										
Crude[1]	978	385	.142 (.032)	< .001**	.152 (.049)	.002**	.087 (.033)	.009*[i]	.133 (.038)	< .001**
Multivariable adjusted [2]	961	362	.128 (.033)	< .001**	.157 (.053)	.003**	.084 (.033)	.012*[i]	.158 (.042)	< .001**
Total no. of positive events:										
Crude[1]	978	385	.087 (.031)	.004**	.243 (.057)	<.001**	-.009 (.014)	.723[i]	.024 (.037)	.519
Multivariable adjusted [2]	961	362	.071 (.031)	.021 *	.238 (.062)	<.001**	-.005 (.031)	.501[i]	.043 (.041)	.296

[1]: adjusted for time and mood

[2]: adjusted for time, gender, age, level of education, and medication use (antipsychotic, antidepressants, benzodiazepines, lithium, and anticonvulsive agents) and mood using multilevel regression analysis (i.e. mixed models).

* p-value < .05

** p-value <.001

Table 3.2 | Stressful life events preceding mood symptom/functional impairment at follow-up in 173 patients with BD.

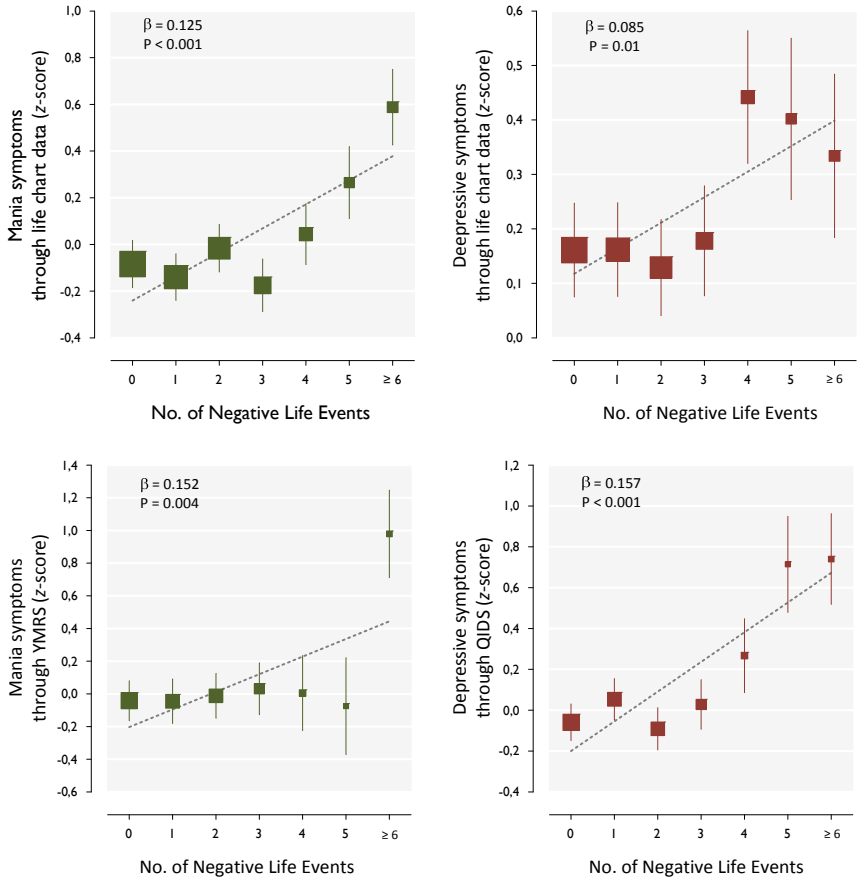

Figure 3.2 | Plots of the association between number of negative life events and the standardized score mood severity (QIDS/YMRS/Life Chart). The size of each square is proportional to the number of participants. Vertical lines indicate standard errors. Data are adjusted means by linear mixed models.

	No. of data points	Total number of negative life events		Total number of positive life events	
		Beta (SE)	P-value	Beta (SE)	P-value
Mania symptoms according to life chart method:					
Crude	992	.022 (.028)	.445	.014 (.032)	.673
Multivariable adjusted	932	.001 (.029)	.973	-.002 (.034)	.964
Mania symptoms according to YMRS:					
Crude	385	.079 (.047)	.094	.136 (.048)	.004*
Multivariable adjusted	374	.049 (.049)	.306	.124 (.048)	.010*
Depressive symptoms according to LCM:					
Crude	992	.043 (.029)	.140	.039 (.033)	.228
Multivariable adjusted	932	.051 (.031)	.088	.043 (.034)	.211
Depressive symptoms according to QIDS:					
Crude	386	.198 (.052)	<.001**	-.016 (.055)	.768
Multivariable adjusted	359	.151 (.049)	.002**	.005 (.056)	.926

[1]: adjusted for time and life events

[2]: adjusted for time, gender, age, level of education, and medication use (antipsychotic, antidepressants, benzodiazepines, lithium, and anticonvulsive agents) and life events using multilevel regression analysis (i.e. mixed models).

* p-value < .05

** p-value <.001

Table 3.3 | Mood symptoms/functional impairment preceding stressful life events at follow-up in 173 patients with BD.

The life chart data reflect mood dependent functional impairment of the past three months, the QIDS and YMRS reflects current mood, with the last measure being temporarily more proximal to the subsequently assessed life events (see Figure 3.1). However, also when life chart functional impairment of only the last month of the three life chart months was included in analyses, life chart severity neither preceded life events (data not shown).

Additional analyses showed that mood/functional impairment did not preceded certain types of life events or life event categories (data not shown).

3.3.4 Bipolar I versus bipolar II patients

Finally we examined BD subtype as a possible moderator of the relationship of life events with subsequent functional impairment and mood. First, differences between BD I (N=121)and II (N=52) at study entry were analyzed (Table 3.1). BD II patients reported significantly higher QIDS scores at study entry and more previous hypomanic episodes and depressive episodes. Further in the BD I group lithium and anti-psychotics were used significantly more often. With respect to the other variables at study entry no differences were found. During follow-up no differences were found in mean QIDS and YMRS scores, functional impairment based on the life chart, and reported total number of positive and negative life events.

Results of the moderation analyses are presented in Table 3.4. These results show that only in the BD I group negative life events are significantly associated with subsequent depression and mania severity on the lifechart, QIDS and YMRS. Moreover, the number of positive events was significantly associated with subsequent manic symptomatology and functional impairment in the BD I patients, but not in the BD II patients. Further, negative life events even seemed to have opposite effects in the two diagnostic groups, in the BD I group negative events are associated with increase in mania severity, whereas in the BD II group negative life events were associated with a decrease in mania severity.

In order to examine whether the differences in number of previous mood episodes between BD I and II might explain the difference in association between life events and mood, we additionally adjusted for number of previ-

	Mania symptoms				Depressive symptoms			
	Life chart data		YMRS		Life chart data		QIDS	
	Beta (SE)	P-value for interaction	Beta (SE)	P-value for interaction	Beta (SE)	P-value for interaction	Beta (SE)	P-value for interaction
Total no. of negative events:								
BD I	.197 (.043)	< .001**	.230 (.063)	.001**	.094 (.039)	.717	.216 (.049)	.036*
BD II and BD NOS	-.027 (.045)		-.201 (.082)		.081 (.063)		-.035 (.092)	
Total no. of positive events:								
BD I	.049 (.039)	.376	.329 (.081)	.019 *	.011 (.036)	.563	.008 (.049)	.410
BD II and BD NOS	.119 (.045)		.024 (.079)		-.049 (.064)		.071 (.081)	

Adjusted for time, mood, gender, age, level of education, and medication use (antipsychotic, antidepressants, benzodiazepines, lithium, and anticonvulsive agents) and mood using multilevel regression analysis (i.e. mixed models).

* p-value < .05

** p-value <.001

Table 3.4 | Effects of life events on mood state at follow-up in patients with BD I (N=121) versus BD II (N=52).

ous manic and depressed episodes in the moderation analyses. This did not lead to different results, suggesting that differences in stress vulnerability are unlikely to be due to differences in number of previous episodes (kindling) (data not shown). Since in the BD II group comorbidity was slightly more common, additional adjustments for comorbidity were made as well, but again this did not lead to different results. For the opposite temporal directions, mood preceding life events, no differences between BD I and II were found.

3.4 Discussion

The aims of the current study were to examine the strength of both temporal associations between life events and mood disturbances in bipolar disorder, with respect to both functional impairment as well as mood severity. Additionally, we aimed to examine possible differences in these associations between BD I and II patients. The most important findings were that negative life events preceded both (hypo-) manic and depressive symptoms and functional impairment, while positive life events predicted only (hypo-) manic mood and functional impairment due to mania. The significant associations were predominantly found in the BD I group and not in the BD II group. For the opposite temporal direction, we found that mania symptoms preceded positive life events and depressive symptoms preceded negative life events. Functional impairment did not precede life events and no differences be-

tween BD I and II patients were found.

3.4.1 Life events preceding mood symptoms and functional impairment

In the current study negative life events were significantly and consistently associated with subsequent depressive mood and depression dependent functional impairment, which is in line with previous studies (31, 32, 98). Further, positive life events preceded manic symptoms/functional impairment, which is somewhat in line with a recent longitudinal study among BD I patients showing goal attainment life events (events that involve striving, or achieving a goal) to be predictors of increases of subsequent (hypo) manic symptoms. As the present study did not assess goal attainment life events our results cannot be directly compared to previous studies reporting that especially life events involving goal attainments and not positive life events in general are predictors of manic symptoms (31, 111, 118). Nevertheless, life events involving goal attainments importantly overlap with our positive life events.

Interestingly, we found clear indications that negative life events also predicted mania severity and mania dependent functional impairment in the subsequent months. These findings are not reported in other prospective studies (31, 32, 98, 109). A possible explanation for the fact that we do observe this association, whereas other failed to do so, might be related to the fact we used continuous mood data, while previous studies evaluated the effect of life events on relapse (dichotomous) into full (hypo-) manic episodes (32, 98, 109). Assessing mood as a continuous variable in the present study may have led to increased statistical power to detect possible associations. In sum, our findings provided support for the notion that negative life events may also precede mild manic symptomatology.

Further, additional analyses showed that no specific single life events or categories of life events in specific life domains (e.g. interpersonal problems, financial problems) are associated with subsequent mood/functional impairment. However, there is a cumulative effect of life events on mood/functional impairment, with the occurrence of single life events causing small mood fluctuations, but when larger numbers of negative life events occur, severity

of mood symptoms and functional impairment increase quite dramatically in the following months. This is in line with Boland et al.(125), who stated that it may not be the specific type of life event that is important but the overall level of disruption caused by the event. It is likely that the occurrence of several different stressful events can highly disturb daily life and thus daily structure and social rhythms, while single life events might not have this disturbing effect. Since social rhythm disruptions are associated with manic and depressive symptoms (126, 127), this might be an additional explanation for the association we found between negative life events and mania. For positive life events not such a threshold effect was found. This may be due to the fact that positive life events are relatively underrepresented compared to the negative life events in the used questionnaire.

3.4.2 Mood symptoms and functional impairments preceding life events

Our results also provide support for the idea that mood symptoms induce life events in BD patients. Hypomanic symptomatology predicted positive events and depressive symptoms predicted negative events. However, mood dependent functional impairment assessed with the life chart was not associated with subsequent life events. The fact that the QIDS and YMRS are more appropriate for the detection of subclinical mood symptoms, than the more crude monthly life chart might explain the different findings, since the literature on unipolar depression indicates, is that both mood episodes as well as subclinical mood symptoms are predictors of life events (128, 129). Moreover, the life chart scores depended on the degree of functional impairment arising from the mood symptoms and does not assess mood symptoms itself. This indicates that increases in number and severity of symptoms is associated with an increase in the occurrence of subsequent number of life events, and that this association may be less strong for functional impairment. The current findings are partly in line with the only other prospective study on stress generation in BD (50), in which (hypo-) manic symptoms were also found to precede positive life events, but no association with depressive symptoms was found previously. Both the current and previous findings seem to indicate that bipolar mood symptoms may induce life events.

3.4.3 Bipolar I versus bipolar II

Another interesting finding is that life events predicted subsequent mood severity and mood dependent functional impairment in the BD I group only, and not in the BD II group. In previous studies BD I and II have already been implicated to be different disorders with respect to several clinical features. BD II compared to BD I is associated with a more chronic course with more frequent episodes (25, 26). This chronic course may indicate that mood symptoms in BD II occur more independently from external factors, such as life events. Further BD II is associated with more comorbidity of psychiatric illness (116, 130), making this a more heterogeneous patient group in which consistent associations between external factors and mood symptoms are more difficult to disentangle. In the current sample BD II patients also seem to have more frequent episodes, since they reported a significantly higher number of previous manic and depressed episodes at study entry compared to BD I patients. However, after additionally adjusting for number of previous manic and depressed episodes, results with respect to the effect of life events on mood remained unchanged. Also psychiatric comorbidity did not seem to account for the differences found between BD I and II. It should be taking into account however, that the BD II group was smaller (N=52) than the BD I group (N=121), hence, the lack of power in the BD II group may also account for the failure to find an association between mood and stressful life events.

Another difference found between BD I and II, was that negative life events seemed to have an opposite effects in the two diagnostic groups, in the BD I group negative events are associated with increase in mania severity, whereas in the BD II group negative life events were associated with a decrease in mania severity. This is in contrast with earlier findings by Johnson et al. (31) showing negative life events to be associated with decrease in mania severity in a group of only BD I patients. To what extent life events have different effects on BDI and II patients and whether the lack of associations found in the current study also hold in larger BD II samples has to be further explored.

3.4.4 Strengths and limitations

Strengths of our study include reliability due to a relative large sample size and internal validity as we were able to adjust for several important confounders. To our knowledge this study contained one of the largest bipolar samples up to date to prospectively investigate the association between life events and mood over a 2 year period of time. This study was also novel in investigating both temporal directions between life events and mood in the same sample and in distinguishing between BD I and II subtype. Further, although there were several dropouts during follow up, a relatively small number of patients dropped out in the first year of follow-up. More importantly, no significant differences were found between completers and study drop-outs.

However there are also some limitations to the current study. First, the largest limitation is the use of a self-report questionnaire for the assessment of life events. Previous reviews emphasized the superiority of life-events interviews over self-report lists (131-133). The most important limitations of self-report relate to patients subjective interpretation as to what counts as a certain life event and misdating of events, making it difficult to distinguish whether the life events are cause or consequence of mood symptoms. Moreover, certain life events may have caused other life events, which we could not take into account. Together with the relative longer periods between follow up measurements (three to six months) it is difficult to distinguish cause from effect. However, we tried to minimize this bias by the frequent assessment of life events and analyzing both directions of the temporal relationship. This has diminished the chance that we faulty indicated mood dependent life events as predictors of mood.

Second, the results can only be generalized to relatively stable bipolar outpatients, as the number of severely depressed as well as severely manic patients was low. Further the life events questionnaire oversamples negative life events compared to positive life events, which may have resulted in lack of power to detect threshold effects of positive life events.

3.4.5 Conclusive remarks

Bipolar disorder is a severe and disabling mood disorder, with a relatively unpredictable disease course that varies strongly among individuals. This study underlines that it is highly important that both positive and negative life events should be clinically evaluated, as they are associated with occurrence of manic and depressed symptoms and functional impairment. Moreover, clinicians should be aware that life events can also occur as a consequence of mood symptoms. To date, both psychoeducation programmes (134, 135) and specific psychotherapeutic treatments (136) already aim to diminish the impact and occurrence of life events and stress in BD patients to some extent. The importance of these therapies is emphasized by the current study. Further, BD I patients may be more vulnerable to life events than BD II patients and if these findings hold in replication studies, interventions addressing stress and life events may especially be important to BD I patients.

Finally, numerous factors may alter the strength of the association between life events and mood, such as clinical factors like BD subtype, subjective appraisal of the life event, social support, coping styles, personality, disease characteristics, and genetic or biological factors. Future research is needed to identify those factors that may amplify the effect that life events have on the bipolar mood course.