Predictors, symptom dynamics and neural mechanisms of bipolar disorders

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CHAPTER 3

Anger and cluster B personality traits and the conversion from unipolar depression to bipolar disorder

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Abstract

Introduction
Feelings of anger and irritability are prominent symptoms of bipolar disorder (BD) that may occur during (hypo)manic, depressive and, especially, during mixed mood states. We aimed to determine whether such constructs are associated with (the conversion to) BD in subjects with (a history of) unipolar depression.

Methods
Data were derived from the depressed participants of Netherlands Study of Depression and Anxiety with 9 years of follow-up. (Hypo)mania was ascertained using the Composite International Diagnostic Interview at 2, 4, 6, and 9 years follow-up. Cross-sectionally, we studied the association between prevalent (hypo)mania and anger related constructs with the 'Spielberger Trait Anger subscale', the 'Anger Attacks' questionnaire, the cluster B personality traits part of the 'Personality Disorder Questionnaire', and 'aggression reactivity'. Prospectively, we studied whether aggression reactivity predicted incident (hypo)mania using Cox regression analyses.

Results
Cross-sectionally, the bipolar conversion group (n = 77) had significantly higher scores of trait anger and aggression reactivity, as well as a higher prevalence on 'anger attacks', 'anti-social traits', and 'borderline traits' compared to current (n = 349) as well as remitted (n = 1,159) depressive patients. In prospective analyses in 1,744 participants, aggression reactivity predicted incident (hypo)mania (n = 28), with a multivariate-adjusted hazard ratio of 1.4 (95% CI: 1.02-1.93; $p = 0.037$).

Conclusions
Anger is a risk factor for conversion from unipolar depression to BD. In addition, patients who converted to BD showed on average more anger, agitation and irritability than people with (a history of) unipolar depression who had not converted.

3.1 Introduction

Bipolar disorder (BD) is a severe and debilitating mood disorder, characterised by (hypo)manic and depressive episodes[1]. Most patients with BD have experienced one or more episodes of depression prior to the onset of (hypo)mania[2, 3], and as a consequence are initially diagnosed with an unipolar depression. Since the treatment for unipolar depression is different from BD and may instigate (hypo)mania[4], earlier detection of a vulnerability to BD would benefit these patients. Moreover, risk factors for the conversion to BD may yield anchor points for (psychological) interventions, for early recognition and appropriate treatment.

Previous studies showed that a parental history of BD, more severe depression, comorbid psychotic symptoms, childhood trauma and atypical symptoms of depression were risk factors for a conversion from unipolar to BD[3, 5, 6]. Irritability and anger in unipolar depression appeared to be a robust clinical marker of undiagnosed or subthreshold bipolar disorder, or so-called bipolar spectrum illness[7, 8]. It is important to examine the association between anger and BD, because of its impact on the patient and family and loved ones. Knowing there is an association can help us to target treatment. It is also important to properly investigate whether experiencing irritability/anger would have predictive value in the development of BD.

Anger can be divided into feelings and expressions. The feeling of anger involves different constructs, encompassing: trait- and state anger[9, 10]. Trait anger is defined by the constant tendency to experience anger upon the slightest provocation. It is a chronic condition that is intertwined in one's personality. A high level of anger can be a personality trait[11]. State anger is defined as the temporary psychological, emotional feeling at a particular time and situation that can vary in intensity from mild irritation to intense fury and rage[12]. These angry feelings could lead to the expression of anger including anger attacks and aggression. Attacks are spells of anger of a sudden surge of autonomic arousal with symptoms such as tachycardia, sweating, flushing, and a feeling of being out of control. They are experienced as uncharacteristic and may occur in inappropriate situations[13]. Anger attacks are associated with verbal and physical aggression, which in turn can cause social avoidance in order to prevent a future anger attack and has certainly a negative impact on interpersonal relations[14]. All emotional states of anger, agitation and irritability will be referred to as anger in the current paper.

Anger might be part of emotion regulation problems and it has been hypothesized that heightened emotionality is an enduring characteristic of BD[15]. This suggests that people with BD experience more intense and more frequently fluctuating negative and positive emotions (apart from their mood episodes). This might increase their risk of developing mood episodes. Most previous studies found cross-sectional associations between anger and bipolarity[16, 17, 18, 19, 20]. In one prospective study (255 BD, 85 non-BP psychopathology and 84 healthy controls) BD patients reported persistently higher scores on self-report questionnaires on anger and feelings of aggression compared to psychiatric and healthy controls across a four-year follow-up[21]. There are indications that people with BD show stronger emotional reactivity compared to healthy controls on self-report questionnaires[22, 23], or specifically report more anger and frustration during euthymic states[24, 25], but contradictory findings have been reported as well[26].

Emotional instability in BD is often mistaken for comorbid personality disorder, since this is such a core characteristic of especially cluster B personality disorders. Ecological momentary assessments (EMA) studies have shown that BD patients in remission report more overall negative affect[27, 28] and more fluctuations in both negative and positive emotionality compared to healthy controls[29]. Earlier cross-sectional studies have found that some of the symptoms of BD (e.g. irritability, anger and emotional instability) overlap with personality disorders such as borderline personality disorder and antisocial personality disorder[30, 31]. In total, 44% of patients diagnosed with borderline personality disorder were found to meet strict diagnostic criteria for BD[32]. Moreover, 55% of newly diagnosed BD patients (without comorbid personality disorder) showed signs of juvenile antisocial behaviour in a retrospective study[33]. These findings suggest that borderline and antisocial personality disorders have construct overlap with BD. Especially affective instability and impulsivity were traits that may link BD to personality disorders[34].

In sum, the majority of the studies have shown a relation between BD and emotional instability, and specifically of anger, also in stable periods. In the current study, we investigated whether patients who converted to BD showed more feelings of anger, irritability and antisocial and borderline personality traits than people with (a history of) unipolar depression who did not convert. Second, we aimed to determine whether increased aggression reactivity increases the risk of conversion from depression to BD.

3.2 Methods

3.2.1 Study sample

Data were derived from the Netherlands Study of Depression and Anxiety (NESDA) with measurement points at baseline and at the 2-, 4-, 6-, and 9-year follow-up. NESDA is an ongoing longitudinal cohort study, consisting of 2,981 participants (18-65 years). Participants were recruited at baseline from community care (19%), primary care (54%), and specialized mental health care (27%) in the Netherlands. Individuals included in the NESDA study were participants with current or remitted depressive disorders and/or comorbid anxiety. The control group consisted of participants without lifetime psychiatric disorders. Exclusion criteria included (1) the presence of other psychiatric disorders (e.g., psychotic, obsessive-compulsive, bipolar, or severe addiction disorder) and (2) not being fluent in Dutch. Participants gave written informed consent before enrolment, and ethical approval was granted by all ethical committees of participating universities (VU University Medical Center, Leiden University Medical Center and University Medical Center Groningen). A detailed description of NESDA is given elsewhere[35]. Specially trained research staff administered the diagnostic interviews using the Composite International Diagnostic Interview (CIDI, version 2.1) to assess remitted or current depressive disorders and incidents of (hypo)mania which is indicative for BD. In the current study, we analysed data cross-sectionally and prospectively (with survival analysis).

Cross-sectional analysis sample: data on anger related questionnaires (i.e., trait anger, aggression reactivity, anger attacks, and personality traits associated with more anger) were gathered only at the 4th wave at 4-year follow-up. Therefore, we selected participants who completed the 4th wave (n = 2,402; 80.6%) to examine the construct of anger cross-sectionally. Participants suffering from a remitted and current depressive disorder and BD patients who converted between baseline and 4 years of follow-up were included. In a previous NESDA study[36], healthy controls showed significantly less trait anger and had lowest prevalence of anger attacks compared with groups of depression with or without comorbid anxiety disorder. For this reason, healthy controls were excluded in the current study. Participants with missing data on questionnaires regarding (hypo)manic episodes, or on one of the anger-related questionnaires were excluded, resulting in a total sample of 1,585 (53.2%) of the 2,981 participants for the cross-sectional analyses (see Flowchart in Figure 3.1).

Prospective analysis sample: aggression reactivity questionnaire was the only measured anger related instrument at baseline. Therefore, aggression reactivity was used as the predictor for incident (hypo)mania during the 9 years of follow-ups. We included 1,744 (58.5%) of 2,981 participants, with remitted or current depressive disorder with at least one follow-up assessment (Figure 3.1).

3.2.2 Measures

Aggression reactivity. This questionnaire was used in prospective analysis as predictor and in cross-sectional as one of the anger-related constructs. It was measured with the aggression reactivity subscale of the Leiden Index of Depression Sensitivity - Revised (LEIDS-R)[37, 38]. The LEIDS-R contains 34 items with six subscales. Aggression Reactiv-

ity is one of these subscales and has six items (e.g. 'In a sad mood, I do more things that I will later regret'; 'When I feel bad, I feel like more breaking things'; 'In a sad mood I'm more bothered by aggressive thoughts'; 'When I feel down, I more easily become cynical or sarcastic'; 'When I feel sad, I do more risky things'; 'When feel down, I lose my temper more easily'). These items measure how people react in a sad mood. Items are answered on a 5-point Likert scale from 0-4, with total scores ranging from 0-24. The internal consistency (Cronbach's alpha) for the aggression reactivity subscale was 0.80 in the current NESDA sample.

CIDI (hypo)manic episodes. The Composite International Diagnostic Interview (CIDI; WHO version 2.1) is a comprehensive, fully standardized diagnostic interview to screen for mental disorders based on DSM-IV criteria. The CIDI was used to assess remitted or current depressive disorders in the preceding 6 months. Incident cases of (hypo)manic episodes, which were indicative of BD, were ascertained using the CIDI "bipolar" section. The CIDI has high interrater reliability, (BDI: $\kappa = 0.92$, BDII: $\kappa = 0.94$)[39] and is a valid instrument (diagnosis of a lifetime BD sensitivity 0.87 and specificity 0.89)[40] for yielding DSM-IV diagnoses.

Trait anger. Trait anger was assessed via the Dutch adaption of the Spielberger State-Trait Anger Scale (STAS)[41, 42] and was gathered at the 4$^{\text{th}}$ wave at 4-year follow-up. The STAS is divided into two subscales for state and trait anger, whereby only the latter was administered in the current study. Trait anger is described as anger proneness as a personality trait[43]. The trait anger scale is a 10-item, self-report questionnaire. Participants score items on a 4-point Likert scale from 1-4. The total sum score ranges from 10-40. Psychometric properties have shown good item correlations, high test-retest reliability, and high internal consistency values with Cronbach's alphas ranging from 0.75 to 0.91[41, 42]. The internal consistency (i.e., Cronbach's alpha) in our sample was 0.89.

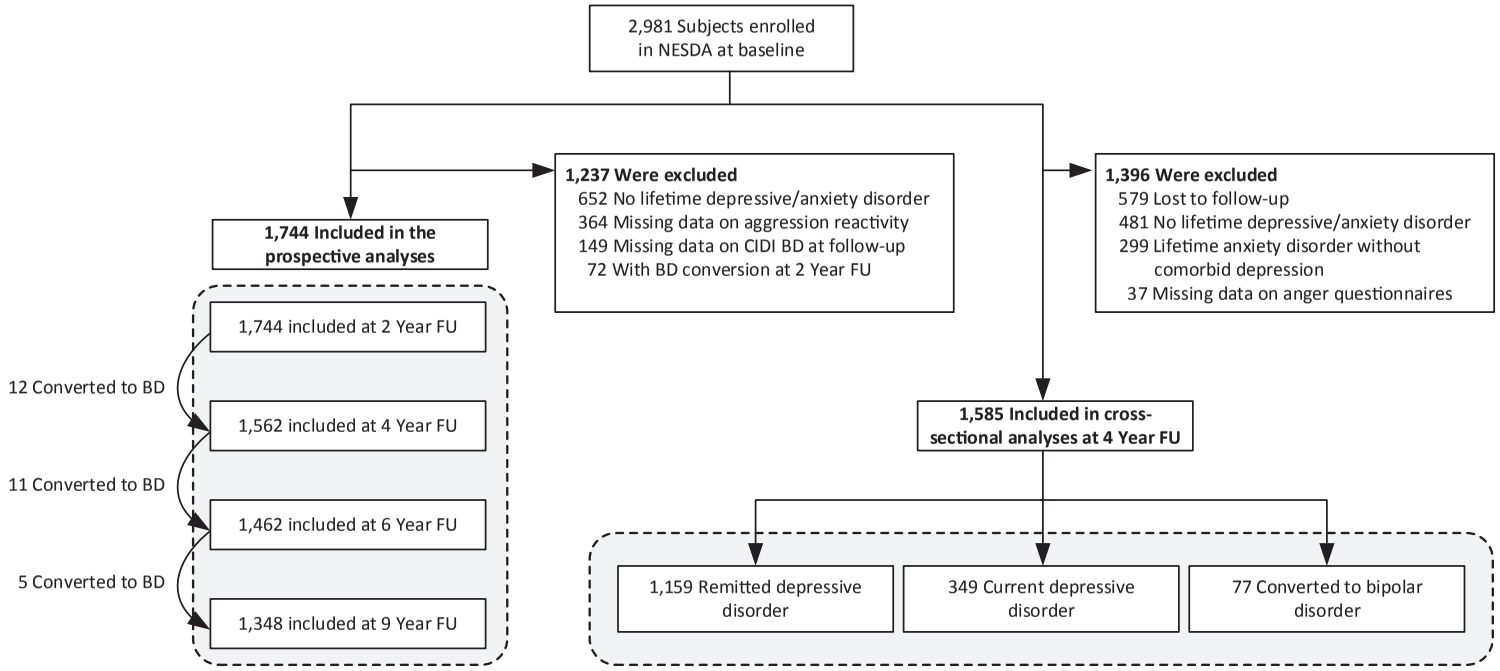

Figure 3.1: Flowchart of included participants in prospective and cross-sectional analyses.

Anger attacks. The Anger Attacks Questionnaire[14] is a self-rated instrument used to measure the presence or absence of anger attacks during the previous 6 months. It was measured at the 4th wave at 4-year follow-up. Anger attacks are sudden spells of anger inappropriate to the situation, accompanied by irritability, a sense of being out of control, and autonomic arousal symptoms[14]. To define who was experiencing anger attacks, the following criteria had to be met the previous 6 months: (1) irritability, (2) overreaction to minor annoyances, (3) inappropriate anger and rage directed at others, (4) incidence of at least one anger attack within the past month, and (5) presence of at least four or more of the following symptoms in at least one of the attacks: tachycardia, hot flashes, tightness of the chest, paraesthesia, dizziness, shortness of breath, sweating, trembling, panic, feeling out of control, feeling like attacking others, attacking physically or verbally, and throwing or destroying objects.

Cluster B personality traits. Antisocial behaviour was assessed with the Dutch adaptation of the Personality Disorder Questionnaire (PDQ-4)[44] and data was gathered at the 4th wave at 4-year follow-up. It was used to identify the key features or possible presence of a personality disorder. Items included in the PDQ-4 were adapted from the diagnostic criteria for personality disorders of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (APA, 1994). In the current study, a shortened version of the PDQ-4 with 37 dichotomous ('true'/'false') was assessed. Items were divided into three subcategories; borderline personality disorder (15 items; e.g. "I have difficulty controlling my anger or temper"); antisocial personality disorder (8 items; e.g. "I don't care if others get hurt so long as I get what I want") and antisocial behaviour before the age of fifteen (14 items; e.g. "I was considered a bully"). Based on items of the subscales for borderline and antisocial personality traits the presence or absence of these symptomatology and characteristics was assessed. The PDQ-4 has a high sensitivity and moderate specificity (Cronbach's alpha = 0.97)[45], and a test-retest reliability of 0.67[46].

Covariates. Sociodemographic covariates were self-reported age, gender, and level of education (in years). Lifetime DSM IV-based alcohol dependency and abuse and drug use were assessed using the CIDI. In addition, the severity of depression during the past week was assessed with the 30-item self-report Inventory of Depressive Symptomatology (IDS)[47]. Items were scored on a 4-point Likert scale (0-3) with total sum score ranges from 0 to 84 (only 28 of the 30 items are rated) The IDS had good internal reliability (Cronbach's alpha = 0.85). This is a 21-item self-report inventory with an internal consistency (Cronbach's alpha) of 0.92[48]. Comorbid current anxiety use was assessed with CIDI.

3.3 Statistical analyses

Sociodemographic and clinical characteristics were summarized according to CIDI using descriptive statistics. Missing values of BMI and smoking status were imputed with the respective values from the previous wave.

Cross-sectional analyses. The CIDI was used to assess remitted or current depressive disorders and incident (hypo)manic episodes in the previous two years for cross-sectional analysis at the 4th wave at 4-year follow-up. Upon completing the CIDI, participants were categorized into one of the following two psychopathology groups: remitted- and current depression. In these two groups a number of participants had experienced a (hypo)manic episode between baseline and 4-year follow-up, thus being classified in the BD converted group. We used analysis of variance (ANOVA) to compare the mean levels of the continuous variables trait anger and aggression reactivity, and chi-squared tests were used to compare the prevalence of the dichotomous variables anger attacks, antisocial and borderline personality traits among the three psychopathology groups (i.e., remitted depression, current depression, converted BD group). Furthermore, analyses were repeated for marginal means, resulting from adjustment for gender, age, level of education, alcohol and drugs use, severity of depressive symptoms and comorbid anxiety disorder using analysis of covariance (ANCOVA) and multivariable logistic regression analyses, when appropriate. The results of these analyses were presented in forest plots.

Moreover, multivariate linear regression analysis was used to analyse all the individual items of all the anger constructs (i.e., trait anger, aggression reactivity, anger attacks, and personality traits associated with more anger). Individual items estimated betas (with error bars representing 95% CI) were summarized and presented in supplementary forest plots. These were sorted by the size of each estimated beta for each construct separately.

Prospective analyses. At baseline, patients with a self-reported or with a professionally reported primary clinical diagnosis of BD were excluded. As the BD section of the CIDI was not conducted at baseline, we applied a lag-time analysis of 2 years, excluding all incident cases of (hypo)manic cases based on the CIDI between baseline and 2-year follow-up. In 1,744 participants, 28 experienced CIDI-confirmed incident (hypo)mania during follow-up (between 2 and 9 years). Kaplan-Meier analysis was used to examine the relationship between baseline aggression reactivity and conversion to BD. Hazard ratios (HR) with 95% confidence intervals (CI) of conversion to BD were estimated by Cox proportional hazards models. The date of inclusion into the cohort was considered the baseline for each patient in the survival analysis. The primary endpoint consisted of all incident cases during the follow-up period, the survival time, and the diagnoses at each time point (based on the CIDI). All follow-up losses as well as patients who did not experience a (hypo)manic episode were censored. We estimated three models: (a) a crude model that did not include any covariates, (b) an adjusted model that included gender, age, and level of education, and (c) a fully adjusted model that also included alcohol dependency, severity of depression symptoms and comorbid anxiety disorder. We tested for a linear trend across tertiles of incidents of (hypo)mania.

Multivariable logistic and Cox regression analyses and ANCOVA were performed using IBM SPSS statistical software (version 25, IBM Corp). The analyses regarding individual

items and forest plots were computed using the R statistical software, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria, 2016. URL: https://www.r-project.org/). A two-sided p value was considered statistically significant at the 0.05 level.

3.3.1 ResultsCross-sectional results

Demographic and clinical characteristics on (hypo)manic episodes of wave 4 (at 4 years follow-up) are shown in Table 3.1. Participants (N = 1,585) were on average 46.3 years old (SD = 12.6) and 68.8% were female. There were 77 (4.9%) patients who had converted from unipolar depression to BD based on CIDI during the two through four year waves (Table 3.1). There were no notable differences found in the sociodemographic between the groups. Patients with current depressive disorder showed more severe symptoms of depression compared with the other two groups. The group of converted patients smoked more often and suffered more from alcohol dependency than the two other groups. These patients also used more benzodiazepines, selective serotonin reuptake inhibitors and psychotropic medication compared to other groups.

Significant differences were present in the crude model for all anger constructs among the 3 groups (all p's < 0.001). The between differences persisted the adjusted models in continuous variables (see forest plot in Figure 3.2) with (F (2, 1582) = 8.20, p $<$ 0.001 for trait anger; F (2, 1456) = 5.61, p = 0.004 for aggression reactivity. In the adjusted models, patients who were converted had the highest marginal mean levels on trait anger and aggression reactivity in comparison with remitted patients (with a mean difference; (MD = 1.87, SE = 0.6, p = 0.001) for trait anger, and (MD = 1.76, SE = 0.5, p = 0.001) for aggression reactivity and current depressed patients (MD = 2.35, SE = 0.6, p $<$ 0.001) for trait anger, (MD = 1.71, SE = 0.6, p = 0.002) for aggression reactivity.

Results of adjusted analysis in categorical variables (see forest plot in Figure 3.3) were also significant with $\chi 2$ (2) = 4.55, p = 0.041 for anger attacks; $\chi 2$ (2) = 5.12, p = 0.02 for antisocial personality traits; and $\chi 2$ (2) = 10.41, p = 0.001 for borderline personality traits. Furthermore, the converted group also had the highest prevalence of anger attacks (22.1%), antisocial personality traits (9.1%) and borderline personality traits (36.4%) compared to those with remitted and current depression.

Results of the individual items of constructs (Supplementary Figures 3.5-3.9) with estimated betas and 95% CI show that anger attack items measuring physical sensation and anger items were most strongly associated with (hypo)mania. Moreover, almost all the items of PDQ borderline personality disorder-subscale were statistically significantly associated with (hypo)mania, and were more prominently associated than the other anger constructs. It was also notable that specifically the items that measure impulsiveness were strongly associated, rather than items that measure anti-sociability such as bullying or harming other people.

Table 3.1: Baseline characteristics of the study sample.
Data are means (with standard errors in parentheses) or number of participants (with percentages in parentheses).
IDS-SR = Inventory of Depressive Symptomatology, self-report.

	Baseline characteristics (*N*=1,744)	**4 year (wave 4) characteristics (*N*=1,585)**		
		Remitted depressive disorder (*n*=1159)	Current depressive disorder (*n*=349)	Converted group bipolar disorder (*n*=77)
All Sociodemographic:				
Female sex, no. (%)	1,290 (68.3%)	796 (68.7%)	253 (72.5%)	41 (53.2%)
Age in years, mean (SD)	42.5 (12.6)	46.2 (12.7)	47.0 (12.3)	44.8 (11.2)
Education, in years, mean (SD)	12.1 (3.3)	12.7 (3.3)	12.2 (3.3)	12.2 (3.3)
Body mass index (BMI), in kg/m^2, mean (SD)	25.7 (5.1)	26.3 (5.0)	26.4 (5.5)	26.9 (5.7)
Smoking, no. (%)	737 (39.0%)	371 (32.0%)	129 (37.0%)	34 (44.2%)
Alcohol dependency, no. (%)	549 (29.1%)	75 (6.5%)	42 (12.0%)	11 (14.3%)
Clinical characteristics:				
Severity depression IDS-SR total score, mean (SD)	33.03 (2.45)	14.95 (9.79)	29.45 (12.63)	24.70 (13.55)
Medication use, no. (%)				
Benzodiazepines	335 (17.7%)	124 (10.7%)	86 (24.6%)	20 (26.0%)
Selective serotonin reuptake inhibitors	411 (21.8%)	186 (16.0%)	65 (18.6%)	17 (22.1%)
Tricyclic antidepressants	63 (3.3%)	30 (2.6%)	17 (2.9%)	5 (6.5%)
Other antidepressants	129 (6.8%)	64 (5.5%)	46 (13.2%)	8 (10.4%)
Antipsychotic	35 (1.5%)	11 (0.9%)	12 (3.4%)	9 (11.7%)
Mood stabilizers	54 (3.1%)	21 (1.8%)	19 (5.4%)	8 (10.4%)

CIDI diagnosis groups	n	Crude mean (95%CI)	Test (crude)	Adjusted mean (95%CI)	Test (adjusted)
Trait anger					
- Remitted depressive disorder	1159	15.57 (15.31–15.84)	F(2, 1582) = 30.5; P < .001	16.12 (15.84–16.39)	F(2, 1582) = 8.20; P < .001
- Current depressive disorder	349	17.19 (16.62–17.76)		15.63 (15.10–16.17)	
- Converted group BD	77	19.15 (17.68–20.62)		18.03 (17.00–19.03)	
Aggression reactivity					
- Remitted depressive disorder	1078	4.92 (4.67–5.17)	F(2, 1466) = 24.39; P < .001	5.26 (5.00–5.51)	F(2, 1456) = 5.61; P = .004
- Current depressive disorder	324	6.24 (5.72–6.75)		5.30 (4.80–5.80)	
- Converted group BD	67	7.92 (6.81–9.03)		7.01 (6.01–8.01)	

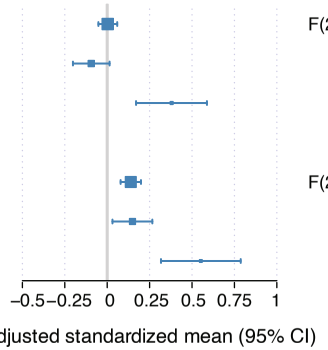

Figure 3.2: Forest plot showing the estimated marginal means (with 95% confidence intervals [CI]) of trait anger and aggression reactivity according to three diagnoses groups.

CIDI diagnosis groups	n (%)	Crude OR (95%CI)	Test (crude)	Adjusted OR (95%CI)	Test (adjusted)
Anger attacks					
- Remitted depressive disorder	99 (8.5%)	1.0 (ref)	X^2 (2) = 26.3, P < 0.001	1.0 (ref)	X^2 (2) = 4.55, P = 0.041
- Current depressive disorder	59 (16.9%)	2.18 (1.54–3.08)		1.55 (0,85–2,83)	
- Converted group BD	17 (22.1%)	3.03 (1.70–5.40)		1.98 (1.03–3.79)	
Antisocial personality traits					
- Remitted depressive disorder	15 (1.3%)	1.0 (ref)	X^2 (2) = 19.1, P < 0.001	1.0 (ref)	X^2 (2) = 5.12, P = 0.02
- Current depressive disorder	14 (4.0%)	3.19 (1.52–6.67)		1.82 (0.72–4.5)	
- Converted group BD	7 (9.1%)	7.63 (3.01–19.31)		3.5 (1.22–10.04)	
Borderline personality traits					
- Remitted depressive disorder	106 (9.1%)	1.0 (ref)	X^2 (2) = 87.5, P < 0.001	1.0 (ref)	X^2 (2) = 10.41, P = 0.001
- Current depressive disorder	93 (26.6%)	3.61 (2.65–4.92)		1.61 (0.93–2.78)	
- Converted group BD	28 (36.4%)	5.68 (3.42–9.41)		3.02 (1.65–5.53)	

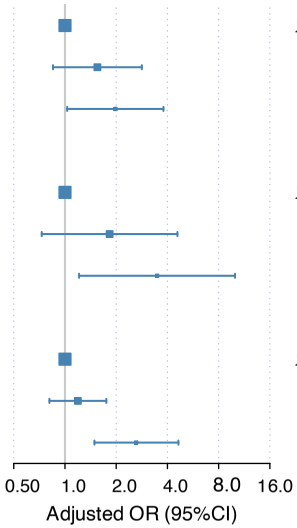

Figure 3.3: Forest plot showing (adjusted) odds ratios of anger attacks, antisocial and borderline personality traits according to three diagnoses groups. The adjusted analyses were adjusted for gender, age, level of education, alcohol dependency, drugs use, severity of depressive symptoms and comorbid anxiety disorder.

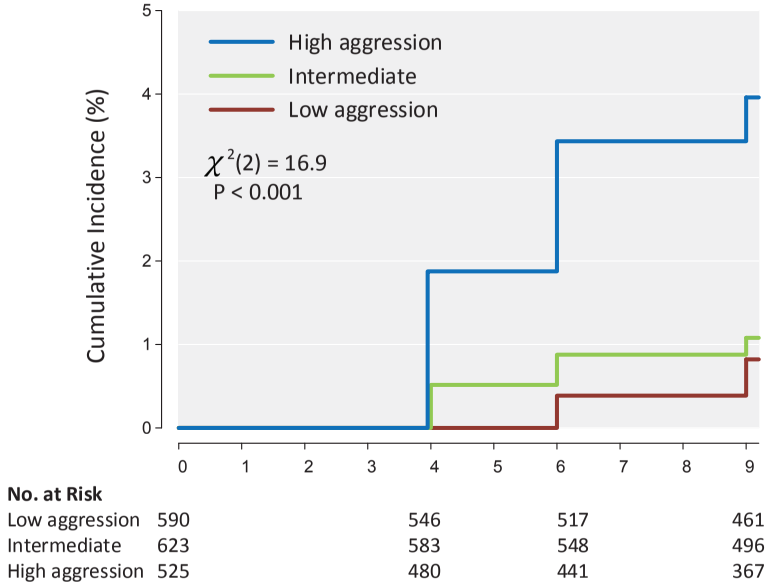

Figure 3.4: Kaplan-Meier curves of incident (hypo)mania according to tertiles of aggression reactivity. P value by log-rank (Mantel-Cox) test.

Table 3.2: Tertiles of aggression reactivity as a predictor of incident of (hypo)mania in sample of patients with depression and/or anxiety disorder.

Data obtained by an analysis of variance for trend, linear term.
∗Adjusted for gender, age, level of education.
∗∗ Additionally adjusted for alcohol dependence and severity of depression symptoms

	Tertiles of aggression reactivity scores			**P-value for**
	Lower	**Intermediate**	**Higher**	**Trend#**
Participants, No.	590	623	525	
Cases, NO. (%)	4 (0.7%)	6 (1.0%)	18 (3.4%)	
Hazard ratio (95% confidence interval):				
Crude	1.0 (ref)	1.41 (0.40-4.99)	5.27 (1.79-15.6)	< 0.001
Adjusted∗	1.0 (ref)	1.37 (0.39-4.88)	4.87 (1.63-14.6)	< 0.001
Fully adjusted model∗∗	1.0 (ref)	1.34 (0.37-4.69)	4.63 (1.54-13.9)	0.037
	Continuous aggression reactivity (z-value)			**P-value**
Hazard ratio (95% confidence interval):				
Crude	1.84 (1.41-2.41)	< 0.001		
Adjusted∗	1.78 (1.36-2.35)	< 0.001		
Fully adjusted model∗∗	1.4 (1.02-1.93)	0.037		

3.4 Prospective results

Baseline characteristics are summarized in Table 3.1. The subjects at baseline (n = 1,744) were on average 42.5 years of age (SD = 12.6) and were predominantly female (68.3%). The sample consisted of 560 (29.7%) patients with remitted depressive and/or anxiety disorder and 1.328 (70.3%) patients with a current depressive and/or anxiety disorder. Based on CIDI 28 cases of (hypo)manic episodes were identified, signalling conversion to BD, from 2 through 9 years of follow-up. Relatively smaller number of incident cases of (hypo)mania in prospective analysis compared with cross-sectional analysis (28 versus 77) is due to the exclusion of all the cases between baseline and 2 years of follow-up in prospective analysis in order to exclude all prevalent cases from the prospective analysis.

Kaplan-Meier analysis of survival with the incident (hypo)manic episode as outcome showed that patients with higher levels of aggression reactivity had higher conversion rates compared to patients with lower levels of aggression reactivity (Figure 3.4). This association is also displayed in Table 3.2; showing that, compared to patients in the lower tertile of aggression reactivity (low is reference with HRs of 1 and intermediate with HRs of 1.34), those in the top tertile had a higher rate (HRs of 4.63) of incident cases of (hypo)mania. In the fully adjusted model, aggression reactivity was a significant predictor, with an HRs 1.4 (95% confidence interval, 1.02-1.93; P = 0.037) per 1-SD increase in aggression reactivity.

3.5 Discussion

The purpose of this study was first to examine the association of different constructs of anger with BD; and second to determine the predictive role of aggression reactivity in conversion to BD. Our study demonstrated a strong and consistent finding in the prospective as well as in the cross-sectional analyses. We found that higher levels of anger in all its variants were consistently associated with bipolarity versus those with (a history of) unipolar depression. Secondly, we found that aggression reactivity was predictive of conversion to BD.

Cross-sectionally, all the different constructs of anger and affective instability (i.e., trait anger, aggression reactivity, anger attacks, and personality traits associated with more anger) showed consistent associations, with the strongest association and highest prevalence in the converted group in comparison to the remitted and current depression groups. These results were in line with previous findings showing that BD patients scored higher on anger-related measures[20, 24] in comparison to unipolar depressed groups.

Regarding our prospective findings, we found that aggression reactivity was a risk factor for the conversion to BD in persons with (a history of) unipolar depression. Although two earlier prospective studies[21, 24] showed that feelings of anger were more frequent during the follow-up waves in BD patients in comparison with subjects with other psychiatric disorders and healthy controls, we are not aware of previous studies that examined the predictive value of an anger construct in relation to conversion to BD.

Affective instability and dysregulation in general seem to be distinctive factors for BD compared to unipolar depression in the current sample, since our results show that both antisocial- and borderline personality traits were more prevalent in the BD conversion group than in the currently depressed and remitted unipolar depression group. Results were most striking for the borderline traits, which is in line with previous findings showing that emotional instability is a core characteristic in both BD and borderline personality disorder.[32] suggest that the current classification may fail to differentiate between the two disorders considering the complexity and heterogeneity within these patient groups and that perhaps borderline and bipolar might be the two extremes of the same spectrum[32]. Additionally, a longitudinal study showed that comorbid borderline and antisocial personality traits predicted the risk of aggression in BD, while controlling for potential confounding factors[49].
Whether emotion regulation problems are more characteristic for BD than unipolar depression is unclear, since the few studies into this topic had contradicting results[50, 51]. We might carefully conclude, based on the current and previous findings, that especially anger and aggression dysregulation are the most distinct affective characteristics for BD when compared to unipolar depression. One important explanation for this finding might be the occurrence of mixed mood states. Although results are not fully conclusive, agitated depression or mixed depression (i.e., depressed episodes with the simultaneous presence of several manic symptoms, like irritability) in unipolar depression might be one of the early signs of conversion to BD since mixed episodes are more prevalent in BD[52]. However, it is unclear to what extent the current and previous findings are associated with the increased occurrence of mixed mood states in BD patients.

Another potential explanation for the more distinct problems in regulation of anger in BD patients compared to unipolar depression patients might reside in differences in emotion regulation styles. Although most dysfunctional emotion regulation styles are comparable between BD and unipolar depression patients (e.g., rumination and catastrophizing)[53, 54] there are indications for important differences. Both on the cognitive and behavioural levels, BD patients seem to have the tendency to upregulate activated mood states. For instance,[55] showed that positive appraisal about activated states predicted BD (in a sample with BD, unipolar depression and healthy controls). BD patients also seem to have more extreme positive self-relevant appraisals of the feelings of activation than healthy controls and unipolar depressed patients[56, 57]. Additionally, at least a subgroup of the bipolar patients are more likely to engage in stimulating and activating behaviour (that potentially induces a (hypo)manic episodes). Although previous studies focussed specifically on activated states such as happiness or euphoria, anger can also be considered as an activated mood state as well.

Feelings of anger might be an important target for early recognition of illness and intervention in BD. Increased feelings of anger in unipolar patients in combination with some other known clinical characteristics such as multiple brief depressed episodes, a lack of response to antidepressants, a family history of BD[58] might help to signal an upcoming conversion to BD. In addition, agitated affective states in BD patients deserve attention for its own sake, as these may have negative consequences for their quality of life and that of their loved ones[59]. Since BD patients experience extensive emotional instability even during euthymic states[15] and seem to use maladaptive strategies[60], it is important that they learn to regulate such feelings in an appropriate way. Psychotherapy, social therapy, and group-oriented approaches can help BD patients to prevent decompensation and to develop healthier social relationships. Other treatment strategies that may especially be apt to improve emotion regulation are dialectical behaviour therapy (DBT) and Systems Training for Emotional Predictability and Problem Solving (STEPPS) program, which is based on cognitive behavioural therapy combined with emotional management skill training[61, 62].

One of the strengths of this study is its longitudinal design and the inclusion of a large group of participants that oversampled patients with (preceding) depression. This is the first study that investigated prospectively the predictive value of feelings of anger in conversion to BD. In addition, this is the first study that examined five different constructs of anger in relation to BD, with strong and consistent findings. There are also limitations that need to be addressed. First, the primary focus of this prospective cohort study on unipolar rather than bipolar depression resulted in a relatively small sample of patients who experienced a (hypo)manic episode during follow-up. Second, even though we adjusted for potential confounders, a family history of BD was not assessed and could not be included as cofounder. Third, the current use of antipsychotic medication and mood stabilizers might have had a dampening effect on anger and aggression, leading to an underestimation rather than an overestimation of our results. However, the group taking these medications was fairly small. Lastly, participants who dropped out or missed scales at follow-ups had probably higher risk of anger or irritability. Exclusion of this specific group might have led to underestimation of our results.

We can conclude that aggression reactivity is a robust risk factor for the conversion from unipolar to bipolar disorder. In addition, patients who had experienced (hypo)mania (and

thus had converted to BD) showed more feelings of anger in comparison with unipolar depressive patients. Identifying the potential risk factors for the development of BD might have clinical value in earlier recognition, prevention of conversion into mania, and better targeted interventions.

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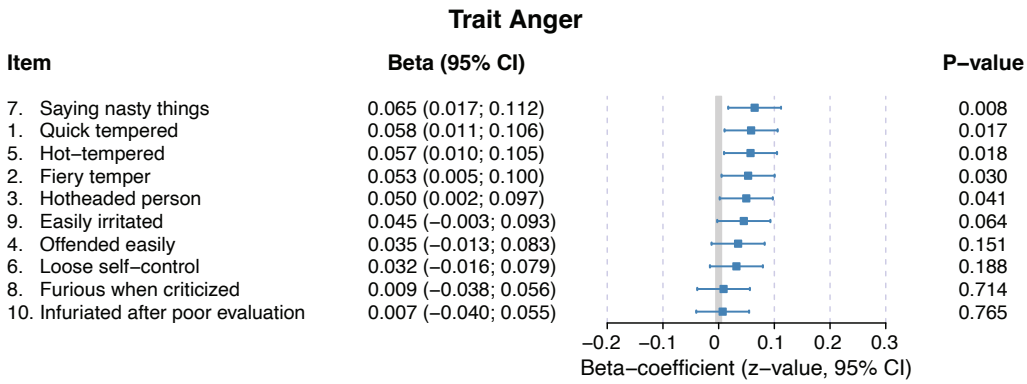
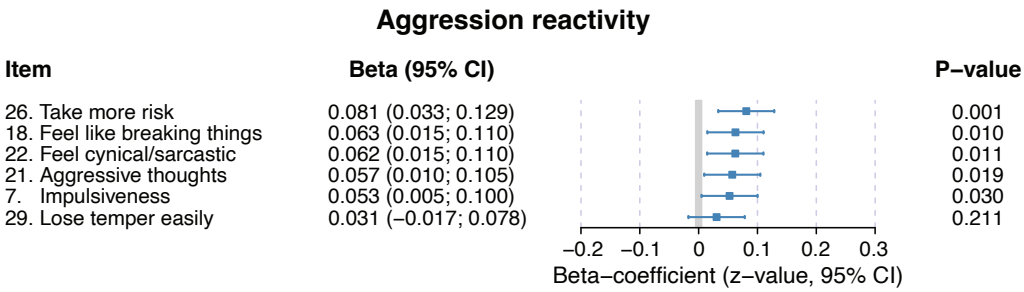
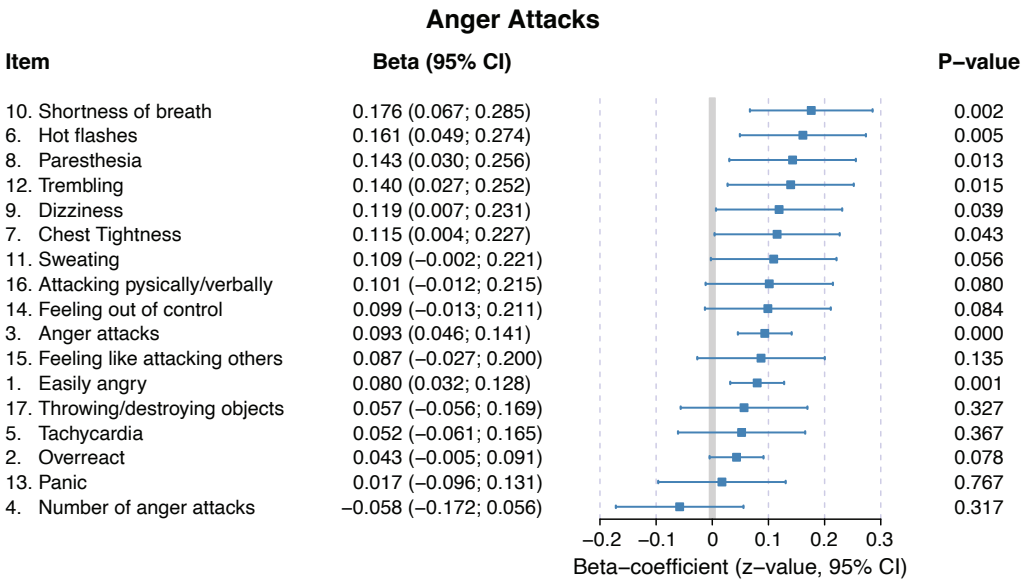
3.6 Supplementary Figures & Tables



Supplementary Figure 1: Associations of individual items of trait anger estimated beta with 95% CI (represented by error bars of those converting to BD versus those with remitted unipolar depression). Analyses were adjusted for gender, age and level of education.



Supplementary Figure 2: Associations of individual items of aggression reactivity estimated beta with 95% CI (represented by error bars of those converting to BD versus those with remitted unipolar depression). Analyses were adjusted for gender, age and level of education.



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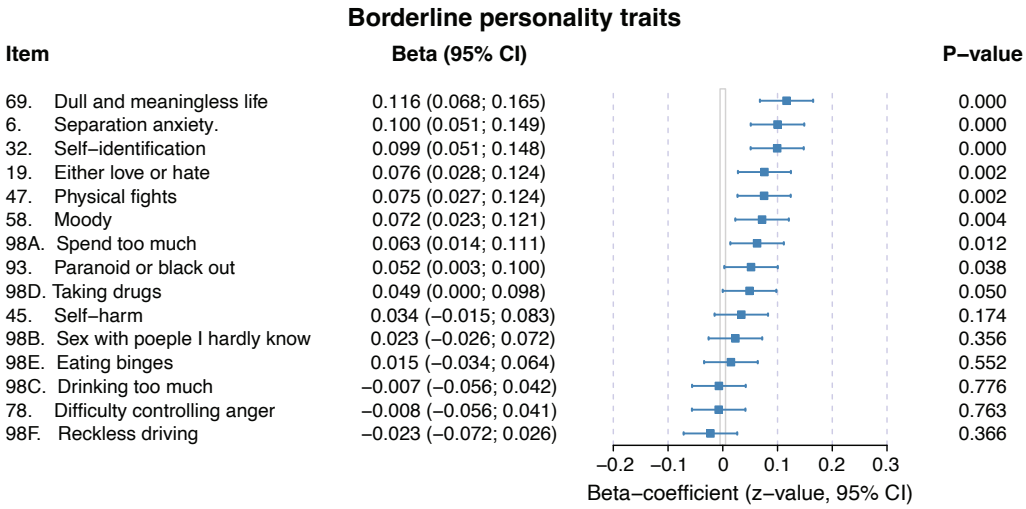
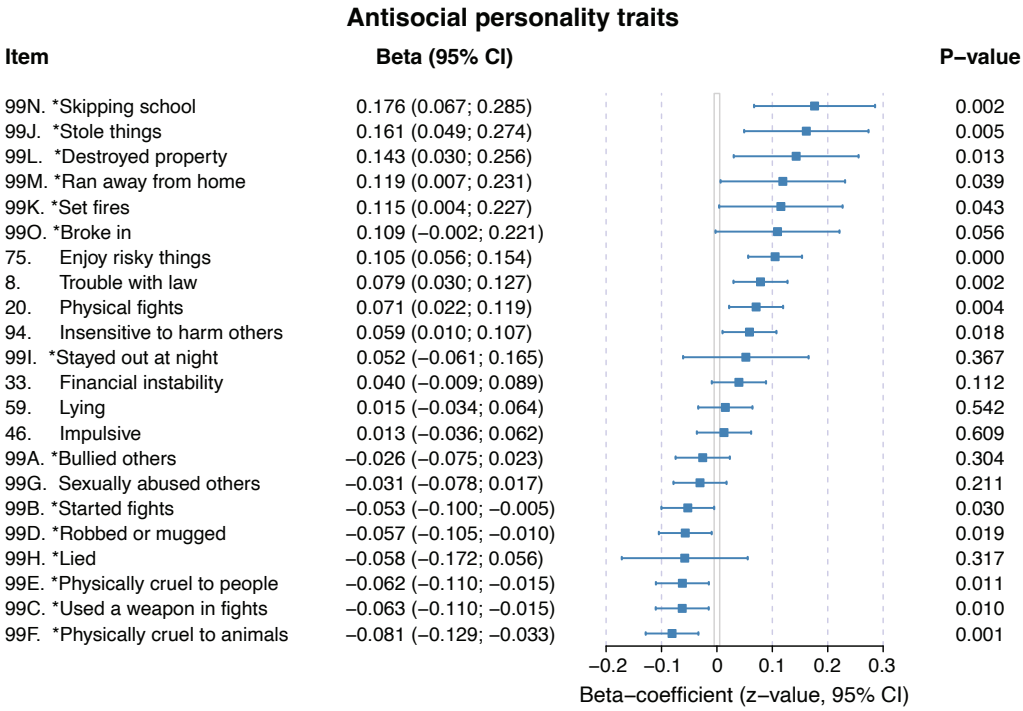


Supplementary Figure 4: Associations of individual items of borderline personality traits estimated beta with 95% CI (represented by error bars of those converting to BD versus those with remitted unipolar depression). Analyses were adjusted for gender, age and level of education.



Supplementary Figure 5: Associations of individual items of antisocial personality traits estimated beta with 95% CI (represented by error bars of those converting to BD versus those with remitted unipolar depression). Analyses were adjusted for gender, age and level of education.
∗Childhood antisocial personality traits.