Predictors, symptom dynamics and neural mechanisms of bipolar disorders

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CHAPTER 2

Personality traits and the risk of incident (Hypo)mania among subjects initially suffering from depressive and anxiety disorders in a 9-year cohort study

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Abstract

Background
Bipolar disorder (BD) is characterized by the alternating occurrence of (hypo)manic and depressive episodes. The aim of the current study was to determine whether personality traits independently predicted the subsequent development of (hypo)manic episodes within a group of patients who were initially diagnosed with depressive and anxiety disorders.

Methods
The Netherlands Study of Depression and Anxiety is a cohort study with measurements taken at baseline and at 2-, 4-, 6-, and 9-year follow-up. Development of a (hypo)manic episode during follow-up was assessed with the Composite International Diagnostic Interview and (hypo)manic symptoms were evaluated with the Mood Disorder Questionnaire. The Big Five personality traits were the independent variables in multivariable Cox regression analyses.

Results
There were 31 incident cases of (hypo)manic episodes (n = 1,888, mean age 42.5 years, 68.3% women), and 233 incident cases of (hypo)manic symptoms (n = 1,319, mean age 43.1, 71.9% women). In multivariable analyses, low agreeableness was independently associated with an increased risk of developing a (hypo)manic episode, with a hazard ratio (HR) of 0.54 (p = 0.002, 95% CI [0.37, 0.78]). This finding was consistent with the development of (hypo)manic symptoms (HR 0.77, p = 0.001, 95% CI [0.66, 0.89]).

Limitations
The 2-year lag-time analysis reduced the number of participants at risk of a (hypo)manic episode.

Conclusions
We conclude that low agreeableness is a personality-related risk factor for incident (hypo)mania among subjects initially suffering from depressive and anxiety disorders. Increased attention to personality deviances could help to recognize BD at an early stage.

2.1 Introduction

Bipolar disorder (BD) is a common mood disorder characterized by alternating periods of (hypo)mania and depression. The lifetime prevalence of BD is estimated around 1% for bipolar I disorder (BDI) and between 1 and 2% for bipolar II disorder (BDII)[1, 2, 3].

A majority of patients with BD experience one or more major depressive episodes prior to an initial (hypo)manic episode[1, 4]. Being able to identify unipolar depressed patients who are at high risk for developing a (hypo)manic episode would help to develop early intervention strategies that could be tailored to target BD. Although increasing numbers of neurobiological markers for the development of BD have been identified[5], these are not yet useful for the early recognition of BD in individual patients in daily clinical practice. More easily assessable psychological variables may be more suitable. Conversion from unipolar depression to BD was predicted by factors including a parental history of BD, more severe depression, comorbid psychotic symptoms, and childhood trauma[4, 6, 7]. However, these factors are rather generic; a more specific profile might help to further identify the early onset of BD. In this study, we focus specifically on personality traits as a risk factor. We investigated whether personality traits independently predicted incidence of (hypo)mania in a group of patients with depressive or anxiety disorder.

Personality traits might also help to identify a "bipolar profile". Personality traits are defined in terms of individual differences in self-concept, which is considered stable and consistent and has developed across a patient's lifespan—particularly during childhood[8]. Previous studies that attempted to identify the personality profile of BD have used different approaches, such as hyperthymic, cyclothymic, and dysthymic temperaments[9]; the hypomanic personality traits[10]; the behavioral inhibition/approach system (BIS/BAS)[11]; and the Big Five personality traits. In the current study, we used the more common Big Five personality traits approach. The Big Five personality traits are neuroticism, extraversion, openness, agreeableness, and conscientiousness, and these are often assessed using the Neuroticism, Extraversion, Openness Five-Factor Inventory (NEO-FFI) questionnaire[12]. However, unlike research on unipolar depressive disorder, only a limited number of studies have focused on the putative association between BD and personality traits[13, 14, 15].

There have been some cross-sectional studies on the Big Five personality traits and BD. Several studies have shown that BD patients have higher neuroticism compared with unipolar depression patients and healthy controls[16, 17, 18, 19, 20]. Higher extraversion in BD patients compared with unipolar depression patients and controls was found in the majority of studies[18, 21, 22, 23, 24]. Patients with BD also demonstrated higher openness compared with healthy controls and other psychiatric groups[24]. In addition, low agreeableness was associated with BD in two cross-sectional studies[16, 20].

Previous prospective findings have been categorized according to the “conversion literature"—i.e., focusing on patient samples with current depressive disorders[15] —or according to the “prediction literature"—i.e., including bipolar patients and/or participants without a current disorder (e.g., healthy participants from the general population)[14, 25].

The “prediction literature" has shown high extraversion and low agreeableness to be

independent risk factors for the development of a (hypo)manic episode in bipolar patients[14, 15, 25, 26]. Three previous prediction studies have included 39[14, 15, 25, 26], 110[14], and 2,247[25] patients with BD and/or healthy participants. These studies had follow-up durations ranging from 6 months[14, 15, 25, 26] to 2 years[14, 25]. These studies consistently showed high neuroticism, high extraversion, and low agreeableness as predictors of manic symptoms[14, 25], but showed different results for high conscientiousness[26].

Only one “conversion" study examined the predictive value of personality traits and conversion to BD[15] with 5 years of follow-up. These findings showed that higher extraversion scores predicted conversion to BD among patients with major depression ($N = 301$), even after adjusting for symptom severity. In the same study, neuroticism was not a predictor for conversion to BD.

In sum, there is evidence from cross-sectional and some prospective studies that higher neuroticism and extraversion and low agreeableness are more prevalent in BD patients than healthy controls. Whether these are also factors that put patients with other affective disorders at risk for developing BD over time is not clear. Larger cohort studies with longer follow-up periods are needed to determine whether and to what extent such traits independently predict the risk of a (hypo)manic episode.

The aim of the current study was to determine whether personality traits independently predicted the subsequent development of (hypo)manic episodes within a group of patients who were initially diagnosed with depressive and anxiety disorders. This was a well-characterized, large, prospective cohort study with a 9-year follow-up period. Since the comorbidity between depression and anxiety is high, and patients with anxiety are at increased risk of BD[27], we also included patients with anxiety disorders. We used survival analysis to investigate the influence of personality traits on incidence of (hypo)manic symptoms and episodes during the 9-year follow-up. Based on previous findings[14, 15, 25, 26], we hypothesized that traits such as higher extraversion and lower agreeableness would have independent predictive value regarding the onset of (hypo)manic symptoms or a (hypo)manic episode.

2.2 Methods

2.2.1 Subjects

Data were obtained from the Netherlands Study of Depression and Anxiety (NESDA). NESDA is a prospective cohort study with measurement points at baseline and at the 2-, 4-, 6-, and 9-year follow-up. At baseline, 2,981 participants were included—of whom 2,483 (83.3%) participated in at least one of the follow-ups. We included only those participants with current and remitted depressive and/or anxiety disorder ($n = 1{,}888$; 63.3%) in our analyses. The total percentage of participants (of 2,981) who participated at each follow-up were 87.1% (2 year), 80.6% (4 year), 75.7% (6 year), and 69.4% (9 year). As we selected only those participants with data available from at least two follow-ups, the number of included participants in our sample were: 1,888 (100.0%) at 2 years, 1,673 (88.6%) at 4 years, 1,563 (82.8%) at 6 years, and 1,434 (76.0%) at 9 years. These participants were between 18 and 65 years of age at baseline and suffered from remitted

(n = 560) or current (n = 1,328) depressive and/or anxiety disorders. Recruitment took place in primary health care and outpatient mental care facilities as well as in communities from the area around Amsterdam, Leiden, and Groningen (the Netherlands). We used the following criteria for exclusion: (a) a primary clinical diagnosis of BD, psychotic disorder, obsessive-compulsive disorder, or severe addiction disorder, and (b) insufficient Dutch language skills. The study design has been extensively described previously[28]. The research protocol was approved by the Ethical Committee of participating universities and all participants provided written informed consent.

For the current study, we selected patients suffering from remitted or current depressive and/or anxiety disorders who had completed at least one follow-up assessment. One hundred and seventeen (6.2%) participants missed one of the CIDI measurements, but participated in the follow-ups. Only one of these 117 participants eventually developed a (hypo)manic episode. Remitted or current depressive and/or anxiety disorders were assessed using the Composite International Diagnostic Interview (CIDI, version 2.1), and specially trained research staff administered the diagnostic interviews.

2.2.2 Measures

Outcome variables. At the 9-year follow-up, a number of individuals experienced a (hypo)manic episode or symptoms thereof. The BD section of the CIDI was not conducted at baseline; therefore, it was not possible to exclude BD patients with certainty at baseline. However, the NESDA had already excluded patients with a self-reported or with a professionally reported primary clinical diagnosis of BD during the initial participant screening. A lag-time analysis of 2 years was applied, meaning that all incidents of (hypo)manic cases based on the CIDI between baseline and the 2-year follow-up were excluded.

CIDI (hypo)manic episodes. The incident cases of (hypo)manic episodes, which were indicative of BD, were ascertained using the CIDI. Trained researchers administered the BD section of the CIDI. The onset of a (hypo)manic episode was based on the presence of a DSM-IV hypomanic or manic episode as assessed with the BD section of the CIDI at the 2-, 4-, 6-, and 9-year follow-up assessments. In the analyses of (hypo)manic episodes, we excluded all participants who met the criteria based on the CIDI between baseline and the 2-year follow-up (n = 86; 71.7% within percentage). Thus, incidents of (hypo)mania were analyzed in 1,888 participants; of these participants, 31 (1.6%) experienced an incidence of (hypo)mania.

The CIDI is highly reliable (BDI: $\kappa = 0.92$, BDII: $\kappa = 0.94$)[29] and is a valid instrument (diagnosis of a lifetime BD sensitivity 0.87 and specificity 0.89)[30] for yielding diagnoses listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).

Mood Disorder Questionnaire (MDQ) of (hypo)manic symptoms. The MDQ is a screening instrument for a history of (hypo)manic symptoms, which for the sake of brevity, we will refer to as “(hypo)manic symptoms". The history of (hypo)manic symptoms was ascertained in all participants during and up to the 9-year follow-up using the MDQ[31].

The MDQ was conducted at baseline and at 2-, 4-, 6-, and 9-year follow-up. The MDQ

includes 15 items and consists of three parts. The first part comprises 13 dichotomous items regarding BD symptoms. The second part assesses the clustering of symptoms, and the third part relates to disease severity. To define (hypo)manic symptoms based on the MDQ, we used the cut-off that was defined in prior NESDA research[32], with slightly modified criteria compared with the most commonly used cut-off according to Hirschfeld[33]. We considered the MDQ total score to show (hypo)manic symptoms when at least seven positive answers were given from a total of 13 items—irrespective of answers on the second or third part. This cut-off demonstrated good psychometric properties when detecting (hypo)manic symptoms, with a sensitivity of 0.83 and a specificity of 0.82[32]. In addition, we excluded all patients who met the criteria for (hypo)manic symptoms based on the MDQ baseline cut-off ($n = 450$; 80.4% with percentage), which we used to analyze our data for (hypo)manic symptoms. In the end, we analyzed the incidents of (hypo)manic symptoms in a total of 1,319 participants, of whom 233 (17.7%) experienced (hypo)manic symptoms.

2.2.3 Baseline Predictor

Personality traits. Personality traits were determined using the NEO-FFI at baseline, which is a short version of NEO Personality Inventory (NEO-PI-R)[12]. The widely used NEO-FFI is a 60-item self-report questionnaire that measures items on a five-point scale (ranging from 0 to 4). This questionnaire measures personality traits within five main personality domains (neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness) each listing 12 items. For each broad domain, item clusters of subcomponents are grouped together, and these mirror the facets of the NEO-PI-R[34].

Internal consistencies for the current study were calculated for the participants NEO-FII domains and yielded Cronbach's α =.90 for neuroticism, Cronbach's α =.78 for extraversion, Cronbach's α =.63 for openness, Cronbach's α =.70 for agreeableness, and Cronbach's α =.79 for conscientiousness. In short, neuroticism includes emotional instability and negative effects. Extraversion is seen as being sociable, assertive, and excited Openness includes intellectual curiosity, need for variety, and non-dogmatic attitudes. Agreeableness involves trust, altruism, and sympathy; individuals who score low on agreeableness tend to be less cooperative and more competitive. Conscientiousness is the predisposition to being disciplined and striving after goals, and a strict adherence to principles[12].

Symptom severity. The current presence of anxiety and/or depressive disorders in patients was assessed according to the respective sections of the DSM-IV, based on the CIDI interview (WHO version 2.1), which has high interrater reliability (any depressive disorder $\kappa = 0.95$)[29] and high validity for depressive and anxiety disorders[35].

The severity of depression was found to be a potential risk factor for the development of a (hypo)manic episode[36]; therefore, we included this as a covariate in the current study. We assessed the severity of depression based on the 30-item self-report Inventory of Depressive Symptomatology (IDS)[37], which has an internal consistency of Cronbach's α =.94. The baseline total score was used as a covariate in the analysis.

Because many patients suffered from anxiety, we adjusted for the severity of anxiety

symptoms, which we assessed according to the Beck Anxiety Inventory (BAI). This is a 21-item self-report inventory with an internal consistency of Cronbach's α =.92[38].

Childhood trauma also predicted the onset of a (hypo)manic episode) and was included as a covariate. Childhood trauma was assessed with the Childhood Trauma Inventory, which is a cumulative index ranging from 0 to 8 that considers the frequency of emotional neglect, psychological abuse, physical abuse, and sexual abuse before the age of 16 years[39].

2.3 Statistical Analysis

We used analyses of variance and χ^2 tests to conduct basic descriptive statistics. The presence of a (hypo)manic episode according to the CIDI was determined at the 4-, 6-, and 9-year follow-up because we applied a lag-time of 2 years. The presence of (hypo)manic symptoms according to the MDQ was determined at each of the time points. We used Cox proportional hazard models to examine the relationship between baseline personality traits and incidence of (hypo)manic episodes and symptoms separately. 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 (including all incident cases of [hypo]manic episodes or symptoms), and the diagnoses at each time point (based on either the CIDI or the MDQ). We censored all follow-up losses as well as patients who did not experience a (hypo)manic episode or symptoms thereof during follow-up. We checked the proportional-hazards assumptions with log-minus-log plots using personality-domain scores categorized into tertiles. These curves did not show any violation, except for a slight violation of the openness personality domain. All personality (sub)domain scores were standardized into z scores. We estimated three models: (a) a crude model that did not include covariates, (b) an adjusted model that included sociodemographic data (i.e., age, gender, and education in years), and current depressive/anxiety disorder based on the CIDI, and (c) a fully adjusted model that included the remaining four Big Five personality traits, severity of depression and anxiety symptoms, childhood trauma, and alcohol dependence. Finally, we used Pearson's correlation to examine the relationship between the Big Five personality traits and the severity of depression and neuroticism.

Two-sided p values were considered statistically significant at the 0.05 level. All analyses were conducted using IBM SPSS statistics software, version 22 (IBM Corp., Armonk, NY, USA).

2.4 Results

2.4.1 Baseline Characteristics

Table 2.1 includes a summary of the basic demographic and clinical characteristics of (hypo)manic episodes and symptoms of all participants. There were 31 cases of (hypo)manic episodes (n = 1,888, mean age = 42.5 years, 68.3% women), and 233 cases of (hypo)manic symptoms (MDQ total score >7) (n = 1,319, mean age = 43.1 years, 71.9% women). The included subjects (based on analyses of [hypo]manic episodes) were on average 42.5 years of age (SD = 12.6) and were predominantly female (68.3%). They also had an average 12.1 years (SD = 3.3) of education.

At baseline, the mean IDS-SR was 24.3 (SD = 13.1), and the mean BAI was 13.5 (SD = 10.2), indicating overall mild depressive and anxiety symptoms. Next, the results of Pearson's correlation between the Big Five personality traits and the severity of depression showed strong associations of neuroticism with IDS-SR (r =.69, p <.001). The other Big Five personality traits were negatively correlated with IDS-SR: extraversion (r = - 0.49, p <.001), openness (r = -.11, p <.001), agreeableness (r = -.28, p <.001), and conscientiousness (r = -.34, p <.001). Moreover, there were only three incident cases of (hypo)manic episodes in patients with remitted depressive and/or anxiety disorders and 28 incident cases of (hypo)manic episodes in patients with current depressive and/or anxiety disorders. When looking to the overlap between the CIDI and MDQ, four (12.9%, N = 31) participants met the criteria of a (hypo)manic episode based on the CIDI but did not have a positive MDQ score.

2.4.2 Predictors of Incident (Hypo)manic Episodes

In the crude models, all the personality domains were significantly associated with subsequent (hypo)manic episodes except for the openness and extraversion domains. In the adjusted models, high neuroticism and low agreeableness remained significant risk factors for the development of a (hypo)manic episode. The hazard ratios (HRs) were 1.70 (p < 0.04, 95% CI [1.03, 2.82]) for neuroticism and 0.52 (p < 0.001, 95% CI [0.37, 0.74]) for agreeableness. In the fully adjusted model, however, only low agreeableness remained an independently associated risk factor for incidence of (hypo)manic episodes (HR 0.54, p = 0.002, 95% CI [0.37, 0.78]) (see Table 2.1).

Kaplan-Meier curves categorized into tertiles show that lower levels of agreeableness were associated with a higher incidence of (hypo)manic episodes (see Figure 2.1A). This finding is in accordance with those from Cox regression models.

	Analyses of (hypo)manic episodes (n = 1,888)	**Analyses of (hypo)manic symptoms** (n = 1,319)
Sociodemographics		
Female sex, no. (%)	1,290 (68.3)	948 (71.9)
Age in years, mean (SD)	42.5 (12.6)	43.1 (12.6)
Education in years, mean (SD)	12.1 (3.3)	12.3 (3.3)
BMI, kg/m^2, mean (SD)	25.7 (5.1)	25.7 (5.0)
Smoking, no. (%)	737 (39.0)	447 (33.9)
Alcohol dependency/abuse, no. (%)	549 (29.1)	312 (23.7)
Clinical characteristics		
Severity measures		
IDS-SR total score, mean (SD)	24.3 (13.1)	22.4 (13.0)
BAI total score, mean (SD)	13.5 (10.2)	12.5 (9.8)
Medication use		
Benzodiazepines, no. (%)	335 (17.7)	230 (17.4)
SSRI, no. (%)	411 (21.8)	291 (22.1)
TCA, no. (%)	63 (3.3)	49 (3.7)
Other AD, no. (%)	129 (6.8)	97 (7.4)
MDQ score, mean (SD)	4.9 (3.3)	2.8 (2.0)
Groups according to psychopathology		
Remitted anxiety and/or depressive disorder, no. (%)	560 (29.7)	433 (32.8)
Current anxiety and/or depressive disorder, no. (%)	1,328 (70.3)	886 (67.2)
Current anxiety disorder, no. (%)	456 (24.4)	17.2)
Current depressive disorder, no. (%)	326 (17.3)	221 (11.9)
Current anxiety and/or depressive disorder, no. (%)	546 (28.9)	346 (18.7)
Five factor personality scales of the NEO−FFI		
Neuroticism, mean (SD)	38.4 (8.1)	37.6 (8.3)
Extraversion, mean (SD)	35.7 (7.0)	35.5 (7.0)
Openness, mean (SD)	38.5 (5.9)	38.3 (5.9)
Agreeableness, mean (SD)	43.7 (5.2)	44.4 (5.0)
Conscientiousness, mean (SD)	40.9 (6.5)	41.6 (6.2)

Table 2.1: Characteristics of the Study Sample of NESDA Participants
Abbreviations:
BMI = Body Mass Index;
IDS-SR = Inventory of Depressive Symptomatology, self-report;
BAI = Beck Anxiety Inventory;
SSRI = Selective Serotonin Reuptake Inhibitor;
TCA = Tricyclic Antidepressant.

2.4.3 Predictors of Incidence of (Hypo)manic Symptoms

Results of the crude models showed significant effects for neuroticism, agreeableness, and conscientiousness on the incidence of (hypo)manic symptoms. In the adjusted models, high neuroticism and low agreeableness remained significantly related to the onset of (hypo)manic symptoms with HRs of 1.21 ($p = 0.03$, 95% CI [1.02, 1.43]) for neuroticism, and 0.74 ($p < 0.001$, 95% CI [0.64, 0.85]) for agreeableness. In the fully adjusted model, again, agreeableness was the only statistically, significant independent predictor, with an HR of 0.77 ($p = 0.001$, 95% CI [0.66, 0.89]) (see Table 2.1 and Figure 2.1B). In addition, when we used the traditional coding of incident cases (a history of [hypo]manic symptoms) for the MDQ, there were 62 incident cases versus 233 cases of slightly modified coding. However, the results were similar, with a multivariate-adjusted HR of 0.59 ($p < 0.001$, 95% CI [0.45, 0.77]) for agreeableness using the 62 incident cases and a HR of 0.77 ($p = 0.001$, 95% CI [0.66, 0.89]) using the 233 cases.

	Crude hazard ratio **[95% CI]**	***p* value**	Adjusted hazard ratio **[95% CI]**∗	***p* value**	Fully adjusted hazard ratio **[95% CI]**∗∗	***p* value**
CIDI (hypo)manic episode ($n = 31/1{,}888$; 1.6%)						
Neuroticism	2.08 [1.32, 3.30]	0.002	1.70 [1.03, 2.82]	0.04	1.29 [0.65, 2.54]	0.46
Extraversion	0.81 [0.56, 1.17]	0.26	0.92 [0.63, 1.36]	0.69	1.44 [0.90, 2.31]	0.13
Openness	1.02 [0.71, 1.46]	0.92	1.11 [0.77, 1.61]	0.57	1.14 [0.79, 1.64]	0.50
Agreeableness	0.49 [0.35, 0.68]	< 0.001	0.52 [0.37, 0.74]	< 0.001	0.54 [0.37, 0.80]	0.002
Conscientiousness	0.70 [0.50, 0.98]	0.04	0.79 [0.56, 1.12]	0.18	0.91 [0.61, 1.36]	0.64
MDQ (hypo)manic symptoms ($n = 233/1{,}319$; 17.7%)						
Neuroticism	1.33 [1.14, 1.54]	< 0.001	1.21 [1.02, 1.43]	0.03	1.03 [0.81, 1.32]	0.79
Extraversion	0.89 [0.78, 1.02]	0.10	0.69 [0.83, 1.11]	0.58	1.15 [0.95, 1.38]	0.14
Openness	0.95 [0.83, 1.08]	0.40	1.05 [0.91, 1.21]	0.47	1.07 [0.93, 1.23]	0.38
Agreeableness	0.69 [0.60, 0.78]	< 0.001	0.74 [0.64, 0.85]	< 0.001	0.77 [0.66, 0.89]	0.001
Conscientiousness	0.85 [0.74, 0.97]	0.01	0.81 [0.78, 1.02]	0.09	0.94 [0.80, 1.01]	0.40

Table 2.2: Personality and the Risk of an Incident (Hypo)Manic Episode or Symptoms in Patients with Anxiety and/or Depressive Disorder.

Personality traits Z scores were used for Cox regression analysis.

∗ Data were adjusted for age, gender, education, and current depressive and anxiety disorders at baseline.

∗∗ Data were additionally adjusted for severity of depression and anxiety, childhood trauma, alcohol dependence, and the four remaining personality traits in the model.

2.5 Discussion

The main goal of the current study was to determine which personality traits are independently associated with the development of a (hypo)manic episode or (hypo)manic symptoms within a group of patients who were initially diagnosed with unipolar depression and anxiety disorders. We found that low agreeableness was a personality-related risk factor that could anticipate the development of a (hypo)manic episode or associated symptoms.

Our results are partly in line with previous studies. A link between low agreeableness and BD was found in a large prospective study[25] and two cross-sectional studies[16, 20].

Our finding that depressed and anxious patients with low agreeableness are at risk of developing (hypo)mania has potential clinical implications. Identifying those patients at increased risk of BD early on would allow preventative intervention. BD is often missed or misdiagnosed by clinicians; this is illustrated by an average treatment delay of up to 10 years after the first major mood episode[40]. Although the criteria for classifying (hypo)mania in patients with BD and unipolar depressive disorder are very clear, it is often not obvious in clinical practice. BD patients start often with predominantly depressive episodes, which are usually later followed by (hypo)manic episodes. (Hypo)manic episodes are regularly unnoticed or not mentioned by patients. An unjustified diagnosis of unipolar disorder can have major disadvantages such as inadequate pharmacological treatment. Inadequate pharmacological treatments are associated with an increased risk of recurrence, non-response, longer illness duration, and possible induction of (hypo)mania[41]. Therefore, it is important to be able to identify BD and distinguish it from unipolar disorder. Specific personality traits may be warning signs of BD, in addition to clinical characteristics such as multiple brief depressed episodes, a lack of response to antidepressants, and a family history of BD[41]. A patient assessment that reveals high emotional instability and a tendency to disagree, compete, and be suspicious could also indicate a heightened risk. Likewise, a lack of being cooperative, trusting, and amiable is a sign of low agreeableness[42]. Our findings are consistent with the idea that BD patients tend to be less agreeable, which might be associated with less willingness to follow advice. Accordingly, euthymic BD groups are more likely to oppose advice given in a computerized goal-directed task after a positive mood induction[43] compared with remitted unipolar and healthy controls. In line with this, BD patients tend to show more anti-social behavior (such as aggression and inappropriate anger attacks) compared with depressive patients and healthy controls[44]. Low agreeableness might also be associated with anti-social behavior. Moreover, BD patients experience extensive emotional instability during their mood episodes and also in between the episodes in their euthymic state. Earlier studies have shown that BD patients more often use maladaptive strategies such as rumination and dampening compared with healthy controls. These maladaptive strategies may adversely impact mood symptoms and severity[45], and were associated with higher scores on maladaptive personality traits (such as neuroticism) and lower scores on adaptive personality traits (such as agreeableness and openness). Our findings match those of previous studies and suggest that such characteristics may signal a risk of BD, even in the euthymic phase.

In contrast to earlier findings, we did not confirm that high neuroticism was an independent predictor of the development of (hypo)mania in our current study; this association

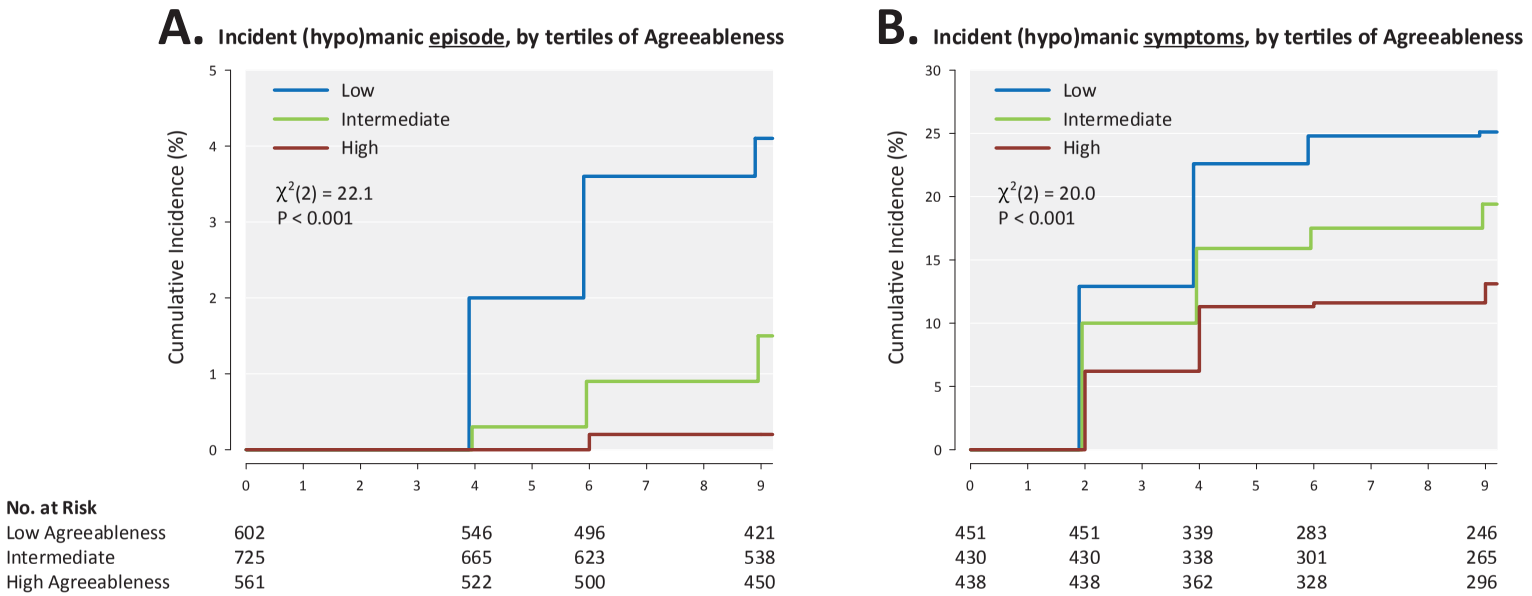

Figure 2.1: (A) Kaplan-Meier curves of incident (hypo)manic episode by tertiles of agreeableness. The cumulative incident of end points is shown in 1888 patients based on (hypo)manic episodes (CIDI). (B) Kaplan-Meier curves of incident (hypo)manic symptoms by tertiles of agreeableness. The cumulative incident of end points is shown in 1319 patients based on (hypo)manic symptoms (MDQ); p-value by log-rank (Mantel-Cox) test.

has been found in several cross-sectional[16, 17, 18, 19, 20] and three predictive studies[14, 25, 26]. In these studies, higher neuroticism correlated with baseline depression symptoms or predicted future depression symptoms, but did not predict future (hypo)manic episode or symptoms. The core features of neuroticism are associated with depression; therefore, it was important for us to adjust for the severity of depression symptoms in the current study. In our sample, neuroticism and the IDS-SR scores were strongly intercorrelated. Adjusting for the severity of depression explains the lack of a significant association with neuroticism in our current analyses.

Another previous finding that we did not confirm was the association between high extraversion and BD, which was found in one predictive study, one conversion study[14, 15], and several cross-sectional studies[18, 21, 22, 23, 24]. Extraversion was mainly related to (hypo)manic symptoms. Although we were not able to differentiate between BDI and BDII, it is plausible that a substantial number of incident cases in our study were BDII. Results from an earlier predictive study[46] indicated that higher neuroticism and lower extraversion were particularly predictive of BDII rather than BDI incident cases. Personality traits could be a distinguishing feature of these two subtypes.

The current study has several strengths over previous studies. The most important strengths are the large sample size and the long follow-up period (the longest to date). Moreover, we took potential confounders such as the presence and severity of depression and anxiety into account. We also assessed incidence of (hypo)mania using a validated instrument and excluded prevalent disorders or symptoms in the subsequent analyses. Unlike the present study, other prospective studies were population-based or conducted with samples of patients already diagnosed with BD at baseline[14, 25, 26]; therefore, these studies could not examine the risk factors for BD development since they already included BD patients at baseline.

The study of[15] is most comparable to our study in terms of design, because their participants were diagnosed with a depressive disorder at baseline, were followed for 5 years, and analyses were adjusted for depression severity. However, our study has important differences. For instance,[15] used the life chart and SCAN interviews to identify BD, and did not exclude prevalent BD patients at baseline. In addition, they only assessed two personality traits (extraversion and neuroticism), and had a smaller sample size ($n = 301$). All in all, our findings corroborate findings from most previous studies and suggest that low agreeableness is a personality-related risk factor that may predict the development of a (hypo)manic episode.

There are some limitations to our study. The exclusion of BD patients based on the CIDI was only possible at the 2-year follow-up because the BD section of the CIDI was not conducted at baseline. However, during the initial screening for participation, patients with a clinical diagnosis of BD were excluded, and we also applied a lag-time analysis which excluded the first 2 years of observation. This resulted in a relatively small sample of patients who had experienced a (hypo)manic episode. Although the attrition in the number of participants over 9 years follow-up was limited, drop-out may not have been at random, leading to potential selective attrition in those with (hypo)manic symptoms compared with participants from the other group, introducing the risk of survival bias. In addition, despite the time-lag analysis, diagnoses of BD, cyclothymia, or subsyndromal

symptoms might have been missed at baseline. Another possible limitation is that the severity of depression or anxiety disorder at baseline might have influenced the personality assessment. An earlier analysis of the current NESDA study[47] examined the influence of depressive and anxiety disorders on personality score, as both mood disorders and the Big Five traits were assessed with a time interval of 4 years. Their results showed that depressive and anxiety disorders both increased neuroticism scores. Extraversion and conscientiousness scores were influenced by depressive disorder, but not by anxiety disorder. Most importantly, agreeableness and openness were influenced by neither. Moreover, data on the Big Five personality characteristics were available but information about formal DSM-IV diagnoses of personality disorders was not. Since many participants suffered from a current mood disorder at baseline, DSM diagnoses of personality disorders cannot be reliably ascertained. Another limitation is the possibility of construct overlap between low agreeableness and hypomania, as low agreeableness could be an expression of over-confidence and following your own goals instead of considering what others want or need[48]. Finally, although we could adjust for the most important confounders, data on the family history of BD were missing.

In summary, we found that low agreeableness increased the risk of (hypo)manic episodes and the symptoms thereof. Clinicians must be aware of these personality characteristics in order to recognize the early signs (usually depression) in patients with depressive and anxiety disorders. Future prospective studies investigating the relationship between personality traits and people at high risk for the development of (hypo)mania (e.g., first-line relatives or offspring of BD patients) are needed to confirm and deepen our understanding of this relationship. The potential benefit of psychotherapeutic interventions to treat low agreeableness in patients at risk of BD also warrants further attention.

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