Personality and the Long-Term Outcome of First-Episode Depression:

A Prospective 5-Year Follow-Up Study

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ABSTRACT

Objective: To determine the impact of the personality traits neuroticism and extraversion as well as comorbid personality disorders on the rate of remission, recurrence, and conversion to bipolar disorder after the first lifetime episode of depression.

Methods: A total of 301 inpatients or outpatients aged 18–70 years with a validated diagnosis of a single depressive episode according to *ICD-10* were assessed by the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders and the Eysenck Personality Questionnaire from 2005 through 2007. At 5-year follow-up, 262 patients were reassessed by means of the Life Chart Method and diagnostic interviews from 2011 through 2013. Cox regression analyses were used to estimate the effect of personality factors on the rates of remission, recurrence, and conversion to bipolar disorder, respectively.

Results: A comorbid cluster C personality disorder decreased the rate of remission by 30% (HR = 0.7; 95% CI, 0.5–0.9; $P = .02$) and increased the rate of recurrence after remission of the first depression by 80% (HR = 1.8; 95% CI, 1.0–3.0; $P = .04$). A higher neuroticism score at baseline decreased the rate of remission by 20% for each increase of 1 SD (HR = 0.8; 95% CI, 0.7–0.9; $P = .002$), and a higher level of extraversion increased the rate of conversion to bipolar disorder by 60% for each increase of 1 SD (HR = 1.6; 95% CI, 1.0–2.5; $P = .05$).

Conclusions: Comorbidity of cluster C personality disorders and the level of neuroticism and extraversion have significant impact on the long-term prognosis of depression. The identified predictors of the course of illness should guide patients and clinicians for individualized tailored treatment of comorbid conditions in depression.

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Results from prior studies have suggested that personality traits and disorders influence the outcome of depression in several ways. Comorbidity of personality disorders and increased level of the temperamental dimension neuroticism[1] have been found to be associated with a poorer response to antidepressant treatment,[2,3] longer time to remission of a depressive episode,[4,5] increased risk of a chronic course of illness,[6] higher rates of recurrence of depression,[4,7,8] and increased risk of subsequent conversion to bipolar disorder.[9–12] On the other hand, a higher level of extraversion, the other major personality dimension included in the personality theories of Eysenck and Eysenck,[1] may predict a better outcome of depression.[13]

Nevertheless, previous research on the relation between depression and personality suffers from limitations, which make firm conclusions difficult to draw. Most important, personality traits and symptoms of personality disorders are not stable over time.[14,15] Among patients with depression, diagnoses of comorbid personality disorder have been found to show only low-to-moderate stability,[16] and personality traits seem to correlate with the number of preceding lifetime depressive episodes.[17] In a recent 2-year follow-up study of 722 patients with depression, Spinhoven et al[13] found that the impact of neuroticism and extraversion on time to remission was greatly reduced after controlling for covariates including baseline severity and the history of depressive symptoms. These results strongly indicate that the associations between outcome of depression and personality traits or comorbid personality disorders are prone to confounding by the illness history. However, prior studies[4–6,8,10,13] in this field have included patients with diverse illness histories, eg, a mixture of patients with first-episode depression and a various number of previous depressive episodes. Hence, it becomes difficult to determine whether the personality traits or personality disorders are actually predictors of the course of illness present from onset of the illness or rather a consequence of a more chronic or recurrent course of illness.[2] Prospective investigations of the impact of personality on the long-term outcome of depression from onset of the first lifetime episode are therefore needed, the findings of which can potentially guide patients and clinicians for individualized treatment.

In the present 5-year follow-up study, we aimed to assess, by use of survival analysis techniques, the influence of the personality traits neuroticism and extraversion as well as comorbid personality disorders on the long-term outcome of first-episode depression in terms of remission, recurrence of depression, and conversion to bipolar disorder.

METHODS

Baseline Assessment

The present study is part of a larger study of gene-environment interaction in first-episode depression and predictors of the course of affective disorders. We have previously described the baseline study[18]

Clinical Points

- The effects of personality traits and disorders on the long-term course of depression have not been studied prospectively.
- Cluster C personality disorders, neuroticism, and extraversion influence the outcome of first-episode depression in terms of remission, recurrence, and conversion to bipolar disorder.
- Increased attention to personality deviances and comorbid personality disorders at an early stage could improve individualized treatment of depression.

in detail. In short, a total of 301 ethnically Danish patients aged 18–70 years and recently discharged from their first ever admission or outpatient contact to a psychiatric hospital in eastern Denmark (Sealand) with an *ICD-10*[19] diagnosis of a single depressive episode were sampled consecutively in a 2-year period from 2005 through 2007 via the Danish Psychiatric Central Research (DPCR) Register.[20] The DPCR Register comprises information on all psychiatric hospitalizations and outpatient contacts in Denmark. The participants were invited to the study 1–3 months after discharge from admission or outpatient care and were interviewed by 2 experienced medical doctors using standardized semistructured interviews. *ICD-10* diagnoses were established for the episode leading to psychiatric hospital care and for the lifetime before by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).[21] Individuals with significant physical illness, dementia, or mental retardation were excluded (for details, see references 18, 22, and 23). Diagnoses of personality disorders according to *DSM-IV* criteria were assessed by the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders (SCID-II),[24] which was administrated with the self-report questionnaire in accordance with the manual. The items on the SCID-II questionnaire cover all symptoms of personality disorders and set a threshold for a positive response that is considerably lower than that of the corresponding diagnostic criterion in *DSM-IV*; hence, questions answered "no" need to be further explored only if there is a clinical basis to suspect that the item is true or if the number of criteria fulfilled are within 1 item of the diagnostic threshold.[24] Further, the participants completed at baseline the Eysenck Personality Questionnaire[1] (EPQ), 101-item version: range on the N scale (neuroticism) is 0–23, and range on the E scale (extraversion) is 0–20. The severity of residual depressive symptoms was measured by the 17-item Hamilton Depression Rating Scale (HDRS-17).[25]

Assessment at Follow-Up

The study participants were invited to the follow-up study after approximately 5 years (from 2011 through 2013). After providing informed consent, participants were re-interviewed by one senior researcher and specialist in psychiatry (J.D.B.), who also had assessed half of the patients at baseline. The longitudinal course of illness was evaluated by the Life Chart Method.[26] Discharge summaries from all hospital contacts were available electronically from a nationwide database. In cases of doubt about diagnoses or treatments, complete case reports were requested. The Danish Ethical Committee (H-3-2011-100) and the Data Inspection (2011-41-6577/2014-331-0644) approved the study.

If the patient was not in remission at baseline (HDRS-17 score ≤7), the date of remission of the first depressive episode was determined retrospectively as the time either when the patient was without clinically significant depressive symptoms for a minimum of 2 months and had returned to his or her usual functional capacity, or when the patient developed a bipolar disorder. Any period with signs of psychiatric illness after remission of the first depressive episode was marked on the life chart, and diagnoses were established for representative periods by means of the SCAN interview.

Outcomes and Predictor Variables

We ascertained the dates of the following outcomes based on the life chart and SCAN interview: (1) remission from the first depressive episode sustained for 8 weeks or more, (2) recurrence of a new depressive episode after remission of the first episode, (3) bipolar disorder (ie, onset of either a manic, hypomanic, or mixed episode), and (4) onset of a psychiatric illness of diagnostic precedence over affective disorder (ie, schizophrenia).

We supposed that personality disorders in the 3 *DSM-IV* clusters would predict the outcomes in a similar way. Therefore, the comorbid personality disorders were grouped in clusters A, B, and C, respectively, in the primary analyses. We further tested the influence of individual personality disorders to determine whether significant effects at the cluster level were related to specific diagnoses within the clusters. Patients diagnosed with more than 1 personality disorder were categorized according to each disorder independently of the concurrent existence of another personality disorder.

Statistics

The occurrence of remission, recurrence (for those who obtained remission), and conversion to bipolar disorder was studied using survival analysis techniques.[27] For participants who were already in remission at the baseline assessment, we assumed that remission had been reached at the midpoint between discharge and the baseline assessment since this assumption resulted in identical estimations as when using interval-censored observations. The cumulative incidences of remission as a function of time since onset of the first depression and conversion to bipolar disorder as a function of time since discharge were estimated by the Kaplan-Meier estimator. Time to recurrence was studied taking into account the competing risk of patients' converting to bipolar disorder; hence, the cumulative incidence of recurrence as a function of time since remission of the first episode of depression was estimated using the Aalen-Johansen estimator.[27]

Cox regression models were used for estimating the effect of comorbid personality disorders and scores on the personality dimensions as assessed at baseline on the rate of remission, recurrence, and conversion to bipolar disorder, respectively. Patients with 3 or more missing items on the EPQ subscales were excluded from the analyses of neuroticism and extraversion. In the case of 1 or 2 missing item scores, the total EPQ score was computed by mean substitution. The neuroticism and extraversion scores were transformed into *z* scores (mean-adjusted raw scores divided by the standard deviation), which means that the hazard ratios (HR) reflect the effect of a change of 1 SD on the scales. All time intervals were right-censored at the date of follow-up if no event occurred during the follow-up period and at the date of onset of a disorder with diagnostic precedence over affective disorder (eg, schizophrenia). Nonparticipants in the follow-up were right-censored at date of the baseline interview. A priori, the analyses were adjusted for the effect of age at onset, sex, and severity of the first depressive episode (mild, moderate, or severe according to *ICD-10* criteria). In post hoc analyses, the regression analyses were further adjusted for additional covariates.

RESULTS

The Sample

The median age at onset was 36 years (quartiles 27–51 years; range, 15–70 years); 199 patients were women (66.1%), and 183 (60.8%) were inpatients at baseline. The severity according to *ICD-10* criteria assessed by the SCAN interview was mild in 24.3% of the cases; 53.5% had a moderate depression, and 22.3% had a severe depression. The median duration from discharge to the baseline assessment was 147 days (quartiles 119–184 days). The mean HDRS-17 score at the time of the baseline interview was 9.3 (SD = 6.2). A total of 93 of the 301 participants in the baseline study (30.9%) fulfilled the diagnostic criteria for 1 or more personality disorders (cluster A: 9 [3.0%], cluster B: 38 [12.6%], cluster C: 51 [6.9%], unspecified personality disorder: 11 [3.7%]). Since the prevalence of cluster A personality disorders was very low, we did not perform further analyses of associations with this category of disorders.

The EPQ was administered to all participants at baseline; the EPQ neuroticism subscale was completed (with ≤ 2 missing items) by 237 participants (78.7%), and the EPQ extraversion subscale was completed (with ≤ 2 missing items) by 235 (78.1%) participants. The mean scores on neuroticism and extraversion were 11.7 (SD = 6.3) and 11.4 (SD = 5.4), respectively. There were no differences in sex, age at onset, prevalence of comorbid personality or anxiety disorders, alcohol abuse, severity of the depressive episode, or HDRS-17 score at baseline between participants with missing EPQ data and participants who completed the EPQ (results not shown). From the baseline study,[28] we previously reported that a higher level of neuroticism and a comorbid cluster C personality disorder were associated with nonremission on the first antidepressant treatment, whereas there was no significant effect of cluster B personality disorders on the rate of remission after first-line treatment.

In the follow-up study, a total of 262 participants at baseline were re-assessed (follow-up rate 87.0%), and 39 were lost to follow-up (withdrawn: 12 [4.0%], deceased: 16 [5.3%], emigrated: 2 [0.7%], unreachable: 7 [2.3%], dementia: 2 [0.7%]). The mean follow-up time was 5.8 years (SD = 0.3 years; range, 5.2–7.7 years). Participation in the follow-up was not associated with any of the personality factors (all $P > .1$).

The cumulative incidence of remission 5 years after onset was 83.3%, the cumulative incidence of recurrence 5 years after remission was 31.5%, and the cumulative incidence of conversion to bipolar disorder after 5 years was 8.6%. The median duration of the first depressive episode was 1.8 years (quartiles 1.0–9.3 years). One patient developed schizophrenia during the follow-up period. Besides personality disorders, the 2 most prevalent comorbid disorders were anxiety (47.5%) and alcohol abuse (15.0%). The majority of the patients obtained remission of anxiety with remission of the depressive episode; however, 9.0% suffered from anxiety disorders after remission of the first depressive episode. Likewise, 7.5% of the patients still had alcohol abuse after remission of the depression. During the entire follow-up period, a total of 230 of the participants in the follow-up study (87.8%) received antidepressant medications and 68 (25.9%) got a mood stabilizer (lithium: 17 [6.5%], antipsychotics: 52 [19.8%], anticonvulsants: 37 [14.1%]), while 32 participants (12.2%) received no psychopharmacologic treatment after the baseline interview.

The Effect of Personality Traits and Disorders on the Outcomes

As can be seen from Table 1, comorbidity of one or more personality disorders at baseline significantly decreased the rate of remission. Analyzed on cluster level, a cluster C personality disorder reduced the rate of remission by 30%, whereas cluster B personality disorders did not significantly influence remission. An increase in neuroticism score decreased the rate of remission by 20% per SD, whereas the extraversion score did not significantly influence remission.

A higher extraversion score increased the rate of conversion to bipolar disorder by 60% per SD, whereas there were no significant effects of neuroticism or personality disorders on the diagnostic conversion to bipolar disorder. However, the presence of an antisocial personality disorder increased the rate of diagnostic conversion significantly, although the prevalence of this disorder was low in the present sample (3%). In the analyses of time to recurrence, only patients with an ascertained time of remission could be included; hence, 19 patients without remission at any time during the entire follow-up period were excluded. Further, 3 nonparticipants in the follow-up assessment who were in remission at baseline were subsequently

Table 1. Effect of Comorbid Personality Disorders and Neuroticism and Extraversion Scores on the Rate of Remission and Recurrence of Depression and Conversion to Bipolar Disorder After the First Lifetime Episode of Depression[a]

						Recurrence		
	Patients (N = 301)	Remission		Conversion to Bipolar Disorder		Patients (n = 246)[b]		
Variable	n (%)	HR (95% CI)	*P*	HR (95% CI)	*P*	n (%)	HR (95% CI)	*P*
Personality disorder of any kind	93 (30.9)	0.7 (0.5–1.0)	.03	1.4 (0.6–3.2)	.5	75 (30.5)	1.4 (0.8–2.4)	.2
Cluster B[c]	38 (12.6)	0.8 (0.5–1.2)	.3	1.8 (0.6–5.4)	.3	32 (13.0)	0.7 (0.3–1.5)	.3
Antisocial	9 (3.0)	0.9 (0.4–1.8)	.7	5.4 (1.6–18.8)	.01	8 (3.3)	…	…
Histrionic	0 (0.0)	…	…	…	…	0 (0.0)	…	…
Narcissistic	1 (0.3)	…	…	…	…	1 (0.4)	…	…
Borderline	35 (11.6)	0.8 (0.5–1.2)	.3	1.0 (0.3–3.5)	1.0	29 (11.8)	0.7 (0.3–1.6)	.4
Cluster C[c]	51 (16.9)	0.7 (0.5–0.9)	.02	1.1 (0.4–2.9)	.9	39 (15.9)	1.8 (1.0–3.0)	.04
Avoidant	30 (10.0)	0.8 (0.5–1.2)	.3	0.6 (0.1–2.4)	.5	25 (10.2)	1.8 (1.0–3.4)	.05
Dependent	12 (4.0)	0.7 (0.3–1.4)	.3	2.4 (0.5–11.1)	.3	9 (3.7)	1.3 (0.4–4.3)	.7
Obsessive-compulsive	19 (6.3)	0.8 (0.5–1.4)	.4	1.7 (0.5–5.9)	.4	15 (6.1)	1.8 (0.8–3.9)	.2
Neuroticism (effect per SD)	237 (78.7)	0.8 (0.7–0.9)	.002	0.8 (0.5–1.3)	.4	198 (80.5)	1.1 (0.8–1.4)	.7
Extraversion (effect per SD)	235 (78.1)	1.1 (1.0–1.3)	.07	1.6 (1.0–2.5)	.05	194 (78.9)	0.9 (0.7–1.2)	.7

[a]Analyses were adjusted for the effect of age at onset, sex, and severity of the first episode of depression.
[b]Nonparticipants (n = 36) and patients without remission (n = 19) were not included in the analysis for recurrence.
[c]Patients could have had more than 1 personality disorder diagnosis.
Abbreviation: HR = hazard ratio. Symbol: … = no patients in this group.

admitted to psychiatric hospital with the diagnosis of recurrent depression according to register information. These 3 nonparticipants were therefore included in the group of patients with recurrence, whereas the remaining 36 nonparticipants in the follow-up (with no further information on the course of illness) were excluded, leaving a total of 246 participants for these analyses.

The presence of a comorbid cluster C personality disorder increased the rate of recurrence with 80%, as did avoidant personality structure when analyzed separately, whereas cluster B personality disorders and the level of neuroticism and extraversion did not influence recurrence.

Post hoc, we conducted additional analyses to adjust the effects of the explanatory variables, which significantly predicted the outcomes in the primary analyses for potential confounding effects from severity of residual depressive symptoms at the time of the baseline assessment, heterogeneity due to episode length, psychiatric comorbidity, and antidepressant treatment (the latter in order to control for potential effects mediated by antidepressant-induced conversion to bipolar disorder).

First, in the analyses of remission, we included comorbidity of anxiety and alcohol abuse (as diagnosed by the SCAN interview) in the regression models together with sex, age at onset, severity (mild, moderate, or severe according to *ICD-10* criteria) and neuroticism or cluster C personality disorder, respectively (but not duration of depression or HDRS-17 score, since these variables are obviously related to the time to remission). This did not substantially change the results (EPQ N-scale score: HR = 0.8; 95% CI, 0.7–0.9; *P* = .005; cluster C personality disorder: HR = 1.5; 95% CI, 1.1–2.1; *P* = .02). Cluster C personality disorder and neuroticism were strongly associated; among patients with cluster C personality disorder, the mean neuroticism score was 15.7 (SE = 0.9) compared to patients without cluster C personality disorder who had a mean neuroticism score of 10.9 (SE = 0.4) (*P* < .0005), probably due to common etiologic factors. Hence, including both cluster C personality disorder and neuroticism in the regression analyses would lead to overcorrection.

Second, in the analyses of recurrence, we included the HDRS-17 score, duration of the first depressive episode, and anxiety and alcohol abuse after remission of the first depression together with sex, age at onset, severity, and cluster C personality disorder. This did not substantially change the result (HR = 1.7; 95% CI, 1.0–2.9; *P* = .06).

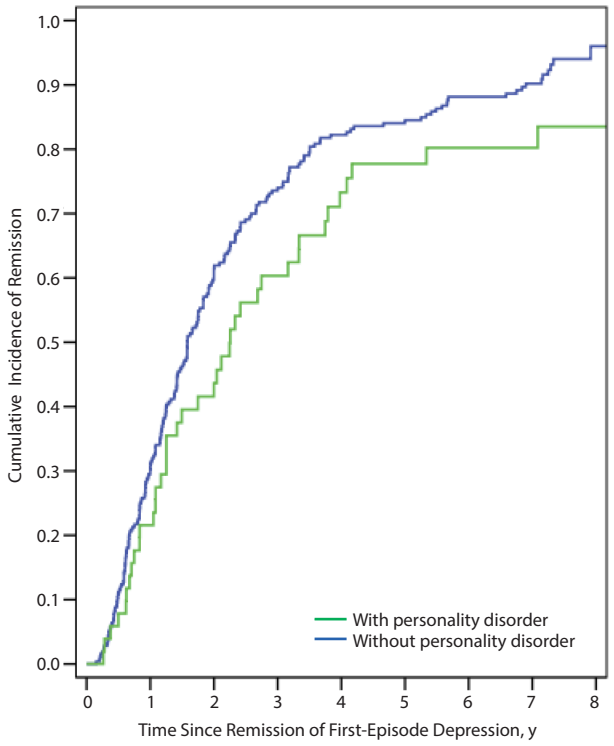
Third, in the analyses of conversion to bipolar disorder, we included the HDRS-17 score, duration of the first depressive episode, comorbidity of anxiety and alcohol abuse, and ongoing treatment with antidepressant medication at baseline together with /sex, age at onset, severity, and extraversion score. This did not substantially change the result (HR = 1.5; 95% CI, 1.0–2.4; *P* = .07).

Figure 1 presents the cumulative incidences of remission as function of time since onset of the first depression for patients with and without a comorbid cluster C personality disorder (Figure 1A) and for patients with a neuroticism score at baseline above and below the mean score of 11.7 (Figure 1B). Figure 2 presents the cumulative incidences of recurrence as a function of time since remission for patients with and without a comorbid cluster C personality disorder, respectively. Figure 3 presents the cumulative incidences of conversion to bipolar disorder as a function of time since discharge with a diagnosis of first-episode depression for patients with an extraversion score at baseline above and below the mean score of 11.4, respectively.

Finally, we tested the effect of the third personality dimension of EPQ, psychoticism, on the rate of remission, recurrence, and conversion to bipolar disorder, respectively, in Cox regressions analyses (adjusted for age at onset, sex, and severity of the first depression). Psychoticism did not influence any of the outcomes (all *P* ≥ .2).

Figure 1. Remission After the First Lifetime Episode of Depression

A. Patients With and Without a Comorbid Cluster C Personality Disorder



B. Patients With a Neuroticism Score at Baseline Above and Below the Mean Score

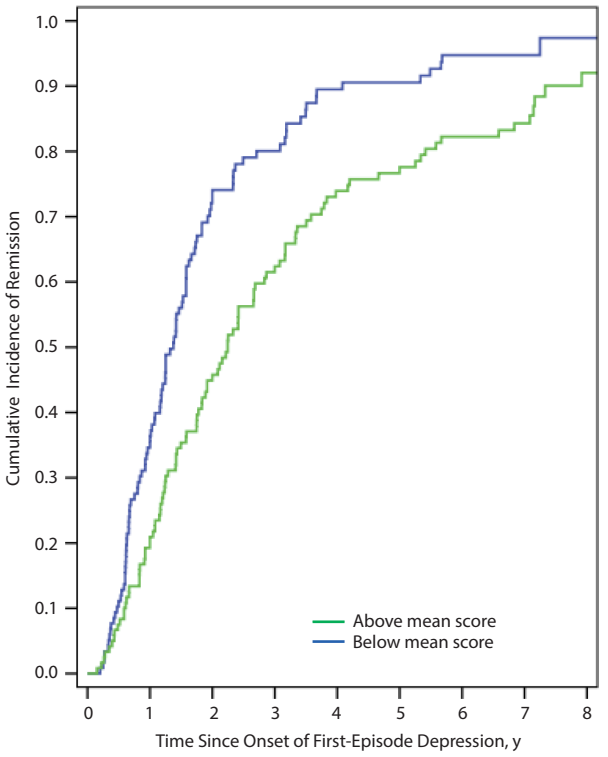


Figure 2. Recurrence After Remission of the First Lifetime Episode of Depression Among Patients With and Without a Comorbid Cluster C Personality Disorder

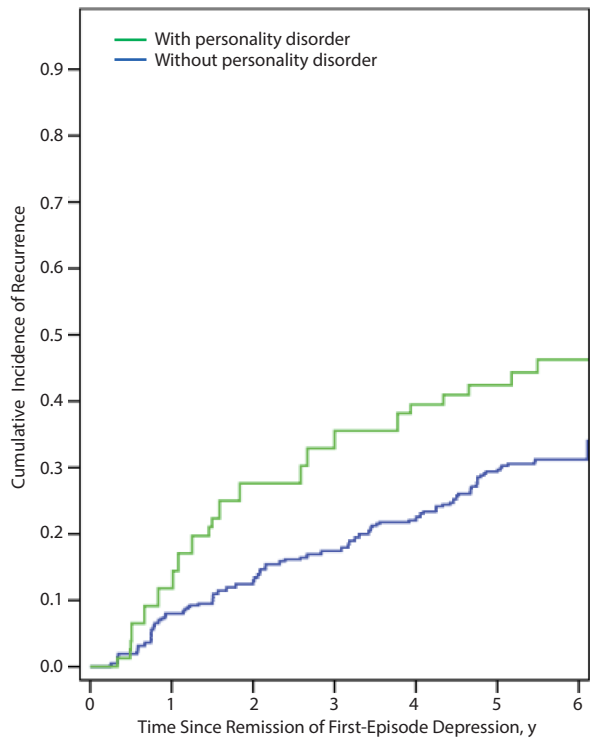
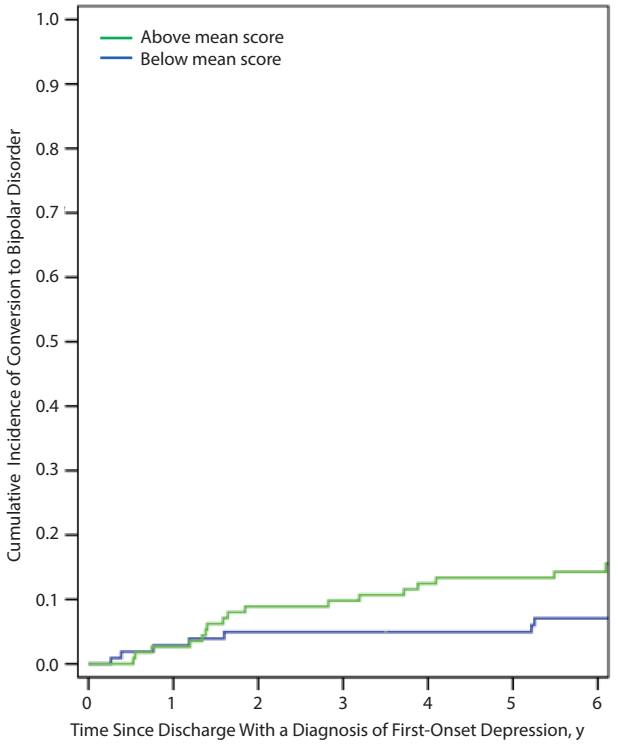


Figure 3. Conversion to Bipolar Disorder After Discharge With a Diagnosis of First Lifetime Episode of Depression Among Patients With an Extraversion Score at Baseline Above and Below the Mean Score



DISCUSSION

This is the first prospective study on the influence of personality traits and comorbid personality disorders on the course of illness following the first lifetime episode of depression. We found that the rate of remission decreased with higher neuroticism score and comorbidity of a cluster C personality disorder, and that the rate of recurrence was increased among patients with a comorbid cluster C personality disorder. Further, the rate of conversion to bipolar disorder was increased by a higher level of extraversion. Analyzed separately, an avoidant personality structure increased the rate of recurrence, and an antisocial personality structure increased the rate of conversion to bipolar disorder. Additional analyses controlling for a number of covariates did not indicate that the results were confounded by age at onset, sex, severity or duration of the first depression, residual depressive symptoms at the baselines assessment, or psychiatric comorbidity in terms of anxiety and alcohol abuse. The majority of participants were treated with various antidepressants or mood-stabilizing medications during the follow-up period. The heterogeneity of treatment due to the naturalistic settings made detailed adjustments for the effects of treatment difficult to accomplish. However, we also included antidepressant treatment at baseline in the analyses of conversion to bipolar disorder because such treatment might have increased the risk of subsequent antidepressant-induced manic or hypomanic episodes. In the post hoc Cox regression models with additional covariates the effects of cluster C personality disorder and extraversion on recurrence and conversion to bipolar disorder, respectively, were of the same numerical magnitude as in the primary analyses, though the results only reached borderline significance (*P* values, .06–.07), probably due to inclusion of more covariates and reduction of statistical power in the additional analyses.

In a recent review, Friborg et al[29] stated that personality disorders should ideally be assessed before the depressive disorder occurs in order to avoid confounding from the previous history of depression, even though the authors also admit that this is virtually impossible to accomplish. This method is definitely ideal when it comes to clarification of the true nature of the interrelations between depression and personality.[14] Ultimately, it might not be possible to separate personality abnormalities conceptually and operationally from intermittent and subthreshold affective symptomatology.[30] However, from a clinical point of view, we find it equally relevant to study the association between personality and outcome of depression from onset of the first depressive episode. First, because this design diminishes the confounding effect from previous depressive episodes, treatment trials, and psychosocial consequences of repeated depressive episodes, and second, because onset is when the clinician meets the patient and decisions about treatments are made. Increased knowledge of the predictors of long-term outcome of depression identifiable from onset of the illness is a prerequisite for individualized, tailored treatment. The present results indicate that screening for (eg, using the Standardized Assessment of Personality–Abbreviated Scale[31]) and eventually conducting a more comprehensive evaluation of cluster C personality disorders especially are already relevant at the first lifetime episode of depression. However, it remains an open question whether a more specific (eg, psychotherapeutic) treatment of comorbid personality disorders could increase the rate of remission and decrease the rate of recurrence, thus calling for randomized long-term studies of the effect of intensified treatment of comorbid conditions in depression. Further, our results suggest that even though the extraversion score has been found to be decreased among patients with both unipolar depression and bipolar disorder compared to healthy controls,[32] depressed patients with a relatively higher level of extraversion are at increased risk for conversion to bipolar disorder. Patients suffering from treatment-resistant depression with a high level of extraversion might therefore benefit from treatment with lithium or other mood stabilizers at an earlier stage, although the preventive effects of such strategies also await further investigation in a randomized controlled trial.

The inclusion of patients suffering exclusively from first-episode depression and the prospective design are major advantages of the present study. Further, one senior researcher and consultant in psychiatry conducted half of the psychiatric interviews at baseline and all interviews at follow-up, which ensured a high validity of both the inclusion diagnoses and the outcomes, and reduced interrater variation. Further, a very high follow-up rate (87.0%) reduced the risk of selection bias. Finally, there were few exclusion criteria, which increases the generalizability of our findings to patients treated in psychiatric hospital settings as inpatients or outpatients. Nevertheless, some limitations should be taken into account. It cannot be excluded that milder episodes have not been recognized and that the lack of assessments between baseline and the 5-year follow-up might have impaired the exact dating of the time of remission and new events. While this possible imprecision is not likely to undermine the significant findings, it might account for the nonsignificant results (eg, lack of associations with cluster B personality disorders). In the present study, interviews were conducted some time after discharge from hospital (median = 147 days; quartiles, 119–184) to minimize the effects of the acute mental state; however, some bias from residual depressive symptoms at the time of assessment is still possible. The personality factors were assessed after onset of the first depressive episode; hence, recall bias might have influenced the results. There was no blinding since the same interviewer made the assessments at baseline and follow-up. Treating the specific personality disorders as dimensions (ie, number of positive diagnostic criteria) rather than a categorical diagnosis, as done in some other studies,[10] might have given different results. We used the SCID-II interview with the screening questionnaire and did not probe questions answered "yes" if the number of positive items was well below the threshold for the disorder; hence, our data were not suitable for noting personality traits when there was an insufficient number to

qualify for a personality disorder diagnosis. Even though this is the largest prospective study to date of patients with first-episode depression, the sample size might still be too small to detect effects of individual personality disorders, especially on the rate of conversion to bipolar disorder, since this outcome is less frequent.

In conclusion, we suggest that, from the first lifetime episode of depression, clinicians and patients already pay attention to personality deviances and comorbid personality disorders since these clinical characteristics are associated with the long-term risk of nonremission, recurrence of depression, and conversion to bipolar disorder.

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REFERENCES

1. Eysenck HJ, Eysenck SGB. *The Manual of the Eysenck Personality Questionnaire*. London, UK: Hodder and Stoughton; 1975.
2. Mulder RT. Personality pathology and treatment outcome in major depression: a review. *Am J Psychiatry*. 2002;159(3):359–371.
3. Newton-Howes G, Tyrer P, Johnson T, et al. Influence of personality on the outcome of treatment in depression: systematic review and meta-analysis. *J Pers Disord*. 2014;28(4):577–593.
4. Grilo CM, Stout RL, Markowitz JC, et al. Personality disorders predict relapse after remission from an episode of major depressive disorder: a 6-year prospective study. *J Clin Psychiatry*. 2010;71(12):1629–1635.
5. Steffens DC, McQuoid DR, Smoski MJ, et al. Clinical outcomes of older depressed patients with and without comorbid neuroticism. *Int Psychogeriatr*. 2013;25(12):1985–1990.
6. Skodol AE, Grilo CM, Keyes KM, et al. Relationship of personality disorders to the course of major depressive disorder in a nationally representative sample. *Am J Psychiatry*. 2011;168(3):257–264.
7. Alnaes R, Torgersen S. Personality and personality disorders predict development and relapses of major depression. *Acta Psychiatr Scand*. 1997;95(4):336–342.
8. Hardeveld F, Spijker J, De Graaf R, et al. Recurrence of major depressive disorder and its predictors in the general population: results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Psychol Med*. 2013;43(1):39–48.
9. Akiskal HS, Maser JD, Zeller PJ, et al. Switching from 'unipolar' to bipolar II: an 11-year prospective study of clinical and temperamental predictors in 559 patients. *Arch Gen Psychiatry*. 1995;52(2):114–123.
10. Holma KM, Melartin TK, Holma IA, et al. Predictors for switch from unipolar major depressive disorder to bipolar disorder type I or II: a 5-year prospective study. *J Clin Psychiatry*. 2008;69(8):1267–1275.
11. Parker G, Fletcher K, McCraw S, et al. Identifying antecedent and illness course variables differentiating bipolar I, bipolar II and unipolar disorders. *J Affect Disord*. 2013;148(2–3):202–209.
12. Azorin JM, Kaladjian A, Adida M, et al. Factors associated with borderline personality disorder in major depressive patients and their relationship to bipolarity. *Eur Psychiatry*. 2013;28(8):463–468.
13. Spinhoven P, Elzinga BM, Hovens JG, et al. Positive and negative life events and personality traits in predicting course of depression and anxiety. *Acta Psychiatr Scand*. 2011;124(6):462–473.
14. Clark LA, Watson D, Mineka S. Temperament, personality, and the mood and anxiety disorders. *J Abnorm Psychol*. 1994;103(1):103–116.
15. Skodol AE, Gunderson JG, Shea MT, et al. The Collaborative Longitudinal Personality Disorders Study (CLPS): overview and implications. *J Pers Disord*. 2005;19(5):487–504.
16. Mulder RT, Joyce PR, Frampton CM. Personality disorders improve in patients treated for major depression. *Acta Psychiatr Scand*. 2010;122(3):219–225.
17. Jylhä P, Melartin T, Rytsälä H, et al. Neuroticism, introversion, and major depressive disorder—traits, states, or scars? *Depress Anxiety*. 2009;26(4):325–334.
18. Bukh JD, Bock C, Vinberg M, et al. Gender differences among patients with a single depressive episode. *Psychopathology*. 2010;43(3):159–169.
19. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva, Switzerland: World Health Organization; 1992.
20. Munk-Jørgensen P, Mortensen PB. The Danish Psychiatric Central Register. *Dan Med Bull*. 1997;44(1):82–84.
21. Wing JK, Babor T, Brugha T, et al; Schedules for Clinical Assessment in Neuropsychiatry. SCAN. *Arch Gen Psychiatry*. 1990;47(6):589–593.
22. Bukh JD. *First episode depression: gender, age-of-onset, and gene-environment interaction* [dissertation]. Copenhagen, Denmark: 2009.
23. Bukh JD, Bock C, Vinberg M, et al. Differences between early and late onset adult depression. *Clin Pract Epidemol Ment Health*. 2011;7(1):140–147.
24. First MB, Gibbon M, Spitzer RL, et al. *The Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)*. Washington, DC: American Psychiatric Press; 1997.
25. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
26. Post RM, Roy-Byrne PP, Uhde TW. Graphic representation of the life course of illness in patients with affective disorder. *Am J Psychiatry*. 1988;145(7):844–848.
27. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. 2nd ed. New York, NY: Wiley; 2002.
28. Bock C, Bukh JD, Vinberg M, et al. The influence of comorbid personality disorder and neuroticism on treatment outcome in first episode depression. *Psychopathology*. 2010;43(3):197–204.
29. Friborg O, Martinsen EW, Martinussen M, et al. Comorbidity of personality disorders in mood disorders: a meta-analytic review of 122 studies from 1988 to 2010. *J Affect Disord*. 2014;152–154:1–11.
30. Akiskal HS, Kilzieh N, Maser JD, et al. The distinct temperament profiles of bipolar I, bipolar II and unipolar patients. *J Affect Disord*. 2006;92(1):19–33.
31. Bukh JD, Bock C, Vinberg M, et al. Clinical utility of Standardised Assessment of Personality—Abbreviated Scale (SAPAS) among patients with first episode depression. *J Affect Disord*. 2010;127(1–3):199–202.
32. Jylhä P, Mantere O, Melartin T, et al. Differences in neuroticism and extraversion between patients with bipolar I or II and general population subjects or major depressive disorder patients. *J Affect Disord*. 2010;125(1–3):42–52.