Temperament, character and suicide attempts in unipolar and bipolar mood disorders

Pekka J. Jylhä, MD, PhD (1,2)

Tom Rosenström, PhD (4)

Outi Mantere, MD, PhD (1,3)

Kirsi Suominen, MD, PhD (1,5)

Tarja K. Melartin, MD, PhD (1,3)

Maria S. Vuorilehto, MD, PhD (1,3)

Mikael K. Holma, MD, PhD (1)

Kirsi A. Riihimäki, MD, PhD (1,6)

Maria A. Oquendo, MD, PhD (7)

Liisa Keltikangas-Järvinen, PhD (4)

Erkki T. Isometsä, MD, PhD (1,3,8)

(1) Department of Mental Health and Substance Use,
National Institute of Health and Welfare, Helsinki, Finland
(2) Department of Psychiatry, Jorvi Hospital,
Helsinki University Central Hospital, Espoo, Finland
(3) Department of Psychiatry,
Helsinki University Central Hospital, Helsinki, Finland
(4) IBS, Unit of Personality, Work and Health Psychology,
University of Helsinki, Helsinki, Finland
(5) City of Helsinki, Health Centre, Psychiatry, Helsinki, Finland
(6) Hospital District of Helsinki and Uusimaa, Hyvinkää Hospital Area, Tuusula Finland

(7) Department of Psychiatry, New York State Psychiatric Institute and Columbia University, New York, NY, USA

(8) Department of Psychiatry, Institute of Clinical Medicine, University of Helsinki, Helsinki, Finland

Funding/support: Funding for this study was provided by The Academy of Finland (E.I.), (L.K-J., grant number258711) and the Department of Psychiatry at Helsinki University Central Hospital (E.I.).

Role of Sponsor: The funding sources had no role in the design, conduct and reporting of the study.

Conflict of Interest: Dr. Oquendo has received royalties for the commercial use of the Columbia Suicide Severity Rating Scale and received financial compensation from Pfizer for the safety evaluation of a clinical facility, unrelated to the current manuscript. She was the recipient of a grant from Eli Lilly to support a year's salary for the Lilly Suicide Scholar, Enrique Baca-Garcia, MD, PhD. She has received unrestricted educational grants and/or lecture fees from Astra-Zeneca, Bristol Myers Squibb, Eli Lilly, Janssen, Otsuko, Pfizer, Sanofi-Aventis, and Shire. Her family owns stock in Bristol Myers Squibb. All other authors declared no conflicts of interest.

Correspondence:
Erkki T. Isometsä, MD, PhD
Professor of Psychiatry
Department of Psychiatry
Institute of Clinical Medicine
University of Helsinki
P.O. Box 22
FI-00014 Helsinki, Finland
Tel: +358 9 47163728
Fax: + 358 9 47163735
E-mail: erkki.isometsa@hus.fi

Word count of text: 2997

ABSTRACT

Objective: Personality features may indicate risk for both mood disorders and suicidal acts. How dimensions of temperament and character predispose to suicide attempts (SAs) remains unclear.

Method: Patients (n=597) from three prospective cohort studies (Vantaa Depression Study [VDS], Jorvi Bipolar study [JoBS], and Vantaa Primary care Depression Study [PC-VDS]) were interviewed at baseline, at 18 months, and in VDS and PC-VDS at 5 years. Personality was measured with the Temperament and Character Inventory–Revised (TCI-R), and follow-up time spent in major depressive episodes (MDEs) as well as (a) lifetime (total) and (b) prospectively ascertained SAs during the follow-up were documented.

Results: Overall, 219 patients had 718 lifetime SAs; 88 patients had 242 SAs during the prospective follow-up. The numbers of both the total and prospective SAs were associated with low Self-Directedness and high Self-Transcendence. Total, but not prospective, SAs were linked to high Novelty seeking. Prospective, but not total, SAs with high Harm Avoidance and low Reward Dependence, Cooperativeness and Novelty Seeking. No association remained significant if only prospective SAs during MDEs were included. After adjusting for total time spent in MDEs, only high Persistence predicted SAs. Formal mediation analyses of Harm Avoidance and Self-Directedness on prospectively ascertained SAs indicated significant mediated effect through time at risk in MDEs, but no significant direct effect.

Conclusion: Among mood disorder patients, SA risk is associated with temperament and character dimensions. However, their influence on predisposition to SAs is likely to be mainly indirect, mediated by more time spent in depressive episodes.

Keywords: *suicide attempt, suicidal behavior, personality, temperament, character, mood disorders, longitudinal studies*

Introduction

Mood disorders are associated with high suicide risk. At least half of all suicides occur in people suffering from mood disorders.[1] The lifetime risk of suicide among mood disorder patients is 5-6%.[2] For suicide prevention, knowing risk factors is of utmost importance. Due to suicide's low base rate, the search for risk factors has largely focused on suicide attempts (SAs) as a proxy for suicide. The risk factors for suicide attempts and suicide are grossly similar, although suiciders are more often male, have psychotic symptoms and use more lethal methods.[3, 4]

Social, psychological and clinical risk factors for suicide attempts in mood disorders include younger age, hopelessness, poor perceived social support, impulsive-aggressive traits and concurrent cluster B personality and substance use disorders (for reviews, see[3, 4]). Most likely an interaction between multiple risk and protective factors predispose to suicidal behavior.[5] In a series of prospective studies [6-9] we have shown that a major determinant, with consistently high population attributable fraction, is the time spent in high-risk illness phases. Compared with euthymia, the incidence of suicide attempts during major depressive phases is 25-fold and 65-fold in mixed illness episodes.[8] Among mood disorder patients, suicidal acts in the absence of an illness episode are rare.[6-9]

Personality traits are known to predict risk of mood disorders in prospective studies.[10] Specifically, we have recently shown that temperament and character traits also predict future burden of depression.[11] Selected personality traits might

also be useful indicators of risk for suicidal behavior.[12] Personality factors might increase the risk of suicide in mood disorders directly by moderating the impact of other risk factors on suicidal behavior during a suicidal crisis. Indirect causal pathways through a mediating factor could include predisposing to comorbid psychiatric disorders anxiety or substance use disorders,[13] to psychotic symptoms,[14] to poor social support,[15] or by increasing the time spent in high-risk mood states.[11]

In this study, we used Cloninger's unified biopsychosocial theory of personality, which postulates four temperament and three character dimensions[16, 17] (Supplementary material). These dimensions are measured using a self-rating questionnaire, the latest version being the Temperament and Character Inventory - Revised (TCI-R).

Previous studies investigating the relationship between suicide attempt and TCI in mood disorders have been cross-sectional. In these studies the presence of at least one lifetime SA has been associated consistently with high harm avoidance (HA),[18-23] novelty seeking (NS)[20, 23] or high self-transcendence (ST)[24, 25] and low self-directedness (SD)[18, 20, 24, 25] or cooperativeness (C),[23] although negative reports also exist.[26] Overall, cross-sectional studies suggest some personality dimensions are associated with risk of suicidal acts. However, the scarcity of prospective studies and inconsistent adjustment for confounders has prevented solid conclusions regarding the role of personality in risk for suicidal acts. To our knowledge, no prospective longitudinal study among mood disorder patients has specifically

investigated the relationship between personality features and risk of SAs. Moreover, a key predictor of accumulated risk for suicidal acts, the proportion of time a patient spends in major depressive episodes during follow-up[6-9], has not been controlled for in any previous study.

Aims of the study

We have previously reported that TCI dimensions predict vulnerability to mood disorders[27] and future burden of depression,[11] and that time spent in major depressive and mixed episodes is a major determinant of overall risk for SAs in mood disorders.[6-9] In this study, we hypothesized that among patients with mood disorders, high harm avoidance, novelty seeking, and self-transcendence would increase rate of SAs, whereas high self-directedness and cooperativeness would decrease the rate. Furthermore, we hypothesized that these effects would be mediated through increased time spent in major depressive episodes.

To test these hypotheses we investigated the relationship between temperament and character dimensions and 1) lifetime (total retrospective and prospective) SAs, and 2) prospectively evaluated new SAs during follow-up. We also tested whether TCI dimensions act directly on the rate of SAs, or indirectly by increasing the duration of illness relative to chronological age (for lifetime SAs) or more specifically, the duration of major depressive episodes (prospectively evaluated SAs). In final analyses of prospectively evaluated SAs, we controlled for confounding

sociodemographic and clinical risk factors, and conducted formal tests of mediation effects.

Method

Patients came from three cohorts (the Jorvi Bipolar Study, JoBS; the Vantaa Depression Study, VDS; and the Vantaa Primary Care Depression Study, PC-VDS), of collaborative research projects of the Department of Mental Health and Substance Use of the National Institute of Health and Welfare, Helsinki, Finland (Principal investigator EI). The pertinent ethics committee approved the research protocols.

Detailed methodologies have been described elsewhere for JoBS,[28, 29] VDS[30, 31] and PC-VDS.[32, 33] A summary is provided in Table 1.

Screening and baseline evaluation

Patients were screened for BD (JoBS), MDD (VDS) or depressive disorder (PC-VDS) in an acute mood episode. The patients were fully informed about the study and written informed consent was obtained. Diagnoses were based on semistructured interviews (Table 1). In PC-VDS, two thirds of the patients had major depressive disorder (MDD); the rest dysthymia, currently subsyndromal but lifetime MDD, or true minor depression. The final baseline cohorts consisted of 191 DSM-IV BD I and II patients (JoBS), 269 MDD patients (VDS) and 137 depressive disorder patients (PC-VDS). Interrater agreement in diagnostic interviews was excellent (kappa 0.86-1.00).[29, 30, 32]

Information was also gathered on demographic characteristics, current symptomatology using the 17-item Hamilton Depression Scale, HAM-D,[34] the 21-item Beck Depression Scale, BDI,[35] the 21-item Beck Anxiety Scale, BAI,[36] and the Young Mania Rating Scale, YMRS,[37] and illness history using a retrospective life-chart.

Follow-up

After baseline assessments, patients were interviewed at 6 (JoBS and VDS) and, at 18 (JoBS, VDS and PC-VDS) months and at 5 years (VDS and PC-VDS). Repeated SCID-I/P[38] (JoBS and PC-VDS at all follow-ups, and VDS at 5 years), SCAN 2.0[39] (VDS at 18 months), and SCID-II interviews and all observer- and self-reported symptom scales were included at all follow-up assessments. Information on course of illness was then integrated into a prospective life-chart based on DSM-IV criteria.[29, 31, 32, 40] Criteria for hypomania were as in the DSM-IV, except duration of at least 2 days. The sociodemographic characteristics of the patients are shown in Table 2.

Personality assessment

Patients were instructed to think of the way they would typically act or feel when filling -in the 240-item Temperament and Character Inventory- Revised.[41] TCI-R was included in JoBS, and PC-VDS at baseline and at the 18-month follow-up and in VDS at the 5-year follow-up.

Suicide attempts

A suicide attempt was defined as a self-injurious behavior with non-fatal outcome accompanied by evidence that the person had at least some degree of intent to die.[6-9] At baseline, the information of previous SAs was obtained by interviews and psychiatric records. The information regarding SAs during follow-up was based on both patient interview and medical records. In follow-up, we assessed episodes of depression and SAs independently, by questioning patients first about their life events and mood, and then about SAs, to avoid automatically attributing the disorders to each other, or the acts to the episode.

Study design

We examined whether TCI-R dimensions predicted number of prospectively ascertained SAs, or were associated with number of lifetime (including prospective) attempts. To minimize the effect of mood, each patient's personality dimensions were determined at an index interview conducted when the HAM-D scores (PC-VDS) or HAM-D and YMRS scores (JoBS) were at a minimum or at 5-year follow-up (VDS). If HAM-D and YMRS were at a minimum in different evaluations (n=28), the time-point when the patient was clinically healthier was chosen. In some cases (n=28) only a single evaluation was available.

Statistical methods

Poisson regression was applied in modeling the number of SAs during the (participant-specific) time of exposure as a function of explanatory covariates[42].

Existence of overdispersal was first tested for using dispersiontest in "AER" R-package version 1.2-1[43], and quasi-Poisson models were used only in the presence of clear overdispersal. Regression estimates were computed by standard Generalized Linear Modeling (glm-function) in R-software 64-bit Linux-version 2.15.3.[44] Formal tests of mediation[45] were conducted for the two dimensions with most robust effect on SA risk (HA and SD). Methodological details are presented in the Supplementary material.

Missing-data modeling was performed using Multiple Imputation by Chained Equations implemented with "mice" R package version 2.17.[46] Details of missing-data modeling along with imputed and non-imputed sensitivity analysis[47] are presented in the supplementary material. As a sensitivity analysis, we studied whether personality is differentially associated with having attempted suicide *versus* the number of attempts. The status outcome was modeled using standard Logistic Regression models.[42]

Results

In total, 219 (36.7% of the 597) patients had had one or more lifetime suicide attempts (SAs); 88 patients made one or more attempts during their prospective, life-charted follow-up period. Total number of lifetime SAs in the sample was 718, with the average being 1.20 (s.d = 2.79). Altogether, 242 prospectively ascertained SAs were observed during the participant-specific follow-up periods, with the average rate being 0.018 attempts/month (s.d. = 0.074).

Univariate associations between personality traits and number of lifetime and new SAs

Table 3 shows which (standardized) personality traits (a) were associated with number of lifetime SAs, (b,d) number of new SAs, and (c) number of new SAs during a major depressive episode (MDE). All models for lifetime SAs tested positive for overdispersal ($p < 0.01$), requiring the use of quasi-Likelihood method (see Methods), whereas models for prospective SAs did not show significant overdispersal. Most associations were in the same direction for numbers of lifetime (total) and prospective SAs, but NS was weakly positively associated with the number of lifetime SAs and (weakly) negatively associated with the number of prospective SAs.

For example, an increase of two standard deviations higher HA nearly doubled the monthly rate of SAs compared to the population mean in HA [exp(0.322 × 2 s.d.) = 1.90-fold rate; one s.d. implied exp(0.322) = 1.38-fold rate]. Effects on lifetime attempts are similarly reported but in terms of annual rates over lived years of life. While considerable in magnitude, the effects of personality were still modest in comparison to a previous SA, which implied a 3.27-fold increase in the expected participant-specific rate of new attempts. Missing-data modeling did not have a significant effect on the estimates, but restricting analysis to the periods during MDE did. All personality traits were non-significant predictors for the number of prospective SAs occurring during MDEs (Table 3).

Duration of illness and time spent in MDEs

Lifetime duration of illness, as assessed here, was not significantly related with the number of lifetime SAs (β = -0.030, S.E. = 0.384, p = 0.938). However, prospectively each month of MDE in the life chart increased the rate of new SAs by 1.05-fold (β = 0.049, S.E. = 0.004, p < 0.001). That is, a year-long MDE was associated with 1.80 -fold rate of new SAs.

The associations between personality traits and the number of lifetime SAs were unaffected by adjustment for life-time duration of illness (e.g., SD had β = -0.276 with p = 0.004, and ST had β = 0.287 with p = 0.002), or age-normalized duration of illness (β = -0.277 and 0.288, respectively). However, when controlling for prospective time spent in MDEs, all associations between personality traits and the number of new SAs lost significance (Table 4), with the exception of Persistence (P), which became a statistically significant predictor of the number of new SAs.

In general, adjusting for risk factors other than time spent in MDEs during follow-up did not explain associations between personality and number of new SAs, although the effects of Reward dependence (RD) may be mediated through perceived social support and hopelessness (Table 4). Adjusting for all other personality traits, however, attenuated all associations except that between SD and new SAs (Table 4). Sensitivity analyses are given in Supplementary material.

Formal analyses of mediation

The direct and indirect effects of HA and SD on prospectively ascertained SAs indicated significant indirect mediated effect through time at risk in MDEs, but no significant direct effects (Figure 1), details in the Supplementary material.

Discussion

We investigated the relationship between temperament and character and suicide attempts in three prospectively studied mood disorder cohorts. In these regionally representative samples, the influence of individual temperament and character on suicide attempt risk was mediated by time spent in high-risk states, i.e. major depressive episodes (MDEs). There was no evidence for a major moderating effect on risk for suicide attempts occurring during MDEs.

This study has numerous methodological strengths. It is the first to evaluate the effect of time at risk on suicidal behavior in conjunction with personality, made possible by use of graphic life charts. Information on SAs was gathered both retrospectively and prospectively during the follow-up, with mostly consistent findings. The most important strength was availability of life charts with information on illness course and timing of SAs, allowing testing of mediator and moderator hypotheses. TCI-R was available at several evaluations, thus reducing the effect of current mood on self-assessment. Patients were assessed prospectively with semi-structured interviews with excellent inter-rater reliability and both objective and subjective structured and semi-structured measures. Information regarding all comorbid Axis I and II disorders at baseline was also available. We investigated a broad range of risk and protective factors from several domains, including axis I and II comorbid disorders and symptoms, history of suicidal behavior, and psychosocial factors in the risk of suicide attempts. All cohorts employed similar methodology allowing valid comparisons and pooling of data.

Nevertheless, limitations exist. The lengths of follow-up differed, as the five-year follow-up data from JoBS was not yet available. The data was therefore modeled in Poisson regressions via the standard offset, or length-of-exposure, term. Second, similarly to any retrospective study, depression might affect recall of previous SAs. Third, it was only possible to investigate time spent in crudely classified risk states instead of detailed temporal tracking of individual-specific risk states. Risk for attempts likely covaries significantly with levels of depression, hopelessness, and possibly anxiety, none of which were measured on daily basis. Thus, the observed gradient between symptom states[6-9] is likely an underestimate. Fourth, as we modeled sample rates, the usual precautions apply for causal inferences at the individual level. Fifth, the study was naturalistic, and treatment was not controlled for. Treatment could influence the risk for SAs by reducing the time ill and, perhaps, by modifying the risk in illness phases independent of the influence of mood. Sixth, we cannot exclude the possibility that some personality dimension e.g. impulsive or nonimpulsive aggressive traits[48, 49-51] not sufficiently captured by the dimensions of the TCI-R might have important moderating effects on risk for suicidal acts. Seventh, in the analyses we controlled for numerous risk factors besides the time ill hypothesized to mediate effects of temperament and character. However, there are other risk factors such as reasons for living that were not measured. Eighth, while we controlled for most known confounders in the mediation analyses, the sequential ignorability assumption[45] cannot be explicitly tested; proof of causality remains unattainable. Finally, we investigated suicide attempts among patients with mood disorders, and generalizability of findings to completed suicides among them, or to suicidal behavior among other types of patients requires further confirmation.

The associations of TCI-R dimensions with SAs among patients with mood disorders were mostly consistent and expected. Like earlier studies with mood disorder patients[18-23] we found the rate of lifetime SAs to be associated with high NS and also, as a trend, with high HA. Moreover, the rate of prospectively evaluated SAs was also associated with high HA. Contrary to findings regarding lifetime SAs in our study and from a birth cohort study,[52] the rate of prospective SAs was associated with low NS, which was mostly due to BD patients. RD was negatively associated with the number of prospective SAs. Most,[18-20, 23-26] but not all[21, 22] former studies among mood disorder patients have found no association with lifetime SAs and RD; we found the possible effect of RD to derive from its correlation with perceived social support. Prospectively evaluated SAs were associated with high Persistence in BD patients which, after adjusting for the time spent in MDEs, resulted in a slight positive finding among all patients. This unexpected finding appears specific to BD, and requires an independent replication. The number of both lifetime and prospectively evaluated SAs were associated with high ST and low SD and C. These findings are in accordance with most studies among mood disorder patients evaluating the association of lifetime SAs with ST,[24, 25] SD[18, 20, 24, 25] and C.[23] Of these traits, the role of SD seems central, as only it persisted as independently significant when the effects of the traits were adjusted for each other (Table 4). Nevertheless, it appears that whatever the precise mechanisms through which these traits exert their influence, they must be indirect rather than direct or moderating effects on risk.

In a series of previous studies,[6-9] we have shown total time spent in mood episodes during follow-up to be a major determinant of risk for suicidal acts among patients

with mood disorders. Here, we observed total duration of MDEs to covary with personality in explaining SA rates. When the effects of MDEs were partialled out, personality did not predict SAs. The statistical analysis of mediation further supported indirect effects. Thus, most of the effects are likely to be mediated through time spent in high-risk states. It is noteworthy that none of the other risk factors we investigated seemed to have a similar mediating role. As we have shown, the analogous associations exist between the personality traits and prospectively evaluated low/dysphoric mood episodes in the general population.[11] Thus, the mediating effect of mood states is a credible mechanism for explaining associations between personality and SAs.

In conclusion, risk of SAs among mood disorder patients is associated with temperament and character dimensions. However, these associations lose significance after adjusting for time spent in MDEs, and mediation analyses support indirect rather than direct effects. Thus their influence on predisposition to SAs is likely to be mainly indirect, mediated by increased time spent in depressive episodes.

Clinical Points:

- Temperament and character predict suicidal acts, but their effect is mainly indirect.
- The influence of these traits on the risk of suicide attempts is largely mediated by longer time spent in depressive episodes, i.e. high-risk states.

- Treatments that shorten and prevent major depressive episodes are credible measures in reducing risk for suicidal acts.
- Understanding role of temperament and character in predisposing to depressive episodes may be helpful in targeting treatment to patients at risk.

References

1. Cavanagh JT, Carson AJ, Sharpe M, et.al. Psychological autopsy studies of suicide: a systematic review. *Psychol Med.*2003;33(3):395-405.

2. Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. *Arch Gen Psychiatry.*2011;68(10):1058-1064.

3. Isometsa E. Suicidal behaviour in mood disorders--who, when, and why? *Can J Psychiatry.*2014;59(3):120-130.

4. Hawton K, Casanas ICC, Haw C, et.al. Risk factors for suicide in individuals with depression: a systematic review. *J Affect Disord.*2013;147(1-3):17-28.

5. Mann JJ, Waternaux C, Haas GL, et.al. Toward a clinical model of suicidal behavior in psychiatric patients. *Am J Psychiatry.* 1999;156(2):181-189.

6. Riihimaki K, Vuorilehto M, Melartin T, et.al. Incidence and predictors of suicide attempts among primary-care patients with depressive disorders: a 5-year prospective study. *Psychol Med.*2014;44(2):291-302.

7. Valtonen HM, Suominen K, Haukka J, et al. Differences in incidence of suicide attempts during phases of bipolar I and II disorders. *Bipolar Disord.*2008;10(5):588-596.

8. Holma KM, Haukka J, Suominen K, et al. Differences in incidence of suicide attempts between bipolar I and II disorders and major depressive disorder. *Bipolar Disord.* 2014; 16(6):652-661.

9. Holma KM, Melartin TK, Haukka J, et.al. Incidence and predictors of suicide attempts in DSM-IV major depressive disorder: a five-year prospective study. *Am J Psychiatry.* 2010;167(7):801-808.

10. Klein DN, Kotov R, Bufferd SJ. Personality and depression: explanatory models and review of the evidence. *Annu Rev Clin Psychol.* 2011;7:269-295.

11. Rosenström T, Jylha P, Cloninger CR, et al. Temperament and character traits predict future burden of depression. *J Affect Disord.*2014;158:139-147.

12. Brezo J, Paris J, Turecki G. Personality traits as correlates of suicidal ideation, suicide attempts, and suicide completions: a systematic review. *Acta Psychiatr Scand.* 2006;113(3):180-206.

13. Kotov R, Gamez W, Schmidt F, et.al. Linking "big" personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. *Psychol Bull.* 2010;136(5):768-821.

14. Cortes MJ, Valero J, Gutierrez-Zotes JA, et al. Psychopathology and personality traits in psychotic patients and their first-degree relatives. *Eur Psychiatry.*2009;24(7):476-482.

15. Leskela U, Melartin T, Rytsala H, et al. Influence of personality on objective and subjective social support among patients with major depressive disorder: a prospective study. *J Nerv Ment Dis.*2009;197(10):728-735.

16. Cloninger CR. A systematic method for clinical description and classification of personality variants. A proposal. *Arch Gen Psychiatry.*1987;44(6):573-588.

17. Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. *Arch Gen Psychiatry.*1993;50(12):975-990.

18. Conrad R, Walz F, Geiser F, et.al. Temperament and character personality profile in relation to suicidal ideation and suicide attempts in major depressed patients. *Psychiatry Res.*2009;170(2-3):212-217.

19. Ekinci O, Albayrak Y, Ekinci AE. Temperament and character in euthymic major depressive disorder patients: the effect of previous suicide attempts and psychotic mood episodes. *Psychiatry Investig.*2012;9(2):119-126.

20. Perroud N, Baud P, Ardu S, et al. Temperament personality profiles in suicidal behaviour: an investigation of associated demographic, clinical and genetic factors. *J Affect Disord.*2013;146(2):246-253.

21. Joyce PR, Light KJ, Rowe SL, et.al. Self-mutilation and suicide attempts: relationships to bipolar disorder, borderline personality disorder, temperament and character. *Aust N Z J Psychiatry.*2010;44(3):250-257.

22. Engstrom C, Brandstrom S, Sigvardsson S, et.al. Bipolar disorder. III: Harm avoidance a risk factor for suicide attempts. *Bipolar Disord.*2004;6(2):130-138.

23. Pawlak J, Dmitrzak-Weglarz M, Skibinska M, et al. Suicide attempts and psychological risk factors in patients with bipolar and unipolar affective disorder. *Gen Hosp Psychiatry.* 2013;35(3):309-313.

24. Sarisoy G, Kacar OF, Pazvantoglu O, et al. Temperament and character traits in patients with bipolar disorder and associations with attempted suicide. *Compr Psychiatry.* 2012;53(8):1096-1102.

25. Bulik CM, Sullivan PF, Joyce PR. Temperament, character and suicide attempts in anorexia nervosa, bulimia nervosa and major depression. *Acta Psychiatr Scand.* 1999;100(1):27-32.

26. Calati R, Giegling I, Rujescu D, et al. Temperament and character of suicide attempters. *J Psychiatr Res.*2008;42(11):938-945.

27. Jylha P, Mantere O, Melartin T, et al. Differences in temperament and character dimensions in patients with bipolar I or II or major depressive disorder and general population subjects. *Psychol Med.*2011;41(8):1579-1591.

28. Mantere O, Suominen K, Leppamaki S, et.al. The clinical characteristics of DSM-IV bipolar I and II disorders: baseline findings from the Jorvi Bipolar Study (JoBS). *Bipolar Disord.*2004;6(5):395-405.

29. Mantere O, Suominen K, Valtonen HM, et al. Differences in outcome of DSM-IV bipolar I and II disorders. *Bipolar Disord.*2008;10(3):413-425.

30. Melartin TK, Rytsälä HJ, Leskelä US, et.al. Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. *J Clin Psychiatry.*2002;63(2):126-134.

31. Holma KM, Holma IA, Melartin TK, et.al. Long-term outcome of major depressive disorder in psychiatric patients is variable. *J Clin Psychiatry.*2008;69(2):196-205.

32. Riihimaki KA, Vuorilehto MS, Melartin TK, et.al. Five-year outcome of major depressive disorder in primary health care. *Psychol Med.*2014; 44(7):1369-1379.

33. Vuorilehto M, Melartin T, Isometsä E. Depressive disorders in primary care: recurrent, chronic, and co-morbid. *Psychol Med.* 2005;35(5):673-682.

34. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960 1960;23:56-62.

35. Beck AT, Ward CH, Mendelson M, et.al. An inventory for measuring depression. *Arch Gen Psychiatry.*1961;4:561-571.

36. Beck AT, Epstein N, Brown G, et.al. An inventory for measuring clinical anxiety: Psychometric properties. *J Consult Clin Psychol.*1988;56(6):893-897.

37. Young RC, Biggs JT, Ziegler VE, et.al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry.*1978;133:429-435.

38. First M, Spitzer RL, Gibbon M, et.al. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen*. New York: Biometrics Research, New York State Psychiatric Institute; 2002.

39. Wing JK, Babor T, Brugha T, et al. SCAN: Schedules for Clinical Assessment in Neuropsychiatry. *Arch Gen Psychiatry.*1990;47:589-593.

40. Vuorilehto MS, Melartin TK, Isometsa ET. Course and outcome of depressive disorders in primary care: a prospective 18-month study. *Psychol Med.* 2009;39(10):1697-1707.

41. Cloninger CR. *The temperament and character inventory (TCI) : a guide to its development and use*. 1st ed. St. Louis, Mo.: Center for Psychobiology of Personality, Washington University; 1994.

42. Gelman A, Hill J. *Data Analysis Using Regression and Multilevel/Hierarchial Models.* New York, NY.: Cambridge University Press; 2007.

43. Cameron AC, Trivedi PK. Regression-based tests for overdispersion in the Poisson model. *J Econometrics.*1990;46:347-364.

44. *R: A Language and Environment for Statistical Computing* [computer program]. Version. Vienna, Austria: R Foundation for Statistical Computing; 2012.

45. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods.*2010;15(4):309-334.

46. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equation in R. *J Stat Software.*2011;45(3):1-67.

47. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med.*2011;30(4):377-399.

48. Mann JJ, Arango VA, Avenevoli S, et al. Candidate endophenotypes for genetic studies of suicidal behavior. *Biol Psychiatry.*2009;65(7):556-563.

49. McGirr A, Renaud J, Bureau A, et.al. Impulsive-aggressive behaviours and completed suicide across the life cycle: a predisposition for younger age of suicide. *Psychol Med.* 2008;38(3):407-417.

50. Keilp JG, Gorlyn M, Oquendo MA, et al. Aggressiveness, not impulsiveness or hostility, distinguishes suicide attempters with major depression. *Psychol Med.* 2006;36(12):1779-1788.

51. Dalca IM, McGirr A, Renaud J, et.al. Gender-specific suicide risk factors: a case-control study of individuals with major depressive disorder. *J Clin Psychiatry.* 2013;74(12):1209-1216.

52. Fergusson DM, Woodward LJ, Horwood LJ. Risk factors and life processes associated with the onset of suicidal behaviour during adolescence and early adulthood. *Psychol Med.*2000;30(1):23-39.

Tables

Table 1. Methods used in the Jorvi Bipolar Study (JoBS), the Vantaa Depression Study (VDS), and the Vantaa Primary Care Depression Study (PC-VDS).

Phase	JoBS	VDS	PC-VDS
Timing of screening	Jan 1, 2002 to Feb 28, 2003	Feb 1, 1997 to May 31, 1998	Jan 1, 2002 to Dec 31, 2002
Catchment area	Adjacent cities of Espoo, Kauniainen, and Kirkkonummi (population 261 100 in 2002)	City of Vantaa (population 169 000 in 1997)	Two districts in the city of Vantaa (population of 63 400 in 2002)
Setting	Department of Psychiatry, Jorvi Hospital, Helsinki University Central Hospital, Espoo, Finland	Department of Psychiatry of the Peijas Medical Care District, Helsinki University Central Hospital, Vantaa, Finland	Primary Health Care Organization of the City of Vantaa, Finland Three health centers Two maternity clinics served by 30 general practitioners with population-based responsibility
Target group	All psychiatric patients aged 18-59 years (1) seeking treatment (2) referred to treatment, or (3) already in treatment with an acute deteriorating clinical state	All psychiatric patients aged 20-59 years (1) seeking treatment (2) referred to treatment, or (3) already in treatment with an acute deteriorating clinical state	Consecutive primary care patients aged 20-59 years in general practitioners' waiting room
Exclusion from screening	ICD-10 schizophrenia	ICD-10 Schizophrenia, BD I	Poor general health status prohibiting completion of screening form
Screening procedure	(1)Mood Disorders Questionnaire, 7/13 items positive, or (2)Clinical suspicion of BD (N=28)	(1)Five screening questions for depression from SCAN, 1 positive, or (2)Scale for Suicide Ideation, score ≥ 6	(1) PRIME-MD: one positive mood disorders item, and (2) telephone interview: one or more main symptoms of depression according to the SCID-I/P
Total Screened	1630	806	1111(eight refused)
Screened positive	546	703	402
Refusals	Screening 46 (2.8% of all screened), Interview 49 (9.0% of positive screens)	161 (22.9%)	37 (9.2%)
Diagnostic Interview	After informed consent, DSM-IV (SCID-I/P and SCID-II)	After informed consent, DSM-IV (Axis I, SCAN) and DSM-III-R (SCID-II, modified to DSM-IV)	After informed consent DSM-IV (SCID-I/P and SCID-II)
Inclusion criteria	DSM-IV type I or II with a new depressive, manic, hypomanic, mixed, or depressive mixed episode of BD.	DSM-IV MDD with a new depressive episode	DSM-IV MDD with no current treatment in psychiatric care
Cohort	191 (65 inpatients and 126 outpatients)	269 (46 inpatients, 223 outpatients)	137 outpatients from primary car
Number of patients at 6-month follow-up	176 (92.1%)	229 (85.1%)	-
18-month follow-up Number of patients	161 (84.3%)	198 (77.3%)	92 (88.5%)

Participants vs. non-participants Mean time for interview	Somewhat older (mean 39.0 years, SD 11.9 vs. 33.7 years, SD 12.1, t=2.711, df=189, p=0.007) 19.8±3.0 months		
5-year follow-up Number of Patients Switch of diagnosis Participants vs. non participants Mean time for interview	-	182(67.7%) 29 BD, 1 schizophrenia, 2 schizoaffective disorder More often female (72.1% vs. 55.6%, χ^2=6.581, p=0.010), married or cohabiting (75.6% vs. 59.7%, χ^2=7.725, p=0.005), less alcohol dependence at baseline (39.5% vs. 72.3%, χ^2=16.064, p<0.001) 5.2 years	112 (82.0%) 5 BD No difference in age, gender, or baseline depression severity. 5.2 years
Diagnostic reliability at baseline	20 videotaped diagnostic interviews; kappa coefficient for BD=1.0	20 videotaped diagnostic interviews; Kappa coefficient for current MDD= 0.86 (95% CI= 0.58 to 1.00); not tested for comorbidity	20 videotaped diagnostic interviews; kappa coefficient for current MDD= 1.0; not tested for comorbidity
Symptom assessment	YMRS, HAM-D, BDI, BAI (baseline and 18 months)	HAM-D, BDI, BAI (baseline, 18 months and 5 years)	HAM-D, BDI, BAI (baseline, 18 months and 5 years)
Personality assessment	TCI-R (baseline and 18 months)	TCI-R (5 years)	TCI-R (baseline and 18 months)
Internal consistencies of the scales	(Cronbach´s alphas) for the scales used were good in patient cohorts in all time-points [TCI-R (0.81-0.94), BDI (0.86-0.95), BAI (0.89-0.93), HAM-D (0.70-0.88) and YMRS (JoBS: 0.59-0.88)].		

BAI= Beck Anxiety Inventory; BD= Bipolar disorder; BDI= Beck Depression Inventory; HAM-D= Hamilton Depression Rating Scale; MDD= Major Depressive Disorder; PRIME-MD= Primary Care Evaluation of Mental Disorders; SCID-I/P= Structured Clinical Interview for DSM-IV Axis I Disorders, research version, patient edition with psychotic screen; SCID-II= Structured Clinical Interview for DSM-IV Personality Disorders; TCI-R= Temperament and Character Inventory –Revised; WHO SCAN= World Health Organization Schedules for Clinical Assessment in Neuropsychiatry, version 2.0; YMRS= Young Mania Rating Scale

Table 2. Sociodemgraphic characteristics, and mean scores and standard deviations (SD) of Beck Depression Inventory (BDI), Beck Anxiety Disorder (BAI), Hamilton Rating Scale for Depression (HAM-D), dimensions of Temperament and Character Inventory (TCI) and Perceived Social Support Scale –Revised (PSSS-R) of patients with (n=219) or without (n=378) lifetime suicide attempt.

	Patients with lifetime suicide attempt (n=219)		Patients without lifetime suicide attempt (n=378)			
	n	%	n	%	χ^2	p
Gender						ns
Female	155	70.8	247	65.3		
Male	64	29.2	131	34.7		
Education[f]						ns
University or polythecnic	70	32.2	150	37.7		
Vocational	52	24.0	93	25.1		
None	95	43.8	138	37.2		
Marital status[g]					4.354	0.037
Married or cohabiting	94	43.1	194	52.0		
Single	124	56.9	179	48.0		
Work status[h]						ns
Employed	147	68.1	259	69.4		
Unemployed	69	31.9	114	30.6		
Comorbid disorders evaluated at baseline						
Any anxiety disorder	125	57.1	171	45.2	7.775	0.005
Alcohol dependence, current	33	15.1	38	10.1		ns
Any personality disorder, current	121	55.3	150	39.7	13.559	<0.001
Psychotic features, lifetime	82	37.4	62	16.4	33.541	<0.001
	Mean	SD	Mean	SD	t	p
Age	38.8	12.2	41.2	12.4	2.241	0.025
BDI, bl	27.1	11.1	22.6	10.0	-5.166	<0.001
BAI, bl	24.2	12.5	19.4	11.3	-4.782	<0.001
HAM-D, bl	16.0	7.3	13.1	5.9	-5.305	<0.001
BDI, HAM-D min	18.2	12.9	11.6	10.2	-6.914	<0.001
BAI, HAM-D min	17.8	12.7	12.0	10.2	-6.100	<0.001
HAM-D min	12.6	8.6	8.9	6.7	-5.829	<0.001
TCI						
Harm avoidance[a]	107.5	20.9	105.2	18.6	1.271	ns
Novelty seeking[b]	107.2	18.8	101.6	16.6	3.405	0.001
Reward dependence[c]	98.1	15.1	99.1	15.7	-0.642	ns
Persistence[c]	106.2	21.3	105.8	19.4	0.217	ns
Self-directedness[d]	129.3	22.7	136.7	19.5	-3.797	<0.001
Cooperativeness[c]	128.4	19.6	131.9	16.8	-2.035	0.042
Self-transcendence[a]	70.8	16.1	65.1	15.5	3.868	<0.001
PSSS-R[e]	42.0	12.6	43.2	12.6		ns

[a]missing data 31/219, 86/378, [b]missing data 31/219, 87/378, [c]missing data 30/219, 87/378, [d]missing data 32/219, 87/378, [e]missing data 19/219, 33/378, [f]missing data 2/219, 7/378, [g]missing data 1/219, 5/378, [h]missing data 3/219, 5/378

Table 3. Quasi-Poisson regression coefficients for temperament and character traits predicting life-time number of suicide attempts, and Poisson regression coefficients when predicting number of new suicide attempts.

	Life-time attempts[a]				**New attempts**[b]			
Variable	**Coefficient**	**S.E.**	***p*-value**	n[e]	**Coefficient**	**S.E.**	***p*-value**	n[e]
Novelty seeking	**0.195**	**0.099**	**0.050**	**479**	**-0.137**	**0.069**	**0.047**	**457**
Harm avoidance	0.184	0.098	0.062	480	**0.322**	**0.071**	**< 0.001**	**458**
Reward dependence	-0.134	0.103	0.196	481	**-0.274**	**0.072**	**< 0.001**	**459**
Persistence	-0.136	0.097	0.161	481	-0.008	0.070	0.911	459
Self-directedness	**-0.266**	**0.091**	**0.004**	**479**	**-0.294**	**0.064**	**< 0.001**	**457**
Cooperativeness	-0.096	0.098	0.326	481	**-0.181**	**0.065**	**0.005**	**459**
Self-transcendence	**0.287**	**0.094**	**0.002**	**480**	**0.223**	**0.072**	**0.002**	**458**
Number of previous attempts	-	-	-	-	**0.122**	**0.032**	**< 0.001**	**555**
Had previous attempt	-	-	-	-	**1.185**	**0.328**	**< 0.001**	**555**
	New attempts during MDE[c]				**New attempts, multiple imputation**[b,d]			
Novelty seeking	0.020	0.101	0.842	386	-0.143	0.083	0.089	555
Harm avoidance	0.137	0.109	0.210	386	**0.320**	**0.084**	**< 0.001**	**555**
Reward dependence	-0.111	0.105	0.289	387	**-0.249**	**0.087**	**0.005**	**555**
Persistence	-0.130	0.094	0.169	387	-0.019	0.099	0.851	555
Self-directedness	-0.132	0.108	0.221	385	**-0.295**	**0.079**	**< 0.001**	**555**
Cooperativeness	-0.112	0.099	0.261	387	**-0.160**	**0.079**	**0.044**	**555**
Self-transcendence	-0.042	0.108	0.696	386	**0.194**	**0.095**	**0.042**	**555**
Number of previous attempts	**0.110**	**0.027**	**<0.001**	**452**	**0.122**	**0.032**	**< 0.001**	**555**
Had previous attempt	**0.836**	**0.208**	**< 0.001**	**452**	**1.185**	**0.328**	**< 0.001**	**555**

MDE=major depressive episode

a) Life-time attempts were adjusted for sex, and data-set (VDS, PC-VDS, or JoBS) covariates
b) New suicide attempts were adjusted for age, sex, data-set, number of previous attempts, and an indicator for having had an attempt before the life-charted follow-up period. Age- and sex adjusted coefficients for the latter two are also shown for comparison.
c) The analysis for new suicide attempts was repeated using only new attempts during MDE as the outcome (exposure was months in MDE and patients without MDEs were excluded)
d) Herein, missing-data modeling was used for bias correction, approximating the situation with 555 complete observations
e) Number of patients is shown per analysis, as different covariates had different amounts of missing values

Table 4. Regression-coefficient estimates for prospectively evaluated new suicide attempts with various adjustments and sensitivity analyses

Variable	Novelty seeking	Harm avoid-ance	Reward dependence	Persistence	Self-directedness	Coopera-tiveness	Self-transcend-ence
Original	-0.143	**0.320*** **	**-0.249** **	-0.019	**-0.295*** **	**-0.160***	**0.194***
Time spent in MDE	-0.102	-0.124	-0.094	**0.190***	-0.001	-0.048	0.149
BDI	-0.119	**0.210***	**-0.187***	-0.003	**-0.224** **	-0.117	**0.189***
BAI	-0.138	**0.245** **	**-0.218***	-0.004	**-0.231** **	-0.119	0.192
Psychotic symptoms	-0.150	**0.296*** **	**-0.279** **	-0.003	**-0.245** **	-0.130	0.138
Hopelessness	-0.121	**0.207***	-0.162	0.069	**-0.211***	-0.086	**0.232***
Social support	-0.090	**0.184***	-0.006	0.079	**0.196***	-0.074	**0.222***
Married	-0.122	**0.338*** **	**-0.221***	-0.052	**-0.294*** **	-0.151	0.162
Substance use	**-0.201***	**0.296*** **	**-0.245** **	-0.011	**-0.250** **	-0.122	0.176
All other traits	-0.181	0.094	-0.206	0.012	**-0.274***	0.106	0.178
Depressed only	0.049	**0.321***	-0.159	-0.264	**-0.473*** **	**-0.235***	0.258
Bipolars only	**-0.383*** **	**0.298** **	**-0.350** **	**0.376*** **	0.009	-0.006	0.107
Bipolars type I only	**0.496** **	0.011	**-0.708*** **	0.016	**-0.432***	**-0.742*** **	0.179
Bipolars type II only	**-0.620*** **	**0.441*** **	-0.223	**0.691*** **	0.187	**0.345***	0.080
Logistic models	0.159	**0.328***	**-0.340***	-0.174	**-0.537*** **	**-0.323***	0.191

Note: "*" = "$p < 0.05$"; "**" = "$p < 0.01$"; "***" = "$p < 0.001$". First row shows the original (multiply imputed) coefficients from Table 3 (n = 555) for comparison, whereas the other coefficients show how these change when adding the indicated covariate to the model: Time spent in MDE= proportion of time in major depressive episode; BDI = Beck's Depression Inventory; BAI = Beck's Anxiety Inventory; Psychotic symptoms (yes/no); Hopelessness score; (perceived) social support score; Married (yes/no); Substance use (yes/no); Then, all other personality traits adjusted were adjusted for. "Depressed only" shows the original estimates in the 379 patients from Vantaa and Primary-Care Vantaa Depression Studies, whereas the "Bipolars only" show the estimates in the 176 patients from Jorvi Bipolar Study. "BD type I only" shows estimates in the 81 Bipolar patients that are of the type I, whereas the "BD type II only" shows the same estimates for the 95 Bipolar Type II patients. Finally, "Logistic coefficients" show the original analysis but predicts the status of having made a new suicide attempt instead of the number of new attempts, adjusting for a possible attempt before the baseline and the number of such attempts.

Figure 1. Average Causal Mediation Effects (ACME) and Average Direct Effects (ADE) of Harm avoidance and Self-directedness personality traits on the patients' rate of suicide attempts trough their time spent in major depressive episodes (MDEs).

The panels on the left side show estimated effect of one standard deviation (s.d.) difference in personality trait mediated through time spent in MDE (ACME) and directly 'caused' by the trait (ADE). An interaction analysis examined whether these effects differ between those who are 1 s.d. above the mean in the trait (solid line) and those who are 1 s.d. below the mean (dotted line). Also the total effect of the traits is shown. The panels on the right side adjust for possible confounding due to baseline depressive symptoms, anxiety symptoms, psychotic symptoms, hopelessness, perceived social support, marital status, and substance use. The number of complete observations per condition is shown in parentheses in the panel titles.