THE JOURNAL OF CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

# Supplementary Material

**Article Title:** Temperament, Character and Suicide Attempts in Unipolar and Bipolar Mood Disorders

**Authors:** Pekka J. Jylhä, MD, PhD; Tom Rosenström, PhD; Outi Mantere, MD, PhD; Kirsi Suominen, MD, PhD; Tarja K. Melartin, MD, PhD; Maria S. Vuorilehto, MD, PhD; Mikael K. Holma, MD, PhD; Kirsi A. Riihimäki, MD, PhD; Maria A. Oquendo, MD, PhD; Liisa Keltikangas-Järvinen, PhD; and Erkki T. Isometsä, MD, PhD

**DOI Number:** 10.4088/JCP.14m09472

## List of Supplementary Material for the article



## Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

**Supplementary material**

## 1. Cloninger's unified biopsychosocial theory of personality

Cloninger's unified biopsychosocial theory of personality postulates four temperament and three character dimensions.[1, 2] The different temperament dimensions are defined in terms of basic stimulus-response characteristics, and character refers to individual differences in higher cognitive functions underlying a person's goals and values and voluntary rational processes. Novelty Seeking (NS) is thought to be related to the behavioral activation system, Harm Avoidance (HA) to the behavioral inhibition system, Reward Dependence (RD) to the behavioral maintenance system, and Persistence (P) to perseverance in behavior despite frustration and fatigue. Of the character dimensions, Self-directedness (SD) refers to an individual's ability to control, regulate and adapt their behavior in accord with chosen goals and values, Cooperativeness (C) to their tendency towards social tolerance, empathy, compassion and helpfulness, and Self-transcendence (ST) to their identification with nature and ability to accept ambiguity and uncertainty.

## 2. Sensitivity analyses between the cohorts

In interaction tests, the observed negative association between NS and the number of new suicide attempts (Table 3 in main manuscript) were mostly due to BD patients (Table 4 in the main manuscript), who showed a clear NS effect ($\beta$ = -0.383) compared to depression patients ($\beta$ = 0.049). BD patients also lacked the association between C and the number of new suicide attempts, or for SD and number of new attempts. That is, low SD was a strong predictor of the number of new suicide attempts in depression patients, but it was not associated with suicide attempt-rates in the BD patients ($\beta$ = 0.009, p = n.s.). P mainly had an effect for BD patients (β = 0.376). In addition to differences between the depression patients and BD patients, there were also many significant interactions with personality traits in predicting the number of new suicide attempts in BD I *versus* BD II patients. Finally, we assessed (dimensionally) whether predicting the number of new suicide attempts yielded different implications than predicting (categorically) who makes an attempt. As the lower right coefficients of the Table 4 show, predictions are qualitatively similar for the number of new attempts and the attempter status (one or more attempts) outcomes. Imputation analysis did not reveal prominent missing-data effects (Table 3).

## 3. Poisson regression

As our primary approach, Poisson regression was applied in modeling the number of suicide attempts during the (participant-specific) time of exposure as a function of explanatory covariates.[3] Observed number of suicide attempts, $y_i$, for patient $i$ was modeled as a Poisson distributed random variable. The participant-specific rate of attempt occurrences, $\lambda_i$, was modeled by a logarithmic link function: the natural log of $\lambda_i$ was a sum of an exposure offset, $a_i$, a linear model on covariates (i.e., independent variables), and a normally distributed random-effect perturbation, $\xi_i$, for overdispersal modeling.[3] In sum, the model was

$$y_i \sim \text{Poisson}(\lambda_i),$$
$$\log(\lambda_i) = \log(a_i) + \Sigma_k \beta_k x_{i,k} + \xi_i,$$
$$\xi_i \sim \text{Normal}(0, \sigma^2),$$

where "~" signifies "distributed as". The offset, $a_i$, stands for the number of follow-up months (length of 'exposure') for the patient $i$ when modeling new suicide attempts, for the patients age when modeling life-time attempts, and for the months in MDE when modeling new suicide attempts that occurred during MDE. Thus, $\lambda_i / a_i = E(Y|X_i)$, or in other words, the expected rate of suicide

attempts per unit time in patients with covariate values $X_i$. This way, exponential of a regression coefficient $\beta_k$ for the covariate $k$, $\exp(\beta_k)$, directly yields a multiplicative coefficient for the expected rate of suicide attempts for those participants with covariate $k$ one s.d. above the mean. Or if the covariate is dichotomous instead of a standardized $z$-score, $\exp(\beta_k)$ yields the multiplicative increase in patient $i$'s suicide-attempt rate due to the group membership indicated by $x_{i,k} = 1$ (as opposed to a patient $j$ with $x_{j,k} = 0$).

Standard Poisson regression model assumes equality of outcome mean and variance, and when this assumption is not satisfied, overdispersal is said to occur. In that case, parameter $\sigma^2 \neq 0$ captures the difference between mean and variance. Since the modeling of overdispersal (estimation of $\sigma^2$) decreases statistical power, however, existence of overdispersal was first tested for dispersiontest in "AER" R-package version 1.2-1[6]; if existing, $\sigma^2$ was estimated, and otherwise simply set to $\sigma^2 = 0$. Quasi-Poisson (overdispersal) or Poisson (no overdispersal) regression models were estimated using the standard Generalized Linear Modeling (glm-function) in R-software 64-bit Linux-version 2.15.3,[5]the former being a standard approximation for an explicit random effect ($\xi_i$) typically used in Bayesian framework.[3]

## 4. Multiple imputation

The following strategy, based on multiple imputation by chained equations"mice" R package version 2.17[6] was taken. Method of imputation was predictive mean matching. First, initial imputation model was created using "quickpred" function of mice for prediction selection, with default options.[6,7] Then predictors that lead to convergence problems or yielded bad imputations were further dropped from imputation model (e.g., long-tailed suicide-attempt distributions were ill-suited predictors and exposure time variable highly correlated with sample indicators). After a suitable and well-behaving imputation model was established, 35 imputation chains were initiated and then iterated for 30 iterations of mice-algorithm; standard regression estimates in the resulting 35 imputation data sets were pooled using moment-based statistics and an $F$ reference distribution.[8] Table e1 summarizes variables in our data and their abbreviations in this supplement. Figure e1 summarizes the missing-data pattern. Figure e2 shows that distributions of imputed values satisfactorily captured those of the observed values. Ten mice iterations yielded satisfactory mixing of the 35 chains, as is typical,[6] but 30 iterations were run to be on the safe side. Variable selection only by quickpred was insufficient, however, but a good imputation model was achieved by excluding variables marked with star in Table s1 when predicting missing values.

**Table e1. Variables and their abbreviations**

| | |
|---|---|
| sam1 | Jorvi Bipolar Study patient |
| sam2* | Vantaa Depression Study patient |
| sam3 | Primary-care Vantaa Depression Study patient |
| age | Age in years |
| sex | Gender indicator |
| y* | Number of new suicide attempts |
| ybl* | Number of previous suicide attempts |
| ns | Novelty seeking (personality trait) |
| ha | Harm avoidance (personality trait) |
| rd | Reward dependence (personality trait) |
| ps | Persistence (personality trait) |
| sd | Self-directedness (personality trait) |
| co | Cooperativeness (personality trait) |
| st | Self-transcendence (personality trait) |
| exposure* | Length of follow up in months |
| bdi* | Beck's Depression Inventory |
| bai* | Beck's Anxiety Inventory |
| hss* | Hopelessness score |
| pssup* | Perceived Social Support |
| msta | Marital status (married/not) |
| psys | Psychotic symptoms (yes/no) |
| subu | Substance use (yes/no) |
| mdet | Proportion of exposure under Major Depressive Disorder |
| jobs_bd1 | Indicator for Type I Bipolar Disorder for JoBS patients (as opposed to Type II) |
| vds_bipo | Indicator for MDE turning to BD during VDS follow-up |

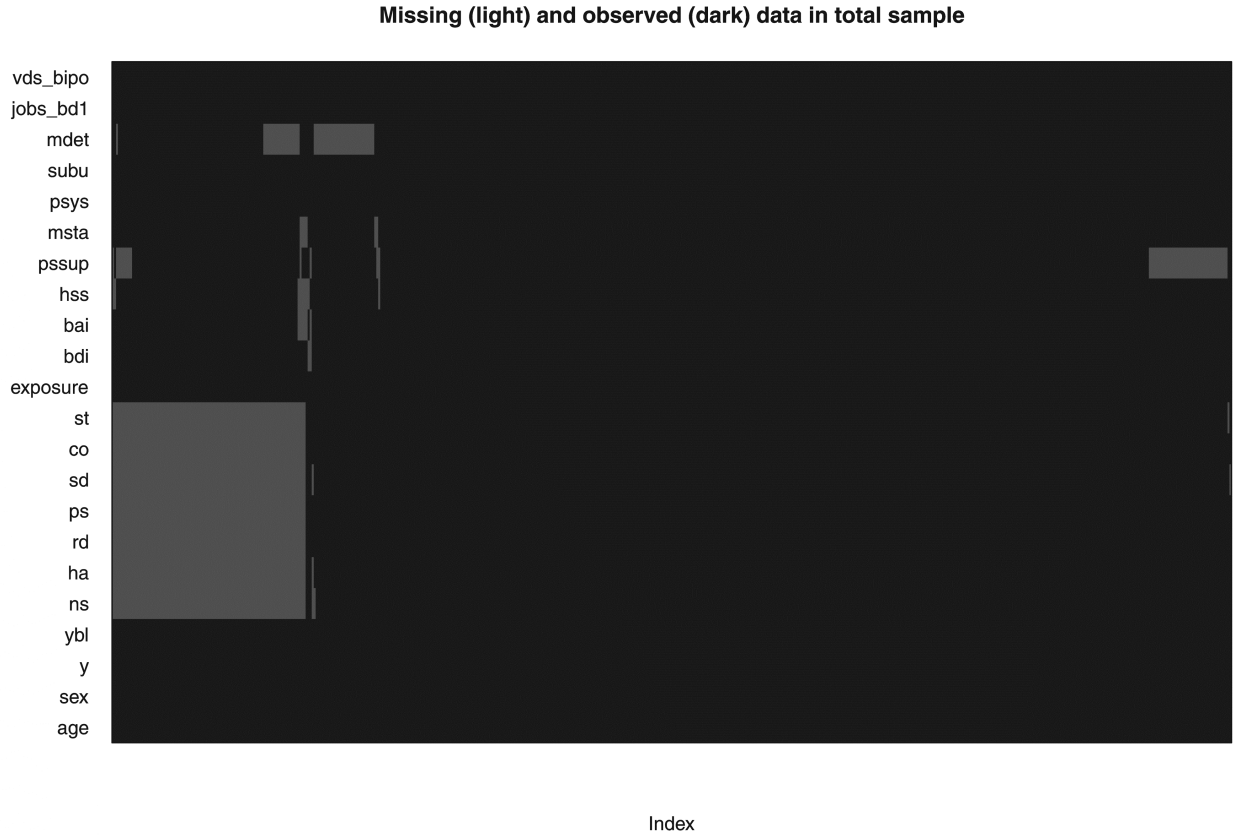


**Figure e1. Clustered missing-data pattern.**

Index/x-axis shows observations and y-axis variables; missing values are marked with light gray, whereas observed values with darker gray.

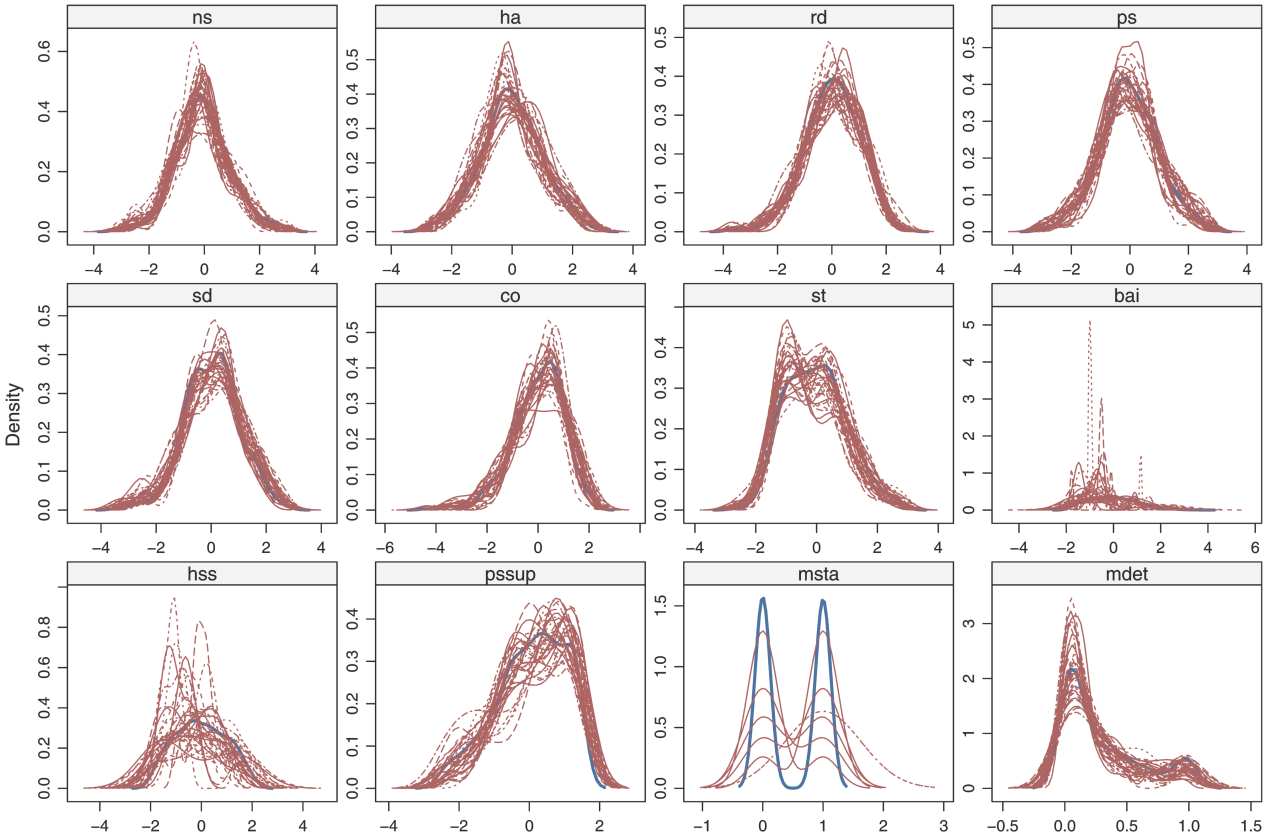


**Figure e2. Density estimates of imputed (red) and observed (blue) values.**
Densities of imputed values are separately shown for all the 35 chains, demonstrating good correspondence with observed distributions. Other variables than personality traits had so few missing values that single density estimates necessarily appear to vary, although good overall correspondence existed.

## 5. Formal analyses of mediation

For cases with a clear possibility that another variable mediates a personality trait's effects to new suicide attempts, we conducted a formal mediation analysis using a general approach to causal mediation analysis and version 4.4.2 of the "mediation" R package that implements it[9,10] ( robust standard-error estimates and 1000 quasi-Bayesian simulations, linear regression model for mediating variable, and Poisson regression model for the outcome). Because it can be difficult to say whether a covariate should be thought as a confounder for personality, we studied both a minimal set of confounding covariates and all possible confounders. The minimal set contained age, sex, having had a previous suicide attempt, number of previous suicide attempts, and cohort indicators. All covariates contained the aforementioned plus baseline BDI and BAI, psychotic symptoms, hopelessness, perceived social support, marital status, and substance use (excluding the studied mediator, of course). For the mediating variable candidate, we estimated the Average Causal Mediation Effect (ACME), Average Direct Effect (ADE), and total effect for the personality trait in question. In text, we report just these estimates that assume no interaction between personality status and the mediator[9], with 95% confidence intervals, but in a Figure 1, we also show the mediated and direct effects separately by "treatment" status. That is, we study whether the mediating variable mediates effects of both high and low poles of the continuous personality traits or just one or other. The hypothetical high-pole "treatment" group was defined as the studied personality trait being 1 s.d. above the sample mean, *versus* the low-pole "control" group with the trait 1 s.d. below the mean. We also studied simple moderation by assessing statistical significance of interaction terms for selected variables and traits.

Upon examining the Table 4, one sees that both Harm avoidance and Self-directedness showed robust effects despite adjustments for other covariates than the time spent in MDE. Thus, these personality traits were selected for further mediation analyses that assess the possibility that their effects on suicide attempts were mediated by increased time spent in MDE. Indeed, 1 s.d. higher Harm avoidance were estimated to imply 0.014 more suicide attempts per month via the increased time spend in MDE (95% CI = 0.007 – 0.031, $p < 0.01$), and not at all due to direct effects of Harm avoidance (ADE = -0.007, CI = -0.027 – 0.005, $p = 0.30$). For Self-directedness, the ACME was -0.013 (CI = -0.034 – -0.005, $p < 0.01$) and ADE virtually non-existent, 0.005 (CI = -0.009 – 0.034, $p = 0.62$). Taking into account all the other covariates attenuated, but did not remove, these mediated effects, and the mediated effects were similar in both poles of the traits (Figure 1). No interaction (or "moderation") effects were observed for the time spent in MDE and Self-directedness ($p = 0.39$ for interaction term in Poisson regression), but Harm avoidance may have minor interactions with time spent in MDE ($p = 0.051$). The supplementary figure e3 shows how the canonical link function changed by the levels of standardized Harm avoidance and standardized (z-score of) months spent in MDE.

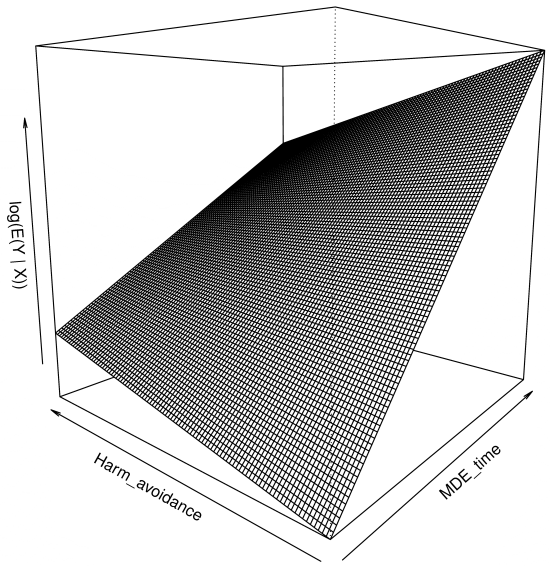


**Figure e3 on moderation/interaction. MDE-time-by-Harm avoidance interaction**.
A generalized linear (Poisson regression) model was estimated with the minimal set of covariates (see Methods) plus MDE-time, Harm avoidance, and their interaction term. The figure shows how the link function (log of suicide-attempt rate) changes by the joint levels of Harm avoidance and time spent in major depressive episodes (MDE). A borderline significant interaction was observed, with those low in Harm avoidance showing a stronger effect of MDE time on suicide-attempt rate compared to those high in Harm avoidance.

## 6. Supplementary material References


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

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

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

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

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

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

**7.** van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med.* 1999;18(6):681-694.

**8.** Li KH, Raghunathan TE, Rubin DB. Large-sample significance levels from multiply imputed data using moment-based statistics and an F reference distribution. *J Am Stat Assoc.* 1991;86(416):1065-1073.

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

**10.** Pearl J. The causal mediation formula--a guide to the assessment of pathways and mechanisms. *Prev Sci.* Aug 2012;13(4):426-436.