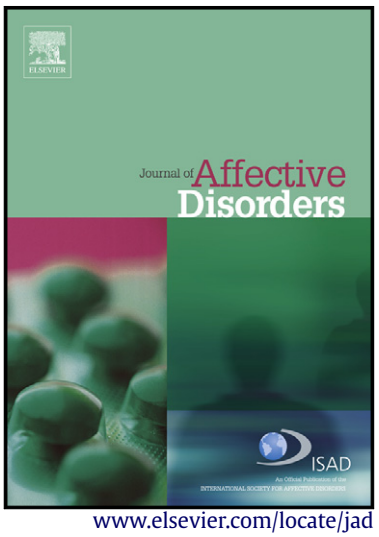

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Temperament and character traits predict future burden of depression

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Abstract

Background. Personality traits are associated with depressive symptoms and psychiatric disorders. Evidence for their value in predicting accumulation of future dysphoric episodes or clinical depression in long-term follow-up is limited, however.

Methods. Within a fifteen-year longitudinal study of a general-population cohort (N=751), depressive symptoms were measured at four time points using Beck's Depression Inventory. In addition, 93 primary care patients with DSM-IV depressive disorders and 151 with bipolar disorder, diagnosed with SCID- I/P interviews, were followed for five and 1.5 years with life-chart methodology, respectively. Generalized linear regression models were used to predict future number of dysphoric episodes and total duration of major depressive episodes. Baseline personality was measured by the Temperament and Character Inventory (TCI).

Results. In the general-population sample, one s.d. lower Self-directedness predicted 7.6-fold number of future dysphoric episodes; for comparison, one s.d. higher baseline depressive symptoms increased the episode rate 4.5-fold. High Harm-avoidance and low Cooperativeness also implied elevated dysphoria rates. Generally, personality traits were poor predictors of depression for specific time points, and in clinical populations. Low Persistence predicted 7.5% of the variance in the future accumulated depression in bipolar patients, however.

Limitations: Degree of recall bias in life charts, limitations of statistical power in the clinical samples, and 21%-79% sample attrition (corrective imputations were performed).

Conclusion. TCI predicts future burden of dysphoric episodes in the general population, but is a weak predictor of depression outcome in heterogeneous clinical samples. Measures of personality appear more useful in detecting risk for depression than in clinical prediction.

Keywords: Personality, major depressive disorder, bipolar disorder, mood disorders, longitudinal data, prevention

1. Introduction

Depression is a common disorder with a high risk of episode recurrence over time (Vos *et al.,* 2012; Hardeveld *et al.,* 2013). Predicting future chronicity and recurrence of depression is clinically important, for targeting treatment. Preceding episodes, family history of depression (Hardeveld *et al.,* 2013), and comorbidity (Melartin *et al.,* 2004) predict recurrence; less obvious factors, such as body-image dissatisfaction (Rosenström et *al.,* 2013), may contribute. Previous studies have also found that personality traits, such as those defined by the Psychobiological Model of Personality (Cloninger, 1987; Cloninger *et al.,* 1993), are predictive of depressive symptoms measured three months (Naito *et al.*, 2000), a year (Cloninger *et al.,* 2006), and four years (Elovainio *et al.,* 2004; Farmer and Seeley, 2009) later, suggesting a more general background behind accumulation of depressive and dysphoric episodes. Other evidence that personality predicts risk of depression has been obtained with measures of coping in relation to concurrent and future depression in community samples (Rohde *et al.,* 1990) and with antecedent personality traits in never-depressed siblings of depressives compared to never-depressed siblings of controls (Farmer *et al*., 2003).

Prior work with Cloninger's psychobiological model of personality shows that the risk of depression is associated with high Harm Avoidance, low Self-directedness, and low Persistence (Cloninger *et al.,* 2012; Cloninger *et al.,* 2010; Farmer *et al.,* 2003). Conversely, resilience is associated with low scores in Harm Avoidance, and high scores in Self-directedness, Cooperativeness, and Persistence (Eley *et al.,* 2013). A brain imaging study showed that these personality traits can be linked with a specific brain circuit that modulates mood and reward-seeking behavior (Gusnard *et al.,* 2003; Cloninger *et al.,* 2012). Dysfunctional attitudes that increase the risk of depression are largely explained by low Self-directedness, as expected from the cognitive theory of depression, but the other personality variables influence in particular circumstances (Luty *et al.,* 1999; Richter and Eisenmann, 2002; Otani *et al.,* 2013).

Dysphoric, or subclinical, symptoms are strongly associated with functional impairment (Karsten *et al.,* 2010), and show no clear empirical boundary with respect to more severe forms of

depression (Haslam *et al.,* 2012). Sample differences among general and clinical populations are likely, however. Simultaneously studying longitudinal accumulation in clinical and general populations offers the opportunity to examine which personality traits have prognostic value under what starting points (*e.g.*, for randomly chosen individual *versus* randomly chosen mood-disorder patient). The potential differences among different clinical populations are studied herein using two separate clinical populations; one with bipolar disorder and another with unipolar depressive disorder. We concentrate on the predictive value of personality traits for future dysphoric/depressive episode accumulation rather than on future depression at single time points. In the general population, the outcome is rate of future dysphoric episodes; in clinical populations, the outcome is the proportion of follow-up with participant fulfilling the DSM-IV criteria for a major depressive episode.

The aim of this study was to provide an answer to two questions. First, are there personality traits that predispose people to a higher or lower rate of future dysphoric episodes compared to the base rate in the general population? Second, which personality traits predict future burden of major depressive episode for unipolar and bipolar mood disorder patients? These results may have clear and immediate clinical utility, as the importance of prevention efforts for depression has been recently emphasized (Ghaemi *et al.,* 2013). Personality is an attractive candidate for detection of at-risk groups, as it is malleable, yet more stable than the actual target of prevention—depressive episodes (Klein *et al.,* 2011).

2. Methods

This study used one data set with a random sample from the general population and two samples from clinical populations of psychiatric patients.

2.1. Participants from Young Finns Study (YFS)

YFS is an ongoing prospective study with the first data collection in 1980 (Raitakari *et al.,* 2008).

The original sample consists of 3596 healthy Finnish children and adolescents (1832 women, 1764 men) sampled from six birth cohorts with approximately equal frequency (born 1962, 1965, 1968, 1971, 1974, or 1977). In order to select a broadly sociodemographically representative sample, Finland was divided into five areas according to locations of university cities with a medical school (Helsinki, Kuopio, Oulu, Tampere, and Turku). In each area, urban and rural boys and girls were randomly selected on the basis of their unique personal social-security number. All participants gave written informed consent and the study was approved by the ethical committee of the Varsinais-Suomi's hospital district's federation of municipalities. The sample has been followed subsequently in 8 data collection waves in 1983, 1986, 1989, 1992, 1997, 2001, 2008, and 2012, but only data from the four latter waves contained the required measures of both depressive symptoms and personality. Data from the year 1997 formed the baseline data, whereas the 2001, 2008, and 2012 follow-ups were used for evaluating future dysphoria and depressive symptoms.

Altogether 751 participants (256 men and 495 women) provided all data needed for the intended analyses in YFS data. The study attrition was 79% from the initial year-1980 sample, and 56% from those with baseline data available (n=1690). Often, those who lack data in YFS have more psychopathology-related personality traits and depressive symptoms, and are more likely to be young and male, compared to retained participants (Rosenström *et al.,* 2012, a, b). Correlates of attrition are same in clinical studies (Melartin *et al.*, 2004). Supplementary on-line material presents an imputation analysis, indirectly testing the sensitivity of the findings for missing observations. For simplicity, the main manuscript presents non-imputed estimates; both should be provided in some form, when possible (White *et al.,* 2011).

2.2. Participants from Primary Care - Vantaa Depression Study (PC-VDS)

Baseline data collection of the PC-VDS was based on stratified sampling from two districts within the city of Vantaa, Finland, during the year 2002 (population 63 400). Primary care patients aged 20-69 from general practitioners' waiting rooms were screened by Primary Care Evaluation of

Mental Disorders, PRIME-MD (Spitzer *et al.,* 1994), from three health centers and two maternity clinics. A total of 1119 participants were addressed, of which 402 screened positive for depressive symptoms; 37 of these refused to participate in the study and the rest gave their written informed consent. In the second phase, a diagnosis was made by a psychiatrist using the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I/P; First *et al.,* 2002). All available information from face-to-face interviews and psychiatric records was used; if the diagnosis was uncertain, other informants were contacted. To exclude substance-induced mood disorder, patients who were currently abusing alcohol or other substances were interviewed after 2–3 weeks of abstinence. The final baseline cohorts consisted of 137 depressive disorder patients. Two thirds had major depressive disorder (MDD), the rest being diagnosed with dysthymia, subsyndromal MDD with 2-4 symptoms (minimum one core symptom) and lifetime MDD, or minor depression otherwise similar to subsyndromal MDD, but without history of MDD. Distress or functional impairment was required. Interrater reliability for current depressive disorder, evaluated from 20 randomly selected videotaped interviews, was perfect [κ =1.0 (Vuorilehto *et al.,* 2005, 2009; Riihimäki *et al.,* 2011)].

The participants were followed again after six and after 18 months, and after five years from the baseline. A life chart of the entire five-year follow-up period was constructed for the patients by one of the two interviewers to determine the duration of the index episode and the timing of possible relapses and recurrences using all available medical and psychiatric records to complement the information. Altogether 93 participants provided the necessary personality and depression inventories at the baseline, and the full life-chart information. Hence, study attrition was between 32% and 47%, depending on the unknown clinical status of refused patients. Further details of the sample can be found from previous publications (Vuorilehto *et al.,* 2005, 2009; Jylhä *et al.*, 2011; Riihimäki *et al.,* 2011).

2.3. Participants from Jorvi Bipolar Study (JoBS)

The patients for the JoBS were screened from those of the Department of Psychiatry at the Jorvi

Hospital (part of Helsinki University Central Hospital), serving the adjacent cities of Espoo, Kauniainen, and Kirkkonummi in Finland during the year 2002 (population 261 100). All patients, excluding those with schizophrenia (n=1630), were screened with the Mood Disorder Questionnaire (MDQ); and 546 positive screens for bipolar disorder (BD) were found; 91 participants refused and the rest gave their written informed consent. In the second phase, a diagnosis was made by one of six psychiatrist using the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I/P; First *et al.,* 2002). All available information from face-to-face interviews and psychiatric records was used; if the diagnosis was uncertain, other informants were contacted. Altogether 191 patients were assigned a research diagnosis of DSM-IV type I or type II BD; interrater reliability of BD and type I or II diagnoses, evaluated by 20 randomly selected interviews ,was perfect (κ=1.0). Details of baseline methodology have been published elsewhere (Mantere *et al.,* 2004).

The participants were followed again after 6 and after 18 months. Graphic life charts of the follow-up period were constructed individually for each patient, as in PC-VDS. Altogether 151 patients provided the necessary personality and depression inventories at the baseline, and the full life-chart information. Hence, study attrition was between 21% and 46%, depending on the unknown diagnostic status of refused patients. Further methodological details can be found from previous publications (Jylhä *et al.,* 2011; Mantere *et al.,* 2008).

2.4. Measures

A modified version of the Beck's Depression Inventory (mBDI) was used in the general-population YFS to measure depressive symptoms (Cronbach's α = 0.91 in 1997, 0.92 in 2001, 0.93 in 2008, and 0.93 in 2012). In the modified version, subject ranks to what degree (a 5-point scale from 'no' to 'very much') he or she suffers from the ailment presented in the second mildest symptom description of the original Beck's Depression Inventory; such modified versions of clinical scales are frequently used because they better represent the general-population variation in the symptoms than the original clinically oriented scales (Rosenström *et al.,* 2012, b). In year 2008, the

participants also fulfilled Beck's Depression Inventory II (BDI-II, $\alpha = 0.88$) for which a national standardization has been published (Beck *et al.,* 2004); BDI and BDI-II are highly similar measures that are strongly correlated (at 0.93) with each other (Beck *et al.,* 1996). Using the 2008 mBDI and BDI-II measures, a general relationship between the mBDI and BDI-II scales was established (see beginning of the Results section). Further psychometric analyses of relationships between mBDI and BDI has been published elsewhere, including Item Response Theory modeling and various attrition analyses (Rosenström *et al.,* 2012, b; Rosenström, 2013, b).

In the national standardization, BDI-II scores above 13 points signify at least mild depression, a state referred to as *dysphoric episode* herein. Via the established mBDI to BDI-II relationship, it was possible to count the dysphoric episodes across all the three follow-ups *after* the baseline. The total number of dysphoric episodes within given number of assessments/follow-ups is referred to as *caseness*, as in previous studies (Jokela *et al.,* 2011). Caseness is, for the population-based YFS, a related measure to the proportion of time a person suffers from a depressive episode as measured from the life chart for the clinical data.

In the clinical data, all collected information was integrated into a graphic of a life chart together with the patient. In addition to symptom ratings, change points in psychopathological states were inquired using probes related to important life-events in order to improve accuracy of the assessment. From the life charts, proportions of time in the follow-up during which the participants fulfilled DSM-IV criteria for MDD (5 or more of the 9 symptoms; SCID-I/P; First *et al.,* 2002) were computed (Holma *et al.,* 2008; Vuorilehto *et al.,* 2009). Accuracy of, or information in, life charts must considerably exceed simple interpolation from face-to-face follow-up assessments (see sections 2.2 and 2.3), but cannot be quantified further, as the patients were not under full-time continuous surveillance. The participants also filled in the Beck's Depression Inventory [BDI (Beck & Steer, 1993), $0.86 \leq \alpha \leq 0.95$].

In addition to the depression assessments, personality as defined by the Psychobiological Model of Personality (Cloninger, 1987; Cloninger *et al.*, 1993) was assessed in the baseline follow-

up of both the population-based YFS study and the clinical studies. The PC-VDS and JoBS used the Revised version of Temperament and Character Inventory (Cronbach's α = 0.81-0.94), while YFS used the Temperament and Character Inventory (internal consistencies below) modified to correspond to the revised version with a 5-point Likert scale (Cloninger *et al.*, 1994). A personality trait is a continuous measure for individual differences occurring along certain dimension of behavior and thought. The main personality traits that were used are briefly described below, and more detailed description has been published elsewhere (Cloninger *et al.,* 1993).

Novelty seeking is a tendency toward excitement and activation of behavior in response to novel stimuli, or in response to cues of potential rewards or potential relief of punishment (40 items, α=0.85 in YFS). *Harm avoidance* is a tendency to inhibit behavior in response to signals of aversive stimuli or frustrative non-reward (35 items, α=0.92). *Reward dependence* is a tendency to form social attachments in response to signals of reward (especially to signals of social approval; 24 items, α=0.80). *Persistence* is a tendency to maintain or resist extinction of behavior previously associated with intermittent rewards or relief from punishment (8 items, α=0.64). *Self-directedness* is a tendency to set and to strive towards self-determined rather than externally influenced life goals, and to attribute causes for the consequences of one's actions to oneself rather than to other peoples or external circumstances (44 items, α=0.89). *Cooperativeness* refers to ability and desire to co-operate with other people (42 items, α=0.91). Finally, *Self-transcendence* is a tendency to be aware of connections with what is beyond the individual self, referring to personal qualities such as spirituality and universal values (33 items, α=0.91).

2.5. Statistical Analyses

Regression models for future accumulation of depression were estimated, with baseline personality traits as predictors. First, 'individual effects' of traits and depression scores in predicting the amount of time a person was depressed were estimated (Model 0). Then, Model I assessed what personality traits contribute when adjustment is made for the baseline depressive-symptoms summary score. In

YFS, we also adjusted for the presence of a dysphoric episode as a dichotomous variable at baseline (Model II). Finally, Model III assessed the contribution of each variable controlling for all the other traits and/or the depression score, that is, a full multiple regression was estimated. Despite this conceptual division, every regression model was adjusted for sex and age (single continuous variable in clinical data; five cohort indicators in YFS).

As the outcome variable was either a count (in YFS) or a proportion (in PC-VDS and JoBS), generalized linear regression models were used (Gelman and Hill, 2007). In YFS, Quasi-Poisson regression was applied (sensitivity analysis with Ordered Logistic regression in on-line supplement). In the clinical data sets, two complementary approaches were taken. Proportions are frequently modeled by transforming them into a continuous variable by Logit transformation, but this does not work when 0 or 1 proportions exist in the data, as the Logit transformation for the former is minus infinity and for the latter plus infinity [the Logit transformation is the map $p \rightarrow \log\{p/(1-p)\}$ from open interval (0, 1) to the real line]. Therefore, we also applied Inflated Beta Regression, which can handle the extreme values as well (Ospina and Ferrari, 2010; Stasinopoulos and Rigby, 2007), thereby allowing the use of all eligible data. In addition to being a sensitivity analysis, the approach with an explicit logit transformation also allows for presenting the coefficient of determinations (R^2) and the change resulting from adding an independent variable into a regression model (ΔR^2). R^2 value signifies the proportion of outcome-variable variance explained by the model; herein, "R^2" always refers to the covariate-number "adjusted R^2" (Gelman and Hill, 2007). Notice that change ΔR^2 for adjusted R^2 can be negative for a bad predictor.

All analyses were performed using R-software 64-bit version 2.15.3, and for the Inflated Beta Regression, GAMLSS R-package (R Core Team, 2012; Stasinopoulos and Rigby, 2007). Statistical comparisons between two linear models were based either on the classical *F*-test or on the Akaike's Information Criterion [AIC (Stasinopoulos and Rigby, 2007)]. Continuous independent variables in regression models were standardized z-scores. The statistical p-values in Table 1 are from two-tailed *t*-test of equal means.

2.6. On the interpretation of outcome variables

In the clinical samples (JoBS and PC-VDS), we were able to explicitly compute the proportion of follow up that a participant suffered from symptoms fulfilling Major Depressive Episode criteria by using the life charts and hospital records. Hence, direct associations between personality measured at baseline and proportion of time depressed could be evaluated. In the general population (YFS), however, the participants were sampled only in discrete time points, without knowledge of their emotional states in between. As the temporal sampling points determined by the study protocol can be considered unrelated to individuals' emotional processes, the number of dysphoric states observed during the sampling times should be monotonically related to their general rate of occurrence. Therefore, estimated *changes* in base rates due to a covariate should be reasonably comparable across partially observed general-population trajectories and more fully observed clinical trajectories. It should be kept in mind, however, that quasi-Poisson models assess relative increases in base rate of dysphoric episodes rather than absolute increases.

In addition to comparability between samples, there was another reason for studying accumulation of discrete dysphoric episodes instead simple sums of symptom sums over several time points. This way one avoids confounding cases of repeatedly elevated scores with cases of a single very high score and several quite low scores.

3. Results

Because the distances among the levels of depressive-symptom severity are encoded differently by mBDI and BDI-II (Rosenström *et al.,* 2012, b), the inclusion of a quadratic component was required in modeling the relationship between the mBDI and the clinically oriented BDI-II ($\beta_{quadratic}$ = 1.48, *S.E.* = 0.07, $p < 0.001$, $\Delta R^2 = 0.085$; see Figure 1A). Further nonlinear components were not needed in the model ($p = 0.998$ and $\Delta R^2 = 0.00$ for a cubic term; other relevant estimates were: $R^2 = 0.695$;

β_{linear} = 4.24 and $\beta_{intercept}$ = 4.02). Correlation between the established model estimate and measured BDI-II was 0.83, which is close to the maximum possible [Cronbach's (alpha) reliability of the BDI-II was 0.88]. A dysphoric episode was defined by this estimated quadratic transformation (*i.e.*, BDI-II modeled by the mBDI) exceeding 13 points of BDI-II score (see Methods/Measures). After the baseline-year 1997, there were 3 non-baseline follow-ups, and hence three dysphoric episodes were maximum number of 'future' episodes in YFS (Figure 1B).

As can be seen from Figure 1A, the predictor/proxy for the BDI-II-defined mild depression had higher specificity (0.98) than sensitivity (0.65). Specificity implied that episodes detected by the model almost always reflected at least mild episodes according to BDI-II. Sensitivity implied that we missed 35% of such episodes, suggesting that regression estimates below are underestimates rather than overestimates. The issue of sensitivity is pertinent, however, only so far as one prefers BDI-II over mBDI in defining dysphoric episodes.

Table 1 presents the basic characteristics of the studied samples. Whereas the proportion of time as depressed is shown for clinical PC-VDS and JoBS data sets, the number of dysphoric episodes in the three non-baseline follow-ups is shown for YFS general-population data that lacks the life chart methodology. On average, the clinical patients had approximately 14-17 points higher BDI compared to the YFS participants' (BDI-II proxy).

3.1. Main results for general population

Table 2 shows regression coefficients from quasi-Poisson models predicting the number of future dysphoric episodes with the baseline measures in general-population participants. Baseline measures included score of depressive symptoms (mBDI), indicator of dysphoric episode at baseline, and personality traits; all independent variables were standardized except dichotomous indicator variables. For all models, low current Self-directedness predicted the greatest increase in the rate of future dysphoric episodes, among personality traits. Also high Harm avoidance, low Cooperativeness, and depressive symptoms contributed strongly. The presence of a dysphoric

episode at baseline was a non-significant predictor after adjusting for the continuous depression score at baseline. All personality-trait coefficients were at least partially attenuated by adjusting for baseline depression score, particularly for Cooperativeness.

The regression-coefficient values in the Table 2 imply, for example, that a one standard deviation lower Self-directedness predicted $e^{0.65} = 1.92$ times higher rate of 'dysphoric-episode caseness' for the following fifteen years compared to the population average (Gelman and Hill, 2007), (linearly) controlling for the present state of the other traits and depressive symptoms. When not considering other covariates, observing the same one standard deviation lower Self-directedness translated to 7.61-fold rate of dysphoric episodes compared to average-population base rate. Current Self-directedness alone was better at predicting the future number of dysphoric episodes than the sum of current depressive symptoms alone (4.53-fold rate for 1 s.d. higher depression score compared to base rate). The effects of Self-directedness and depressive-symptom counts on number of future episodes were only slightly overlapping (Model II in Table 2); that is, complementary rather than redundant.

In addition to predicting the number of dysphoric episodes, one may ask how much variance in a *single* future time-point's depressive-symptom score (mBDI) the baseline personality traits linearly explain, and how much this adds over the baseline symptom score? The score after four years from the baseline was examined (*i.e.*, in the 2001 follow-up). The seven baseline personality traits explained 35.1% of the later symptom score, adding considerably to the explained variance achieved by sex and age/cohort effects alone ($\Delta R^2 = 34.7\%$, $F_{7,737} = 58.55$, $p < 0.001$), but only little compared to that achieved by sex, age/cohort, *and* baseline mBDI ($\Delta R^2 = 1.6\%$, $F_{7,737} = 4.13$, $p < 0.001$). Baseline mBDI alone explained 45.5% of the variance in the mBDI measured four years later. Hence, the information in baseline mBDI and personality traits was redundant rather than complementary when predicting mBDI-values at single future time point.

An online supplementary sensitivity analysis presents results for imputed data, and for an alternative model to quasi-Poisson regression that cannot be biased by the ceiling effect on

caseness. Both the sensitivity analyses provided qualitatively corresponding results, indicating that the non-imputed YFS analyses presented herein were reliable, perhaps conservative, estimates.

3.2. Main results for clinical populations

Table 3 shows regression coefficients in the mood disorder patients for the baseline variables predicting proportion of time as depressed during the follow-up (Figures 1C and 1D), or its logistic transformation. The logistic transformation allows for using ordinary least squares regression, but applying the Inflated Beta Regression model allows for also using the participants with zero or unit proportions (circles in Figure 1C-D). Results for both models are shown in the Table 3. The ordinary linear regression model with logit-transformed outcome variable provided highly similar results compared to Inflated Beta regression models. Continuous baseline depression scores explained 9-11% of variance in the accumulated time as depressed during the subsequent 5 or 1.5 years. Personality showed predictive value in JoBS data, but not in PC-VDS. In the ordinary linear model in PC-VDS, there was only a slight chance for detecting small effects for individual personality traits, however [statistical power was 21.1% for small ($f^2 = 0.02$) effect]; for large effects the power was adequate [99.8% for $f^2 = 0.35$ (Cohen, 1988)].

In the linear model, predicting the logistic transformation of depression-time proportion in JoBS data, baseline Persistence explained 7.5% of variance; most of it (7.2%) non-overlapping with baseline depression score that explained 11.0% by itself and 10.6% adjusting for persistence. Baseline Persistence and baseline BDI did not correlate significantly ($r = -0.02$, $p = 0.792$). Together baseline Persistence and BDI explained 18.2% of variance in the proportion of future time as depressed. This result was specific to major depressive episodes, as we verified that Persistence alone did not significantly predict accumulated mania ($\beta = -0.20$, s.e. = 0.17, $p = 0.241$ in Inflated Beta regression; JoBS included analogous life-chart data on manic episodes).

4. Discussion

In this study we examined whether personality traits, defined by the Cloninger's Psychobiological Model of Personality (Cloninger, 1987; Cloninger *et al.,* 1993), predicted the future number of dysphoric episodes in a general population, and whether the same traits predicted the amount of future time a person suffered from major depressive episode given a current diagnosis of mood disorder (unipolar and/or bipolar). In the general population, personality was better at predicting accumulated dysphoria (number of future episodes) than at predicting depression score values at a single future time point. For example, one standard deviation lower current Self-directedness led to 7.61-fold rate of future dysphoric episodes across 15 years compared to base rate, whereas one standard deviation higher depression score implied only 4.53-fold rate; in contrast, all current personality traits together predicted only 35.1% of the depression-score variance four years later, whereas the current depression score predicted 45.5%. This observation is plausible because past depression scores certainly assess a similar construct to present depression score, whereas personality traits are more temporally stable than depression scores (Cloninger *et al.,* 2006), thereby exerting their potential effects in a more prolonged manner. In addition to the strongest predictor, low Self-directedness, also high Harm avoidance predicted elevated rates of future dysphoria; low Cooperativeness was predictive, but not significantly so after accounting for the baseline depressive symptoms. These findings confirm and extend prior work showing that the risk of depression is predicted by high Harm Avoidance, low Self-directedness, and low Persistence, variables that interact in the modulation of a brain circuit that regulates mood and reward-seeking behavior in the general population (Cloninger *et al.,* 2012; Eley *et al.,* 2013).

In primary-care depression patients, current personality was not particularly informative about future prognosis. For Bipolar patients, however, the baseline level of the trait Persistence predicted 7.5% of the variance in the future accumulated major depressive episodes up to 18 months. This was close to predictive value of baseline depressive symptoms (11.0%), and mostly independent information with respect to the baseline depressive symptoms (a similar effect on mania was not observed). Our finding about the importance of low Persistence in Bipolar patients

extends earlier observations that Persistence is often low in Bipolar patients, even when they are in full remission (Osher *et al.,* 1996, 1999).

Our findings need to be evaluated in light of the methodology of the study. The major strengths of the study were prospective design, outcome measures related to temporal durations of illness states, and a comprehensive picture drawn from three heterogeneous samples. The general-population sample was followed for 15 years; comparable follow-up times with the studied variables are rare or non-existent. The clinical screening-based representative cohorts, diagnosed using SCID-I/P interviews with excellent reliability, were also followed for 1.5 or 5 years. In the clinical samples, the life-chart methodology allowed measures related to temporal durations of illness states. In the general-population sample, predictors for deviations from population-average rate of illness-like states were studied using 751 four-sample time series and statistical models (the plural is due to supplementary analyses available on-line).

The most important limitations include sample attrition, some degree of recall bias (likely underestimates of psychopathology in the life charts), and some limitations of statistical power in clinical samples. In the YFS data that had the largest attrition, supplementary on-line imputation analysis was provided, and did not suggest major changes to results. Such imputations are never perfect, however, and some degree of regression-coefficient inflation due to association between depressive symptoms and study attrition (*e.g.*, Rosenström *et al.,* 2012, b) is possible. In contrast, the ceiling of three observed episodes and sensitivity-to-specificity imbalance in episode detection may have attenuated rather than inflated the coefficients, promoting conservative estimates.

Our results suggested that some personality traits (especially low Self-directedness) predispose one for higher future rate of dysphoric episodes compared to base rate in the general population. In line with present findings, a previous categorical analysis with a baseline and one follow-up measurement suggested that low Self-directedness and Cooperativeness index ones vulnerability to future depressive episodes (Farmer and Seeley, 2009). That study also found a similar role for low Reward Dependence as well, which was not strongly implicated here. Present

study is much stronger in assessing vulnerability to future episodes, however, as it included three follow-ups instead of just a single one. Present and previous studies are generally congruent with predictive role of both low Self-directedness (Cloninger et al., 2006; Farmer and Seeley, 2009, Naito et al., 2000) and high Harm avoidance (Cloninger et al., 2006; Farmer and Seeley, 2009) for future depression.

Teasing apart the "precursor" (shared or similar etiology) and "predisposition" (personality predicts depression onset with other variables mediating/moderating) models for the effects of personality on subsequent depression is a difficult task (Klein *et al.,* 2011). The present results support the predisposition model rather than the precursor model, because in the shared-etiology case there should be no qualitative dissociation between personality- and depression-based predictions for future point-estimates of depression *versus* estimates for future accumulation. The predisposing role of personality traits for risk of depression has also been well-documented in a study of never-ill siblings of depressives: never-depressed siblings of depressives are intermediate between cases and controls for Self-directedness and Harm Avoidance, indicating that these traits influence the predisposition to major depression (Farmer *et al.,* 2003). Similar evidence regarding other disorders is summarized elsewhere (Cloninger *et al.,* 2010).

While importance of prevention efforts for depression has been recently emphasized (Ghaemi *et al.,* 2013), expenses of prevention can often be effectively carried out mainly for well-defined at-risk groups rather than for entire populations, or for indicated/sub-threshold cases where "treatment" might be a more adequate term (Clarke *et al.,* 1995; Lewinsohn *et al.,* 1998; Klein *et al.,* 2011). The support that present study gives for "the predisposition" rather than "the precursor" model underlines the fact that personality is not an equivalent of depression, but is potentially useful in defining at-risk groups. Also, personality traits like Self-directedness can be modified by cognitive-behavioral therapy, and hence directly targeted in an intervention (Anderson *et al.,* 2002; Cloninger, 2006). Hence, personality is an attractive candidate for detection of at-risk groups, because it is more stable than depressive episodes but can be altered (Klein *et al.,* 2011).

In addition to single traits, combinations of personality traits (personality profiles) may offer efficient future predictors (Josefsson *et al.,* 2011; Rosenström *et al.,* 2012, a), but their derivation is subject to analytical difficulties commonly known as the "curse of dimensionality" (Hastie *et al.,* 2009; Wasserman, 2006). The ensuing problem is reminiscent of the statistical challenges in molecular genetics, where either a huge number of observations or solid *a priori* functional information is often needed. Nevertheless, progress is being made towards detection of dynamic interactions among multiple variables that influence the development of complex phenotypes like mood disorders and schizophrenic psychoses (Arnedo *et al.,* 2013).

While past findings regarding genetic associations and cross-sectional factor loadings have suggested that some traits in the Psychobiological theory of personality might not represent separate entities, recent longitudinal research has demonstrated that these traits do have different developmental trajectories (Josefsson *et al.,* 2013). Specifically regarding the two traits associated with depression, Harm avoidance and Self-directedness, the former shows no mean-level changes as a function of age while the latter grows by age (Josefsson *et al.,* 2013). In addition, twin studies show that the genetic determinants of each of the TCI dimensions are largely independent (Gillespie et al, 2003). Hence any correlations observed among the dimensions could be associations produced by self-organization during the development as a complex adaptive system (Cramer *et al.,* 2012, b; Cloninger *et al.,* 1997; Rosenström *et al.,* 2012, a; van der Maas *et al.,* 2006). Such findings call into question the adequacy of describing personality in terms of traits identified by linear factor analysis (Cloninger, 2008; Cervone, 2005), but modern personality inventories actually overlap extensively in their information content and predictive validity despite these theoretical differences (Grucza and Goldberg, 2007). Debate is going on regarding the true nature and origins of both individual differences in behavior in general (Cramer *et al.,* 2012, b; Brown *et al.,* 2011; Buss, 2009) and depression specifically (Cramer *et al.,* 2012, a; Hagen, 2011; Rosenström, 2013, a), and we do not imply having used a flawless model of personality; just that these personality variables have been shown to contain information about other constructs of interest in psychiatry and other

fields (*e.g.*, Cloninger *et al.,* 2010; Grucza and Goldberg, 2007; Määttänen *et al.,* 2013; Svrakic *et al.,* 2002), and are of interest due to their predictive value. Hence, our present contribution is not a theoretical one, but provides empirical facts to be explained by future theory, and possible prognostic tools.

In summary, personality traits were found to be strong predictors for future accumulation of dysphoric episodes in a general-population sample, but weak predictors of future accumulation of depressive episodes in primary-care Depression patients. In the general population, low Self-directedness was the strongest predictor of future burden of dysphoric episodes. In the clinical sample of Bipolar-disorder patients, low Persistence was a strong predictor of future depressive-episode burden. Persistence was also predictive independently of the baseline level of depression, providing prognostic value. Overall, measures of personality (TCI main traits) appeared more useful in detecting risk for future burden of depression than in clinical prediction of future DSM-IV depressive-episode burden in diagnosed cases of unipolar or bipolar mood disorder.

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Tables

Table 1. Basic Sample Characteristics and their Comparison

	PC-VDS			YFS			
Variable	**Median**	**Mean**	**s.d.**	**Median**	**Mean**	**Range/s.d.**	***p*-value**
Age at the baseline	46.15	44.27	13.85	29	27.61	20-35	< 0.001
Age at the final follow up	51.15	49.27	13.85	44	42.61	35-50	-
Proportion/number of episode(s)	0.18	0.32	0.34	0	0.32	0.71	-
BDI or BDI-II proxy at baseline	17	19.54	10.51	3.79	5.63	5.30	< 0.001
					JoBS		
Age at the baseline	-	-	-	37.93	38.54	11.72	0.001
Age at the final follow up	-	-	-	39.43	40.04	11.72	-
Proportion of derpressive episode(s)	-	-	-	0.27	0.35	0.32	-
Logit of depressive-episode proportion	-1.32	-1.17	1.89	-0.55	-0.65	1.65	0.056
BDI or BDI-II proxy at baseline	-	-	-	23	22.07	11.78	0.082

Note: "PC-VDS" = Primary Care Vantaa Depression Study; "YFS" = Young Finns (general-population) Study; "JoBS" = Jorvi Bipolar Study. *p*-value is provided for a column-wise t-test when such test made sense; "s.d." = standard deviation, range is given for age at YFS that had six approximately equally large cohorts.

Table 2. Quasi-Poisson Regression Coefficients for Models Predicting Number of Future Dysphoric Episodes with Prior Dysphoria and Personality in General Population

	Model 0	Model I	Model II	Model III
mBDI	**1.51 (0.10)*****	-	**1.52 (0.16)*****	**1.05 (0.20)*****
Dysphoric episode	**1.77 (0.16)*****	-0.02 (0.22)	-	-0.11 (0.23)
Novelty seeking	-0.02 (0.21)	0.23 (0.17)	0.00 (0.18)	0.36 (0.20)
Harm avoidance	**1.42 (0.14)*****	**0.46 (0.16)****	**0.94 (0.15)*****	**0.58 (0.20)****
Reward dependence	-0.20 (0.20)	0.11 (0.16)	-0.06 (0.18)	-0.06 (0.20)
Persistence	0.02 (0.14)	0.09 (0.12)	0.03 (0.13)	**0.28 (0.13)***
Self-directedness	**-2.03 (0.16)*****	**-0.88 (0.22)*****	**-1.55 (0.19)*****	**-0.65 (0.26)****
Cooperativeness	**-1.15 (0.19)*****	-0.18 (0.19)	**-0.61 (0.19)****	0.05 (0.23)
Self-transcendence	**0.38 (0.14)****	0.15 (0.12)	0.27 (0.13)	0.22 (0.13)

Note: Standard errors in parentheses; "*" = "p-value < 0.05"; "**" = "p-value < 0.01"; "***" = "p-value < 0.001"; "mBDI" = modified version Beck's Depression Inventory score; "Dysphoric episode" = a dichotomous variable for an episode at baseline, preceding the episodes that contributed to the outcome variable; "Model 0" = regression coefficients for model with only age and sex as covariates; "Model I" = Model 0 further adjusted for baseline mBDI; "Model II" = Model 0 further adjusted for a dysphoric episode at baseline; "Model III" = Multiple regression with all predictor variables included in the same model, adjusted for age and sex.

Table 3. Regression Models Predicting Accumulated DSM-IV Major Depressive Episodes in Diagnosed Patients with Baseline Personality and Depression

PC-VDS (5 yr follow)	Variable	Model 0	Model I	Model III	ΔR^2	ΔR^2_{MI}
Logit + linear, n=71	BDI	**0.34 (0.12)****	-	**0.32 (0.14)***	0.09	-
	Novelty seeking	-0.11 (0.12)	-0.06 (0.12)	-0.06 (0.14)	0.00	-0.01
	Harm avoidance	0.18 (0.12)	0.11 (0.12)	0.13 (0.17)	0.02	0.00
	Reward dependence	0.05 (0.13)	0.11 (0.12)	0.10 (0.15)	-0.01	0.00
	Persistence	0.00 (0.12)	-0.03 (0.12)	0.02 (0.14)	-0.02	-0.01
	Self-directedness	-0.12 (0.12)	-0.03 (0.11)	-0.01 (0.17)	0.00	-0.01
	Cooperativeness	0.05 (0.12)	0.09 (0.12)	0.07 (0.15)	-0.01	-0.01
	Self-transcendence	0.01 (0.12)	0.02 (0.12)	0.04 (0.13)	-0.02	-0.01
Inflated Beta, n=93	BDI	**0.40 (0.15)****	-	**0.39 (0.16)***	-	-
	Novelty seeking	-0.11 (0.13)	-0.07 (0.13)	-0.07 (0.14)	-	-
	Harm avoidance	0.19 (0.15)	0.12 (0.14)	0.17 (0.20)	-	-
	Reward dependence	0.06 (0.14)	0.14 (0.14)	0.14 (0.17)	-	-
	Persistence	0.01 (0.14)	-0.02 (0.14)	0.03 (0.16)	-	-
	Self-directedness	-0.13 (0.14)	-0.02 (0.14)	0.00 (0.19)	-	-
	Cooperativeness	0.05 (0.14)	0.09 (0.14)	0.05 (0.16)	-	-
	Self-transcendence	0.01 (0.15)	0.04 (0.15)	0.06 (0.16)	-	-
JoBS (1.5 yr follow)						
Logit + linear, n=118	BDI	**0.38 (0.10)*****	-	**0.35 (0.11)****	0.11	-
	Novelty seeking	-0.10 (0.09)	-0.08 (0.09)	-0.13 (0.10)	0.00	0.00
	Harm avoidance	**0.31 (0.09)*****	0.19 (0.10)	-0.03 (0.13)	0.09	0.02
	Reward dependence	-0.11 (0.09)	-0.05 (0.09)	0.03 (0.11)	0.00	-0.01
	Persistence	**-0.28 (0.09)****	**-0.27 (0.09)****	**-0.26 (0.09)****	0.08	0.07
	Self-directedness	**-0.21 (0.09)***	-0.12 (0.09)	-0.10 (0.11)	0.04	0.01
	Cooperativeness	-0.11 (0.09)	-0.10 (0.09)	-0.10 (0.12)	0.00	0.00
	Self-transcendence	-0.01 (0.09)	-0.01 (0.09)	0.03 (0.09)	-0.01	-0.01
Inflated Beta, n=151	BDI	**0.40 (0.11)*****	-	**0.39 (0.12)****	-	-
	Novelty seeking	-0.11 (0.10)	-0.10 (0.10)	-0.14 (0.11)	-	-
	Harm avoidance	**0.31 (0.10)****	0.19 (0.11)	-0.04 (0.14)	-	-
	Reward dependence	-0.11 (0.10)	-0.05 (0.10)	0.02 (0.12)	-	-
	Persistence	**-0.31 (0.10)****	**-0.30 (0.10)****	**-0.29 (0.10)****	-	-
	Self-directedness	**-0.25 (0.11)***	-0.15 (0.11)	-0.12 (0.14)	-	-
	Cooperativeness	-0.11 (0.10)	-0.10 (0.10)	-0.12 (0.13)	-	-
	Self-transcendence	-0.01 (0.10)	-0.02 (0.10)	0.04 (0.11)	-	-

Note: Standard errors in parentheses, hyphens indicate impossible computations; "*" = "*p*-value < 0.05"; "**" = "*p*-value < 0.01"; "***" = "*p*-value < 0.001"; "n" = available sample size; "BDI" = Beck's Depression Inventory score; "Logit + linear" = ordinary regression applied after logistic transformation to non-infinite transformed values; "Inflated Beta" = Inflated Beta Regression applied to all observed proportions/participants; "PC-VDS" = Vantaa Primary Care Depression Study; "JoBS" = Jorvi Bipolar Study; "Model 0" = regression coefficients for model with only age and sex as covariates; "Model I" = Model 0 further adjusted for baseline BDI; "Model III" = Multiple regression with all predictor variables included in the same model, adjusted for age and sex; "ΔR^{2}" = change in adjusted R^2 due to adding the individual-effect predictor to regression with age and sex; "ΔR^2_{MI}" = the contribution of the predictor to Model I.

Figure caption

Figure 1. Outcome Variables. (A) *Dysphoric episodes in Young Finns Study's (YFS) general population were defined by Beck's Depression Inventory II (BDI-II) score higher than 13 (a national cut-off). BDI-II existed from single year, but was well-predicted (solid line) by quadratic model on more frequently observed modified BDI (mBDI; x-axis is for standardized z-score). Points/circles represent observed values, with jitter (uniformly distributed random values on interval [-1/40, 1/40]) added to both axes so that overlapping points can be discerned.* (B) *Distribution of the number of dysphoric episodes ('caseness' score) across the three non-baseline follow-ups.* (C) *Histogram for the proportions of time that the clinical participants in Primary Care Vantaa Depression Study (PC-VDS) satisfied DMS-IV criteria for major depressive episode. Circles represent numbers of participants without episode accumulation (zero proportion) or with a single full five-year long episode (proportion is one).* (D) *Similar histogram as in panel C, but for the participants of Jorvi Bipolar Study (JoBS).*

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Conflict of interest

No conflict of interest exists for any of the involved authors or data projects.

Contributors

Author TR designed and conducted first data analyses with the aid of PJ, wrote first draft of the manuscript, and modified analyses based on input especially by EI, PJ, LK, but also by others. Authors PJ, OM, KR, MV, and EI have contributed to design and data collection of VDS, PC-VDS, and JoBS studies, whereas MH, LP, ME, and LK have contributed to design and data collection of Young Finns study. All authors contributed to and have approved the final manuscript.

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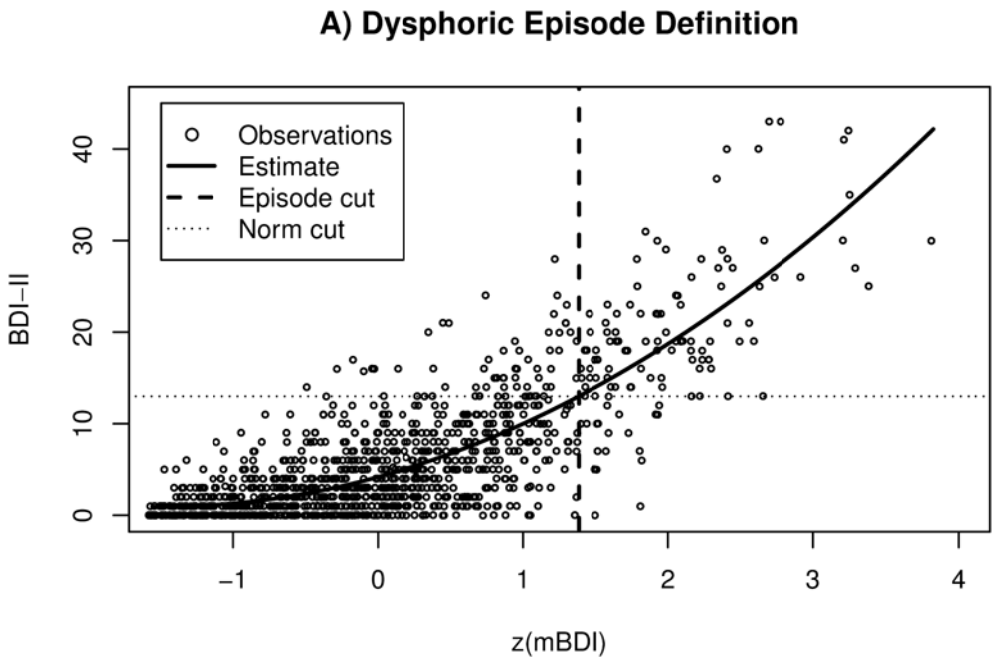
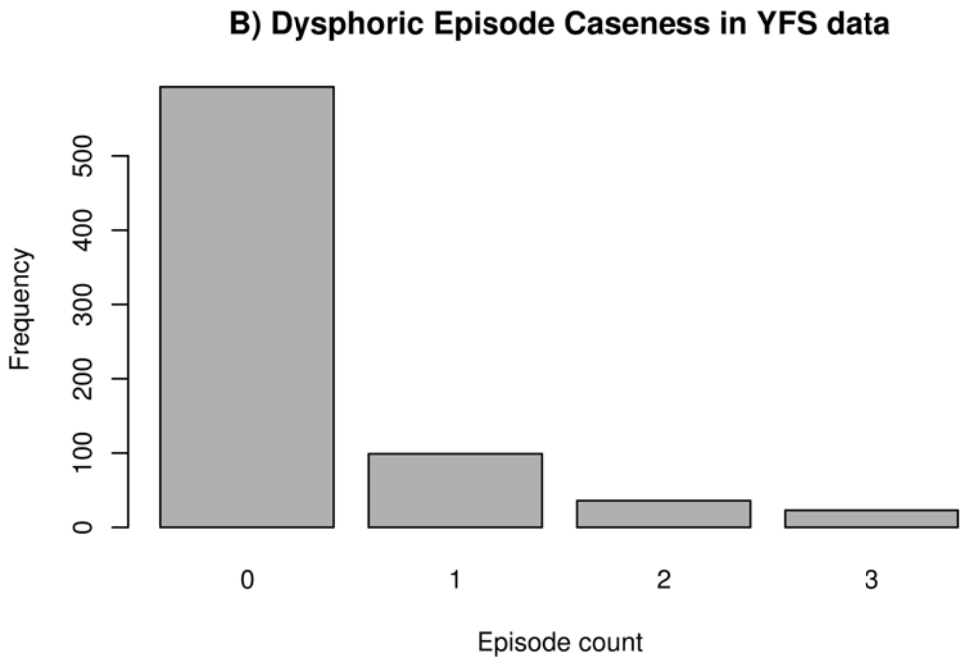
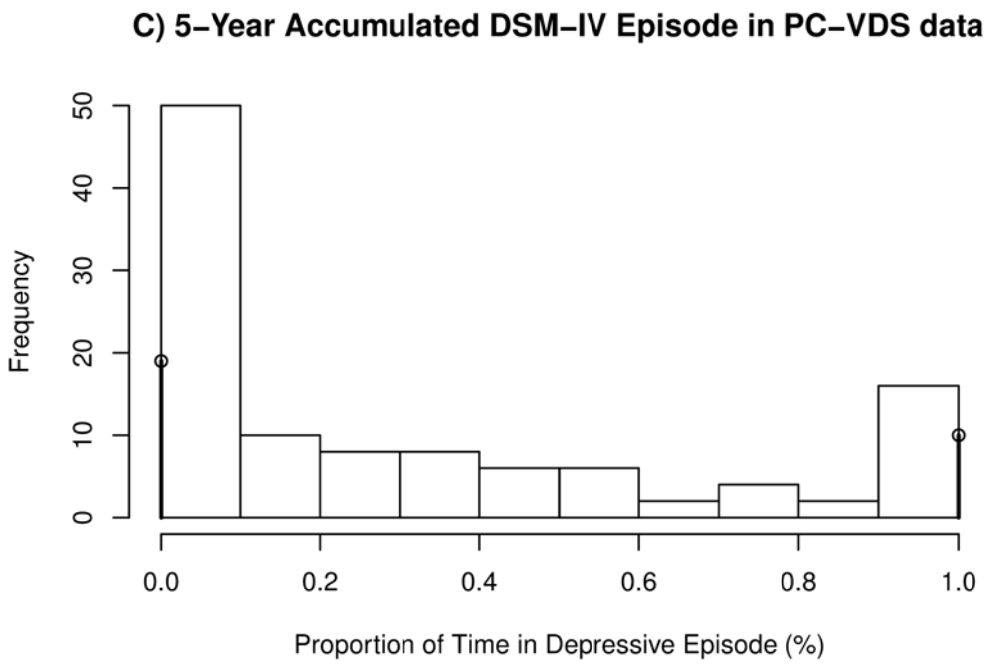
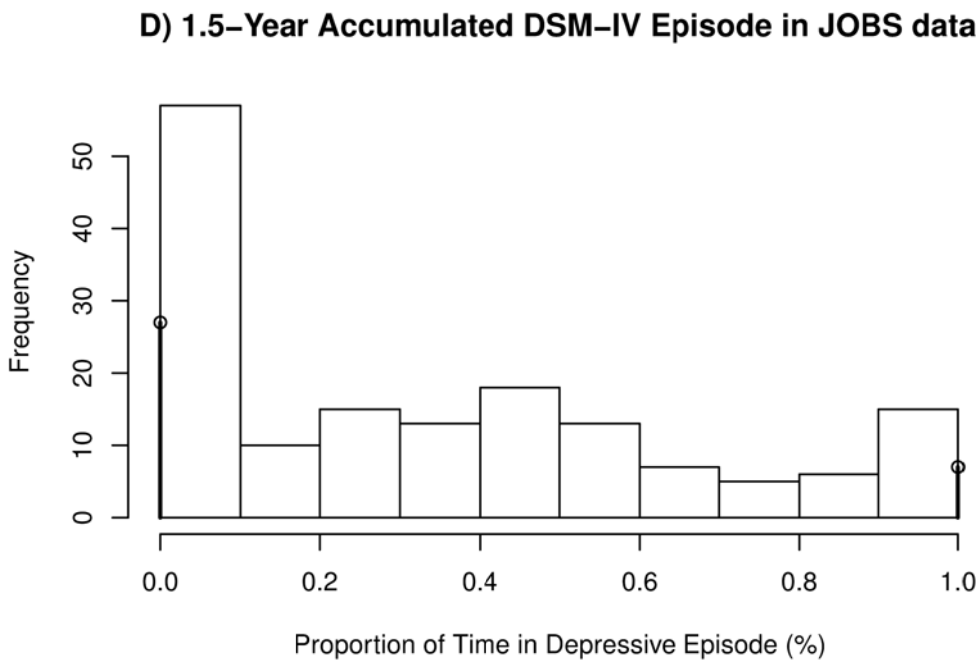

A) Dysphoric Episode Definition
Observations
Estimate
Episode cut
Norm cut
BDI−II
z(mBDI)


B) Dysphoric Episode Caseness in YFS data
Frequency
Episode count


C) 5−Year Accumulated DSM−IV Episode in PC−VDS data
Frequency
Proportion of Time in Depressive Episode (%)


D) 1.5−Year Accumulated DSM−IV Episode in JOBS data
Frequency
Proportion of Time in Depressive Episode (%)