**Supplemental Table 1. Baseline characteristics**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **All data (n=653)** | | |  | **Males (n=427)** | | **Females (n=226)** | |  |  |  |
|  | **mean** | **SE** | **missings (%)** |  | **mean** | **SE** | **mean** | **SE** | **Statisticb** | ***P*** |  |
| **(I) Recent depressive episodea** |  |  |  |  |  |  |  |  |  |  |  |
| Depressed mood | 0.98 | 0.01 | 0.0 |  | 0.97 | 0.01 | 0.99 | 0.01 | 2.61 | 0.106 |  |
| Loss of interest | 0.89 | 0.01 | 0.0 |  | 0.89 | 0.02 | 0.90 | 0.02 | 0.14 | 0.709 |  |
| Appetite loss | 0.50 | 0.02 | 0.0 |  | 0.48 | 0.02 | 0.55 | 0.03 | 2.70 | 0.101 |  |
| ***Appetite gain*** | 0.24 | 0.02 | 0.0 |  | ***0.21*** | ***0.02*** | ***0.29*** | ***0.03*** | ***4.93*** | ***0.026*** | \* |
| Weight loss | 0.27 | 0.02 | 0.0 |  | 0.28 | 0.02 | 0.27 | 0.03 | 0.07 | 0.789 |  |
| Weight gain | 0.20 | 0.02 | 0.0 |  | 0.19 | 0.02 | 0.23 | 0.03 | 1.29 | 0.257 |  |
| Feeling restless | 0.64 | 0.02 | 0.0 |  | 0.66 | 0.02 | 0.60 | 0.03 | 2.10 | 0.147 |  |
| Slowed down | 0.37 | 0.02 | 0.0 |  | 0.39 | 0.02 | 0.35 | 0.03 | 0.71 | 0.400 |  |
| ***Fatigue*** | 0.77 | 0.02 | 0.0 |  | ***0.74*** | ***0.02*** | ***0.83*** | ***0.03*** | ***5.30*** | ***0.021*** | \* |
| Insomnia | 0.65 | 0.02 | 0.0 |  | 0.66 | 0.02 | 0.63 | 0.03 | 0.38 | 0.536 |  |
| Hypersomnia | 0.28 | 0.02 | 0.0 |  | 0.26 | 0.02 | 0.31 | 0.03 | 1.43 | 0.232 |  |
| Concentration difficulties | 0.61 | 0.02 | 0.0 |  | 0.62 | 0.02 | 0.58 | 0.03 | 1.22 | 0.270 |  |
| ***Feeling irritable/angry*** | 0.65 | 0.02 | 0.0 |  | ***0.68*** | ***0.02*** | ***0.58*** | ***0.03*** | ***5.15*** | ***0.023*** | \* |
| Hopelessness | 0.69 | 0.02 | 0.0 |  | 0.70 | 0.02 | 0.67 | 0.03 | 0.26 | 0.607 |  |
| Suicidal ideation | 0.28 | 0.02 | 0.0 |  | 0.30 | 0.02 | 0.25 | 0.03 | 1.57 | 0.211 |  |
| Worthlessness/guilt | 0.59 | 0.02 | 0.0 |  | 0.60 | 0.02 | 0.57 | 0.03 | 0.54 | 0.462 |  |
| Feeling anxious, nervous, worried | 0.75 | 0.02 | 0.0 |  | 0.75 | 0.02 | 0.74 | 0.03 | 0.04 | 0.843 |  |
| Feeling tense | 0.48 | 0.02 | 0.0 |  | 0.47 | 0.02 | 0.50 | 0.03 | 0.34 | 0.562 |  |
| Fear attacks | 0.23 | 0.02 | 0.5 |  | 0.23 | 0.02 | 0.24 | 0.03 | 0.01 | 0.910 |  |
| Cardio-respiratory panic symptoms | 0.15 | 0.01 | 0.5 |  | 0.15 | 0.02 | 0.15 | 0.02 | 0.00 | 1.000 |  |
| Sum of 9 MD criteria | 6.43 | 0.05 | 0.0 |  | 6.42 | 0.06 | 6.45 | 0.08 | -0.31 | 0.754 |  |
| Number of episodes last yearc | 2.08 | 0.08 | 0.2 |  | 2.01 | 0.09 | 2.20 | 0.14 | -1.15 | 0.251 |  |
| Severe work impairment | 0.19 | 0.02 | 0.6 |  | 0.19 | 0.02 | 0.19 | 0.03 | 0.00 | 1.000 |  |
| Severe leisure impairment | 0.36 | 0.02 | 1.1 |  | 0.35 | 0.02 | 0.38 | 0.03 | 0.28 | 0.599 |  |
| Severe social impairment | 0.24 | 0.02 | 0.2 |  | 0.23 | 0.02 | 0.27 | 0.03 | 0.71 | 0.401 |  |
| **(II) Current state** |  |  |  |  |  |  |  |  |  |  |  |
| SCL past 30 daysd | 1.24 | 0.07 | 0.5 |  | 1.29 | 0.09 | 1.14 | 0.12 | 1.05 | 0.294 |  |
| Current age | 35.26 | 0.34 | 0.0 |  | 34.91 | 0.41 | 35.92 | 0.61 | -1.38 | 0.168 |  |
| **(III) Psychiatric history (lifetime)e** |  |  |  |  |  |  |  |  |  |  |  |
| ***Early anxiety*** | 0.39 | 0.02 | 0.0 |  | ***0.34*** | ***0.02*** | ***0.49*** | ***0.03*** | ***12.83*** | ***0.000*** | \*\* |
| History of GAD | 0.18 | 0.02 | 0.0 |  | 0.17 | 0.02 | 0.21 | 0.03 | 1.11 | 0.291 |  |
| Age of MD-onset | 24.80 | 0.43 | 0.0 |  | 25.39 | 0.52 | 23.68 | 0.78 | 1.83 | 0.068 |  |
| Number of MD episodes lifetime | 7.09 | 1.01 | 0.9 |  | 6.50 | 1.36 | 8.20 | 1.41 | -0.87 | 0.385 |  |
| ***History of alcohol dependence*** | 0.43 | 0.02 | 0.0 |  | ***0.51*** | ***0.02*** | ***0.30*** | ***0.03*** | ***25.54*** | ***0.000*** | \*\* |
| **(IV) Family history** |  |  |  |  |  |  |  |  |  |  |  |
| MD father | 0.22 | 0.02 | 7.7 |  | 0.21 | 0.02 | 0.24 | 0.03 | 0.59 | 0.442 |  |
| ***MD mother*** | 0.36 | 0.02 | 3.5 |  | ***0.33*** | ***0.02*** | ***0.42*** | ***0.03*** | ***4.01*** | ***0.045*** | \* |
| GAD father | 0.21 | 0.02 | 11.0 |  | 0.19 | 0.02 | 0.25 | 0.03 | 2.50 | 0.114 |  |
| GAD mother | 0.32 | 0.02 | 5.1 |  | 0.30 | 0.02 | 0.34 | 0.03 | 1.14 | 0.285 |  |
| MD cotwin | 0.40 | 0.02 | 11.9 |  | 0.43 | 0.03 | 0.35 | 0.03 | 3.20 | 0.074 |  |
| GAD cotwin | 0.27 | 0.02 | 21.1 |  | 0.29 | 0.02 | 0.23 | 0.03 | 1.78 | 0.182 |  |
| **(V) Personality** |  |  |  |  |  |  |  |  |  |  |  |
| Neuroticism | 6.25 | 0.14 | 0.5 |  | 6.07 | 0.17 | 6.57 | 0.23 | -1.72 | 0.087 |  |
| Extraversion | 5.34 | 0.10 | 0.5 |  | 5.21 | 0.13 | 5.58 | 0.17 | -1.75 | 0.081 |  |
| **(VI) Early adverse life events** |  |  |  |  |  |  |  |  |  |  |  |
| ***Parental warmth*** | 14.17 | 0.16 | 2.3 |  | ***14.45*** | ***0.19*** | ***13.61*** | ***0.28*** | ***2.49*** | ***0.013*** | \* |
| Parental loss childhood/adolescence | 0.27 | 0.02 | 0.0 |  | 0.28 | 0.02 | 0.27 | 0.03 | 0.07 | 0.789 |  |
| ***Childhood sexual abuse*** | 0.15 | 0.01 | 1.2 |  | ***0.09*** | ***0.01*** | ***0.25*** | ***0.03*** | ***27.48*** | ***0.000*** | \*\* |
| ***Number of lifetime traumas*** | 1.87 | 0.06 | 0.3 |  | ***2.15*** | ***0.07*** | ***1.33*** | ***0.10*** | ***6.65*** | ***0.000*** | \*\* |
| **(VII) Recent adverse life events** |  |  |  |  |  |  |  |  |  |  |  |
| Divorced | 0.33 | 0.02 | 0.0 |  | 0.32 | 0.02 | 0.35 | 0.03 | 0.79 | 0.373 |  |
| Number of stressful life events in past year | 3.57 | 0.10 | 0.0 |  | 3.54 | 0.12 | 3.64 | 0.16 | -0.49 | 0.627 |  |
| **(VIII) Social and economic environment** |  |  |  |  |  |  |  |  |  |  |  |
| Married | 0.44 | 0.02 | 0.0 |  | 0.41 | 0.02 | 0.49 | 0.03 | 2.84 | 0.092 |  |
| ***Never married*** | 0.29 | 0.02 | 0.0 |  | ***0.33*** | ***0.02*** | ***0.20*** | ***0.03*** | ***12.64*** | ***0.000*** | \*\* |
| Low marital satisfaction | 0.26 | 0.02 | 0.0 |  | 0.25 | 0.02 | 0.28 | 0.03 | 0.65 | 0.419 |  |
| ***Number of confidants*** | 2.00 | 0.06 | 0.2 |  | ***1.88*** | ***0.07*** | ***2.22*** | ***0.09*** | ***-3.01*** | ***0.003*** | \* |
| Support from friends | 3.06 | 0.09 | 0.0 |  | 2.97 | 0.11 | 3.24 | 0.14 | -1.52 | 0.130 |  |
| ***Problems with friends*** | 2.13 | 0.07 | 0.0 |  | ***2.26*** | ***0.08*** | ***1.88*** | ***0.11*** | ***2.72*** | ***0.007*** | \* |
| ***Support from relatives*** | 2.96 | 0.07 | 0.0 |  | ***2.82*** | ***0.08*** | ***3.20*** | ***0.11*** | ***-2.78*** | ***0.006*** | \* |
| ***Problems with relatives*** | 2.90 | 0.07 | 0.0 |  | ***2.76*** | ***0.09*** | ***3.18*** | ***0.12*** | ***-2.88*** | ***0.004*** | \* |
| General socialization | 1.31 | 0.06 | 0.0 |  | 1.26 | 0.08 | 1.39 | 0.11 | -0.92 | 0.356 |  |
| Financial problems | 0.24 | 0.02 | 0.0 |  | 0.25 | 0.02 | 0.23 | 0.03 | 0.13 | 0.724 |  |
| Years of education | 13.06 | 0.10 | 0.0 |  | 12.97 | 0.13 | 13.21 | 0.16 | -1.16 | 0.246 |  |

GAD, generalized anxiety disorder; HR, hazard ratio; MD, major depression; SCL, Symptom Checklist; SE, standard error

Bold and italicized rows indicate predictors with significant differences for men and women (p<0.05).

a Characteristics of episode in the year prior to baseline interview (MF1).

b Tests used to asses mean differences between men and women: chi-squared statistic for binary and nominal variables, Cochran-Mental-Haenszal statistic for ordinal variables, t-test for continuous variables.

c Number of MD episodes lasting ≥5 days in the last year (note that only for this predictor variable we used a shorter duration criterion than the 14 days indicated by the DSM-III-R)

d First principal component of depression and anxiety scales of the Symptom Checklist past 30 days.

e Lifetime: prior to last year (≥ 1 year ago).

\* *p*<0.05; \*\* *p*<0.001 (*p*-value after Bonferroni correction)**Supplemental Table 2. Comparison of predictors of MD-recurrence in penalized multivariate Cox models for male-female (MF) twin pairs and female-female twin pairs (FF) in a previous study (van Loo et al. 2015).**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **MF All (n=653)** | **MF Males (n=277)** | **MF Females (n=226)** | **FF Females (n=194)** |
|  | **HRa** | **HRa** | **HRa** | **HR°** |
| **(I) Recent depressive episodeb** |  |  |  |  |
| Loss of interest | 1.11 | 1.12 |  | 1.10 |
| Appetite gain | 1.01 | 1.02 | 1.02 |  |
| Weight loss | 1.02 |  |  | 1.05 |
| Feeling restless | 1.02 | 1.07 |  |  |
| Slowed down |  | 1.04 | 0.98 |  |
| Fatigue | 1.04 |  |  |  |
| Hypersomnia | 1.04 |  | 1.04 |  |
| Feeling irritable/angry | 1.06 | 1.19 |  |  |
| Suicidal ideation |  |  | 1.01 |  |
| Feeling tense | 1.04 |  |  | 1.06 |
| Cardio-respiratory panic symptoms\* | 1.11 | 1.17 | 1.06 |  |
| Severe work impairment |  |  | 1.07 |  |
| Sum of 9 MD criteria | 1.05 | 1.07 |  | 1.02 |
| ≥6 MD episodes last yearc |  | 1.02 |  |  |
| **(II) Current state** |  |  |  |  |
| SCL past 30 daysd | 1.06 | 1.04 | 1.02 | 1.03 |
| **(III) Psychiatric history (lifetime)e** |  |  |  |  |
| Early anxiety | 1.15 | 1.16 | 1.03 | 1.06 |
| History of GAD | 1.76 | 1.62 | 1.67 |  |
| 2-3 MD episodes lifetime | 1.02 |  |  |  |
| ≥6 MD episodes lifetime | 1.14 | 1.42 | 1.04 | 1.05 |
| History of alcohol dependence | 1.03 |  | 1.05 |  |
| **(IV) Family history** |  |  |  |  |
| MD father |  | 1.03 |  |  |
| MD mother | 1.09 | 1.04 | 1.14 |  |
| GAD father |  | 1.13 |  |  |
| GAD mother |  | 1.02 |  |  |
| **(V) Personality** |  |  |  |  |
| Neuroticism |  | 1.01 |  |  |
| Extraversion |  |  | 1.02 | 1.02 |
| **(VI) Early adverse life events** |  |  |  |  |
| Parental warmth |  |  | 0.99 |  |
| Parental loss childhood/adolescence |  |  | 1.01 | 1.03 |
| Childhood sexual abuse\* | 1.19 | 1.17 | 1.16 | 1.04 |
| Traumas 1-2 |  | 1.01 |  |  |
| Traumas ≥5\* | 1.13 |  | 1.19 | 1.06j |
| **(VII) Recent adverse life events** |  |  |  |  |
| Divorced |  |  | 1.10 |  |
| Number of stressful life events in past year | 1.01 |  | 1.03 | 1.03 |
| **(VIII) Social and economic environment** |  |  |  |  |
| Never married |  |  | 0.93 | 1.03 |
| No partner | 1.03 | 1.03 |  | 1.04 |
| Low marital satisfaction\* | 1.13 | 1.07 | 1.08 |  |
| Number of confidants |  |  | 0.96 |  |
| Problems with friends |  |  | 1.02 |  |
| Support from relatives | 0.99 |  | 0.96 |  |
| Problems with relatives | 1.03 |  |  | 1.02 |
| Financial problems\* |  |  | 1.05 | 1.15 |
|  |  |  |  |  |
| **Prediction performance** |  |  |  |  |
| AUC training data | 0.746 | 0.785 | 0.783 | 0.79 |
| AUC test data same sex |  | 0.710f |  | 0.61i |
| AUC test data opposite sex |  | 0.692g | 0.680h |  |

AUC, Area under the Receiver Operating Characteristic curve; GAD, generalized anxiety disorder; HR, hazard ratio; MD, major depression; SCL, Symptom Checklist

Shaded rows indicate predictors that were selected ≥90 out of 100 times as main effects in 100 Lasso regressions on 80% bootstrapped samples of the male-female twins dataset (n=653) including all risk factors and sex-dependent interactions.

° Selected predictors for recurrence of depression in 194 female twins in our previous study based on elastic net Cox regression using 81 predictors (see van Loo et al. 2015). Extra predictors included in this model were appetite loss, weight gain (HR 0.99), insomnia (HR 1.07), concentration difficulties (HR 1.07), feeling anxious (1.03), duration of MD episode (HR 0.98 for 1-3 months and HR 1.03 for ≥3 months), GAD in cotwin (HR 1.06), disturbed family environment (HR 1.02).

\* These predictors have been differently assessed in the former study (van Loo et al. 2015), e.g. with a different type of questionnaire. The former study in the female-female twin pairs included extra predictors that were missing in the current study: duration of most severe MD episode in the past year, duration of most severe MD episode lifetime, family environment, bulimia.

a Penalized hazard ratios of all predictors for recurrence of MD with effect sizes ≤0.99 or ≥1.01 based on elastic net Cox regression for alpha=0.1 including all 70 (dummy) variables. Sex was included as a predictor in the model for all participants (n=653) but not selected in the prediction model. Depressed mood was excluded as a predictor for the females due to too little variation (99% of the females reported depressed mood).

b Characteristics of episode in the year prior to baseline interview (MF1).

c Number of MD episodes lasting ≥5 days in the last year (note that only for this predictor variable we used a shorter duration criterion than the 14 days indicated by the DSM-III-R).

d First principal component of depression and anxiety scales of the Symptom Checklist past 30 days.

e Lifetime: prior to last year (≥ 1 year ago).

f AUC of the male-model in independent, same sex, test data (n=150 male twins)

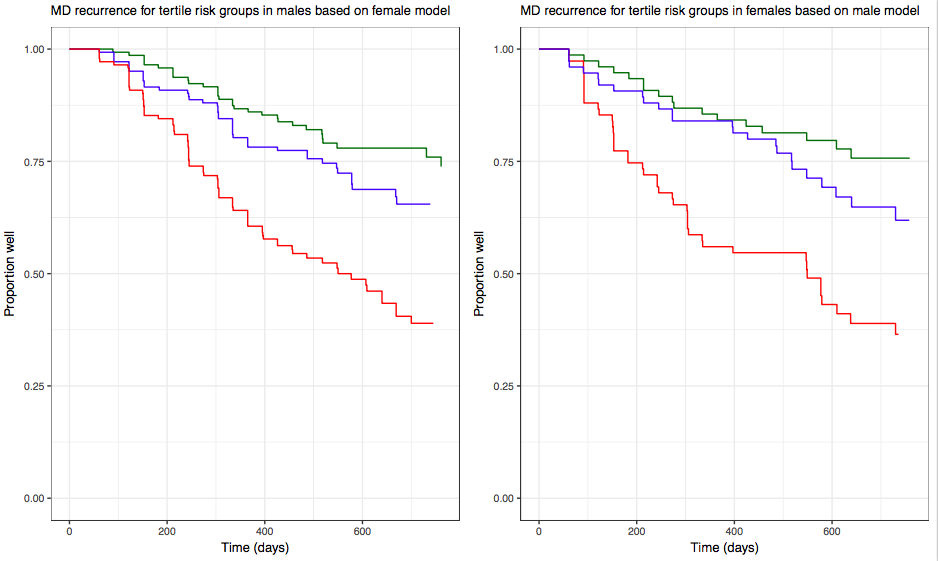
g AUC of the male-model in independent, opposite sex, test data (n=226 female twins)

h AUC of the female-model in independent, opposite sex, test data (n=427 male twins)

i AUC of the female-model in FF1 in independent, same sex, test data (n=133 female twins) with test data having overall lower severity and missing information for some predictors (see van Loo et al. 2015).

j 3-4 traumas lifetime

**Supplemental Figure 1. Recurrence of MD for different risk groups based on opposite sex prediction models**

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Kaplan Meier estimated proportion of male participants without recurrence in different tertile risk groups based on opposite-sex prediction models in males (n=427, left figure) and females (n=226, right figure). Green solid line: subjects predicted in the lowest one third risk; blue solid line: subjects predicted in the intermediate one third risk group, red solid line: subjects predicted in the highest one third risk group.