## Additional Table 3. Prediction models for recurrence of MD across different levels of elastic net/Lasso regularization (alpha)

	Hazard	ratios <sup>b</sup> fo	or all sub	jects (n=	=653)			Hazard	ratios fo	r males	(n=277) <sup>f</sup>				Hazard	ratios fo	or femal	es (n=226	)		
	α=0.05	5 α=0.1	α=0.2	α=0.3	α=0.4	α=0.6	α=1	α=0.0	5 α=0.1	α=0.2	α=0.3	α=0.4	α=0.6	α=1	α=0.0	5 α=0.1	α=0.2	α=0.3	α=0.4	α=0.6	α=1
(I) Recent depressive episode <sup>a</sup>								(I) Recer	nt depressi	ive episo	<u>de</u>				(I) Recei	nt depress	ive episo	<u>de</u>			
Depressed mood	0.98								1						х						
Loss of interest	1.13	1.11	1.08	1.06	1.06	1.04	1.04	1.15	1.12	1.07	1.04	1.01			1.04						
Appetite loss		ļ.						1.03													
Appetite gain	1.04	1.01						1.05	1.02						1.05	1.02					
Weight loss	1.04	1.02						1.02	1	}											
Weight gain	1.01								1												
Feeling restless	1.04	1.02						1.09	1.07	1.04	1.02										
Slowed down		1	ġ.					1.06	1.04	1.01					0.95	0.98					
Fatigue	1.07	1.04						1.04							1.04						
Insomnia		Į						1.03							0.98						
Hypersomnia	1.07	1.04	1.01						1						1.06	1.04					
Concentration difficulties		ţ.							1												
Feeling irritable/angry	1.08	1.06	1.04	1.03	1.03	1.02	1.01	1.18	1.19	1.18	1.18	1.16	1.14	1.11							
Hopelessness		ş							1	1											
Suicidal ideation		ţ.						1.01		1					1.04						
Worthlessness/guilt		ļ							1												
Feeling anxious, nervous, worried		1						1.02	1												
Feeling tense	1.05	1.04	1.03	1.01	1.01				1	}					1.02						
Fear attacks									1												
Cardio-respiratory panic symptoms	1.13	1.11	1.07	1.05	1.03			1.17	1.17	1.15	1.14	1.12	1.09	1.05	1.08	1.06	1.02				
Sum of 9 MD criteria	1.05	1.05	1.06	1.07	1.07	1.07	1.07	1.06	1.07	1.08	1.08	1.08	1.08	1.08							
2-3 episodes last year									1												
4-5 MD episodes last year									1												
≥6 MD episodes last year		ŧ.	1					1.06	1.02												
Moderate work impairment	0.99	Į																			
Severe work impairment	1.03	1.01							1						1.09	1.07	1.04	1.01			
Moderate leisure impairment		1							1												
Severe leisure impairment		8							1												
Moderate social impairment		§							1												
Severe social impairment	1.02	ţ.							1	ļ											
(II) Current state		ţ						(II) Curre	ent state	1					(II) Curr	ent state					
SCL past 30 days <sup>c</sup>	1.05	1.06	1.06	1.07	1.07	1.08	1.08	1.04	1.04	1.04	1.04	1.05	1.05	1.05	1.02	1.02	1.02	1.02	1.01		
Current age									1												
(III) Psychiatric history (lifetime) <sup>d</sup>		Ş						(III) Psvo	hiatric his	tory (life	time)				(III) Psvo	hiatric his	story (life	time)			
Early anxiety	1.15	1.15	1.14	1.14	1.14	1.13	1.13	1.15	1.16	1.15	1.15	1.14	1.12	1.10	1.06	1.03	1				
History of GAD	1.67	1.76	1.87	1.94	2.01	2.05	2.12	1.54	1.62	1.73	1.81	1.85	1.91	1.98	1.56	1.67	1.84	1.92	2.00	2.13	2.25
Age of onset < 16 years									1								1				
Age of onset 16-20		ļ							1												
Age of onset >31		ţ.							1												
1 MD episode lifetime									1												
2-3 MD enisodes lifetime	1 04	1 02							1						1.03						
4-5 MD episodes lifetime	1.02	1.01						1 04	1						0.99						
>6 MD episodes lifetime	1.15	1.14	1.13	1.13	1.13	1.13	1.13	1.38	1.42	1.48	1.54	1.56	1.60	1.62	1.08	1.04	1				
History of alcohol dependence	1.13	1.03	1.02	1.15	1.15	1.15	1.15	1.50	1.72	1.40	1.54	1.50	1.00	1.02	1.00	1.05	1.03				
(IV) Family history	1.0 7	1.05	1.02					(IV) Fam	ilv history						(IV) Fam	nily history	,				
MD father	1 02							1 05	1.03	<u> </u>							ý				
MD mother	1.02	1 09	1.08	1.08	1 09	1.08	1.08	1.05	1.04	1.03	1.02				1 15	1 14	1 14	1 11	1 10	1 07	1 04
GAD father	1.05	1.05	1.00	1.00	1.05	1.00	1.00	1.13	1.13	1.11	1.10	1.08	1.05	1.01	0.98		1	1.11	1.10	1.07	1.04
GAD mother	1 02	Į						1.04	1.02		1.10	1.00	1.05	1.01	0.50		1				
	1.02	5	\$					1.04	1.02	3						3	8				

MD cotwin																1					
GAD cotwin																					
<u>(V) Personality</u>								(V) Perso	<u>nality</u>						(V) Perso	onality	1				
Neuroticism	1.01							1.01	1.01	1.01					1.01						
Extraversion															1.02	1.02					
(VI) Early adverse life events			1					(VI) Early	adverse li	fe events					(VI) Early	/ adverse	life event	<u>s</u>			
Parental warmth															0.99	0.99	0.99	0.99	0.99	0.99	0.99
Parental loss childhood/adolescence															1.03	1.01					
Childhood sexual abuse	1.19	1.19	1.20	1.20	1.21	1.21	1.22	1.19	1.17	1.13 1	12	1.08	1.04		1.16	1.16	1.17	1.16	1.15	1.15	1.14
Traumas 1-2								1.04	1.01							1	1				
Traumas 3-4																					
Traumas ≥5	1.14	1.13	1.11	1.10	1.10	1.09	1.09								1.21	1.19	1.14	1.10	1.07	1.02	
(VII) Recent adverse life events								(VII) Rece	nt advers	e life event	<u>s</u>				(VII) Reco	ent adver	se life eve	ents			
Divorced									3						1.10	1.10	1.08	1.05	1.03		
Number of stressful life events in past year	1.01	1.01													1.03	1.03	1.03	1.03	1.03	1.03	1.03
(VIII) Social and economic environment								(VIII) Soci	al and ecc	nomic env	ironmer	<u>nt</u>			(VIII) Soc	ial and ec	onomic e	nvironme	ent (		
Separated diverced widewed (ref: married)			3						3						1 02		*				
Separateu, ulvorteu, wluoweu (rei. marneu)		5	3					8	3						1.02		8				
Never married (ref: married)	0.97							0.97							1.02 0.91	0.93	0.97				
Never married (ref: married) No partner (ref: normal marital satisfaction)	0.97 1.06	1.03						0.97 1.06	1.03						1.02 0.91	0.93	0.97				
Never married (ref: married) No partner (ref: normal marital satisfaction) Low marital satisfaction (ref: normal marital satisf.)	0.97 1.06 1.14	1.03 1.13	1.11	1.10	1.11	1.10	1.11	0.97 1.06 1.09	1.03 1.07	1.04 1	02				1.02 0.91 1.09	0.93 1.08	0.97 1.06	1.01			
Never married (ref: married) No partner (ref: normal marital satisfaction) Low marital satisfaction (ref: normal marital satisf.) Number of confidants	0.97 1.06 1.14 0.99	1.03 1.13	1.11	1.10	1.11	1.10	1.11	0.97 1.06 1.09	1.03 1.07	1.04 1	02				1.02 0.91 1.09 0.96	0.93 1.08 0.96	0.97 1.06 0.97	1.01 0.99	0.99		
Never married (ref: married) No partner (ref: normal marital satisfaction) Low marital satisfaction (ref: normal marital satisf.) Number of confidants Support from friends	0.97 1.06 1.14 0.99	1.03 1.13	1.11	1.10	1.11	1.10	1.11	0.97 1.06 1.09	1.03 1.07	1.04 1	02				1.02 0.91 1.09 0.96	0.93 1.08 0.96	0.97 1.06 0.97	1.01 0.99	0.99		
Never married (ref: married) No partner (ref: normal marital satisfaction) Low marital satisfaction (ref: normal marital satisf.) Number of confidants Support from friends Problems with friends	0.97 1.06 1.14 0.99	1.03 1.13	1.11	1.10	1.11	1.10	1.11	0.97 1.06 1.09	1.03 1.07	1.04 1	02				1.02 0.91 1.09 0.96 1.03	0.93 1.08 0.96 1.02	0.97 1.06 0.97 1.02	1.01 0.99 1.01	0.99		
Never married (ref: married) No partner (ref: normal marital satisfaction) Low marital satisfaction (ref: normal marital satisf.) Number of confidants Support from friends Problems with friends Support from relatives	0.97 1.06 1.14 0.99 0.98	1.03 1.13 0.99	1.11 0.99	1.10	1.11	1.10	1.11	0.97 1.06 1.09	1.03 1.07	1.04 1	02				1.02 0.91 1.09 0.96 1.03 0.96	0.93 1.08 0.96 1.02 0.96	0.97 1.06 0.97 1.02 0.96	1.01 0.99 1.01 0.96	0.99 0.96	0.96	0.97
Never married (ref: married) No partner (ref: normal marital satisfaction) Low marital satisfaction (ref: normal marital satisf.) Number of confidants Support from friends Problems with friends Support from relatives Problems with relatives	0.97 1.06 1.14 0.99 0.98 1.03	1.03 1.13 0.99 1.03	1.11 0.99 1.03	1.10	1.11	1.10	1.11	0.97 1.06 1.09	1.03 1.07	1.04 1	02				1.02 0.91 1.09 0.96 1.03 0.96 1.01	0.93 1.08 0.96 1.02 0.96 1.01	0.97 1.06 0.97 1.02 0.96 1.00	1.01 0.99 1.01 0.96	0.99 0.96	0.96	0.97
Never married (ref: married) No partner (ref: normal marital satisfaction) Low marital satisfaction (ref: normal marital satisf.) Number of confidants Support from friends Problems with friends Support from relatives Problems with relatives General socialization	0.97 1.06 1.14 0.99 0.98 1.03	1.03 1.13 0.99 1.03	1.11 0.99 1.03	1.10	1.11	1.10	1.11	0.97 1.06 1.09 0.98	1.03 1.07	1.04 1	.02				1.02 0.91 1.09 0.96 1.03 0.96 1.01	0.93 1.08 0.96 1.02 0.96 1.01	0.97 1.06 0.97 1.02 0.96 1.00	1.01 0.99 1.01 0.96	0.99 0.96	0.96	0.97
Never married (ref: married) No partner (ref: normal marital satisfaction) Low marital satisfaction (ref: normal marital satisf.) Number of confidants Support from friends Problems with friends Support from relatives Problems with relatives General socialization Financial problems	0.97 1.06 1.14 0.99 0.98 1.03	1.03 1.13 0.99 1.03	1.11 0.99 1.03	1.10	1.11	1.10	1.11	0.97 1.06 1.09 0.98	1.03 1.07	1.04 1	.02				1.02 0.91 1.09 0.96 1.03 0.96 1.01 1.07	0.93 1.08 0.96 1.02 0.96 1.01 1.05	0.97 1.06 0.97 1.02 0.96 1.00 1.01	1.01 0.99 1.01 0.96	0.99 0.96	0.96	0.97
Never married (ref: married) Never married (ref: married) No partner (ref: normal marital satisfaction) Low marital satisfaction (ref: normal marital satisf.) Number of confidants Support from friends Problems with friends Support from relatives Problems with relatives General socialization Financial problems Education level	0.97 1.06 1.14 0.99 0.98 1.03 1.02	1.03 1.13 0.99 1.03	1.11 0.99 1.03	1.10	1.11	1.10	1.11	0.97 1.06 1.09 0.98	1.03 1.07	1.04 1	.02				1.02 0.91 1.09 0.96 1.03 0.96 1.01 1.07	0.93 1.08 0.96 1.02 0.96 1.01 1.05	0.97 1.06 0.97 1.02 0.96 1.00 1.01	1.01 0.99 1.01 0.96	0.99 0.96	0.96	0.97
Never married (ref: married) Never married (ref: married) No partner (ref: normal marital satisfaction) Low marital satisfaction (ref: normal marital satisf.) Number of confidants Support from friends Problems with friends Support from relatives Problems with relatives General socialization Financial problems Education level Number of included predictors	0.97 1.06 1.14 0.99 0.98 1.03 1.02 34	1.03 1.13 0.99 1.03	1.11 0.99 1.03	1.10	1.11 1.03	1.10	1.11 1.03	0.97 1.06 1.09 0.98 30	1.03 1.07 21	1.04 1	.02	9	9	8	1.02 0.91 1.09 0.96 1.03 0.96 1.01 1.07 35	0.93 1.08 0.96 1.02 0.96 1.01 1.05 25	0.97 1.06 0.97 1.02 0.96 1.00 1.01	1.01 0.99 1.01 0.96	0.99 0.96	0.96	0.97

GAD, generalized anxiety disorder; HR, hazard ratio; MD, major depression; ref, reference class; SCL, Symptom Checklist

<sup>a</sup> Penalized hazard ratios of all predictors for recurrence of MD with effect sizes ≤0.99 or ≥1.01 based on elastic net regression for different values of alpha including all 70 (dummy) variables.

Sex was included as an extra 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.

<sup>b</sup> Characteristics of episode in the year prior to baseline interview (MF1).

<sup>c</sup> First principal component of depression and anxiety scales of the Symptom Checklist past 30 days.

<sup>d</sup> Lifetime: prior to last year ( $\geq 1$  year ago).

<sup>e</sup> Average prediction error for each model in terms of partial likelihood deviance in 100 runs of 10-fold cross-validation on different random folds.

<sup>f</sup> We performed some sensitivity analyses to check for the potential influence of concordant monozygotic twins on the prediction model for males. We randomly excluded one member of each of the 6 concordant monozygotic twins pairs from the male training sample - i.e. dropping a total of six subjects - resulting in a training set of n=271 males. We then reran the elastic net regression analyses on this sample to obtain the selected set of predictors and their estimates. The prediction models were very similar in the types of predictors and directions of effects compared to the original results. Penalized effect sizes were slightly attenuated in the sample of n=271 male of n=271 males (MD father, MD mother, GAD father, GAD mother), the latter three were again retained in the model for the reduced n=271 male sample (alpha = 0.1). This result suggests that the importance of genetic risk factors in males as compared to females is unlikely to be impacted by the inclusion of this relatively small number of concordant monozygotic males.