Online supplement for Halldorsdottir et al., Polygenic Risk: Predicting Depression Outcomes in Clinical and Epidemiological Cohorts of Youths. Am J Psychiatry (doi: 10.1176/appi.ajp.2019.18091014)

Methods

Participants

Clinical Cohort. Cases were recruited from two child and adolescent clinics in Munich. Inclusion criteria for the cases at study entry was an MD disorder diagnosis based on standardized semi-structured clinical interview. Cases were recruited from two child and adolescent clinics in Munich. Inclusion criteria for the cases at study entry was a MD diagnosis based on ICD-10 using a standardized semi-structured clinical interview and intellectual capacity to complete clinical measures. To meet diagnostic criteria according to the ICD-10, the patient must suffer from persistent depressed mood. reduction of energy, and decreased activity. Other symptoms may include decreased enjoyment, interest, concentration and self-esteem and increased feelings of guilt and worthlessness. The depressed mood may also be accompanied by somatic symptoms such as disturbed sleep, psychomotor retardation, agitation, loss of appetite, weight loss. and loss of libido. Patients are diagnosed with mild, moderate of severe depressive episodes in accordance with the number and severity of the symptoms. The main difference between the DSM-5 and ICD-10 criteria for MD is the number of symptoms and their duration needed to meet criteria in the former (at least 5 clinically interfering symptoms present for ≥ 2 weeks) which the ICD-10 does not have and that the ICD-10 distinguishes between mild, moderate and severe depressive episodes based on the number and severity of the symptoms.

The control group was recruited through the clinic's website, flyers and local advertisement. Inclusion criteria for controls were no past or current mental disorder based on the Kinder-DIPS and intellectual capacity to complete clinical measures. Participants in the study received a 20 Euro voucher as composition for participating in the study.

Childhood abuse was measured with four items on a self-report questionnaire(1) adapted from the Life Event Survey (2) and the Munich Event List (3). Specifically, participants were asked if any the following statement applied to them: 1) I have been yelled at or insulted at home; 2) I have been beaten up at home; 3) I have been the victim of violence; 4) Someone has tried to perform unwanted sexual acts to or with me. Each item was rated dichotomously ("yes"/"no").

Epidemiological Cohort. Participants were drawn from a larger study composed of 1,459 students between the ages 12 to 17 recruited from 31 schools in central Portugal in 2013-2014. Of those. 1,450 youth were successfully genotyped and completed the phenotypic measures required for the present study (see Table 1 for sample characteristics). Trained research assistants (master's students and licensed psychologists) administered the assessment battery in the school classroom setting. Following the study entry assessment, participants with elevated levels of depression entered an established prevention program targeting depressive symptoms (4, 5) and are not included in the

follow up analyses in the present study. In the current study, 694 participants with varying levels of depressive symptoms who did not enter the prevention study were tracked over time. with follow up assessments occurring at 6 months, 1-year and 2-years after study entry. An additional assessment occurred at 18-months following study entry. However, given the low participation rate at this timepoint (n = 138), it was not included in this study.

Replication Epidemiological Cohort. Participants were drawn from a larger longitudinal birth cohort study of 1,049 healthy singleton newborns born between 35 and 42 gestational weeks in 1998 in Helsinki, Finland (6, 7). DNA was extracted from blood samples (N=80) and saliva samples (N=277) donated at the 2009-2011 follow-up. In the current study, only genotyped participants with parental report on depressive symptoms at ages 8 and 11 years old were included. After quality control procedures, there were 185 youth with maternal report depressive symptoms and 144 participants with paternal report depressive symptoms at age 8 years old and 317 with maternal report and 236 with paternal report of depressive symptoms at age 11 years old.

Genotyping

Genetic samples from both the German clinical and Portuguese epidemiological cohorts were genotyped using the Illumina Global Screening array at the MPIP and de-identified phenotypic data were also supplied to the researchers at MPIP for analyses. SNPs with Hardy-Weinberg equilibrium (HWE) < 0.0001. with a minor allele frequency (MAF) < 0.05 or a call rate < 95% were excluded following quality control. With the 469.592 SNPs in the clinical cohort and 459.810 SNPs in the epidemiological cohort surviving this quality control. Imputation for additional variants was performed using IMPUTE version 2(8) and the 1000 Genomes Project reference genome. Imputed SNPs were excluded if their posterior probability averages were less than 90% for the most likely imputed genotype (INFO ≥ 0.9). After the imputation process, SNPs with call rate < 98%. HWE p < 0.0001 and MAF < 0.05 were excluded. This yielded a total of 3.984.898 SNPs in the clinical cohort and 3.779.545 SNPs in the epidemiological cohort.

In the replication epidemiological cohort, genotyping was performed using the OmniExpress Illumina array. SNPs with Hardy-Weinberg equilibrium (HWE) < 1*10-6, with a minor allele frequency (MAF) < 0.10 or a call rate < 95% were excluded. Moreover, heterozygosity, gender check and relatedness checks were performed and any discrepancies removed (N=2). This yielded a total of 529.505 SNPs.

Principal components (PCAs) to account for population stratification were calculated using genome-wide complex trait analysis(9). In all analyses, the first 6 PCAs were included to control for population stratification. MDs plots were used to inspect the samples for outliers and outliers more than four standard deviations from the mean were removed.

Data Analysis

Sex differences in completion rates at the 2-year follow up were noted. To address any potential bias. sex was included in the imputation model and controlled for in all analyses. No other differences in terms of demographic and clinical characteristics in participants with completed versus non-completed data at study entry or at the follow up assessments were noted. Multiple imputation of missing data for all considered variables was conducted through the method of chained equations using the Multivariate Imputation by Changed Equations (MICE)(10) in R. The area under the curve (AUC) using survivalROC(11) and power analyses were calculated with avengeme in R(12).

In the polygenic risk score (PRS) analyses(13), the LD threshold was set to r2 <= 0.25 and distance threshold was set to 2000 bp for clumping. After the imputation process, SNPs with MAF <0.01 were excluded; however, there was no further thresholding on MAF applied in the PRS analyses. Table S4 displays the number of SNPs included in each threshold.

In all analyses, depression PRS was a standardized given its small numerical size. In the clinical cohort, MD status was dichotomized (0=control, 1=case) and self-reported depressive symptoms and AAO were continuous measures. The DIKJ and BDI were transformed into z-scores using the 'scale' function in R in order to perform the analyses on the whole sample. In the epidemiological cohort, depressive symptoms were continous measures in the cross-sectional analyses. In the survival analyses, depressive symptoms were dichotomized (none-mild depressive symptoms=0, moderate-severe depressive symptoms=1) and time was coded to reflect the duration between assessments (1=study entry, 2=6-month follow-up, 3=1-year follow-up, 5=2-year follow-up). Exposure to childhood abuse was dichotomized (0=no abuse/none-mild levels endorsed, 1=1 abuse type or more endorsed/moderate-severe levels of emotional, physical or sexual abuse endorsed). In all analyses, covariates were biological sex, chronological age, parental education, and the first six genetic principal components to adjust for population stratification. The interaction analyses of depression PRS and childhood abuse were adjusted for the covariates and the interaction terms of the depression PRS and childhood abuse with each covariate(14).

To examine the specificity of the effect, we ran the analyses using the summary statistics from the latest bipolar disorder (BPD) GWAS(14) to create the BPD PRS. At a p-value threshold of 0.05 (same as used for the depression PRS), the BPD PRS did not significantly predict case-control status (OR = 0.250, p = 0.766), depression severity (β = 0.002, p = 0.964) or age at onset (β = -0.035, p = 0.688) in the clinical cohort. These findings suggest that the predictive effect of genetic markers are specific to the depression PRS when it comes to predicting depression outcomes in youth.

Figures

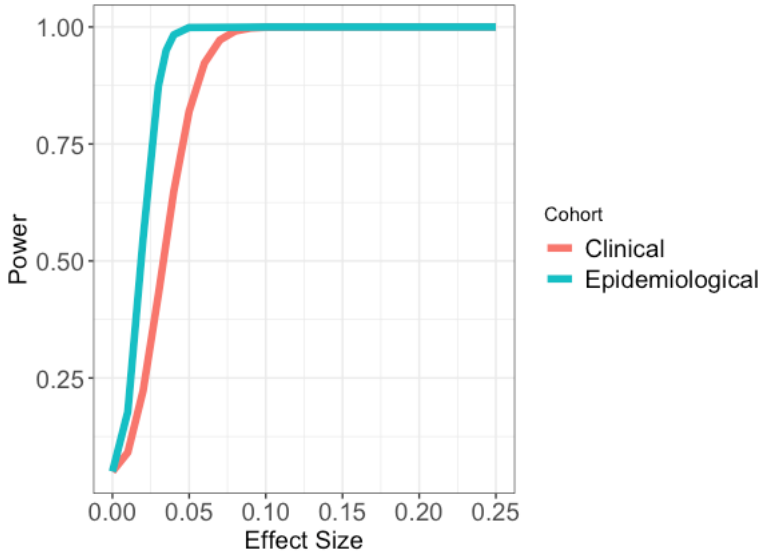

Figure S1. Power curve by effect size for the clinical cohort (red) and epidemiological cohort (blue).

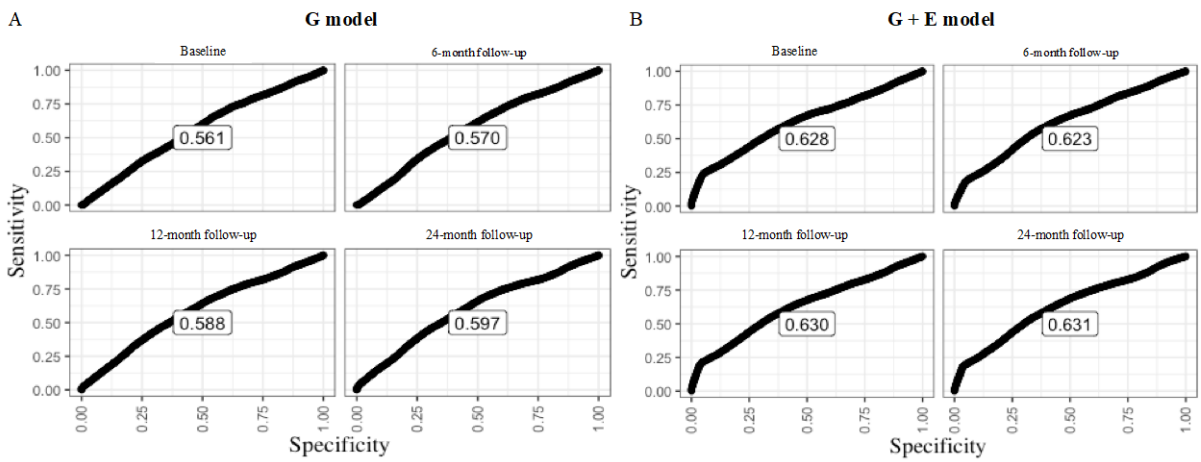

Figure S2. Sensitivity and specificity of the G model (A) and G + E model (B).

Tables

Table S1. Common comorbid diagnoses in the clinical cohort.

Comorbid diagnosis	N	%
Oppositional defiant disorder	26	9.32
Conduct disorder	4	1.43
Separation anxiety	10	3.58
Specific phobia	39	13.98
Social anxiety	22	7.89
Generalized anxiety disorder	11	3.94
Post-traumatic stress disorder	10	3.58
Panic disorder	4	1.43
Agoraphobia	4	1.43
Dysthymia	28	10.04

Table S2. Number of participants meeting diagnostic criteria for MD disorder based on a semi-structured clinical interview (A-LIFE) and within the moderate-severe range on the CDI at the follow-up assessments.

	MD disorder		Moderate-severe depressive symptoms	
	N	%	N	%
Study entry	-		103	15.6
6-month follow-up	15	2.2	104	15.7
12-month follow-up	14	2.1	78	11.8
24-month follow-up	17	2.6	127	19.2

Note. CDI = Children's Depression Inventory; MD = major depression.

Table S3. Number of participants with available data for each outcome.

Outcome		N	Mean	SD
Clinical Cohort				
	Case-control status	466 (279 cases)	-	-
	Depression severity			
	DIKJ	43	17.21	10.19
	BDI	291	19.44	15.66
	Age at onset	245	12.56	2.49
	Abuse measure	434	-	
Epidemiological Cohort 1				
	Baseline analyses (n = 1450)			
	Depressive symptoms	1425	11.46	7.68
	Childhood Trauma Questionnaire	1049	32.27	8.29
	Longitudinal analyses (n = 694)			
	Depressive symptoms at study entry	694	10.86	7.67
	Depressive symptoms at 6-month follow up	570	9.79	7.12
	Depressive symptoms at 1-year follow up	561	9.19	7.11
	Depressive symptoms at 2-year follow up	413	9.03	7.21
Epidemiological Cohort 2				
Depressive Problems t-score at 8 years-old				
	Maternal report	184	52.70	4.40
	Paternal report	144	52.02	3.95
Depressive Problems t-score at 11 years-old				
	Maternal report	317	55.24	6.47
	Paternal report	236	53.60	5.74

Note. Missing data was handled with multiple imputation using the software package *mice* in R. BDI = Beck Depression Inventory. DIKJ = Depression Inventory for Children and Adolescents.

Table S4. Number of SNPs used in the PRS calculations after clumping.

		Number of SNPs	
p-value threshold	Clinical cohort	Epidemiological cohort 1	Epidemiological cohort 2
p < 5e-08	44	44	44
p < 1e-05	237	233	220
p < 1e-04	627	635	558
p < 1e-03	1909	1891	1775
p < 0.01	7008	7133	6636
p < 0.05	19493	19962	18128
p < 0.10	30954	31821	28565

Table S5. Summary of the findings from the null, main effect of PRS, additive, and interaction models with the childhood abuse cutoff of mild to severe in the epidemiological cohort.

Outcome	Model	Variable	β/HR	SE	95% confidence interval		p_{FDR}	original *p*-value	R^2	Model comparison (*p*-value)
					Lower	Higher				
Depressive symptoms (β)										
	Null model	-	-	-	-		-	-		-
	G	PRS	0.557	0.200	0.167	0.947	0.010	0.005	0.075	0.005
	G+E	PRS	0.421	0.193	0.043	0.799	0.044	0.029	0.134	2.200e-16
		Childhood abuse	4.245	0.426	3.410	5.079	6.00e-16	2.00e-16		
	G×E	PRS	0.348	0.226	-0.095	0.791	0.149	0.124	0.134	0.535
		Childhood abuse	4.225	0.427	3.387	5.062	6.00e-16	2.00e-16		
		PRS*Childhood abuse	0.264	0.424	-0.;568	1.095	0.534	0.534		
Prospective moderate-severe depressive symptoms (HR)										
	Null model	-	-	-	-		-	-	0.035	-
	G	PRS	1.202	0.071	1.045	1.383	0.020	0.010	0.044	0.010
	G+E	PRS	1.192	0.076	1.027	1.383	0.025	0.021	0.082	0.002
		Childhood abuse	2.347	0.154	1.748	3.151	4.200e-05	1.400e-8		
	G×E	PRS	1.143	0.085	1.748	3.151	0.025	0.021	0.083	0.411
		Childhood abuse	2.347	1.504	0.968	1.351	4.200e-05	1.400e-08		
		PRS*Childhood abuse	1.192	0.076	1.027	1.383	0.116	0.116		

Note. Age, sex, parental education, and ancestry markers are controlled for in all the analyses. Null models contain only the covariates. The PRS at *p*-value threshold of 0.05 has been standardized in the models.

Table S6. Main effect of the depression PRS on maternal and paternal reported depressive symptoms in the replication epidemiological cohort of youth at ages 8 and 11 years old.

Informant	N	β	SE	*p*-value	R^2
8 years old					
Mother	184	0.929	0.460	0.045	0.011
Father	144	0.138	0.161	0.391	0.001
11 years old					
Mother	317	0.196	0.141	0.164	0.045
Father	236	0.473	0.144	0.001	0.056
Fisher combined probability test				1.273e-3	

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