# Transcriptome-based polygenic score links depression-related corticolimbic gene expression changes to sex-specific brain morphology and depression risk

## SUPPLEMENTARY NOTE

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**SUPPLEMENTARY METHODS**

*Calculation of the transcriptome-based polygenic risk score*

The T-PRS, which captures depression-related changes in gene expression, was developed based on a list of 566 genes generated by a meta-analysis of case-control post-mortem brain transcriptome datasets (n=101 post-mortem subjects; 51 MDD, 50 controls) [1]. Clinical characteristics of the 101 donors and technical parameters associated with each sample are described in the original publication and are additionally available in **Supplementary Table 2.** The original study used a published analytic framework [2] that simultaneously considers correction for confounding variables, selection of effective confounders on an individual gene level, random effects stemming from paired design, and integration by meta

analysis. Within this framework, random intercept models (RIM) with parameter selection using the smallest Bayesian information criterion (BIC) were used to account for several MDD-related potential covariates (e.g. alcohol dependence, antidepressant drug use and death by suicide as well as numerical covariates for age, brain pH, post-mortem interval, etc.). Potential bias in the variable selection procedure was corrected by permutation analysis (500 permutations) that randomly shuffled the disease labels within each pair to generate a null distribution of p values. The final gene list is therefore likely to reflect genes specifically associated with MDD across the three regions of interest, rather than the effects of any confounders.

We used PrediXcan [3] with the Genotype-Tissue Expression (GTEx) 'cortex' tissue from European individuals as a reference transcriptome, to impute gene expression levels in participants in the Duke Neurogenetics Study (DNS) and the Psychiatric Genomics Consortium - Major Depressive Disorder (PGC MDD). This tissue was chosen as a reference for two reasons: 1) it included samples derived from prefrontal regions overlapping those included in the original case-control transcriptome study; and 2) it included the largest number of samples out of any cortical tissue sampled in GTEx (n=119 of European background), hence affording the highest statistical power for identifying reliable cis-expression Quantitative Trait Loci (cis-eQTLs). Gene expression imputation was based on Single Nucleotide Polymorphisms (SNPs) genotyped in peripheral tissue of DNS and PGC-MDD participants. Individual SNP contributions were determined based on weighting in a tissue-specific prediction model (gtex_v7_Brain_Cortex_imputed_europeans_tw_0.5_signif.db).

As described in the original publication [3], PrediXcan expression models were obtained using a Nested Cross-validation Elastic Net approach, in which all SNPs within a cis-window of 1Mb upstream the transcription starting site and 1Mb downstream the transcription end site were used for model training



(sites were determined from Gencode v19). SNPs with non-zero weight found in each cis window were included in a final model if the model was significant. A model was considered significant when the average Pearson correlation between predicted and observed expression during nested cross validation was greater than 0.1 ($R^2$>0.01) and the estimated p-value for this statistic was less than 0.05. Models performed markedly better for genes with higher estimated heritability.

Using these previously published and validated models and parameters, we were able to impute 4220 genes in total (~18% of all protein coding genes), which included 76 out of the 566 'MetaA-MDD' genes. Expression levels were not imputed for the remaining genes, which did not have significant cis-eQTLs identified in the reference tissue, due to low power and/or lower expression heritability [3]. Thus, our rate of 76/566 (13.5%) among the MetaA-MDD genes is slightly lower than that obtained for the entire

genome, which may indicate lower-than-average heritability for those genes consistent with the possibility that the post-mortem transcriptome signature of MDD is likely not primarily genetically driven. Once imputed, expression values were weighted by direction of effect in the original post-mortem meta analysis [1], and T-PRS was computed as the sum of the weighted expression values of the 76 imputed genes, with higher values indicating a more depression-like transcriptome. We have provided a list of the 76 genes included in our T-PRS in **Supplementary Table 3**.

*Neuroimaging sample*

We restricted our analyses to non-Hispanic white participants to match the ethnic background of the post mortem cohorts used to develop our T-PRS, and we further probed the resulting population structure as follows. First, we used proportional identity by descent (PIHAT) to assess the presence of relatedness in the sample. When pairs of individuals with PIHAT > 0.2 were detected, we excluded from the analysis the individual with higher SNP-level missingness (i.e. lower genome-wide call rate). Using this method, we identified two sibling pairs (PIHAT = 0.47, 0.49), and we reduced our sample to 480 subjects. Second, we used a multidimensional scaling (MDS) and clustering method [4], implemented in PLINK v1.9 [5] and using thresholds and recommendations published elsewhere [6,7], to assess population stratification that remained after filtering by self-reported ethnicity. Two individuals from our sample did not cluster with the 1000 Genomes participants of European descent, and they were excluded from subsequent analyses, thereby reducing our sample to 478 subjects. A second MDS analysis yielded 20 principal components (PCs), which were used as covariates in all subsequent neuroimaging analyses.

*MRI preprocessing*



The Freesurfer automated segmentation pipeline (http://surfer.nmr.mgh.harvard.edu, version 6.0) was used to estimate volume in each of seven subcortical regions: accumbens area, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus. This method has been described in detail elsewhere [8,9]. In brief, it performs: registration to standard space, intensity inhomogeneity correction, removal of non-brain tissue, tissue-type classification, and probabilistic anatomical labeling. Regional volumes were averaged over hemisphere to reduce the number of comparisons.

The Freesurfer surface-based processing stream (http://surfer.nmr.mgh.harvard.edu, version 6.0) was used to estimate cortical thickness (CT), cortical surface area (CSA), and local gyrification, quantified using the local gyrification index (LGI) [10], at each vertex on the cortical surface. This method has been described in detail elsewhere [10–12]. In brief, it involves: defining the boundaries between white

matter, grey matter, and cerebrospinal fluid; performing spherical transformation and areal interpolation; measuring the distance between white and pial surfaces (CT); measuring surface area on the inflated sphere (CSA); and quantifying the proportion of concealed versus visible pial surface area (LGI).

Once computed, vertex-wise estimates of cortical surface architecture were registered to the Freesurfer average template and smoothed with a Gaussian kernel (FWHM = 15mm). The latter step was not applied to vertex-wise estimates of LGI as they had comparable intrinsic smoothness. To ensure accuracy, all segmented volumes and reconstructed surfaces were assessed with Freesurfer quality assurance tools and visually inspected by a trained examiner, A.M. LGI computation failed in six subjects, who were excluded from the final sample (n = 472: 221 men, 251 women; aged 19.78 ± 1.24 years).

*PGC symptom severity*

Among all PGC cohorts (n=29,340 after performing QC and removing related individuals), only 4,343 participants from 7 cohorts had data on depressive symptom severity. Among the available data, seven instruments were used to assess depressive symptoms, including the Beck Depression Inventory (BDI, n=6), Center for Epidemiological Studies Depression (CESD, n=6 cases and 18 controls), Composite International Diagnostic Interview - short version (CIDI, n=970, STR), Hamilton Depression Rating Scale - 21 items (HDRS, n=762, available in the Munich Antidepressant Response Signature, MARS, study), Inventory of Depressive Symptomatology (IDS, n= 1359 cases and 290 controls, available in the Netherlands Study of Depression and Anxiety, NESDA), Quick Inventory of Depressive Symptomatology (QIDS, n=932, available in the Sequenced Treatment Alternatives to Relieve Depression, STAR*D, study). In light of the small number of individuals with available CESD and BDI, those measures were not included in analyses. The CIDI is primarily used as a screening tool and may not show sufficient variability in



dimensional analyses. Thus, we tested association of T-PRS, separately, with HDRS in the MARS cohort, IDS in the NESDA/NTR cohort, and QIDS in the STAR*D cohort.

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**Supplementary Table 1.** Participants in the original sample (n=482) meeting criteria for at least one DSM-IV Axis I diagnosis

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**Supplementary Table 5.** Results of post-hoc linear regressions, confirming sex-specific main effects of T PRS on cortical and subcortical morphology when controlling for diagnosis. All values are adjusted for age and 20 genetic components.

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**Supplementary Figure 1.** Forest plot illustrating the standardized mean differences (SMD) of TPRS between women and men per PGC cohort, as well as the overall pooled SMD; Meta-analysis including subjects of 21 PGC cohorts.

**Supplementary Figure 2.** Forest plot illustrating the odds ratio for depression over increasing T-PRS by PGC cohorts, as well as the overall pooled odds ratio; Meta-analysis including both sexes of 21 PGC cohorts.

**Supplementary Figure 3.** Forest plot illustrating the odds ratio for depression over increasing T-PRS by PGC cohorts, as well as the overall pooled odds ratio; Meta-analysis including female subjects only of 21 PGC cohorts.

**Supplementary Figure 4.** Forest plot illustrating the odds ratio for depression over increasing T-PRS by PGC cohorts, as well as the overall pooled odds ratio; Meta-analysis including male subjects only of 21 PGC cohorts.

**Supplementary Figure 5.** Effects of T-PRS on symptom severity in 3 PGC cohorts.



**SUPPLEMENTARY TABLES**

**Supplementary Table 1.** Participants in the original sample (n=482) meeting criteria for at least one DSM-IV Axis I diagnosis

| **DSM-IV Axis I diagnosis** | **n** |
|---|---|

Agoraphobia (with or without history of Panic Disorder) 12
Alcohol Abuse 35
Alcohol Dependence 30
Bipolar Disorder (past) 16
Generalized Anxiety Disorder 5
Major Depressive Disorder (current or past) 26
Obsessive Compulsive Disorder 6
Social Anxiety Disorder 5
Substance Abuse (cannabis) 13
Substance Dependence (cannabis) 7
**Total 114**



**Supplementary Table 2.** Individual post-mortem subject characteristics (as described in [1]).

[see supplementary file]

**Supplementary Table 3.** List of genes included in T-PRS (n=76)

ACOT8 DPY19L1 PPP3CC ADH5 DTNBP1
PRKRIP1 AGA EIF4G3 PRSS3 AGL FAM149A
RABGEF1 ALDH4A1 FIGNL1 RPA1 ALMS1
GALNT13 RPS26 ANKRD10 GAS2L1 RRM1
ARMC1 GCC2 RWDD2B ARSA GGCX SFI1
ATF4 GOSR1 SFT2D1 ATIC GPR98 SIN3B
ATPIF1 HN1L SLC1A1 BPHL IVNS1ABP SNX24
BRMS1 KCNIP3 SPATA7 CAMK2N2 KIAA1467
SPHK2 CCNY KLHL24 STARD10 CHERP LXN
SYT7 CIAO1 MAPK9 TAF1C CLCN3 MMACHC
TBCD COQ5 NEK1 TMEM86B CPNE7 NPHP3
TRAF3 CSRP2 PIK3R1 TTC3 DDT PILRB WWP2
DGCR2 PPIC ZNF558 DIDO1 PPM1D
DOK4 PPP2R3A



**Supplementary Table 4.** Sex-specific main effects of T-PRS and PGC-PRS on vertex-wise cortical morphology for clusters depicted in Figures 2 and 3.

| **Cluster Max CWP Size ($mm^2$) Annot.** | **Phenotype** |
|---|---|
| **T-PRS** | |

| | |
|---|---|
| **Men**<br>1m -2.921 .001 1004 rostral middle frontal, lh 2m 2.310 .015 698 supramarginal, lh 3m -2.430 .001 858 lingual, rh 4m 3.337 .011 637 middle temporal, rh 5m 2.970 .016 609 bankssts, rh **Women**<br>1w -2.983 <.001 2017 rostral middle frontal, lh 2w -2.797 .001 905 paracentral, rh 3w -3.510 .005 765 fusiform, lh 4w -3.337 <.001 1335 paracentral, rh 5w -3.050 .002 838 caudal middle frontal, rh | local gyrification<br>local gyrification<br>local gyrification<br>local gyrification<br>local gyrification<br><br>local gyrification<br>local gyrification<br>local gyrification<br>local gyrification<br>local gyrification |
| **PGC-PRS** | |
| **Men**<br>1 -3.489 <.001 4458 lateral occipital, lh 2 -2.071 <.001 1401 superior parietal, lh 3 -3.122 <.001 1086 fusiform, rh **Women**<br>1 3.310 .015 1660 temporal pole, rh | local gyrification<br>local gyrification<br>local gyrification<br><br>cortical thickness |

*Annot. = Desikan-Killiany atlas label corresponding to the peak vertex; CWP = cluster-wise p-value; Max. = maximum -log10(p) where p is the p-value at the peak vertex*

Clusters in which T-PRS had a significant main effect on vertex-wise local gyrification.

**Supplementary Table 5.** Results of post-hoc linear regressions, confirming sex-specific main effects of T PRS on cortical and subcortical morphology. All values are adjusted for age and 20 genetic components.

| **Region of interest** | **Tested with psychiatric diagnosis as an additional covariate** | **Tested in restricted sample, excluding participants with a psychiatric diagnosis** |
|---|---|---|
| **T-PRS** | | |
| **Men** | **t p** | **t p** |
| Cluster #1m, local gyrification Cluster #2m, local gyrification Cluster #3m, local gyrification | -2.929 .004 | -2.728 .007 |
| Cluster #4m, local gyrification Cluster #5m, local gyrification | 2.490 .014 | 1.124 .263 |
| **Women** | -2.808 .005 | -2.543 .012 |
| Amygdala, volume | 2.973 .003 | 2.413 .017 |
| Cluster #1w, local gyrification Cluster #2w, local gyrification Cluster #3w, local gyrification | 2.688 .008 | 1.516 .132 |
| Cluster #4w, local gyrification Cluster #5w, local gyrification | -3.412 .001 | -3.376 .001 |
| **PGC-PRS** | -3.303 .001 | -2.885 .004 |
| **Men** | -3.026 .003 | -2.273 .024 |
| Amygdala, volume | -2.785 .006 | -2.431 .016 |
| Cluster #1, local gyrification Cluster #2, local gyrification Cluster #3, local gyrification | -3.239 .002 | -3.049 .003 |
| **Women** | -3.001 .003 | -3.100 .002 |
| Cluster #1, cortical thickness | -2.872 .005 | -2.324 .022 |
| | -3.838 <.001 | -2.733 .007 |
| | -2.301 .022 | -1.812 .072 |
| | -3.085 .002 | -2.451 .016 |
| | 4.658 <.001 | 5.118 <.001 |

**Supplementary Table 6.** Sex-specific main effects of familial MDD on volume or local gyrification in T PRS- and PGC-PRS-associated regions or clusters. Bold font indicates significance. All values are adjusted for age.

| Brain-based phenotype | t | p |
|---|---|---|
| **T-PRS** | | |
| **Men pcrit < .010** Cluster #1, local gyrification | **-2.688** | **.008** |
| Cluster #2, local gyrification | -2.511 | .013 |
| Cluster #3, local gyrification | -1.775 | .077 |
| Cluster #4, local gyrification | 1.112 | .267 |
| Cluster #5, local gyrification | 0.667 | .506 |
| **Women pcrit < .008** Amygdala, volume | -0.387 | .699 |
| Cluster #1, local gyrification | 0.885 | .377 |
| Cluster #2, local gyrification | -0.443 | .658 |
| Cluster #3, local gyrification | 0.411 | .681 |
| Cluster #4, local gyrification | 0.928 | .354 |
| Cluster #5, local gyrification | 0.667 | .506 |
| **PGC-PRS** | | |
| **Men pcrit < .0125** Amygdala, volume | -0.387 | .699 |
| Cluster #1, local gyrification | 1.019 | .310 |
| Cluster #2, local gyrification | -1.101 | .272 |
| Cluster #3, local gyrification | -1.028 | .305 |
| **Women pcrit < .05** Cluster #1, cortical thickness | 1.037 | .301 |



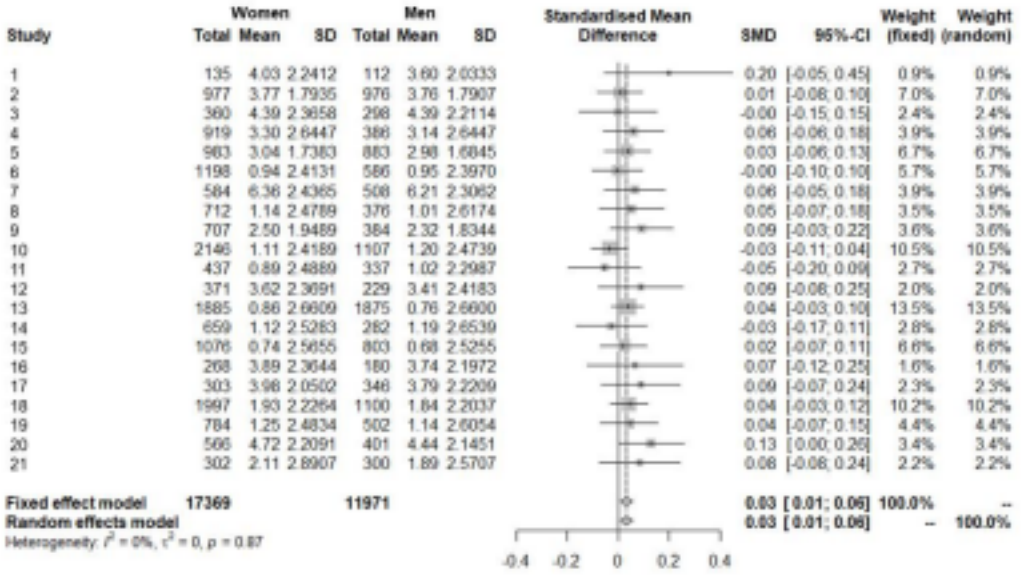
**Supplementary Table 7. Generalized linear model results by PGC cohort for the effect of T-PRS and the interaction between T-PRS and sex**

[see supplementary file]

*N = sample size; N case = sample size in MDD group; N control = sample size in control group; OR = odds ratio for T-PRS in the GLM; 95% C.I. = 95% confidence interval of T-PRS odds ratio in the GLM; P 1s = one sided p-value of T-PRS in the GLM; (T-PRS*Sex) = interaction term for T-PRS and sex in the GLM*

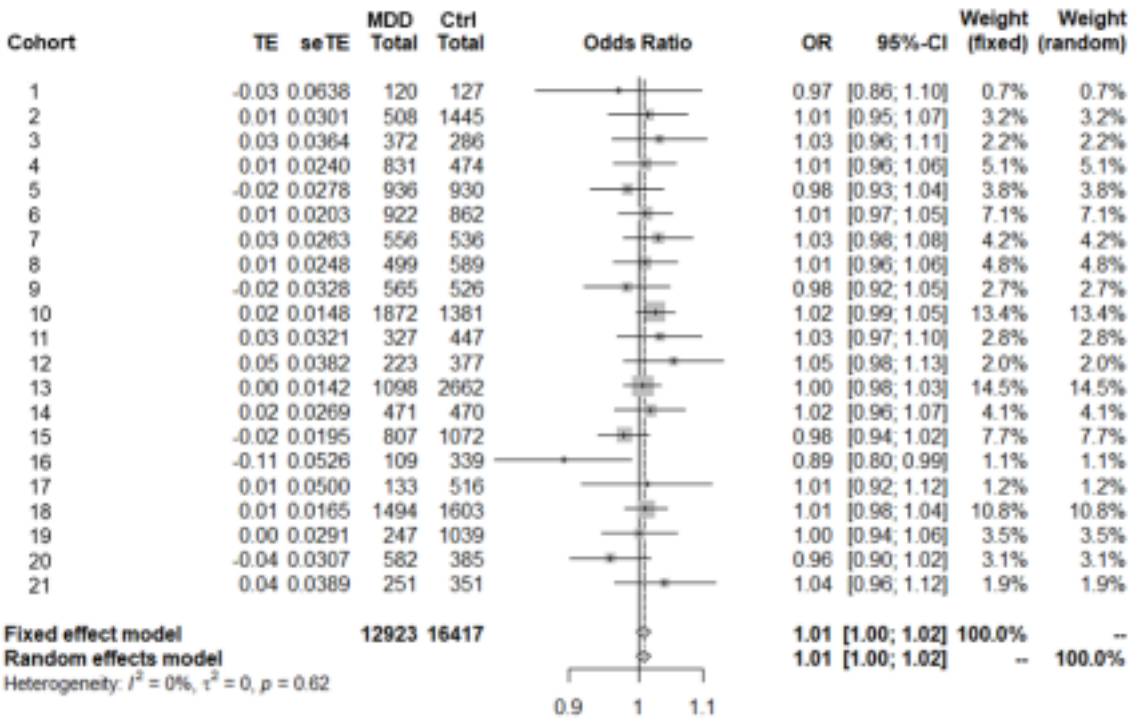
**SUPPLEMENTARY FIGURES**

**Supplementary Figure 1.** Forest plot illustrating the standardized mean differences (SMD) of TPRS between women and men per PGC cohort, as well as the overall pooled SMD; Meta-analysis including subjects of 21 PGC cohorts.






**Supplementary Figure 2.** Forest plot illustrating the odds ratio for depression over increasing T-PRS by PGC cohorts, as well as the overall pooled odds ratio; Meta-analysis including both sexes of 21 PGC cohorts.

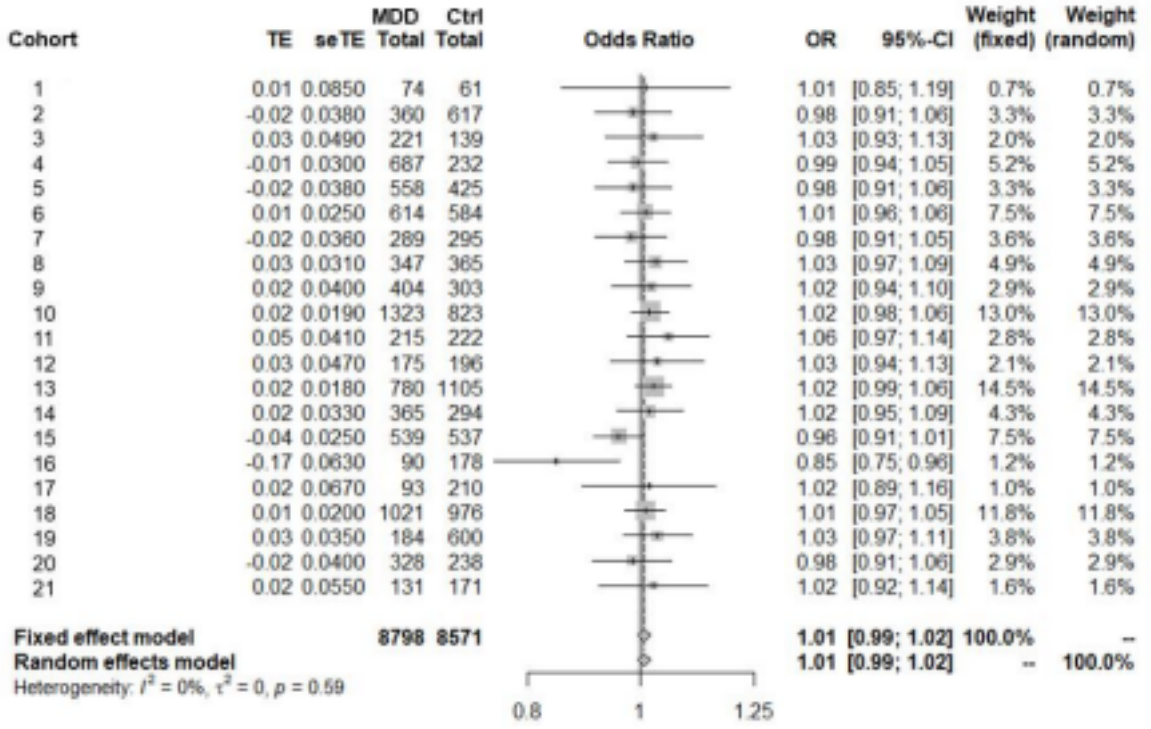



*Abbreviations: TE = Logistic regression coefficient for T-PRS; seTE = standard error of the logistic regression coefficient for T-PRS; MDD Total = Total number of depression cases; Ctrl Total = Total number*

*of controls; OR = odds ratio; 95%-CI = 95% confidence interval; PGC = Psychiatric Genomics Consortium.*

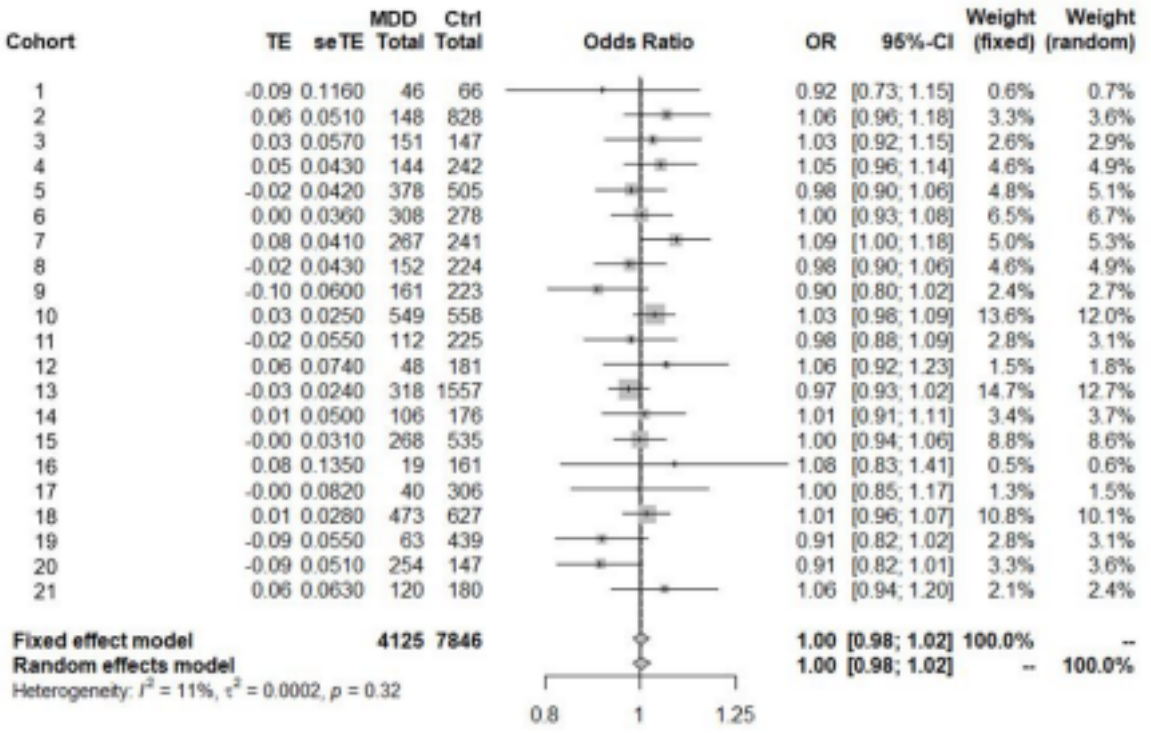


**Supplementary Figure 3.** Forest plot illustrating the odds ratio for depression over increasing T-PRS by PGC cohorts, as well as the overall pooled odds ratio; Meta-analysis including female subjects only of 21 PGC cohorts.



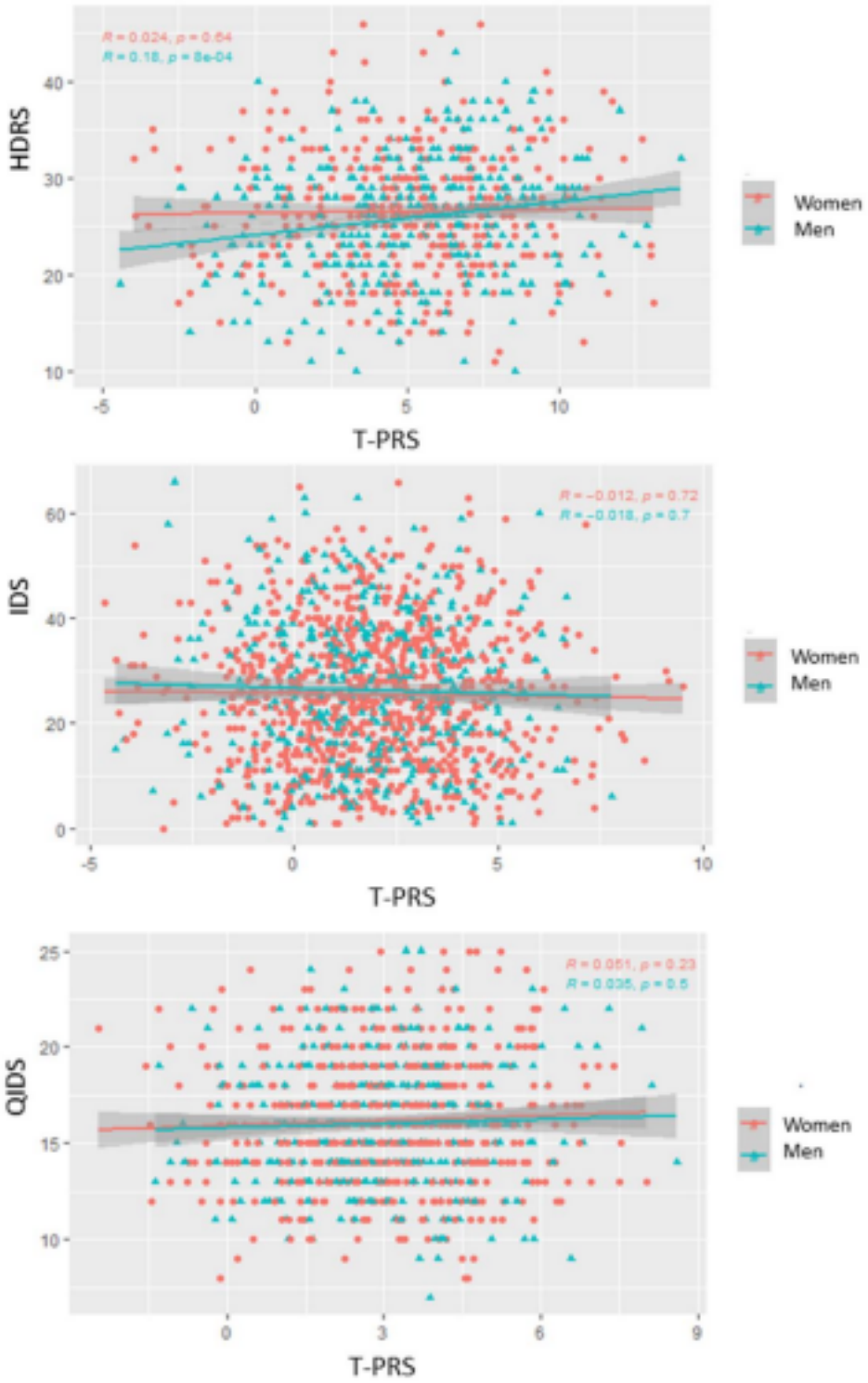

*Abbreviations: TE = Logistic regression coefficient for T-PRS; seTE = standard error of the logistic regression coefficient for T-PRS; MDD Total = Total number of depression cases; Ctrl Total = Total number of controls; OR = odds ratio; 95%-CI = 95% confidence interval; PGC = Psychiatric Genomics Consortium.*

**Supplementary Figure 4.** Forest plot illustrating the odds ratio for depression over increasing T-PRS by PGC cohorts, as well as the overall pooled odds ratio; Meta-analysis including male subjects only of 21 PGC cohorts.




*Abbreviations: TE = Logistic regression coefficient for T-PRS; seTE = standard error of the logistic regression coefficient for T-PRS; MDD Total = Total number of depression cases; Ctrl Total = Total number of controls; OR = odds ratio; 95%-CI = 95% confidence interval; PGC = Psychiatric Genomics Consortium.*

**Supplementary Figure 5.** Effects of T-PRS on symptom severity in 3 PGC cohorts.




*Abbreviations: HDRS = Hamilton Depression Rating Scale; IDS = Inventory of Depressive Symptoms; QIDS = Quick Inventory of Depressive Symptoms.*



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