Bipolar multiplex families have an increased burden of common risk variants for psychiatric disorders

Supplementary Material

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Supplementary Methods

Extended FAM sample description

We included 395 members of 33 families in the present analyses. 166 participants were diagnosed with BD (BD type I (BD-I), n=115; BD type II (BD-II), n=41; not otherwise specified (NOS) BD, n=10), 78 with MDD (recurrent MDD (R-MDD), n=53; single episode MDD (SE-MDD), n=17; NOS MDD, n=8), and 151 without a history of an affective disorder.

Diagnoses were assigned by two trained clinicians according to DSM IV using the best estimate approach. Diagnosis and clinical data were based on the Schedule for Affective Disorders and Schizophrenia (SADS)[1], the Operational Criteria Checklist for Psychotic and Affective Illness (OPCRIT)[2], the Family Informant Schedule and Criteria (FISC)[3], and on clinical records.

A severe impairment during the disorder (see Table 1) corresponded to a level of 3 in the OPCRIT item 87 (no function at all in a major life role for more than two days or in-patient treatment has been required or active psychotic symptoms such as delusions or hallucinations have occurred).

Quality control (QC)

QC of genotype data was conducted in PLINK v1.90b3.36. QC was carried out first on each of both cohorts separately (FAM and CC), followed by a second round of QC on the combined dataset.

Sequence of QC steps:

1. FAM (genotyped on Infinium PsychArray BeadChip (PsychChip))
   Before QC: 395 individuals and 588,454 variants
   - 1.1. Removal of SNPs with call rates <98% or a MAF <1%
   - 1.2. Check for individuals with genotyping rates <98% (*none removed*)
   - 1.3. Check for sex mismatches (*none removed*)
   - 1.4. Removal of non-autosomal variants
   - 1.5. Removal of SNPs with call rates <98%, a MAF <1%, or Hardy-Weinberg Equilibrium (HWE) test *p*-values $<1\times10^{-6}$
   - 1.6. Removal of A/T and G/C SNPs
   - 1.7. Update of variant IDs and positions to the IDs and positions in the 1000 Genomes Phase 3 reference panel
   - 1.8. Alignment of alleles to the reference panel
   - 1.9. Removal of duplicated variants and of variants not present in the reference panel

   After QC: 395 individuals and 258,046 variants

2. CC (Illumina HumanOmni1-Quad and Illumina Human610-Quad, combined and quality-controlled as previously published[4]; the QC described here was conducted on the published data)
   Before QC: 547 individuals and 333,353 variants
   2.1. Removal of SNPs with call rates <98% or a MAF <1%
   2.2. Check for individuals with genotyping rates <98% (*none removed*)
   2.3. Check for sex mismatches (*none removed*)
   2.4. Check for genetic duplicates (*none removed*)
   2.5. Removal of individuals where the autosomal or X-chromosomal heterozygosity deviated from the mean >4 SD (*six removed*)
   2.6. Removal of non-autosomal variants
   2.7. Removal of SNPs with call rates <98%, a MAF <1%, or HWE test *p*-values $<1\times10^{-6}$
   2.8. Removal of A/T and G/C SNPs
   2.9. Update of variant IDs and positions to the IDs and positions in the 1000 Genomes Phase 3 reference panel
   2.10. Alignment of alleles to the reference panel
   2.11. Removal of duplicated variants and variants not present in the reference panel
   After QC: 541 individuals and 315,634 variants

3. Combined dataset of both samples (936 individuals and 116,079 variants)
   3.1. Removal of SNPs with call rates <98% or a MAF <1%
   3.2. Removal of individuals with genotyping rates <98% (*two removed*)
   3.3. Removal of individuals duplicated between both datasets (*31 removed from the CC sample*)
   3.4. Removal of genetic outliers with a distance from the mean of >4 SD in the first eight MDS components (*15 removed from the CC sample*)
   3.5. Removal of individuals where the autosomal heterozygosity deviated from the mean >4 SD (*eleven removed from the FAM sample*)
   3.6. Removal of SNPs with call rates <98%, a MAF <1%, or HWE test *p*-values $<1\times10^{-6}$
   3.7. Removal of individuals from the CC sample that have been recruited as part of the FAM/ABiF cohort (*55 removed*)
   After QC: 822 individuals (384 FAM and 438 CC) and 116,067 variants

Population substructure analysis

For the population substructure analyses, pre-imputation genotype data was used, after the QC steps explained above had been applied. Additional variant filtering steps were: removal of variants with a MAF <0.05 or HWE *p*-value $<10^{-3}$; removal of variants mapping to the extended MHC region (chromosome 6, 25-35 Mbp) or to a typical inversion site on chromosome 8 (7-13 Mbp); LD pruning (command *--indep-pairwise 200 100 0.2*).

Next, the pairwise identity-by-state (IBS) matrix of all individuals was calculated using the command *--genome* on the filtered genotype data. Multidimensional scaling (MDS) analysis was performed on the IBS matrix using the eigendecomposition-based algorithm in PLINK v1.90b5.

In an MDS analysis, the high relatedness between family members leads to artifacts. To avoid such artifacts, only one person per family was included in population substructure analyses. For each of the 33 families, the individual with the highest absolute values in MDS components 1 and 2 was selected to represent the respective family. Afterwards, the MDS analysis was repeated, using only selected individuals from the FAM sample.

Whether MDS components differ between cohorts was analyzed with logistic regression using the following model without additional covariates:
cohort (FAM/CC) ~ MDS components.
The ten calculated MDS components showed association *p*-values with cohort ≥0.30, except for component 3, which was associated with cohort at nominal significance with p=0.036. After correction for multiple testing (ten comparisons), this difference observed for component 3 was not significant.

Imputation of genotype data

Genotypes were aligned to the 1000 Genomes Phase 3 reference panel using SHAPEIT v2 (r837) and PLINK v1.90b3.36. Pre-phasing (haplotype estimation) was conducted for each chromosome separately using SHAPEIT. Imputation was performed using IMPUTE2 v2.3.2 in 5 Mbp chunks with 500 kbp buffers, filtering out variants that are monomorphic in the EUR samples. Chunks with <51 genotyped variants or concordance rates <92 % were fused with neighboring chunks and re-imputed. Imputed variants with a MAF <1% or an INFO metric <0.8 were removed.

Imputed variants in the combined sample after QC: 6,862,461
Imputed variants in the FAM sample after QC: 8,628,089

Note that optimized imputation algorithms for pedigrees exist, for example, GIGI[5]. GIGI mainly improves imputation accuracy of rare variants but does not have a clear advantage over population-based methods regarding common variants. Moreover, GIGI can only impute one pedigree at a time and cannot impute unrelated individuals. As we were only interested in common variation (MAF ≥1%) and also wanted to analyse a mixed sample of related and unrelated subjects, we chose a population-based imputation method using SHAPEIT and IMPUTE2.

Generation and analysis of PRS

The GWAS test statistics and imputed variants in our data were merged based on chromosome, position, and alleles of each variant. Summary statistics were then clumped in PLINK v1.90b5.2, based on best-guess genotype data (hard-call threshold 0.3) using the following parameters:

--clump-kb 500 --clump-r2 0.1 --clump-p1 1 --clump-p2 1

PRS were then calculated in *R* v.3.3 based on imputed (dosage) data. Test statistics and alleles in the GWAS training data were flipped so that effect sizes were always positive. Thus, the weighted PRS represent cumulative, additive risk. PRS were scaled to represent the relative risk load (minimum possible cumulative risk load = 0, maximum = 1). For each disorder, ten PRS with different *p*-value thresholds were calculated: $<5\times10^{-8}$, $<1\times10^{-7}$, $<1\times10^{-6}$, $<1\times10^{-5}$, $<1\times10^{-4}$, <0.001, <0.01, <0.05, <0.1, <0.2.

In the first step of the PRS analyses, residuals were calculated with the GenABEL *polygenic* function using the formula *phenotype ~ covariates* (where the phenotype corresponded to the diagnosis/cohort groups contrasted in a given analysis), including the genetic relationship matrix as random effects. Residuals from this model were then used in a second linear model with the formula *residuals ~ PRS*. Test statistics including 95% CI were calculated using bootstrapping (*R* package boot, nonparametric bootstrapping using ordinary resampling with 2,000 replications).

Supplementary Discussion

FAM_{MDD} cases had higher BD, MDD, and *Shared* PRS than $CC_{controls}$. The SCZ-MDD GWIS PRS were also increased in FAM_{MDD} but the SCZ and SCZ-BD GWIS PRS were not higher. This may be due to the lower genetic correlation of MDD and SCZ compared to the correlation of BD and SCZ[6-9]. However, when interpreting the results for FAM_{MDD} cases, it is important to consider that much fewer MDD than BD cases have been analysed (Table 1). The power of MDD-based analyses in the present study was thus considerably lower than for BD. This lower statistical power is also a possible explanation for why FAM_{MDD} cases only showed a nominally increased MDD PRS over $FAM_{unaffected}$ individuals. In addition to suggesting a cross-disorder illness burden, the increased BD PRS in FAM_{MDD} cases may also indicate that, in some cases, the current MDD diagnosis constituted a prodromal stage of BD[10]. Furthermore, in ABiF families, MDD may be more strongly driven by BD risk variants and therefore have closer etiological proximity to BD than is the case for the average MDD patient from the general population.

Supplementary References

1 Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. *Arch Gen Psychiatry* 1978; **35**: 837–844.

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7 Ruderfer DM, Fanous AH, Ripke S, McQuillin A, Amdur RL, Schizophrenia Working Group of Psychiatric Genomics Consortium *et al.* Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia. *Mol Psychiatry* 2014; **19**: 1017–1024.

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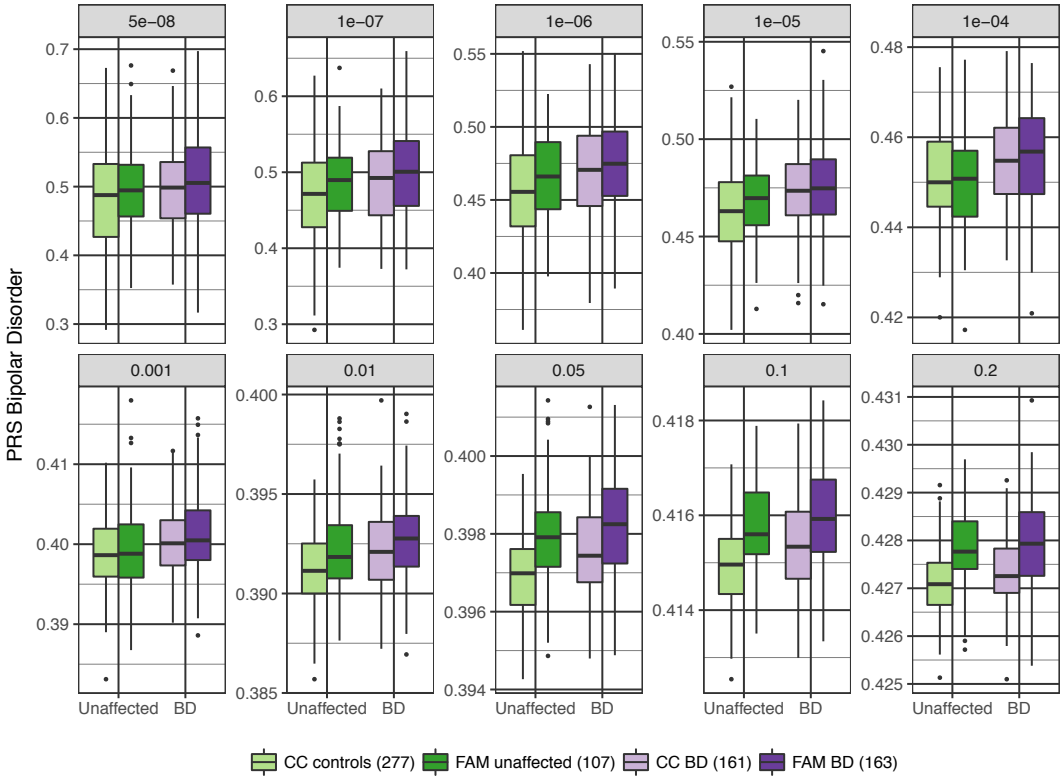
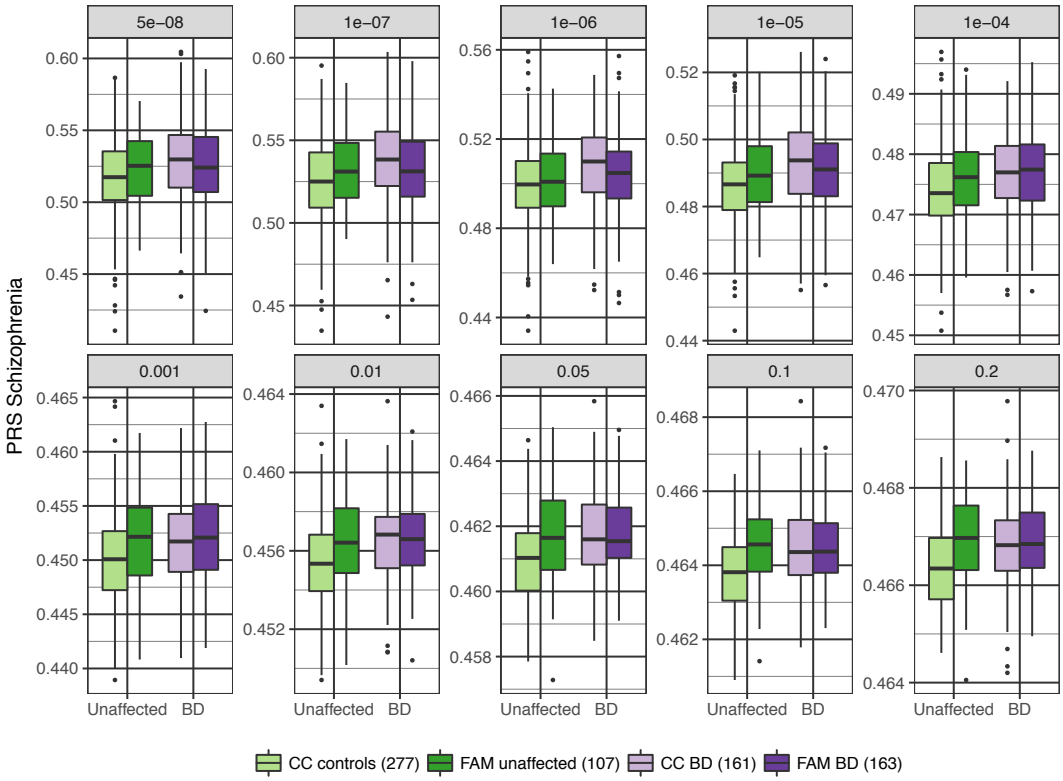
10 Berk M, Dodd S, Callaly P, Berk L, Fitzgerald P, de Castella AR *et al.* History of illness prior to a diagnosis of bipolar disorder or schizoaffective disorder. *J Affect Disord* 2007; **103**: 181–186.

Supplementary Fig. S1: Boxplots of PRS at different *p*-value thresholds for $CC_{controls}$, $FAM_{unaffected}$, and BD cases. FAM samples excluded from the analyses of the combined dataset are not shown in these plots, *i.e.*, family members with a history of substance abuse, married-in family members, or family members diagnosed with MDD. CC = Case/control sample.

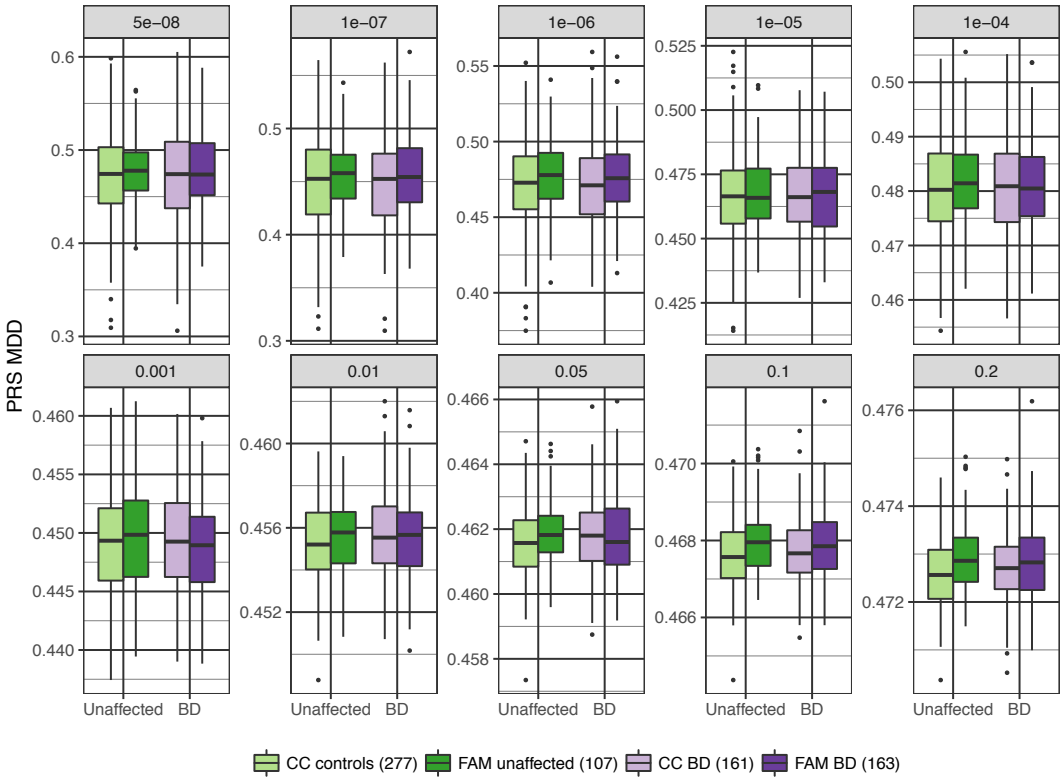
Supplementary Fig. S1A: Boxplots of BD PRS.



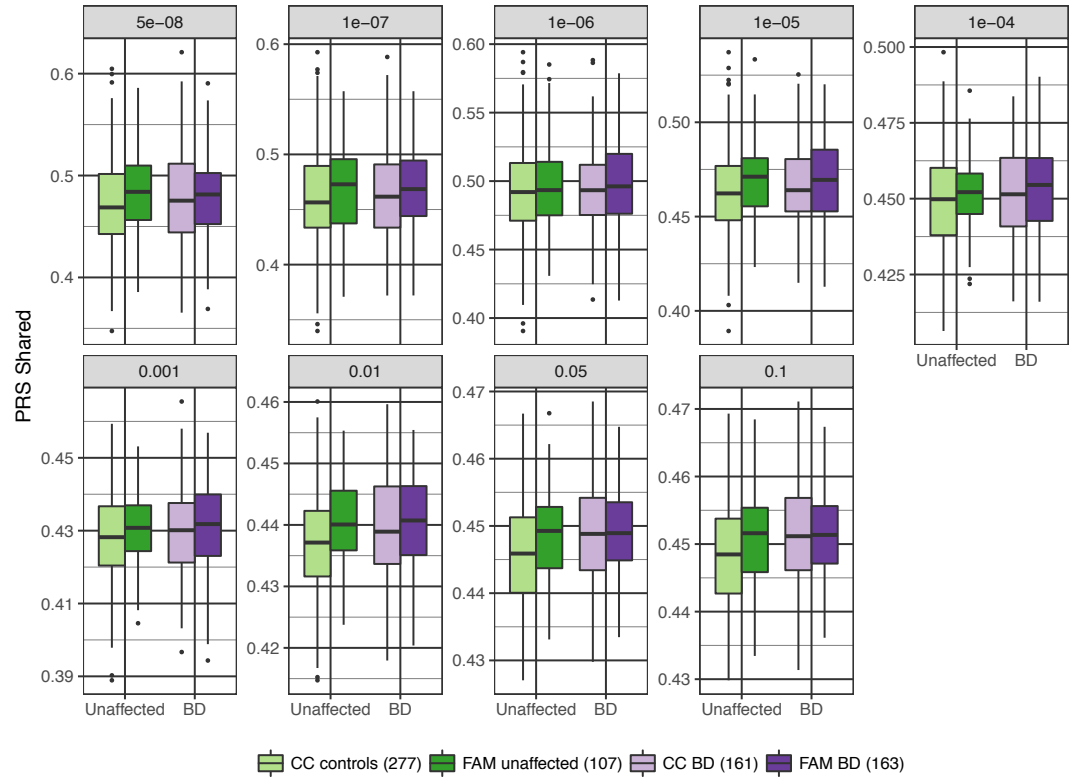
Supplementary Fig. S1B: Boxplots of SCZ PRS.



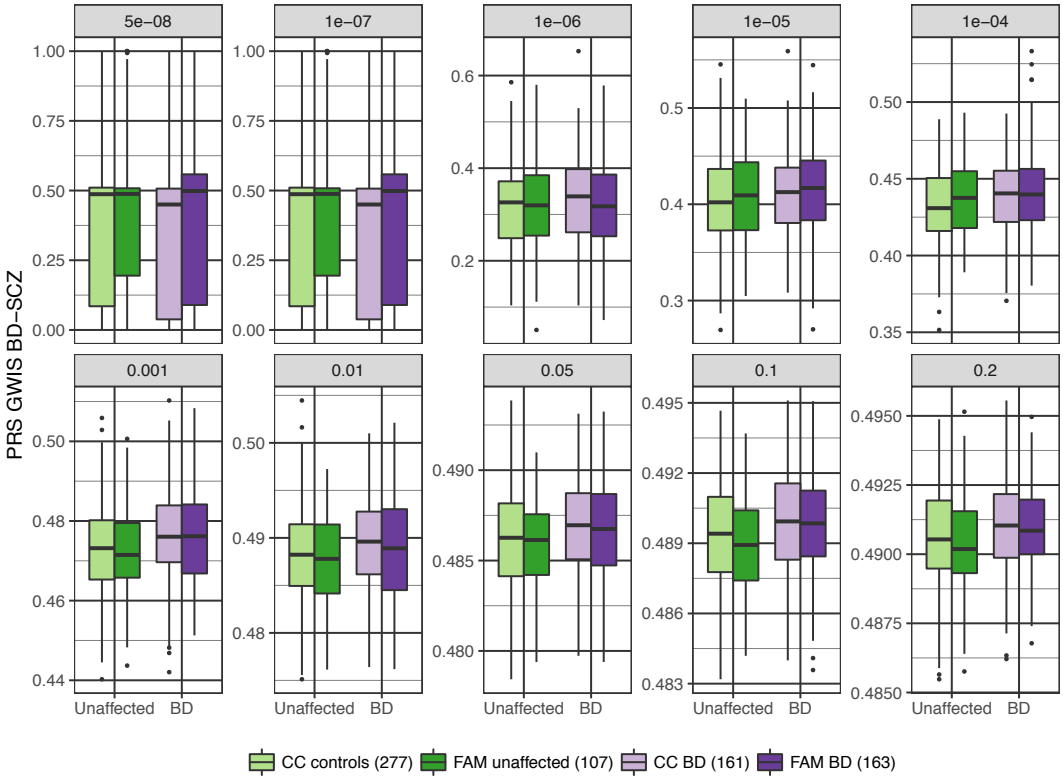
Supplementary Fig. S1C: Boxplots of MDD PRS.



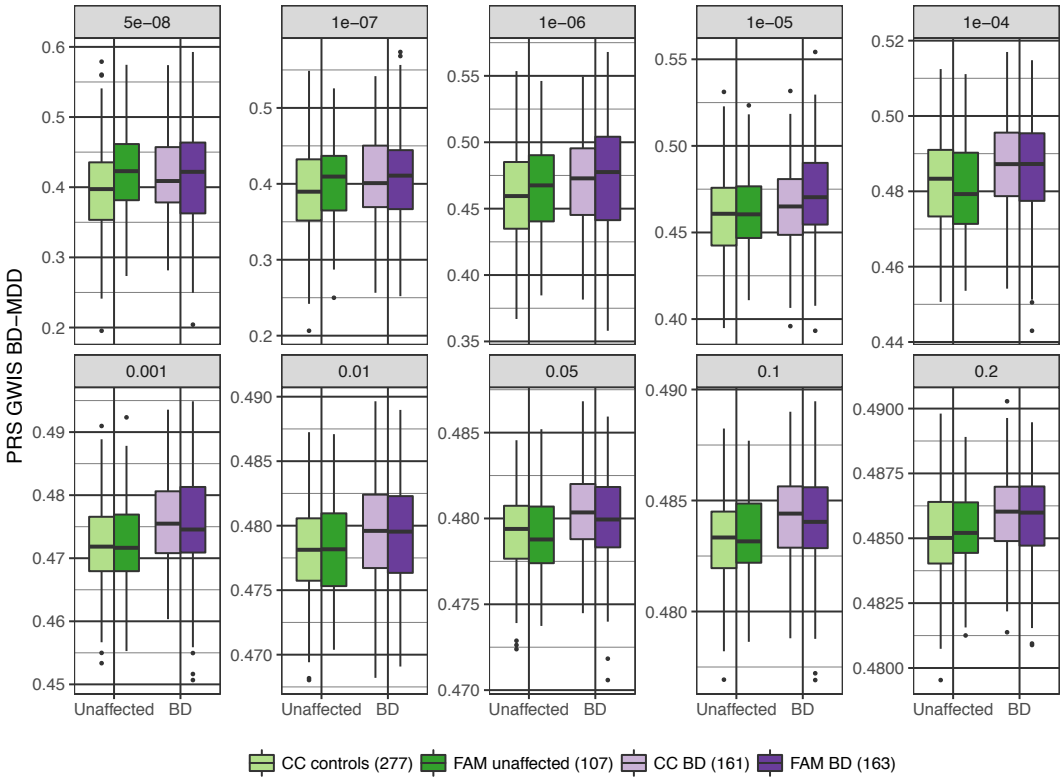
Supplementary Fig. S1D: Boxplots of the BD+SCZ+MDD *Shared* PRS. Note that because of the way this PRS was calculated, the maximum possible threshold was p_{PRS}=0.1.



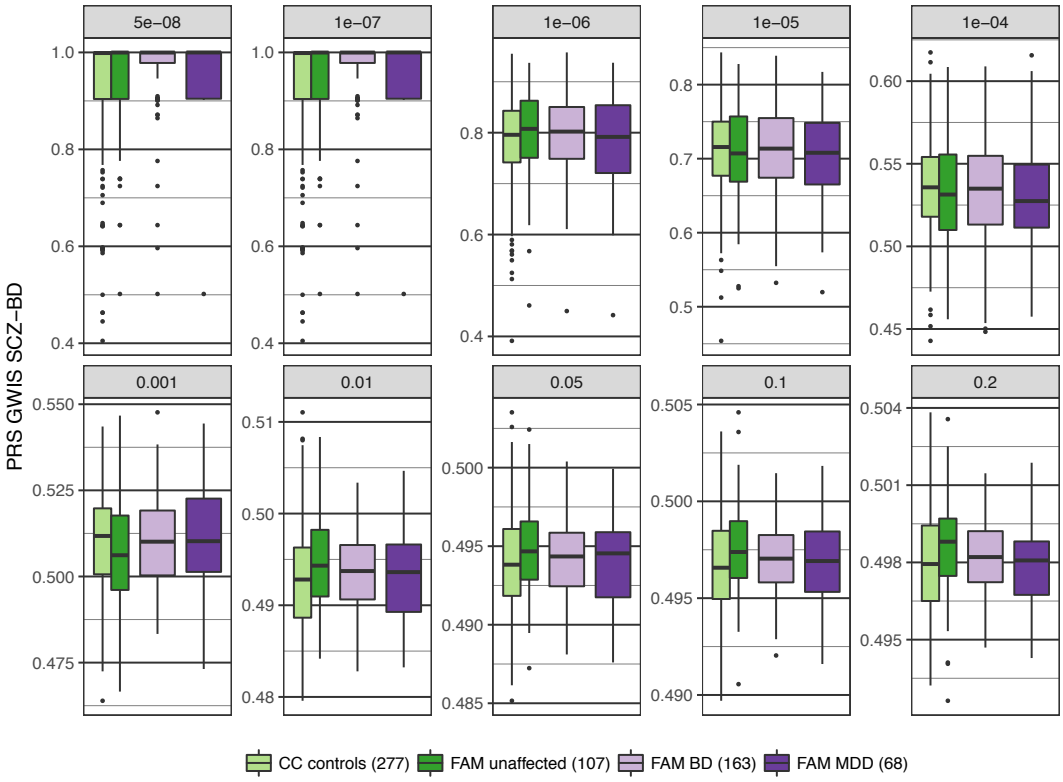
Supplementary Fig. S1E: Boxplots of the BD-SCZ GWIS PRS.



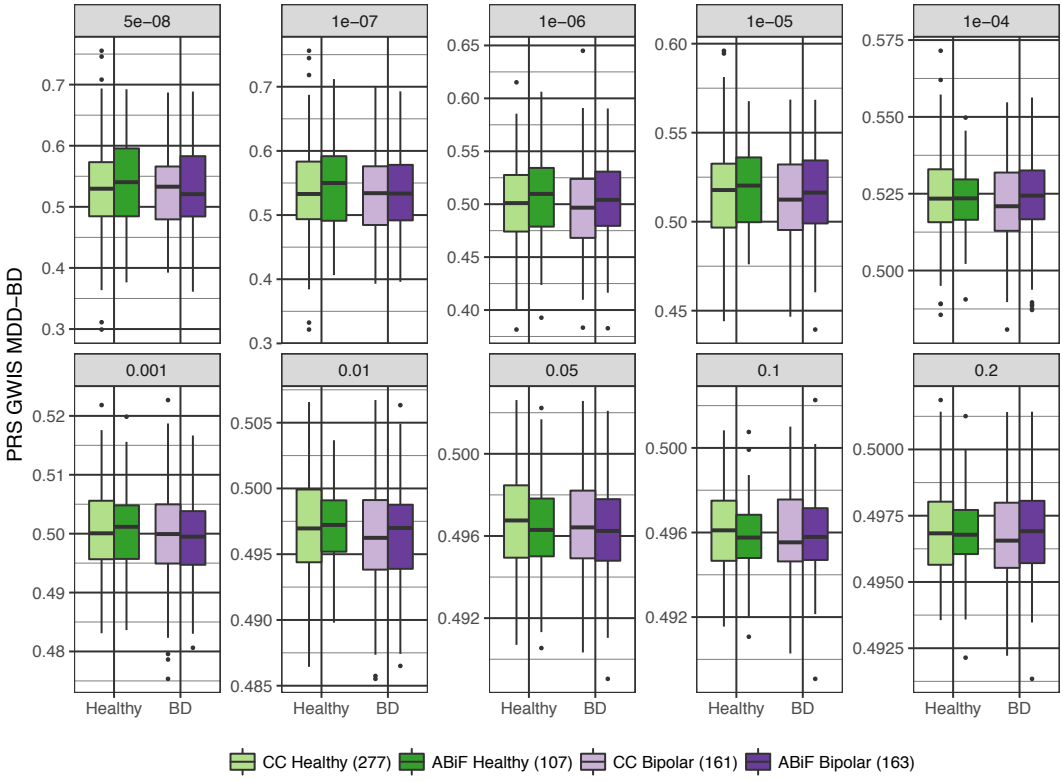
Supplementary Fig. S1F: Boxplots of the BD-MDD GWIS PRS.



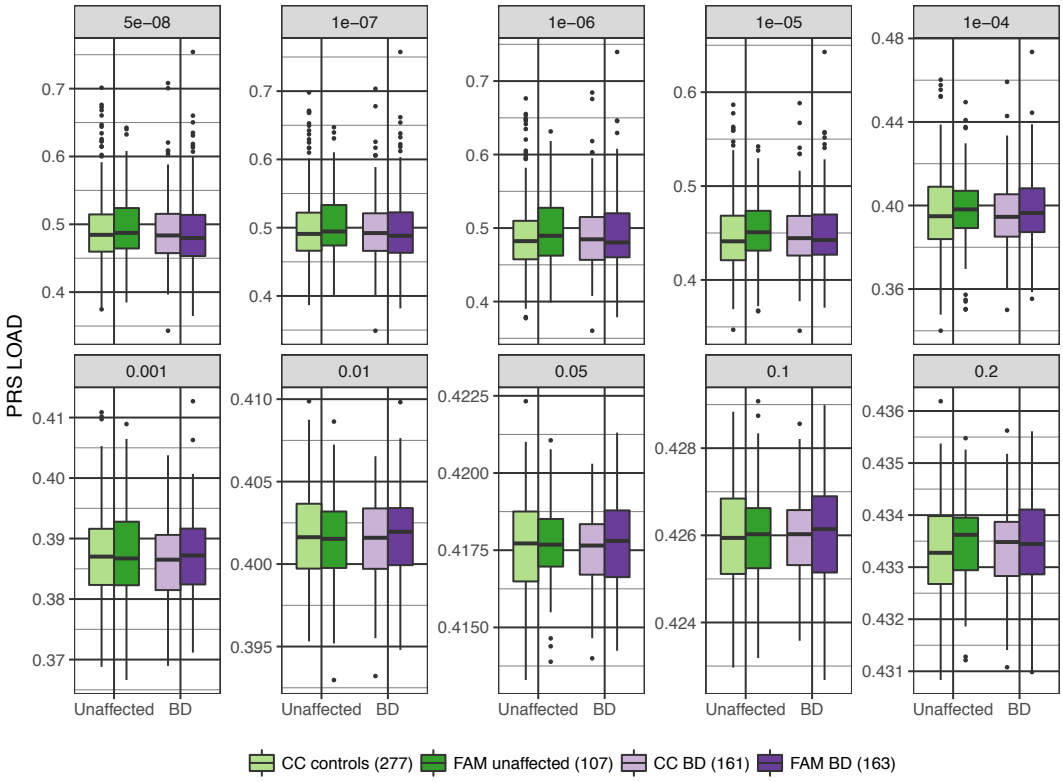
Supplementary Fig. S1G: Boxplots of the SCZ-BD GWIS PRS.



Supplementary Fig. S1H: Boxplots of the MDD-BD GWIS PRS.

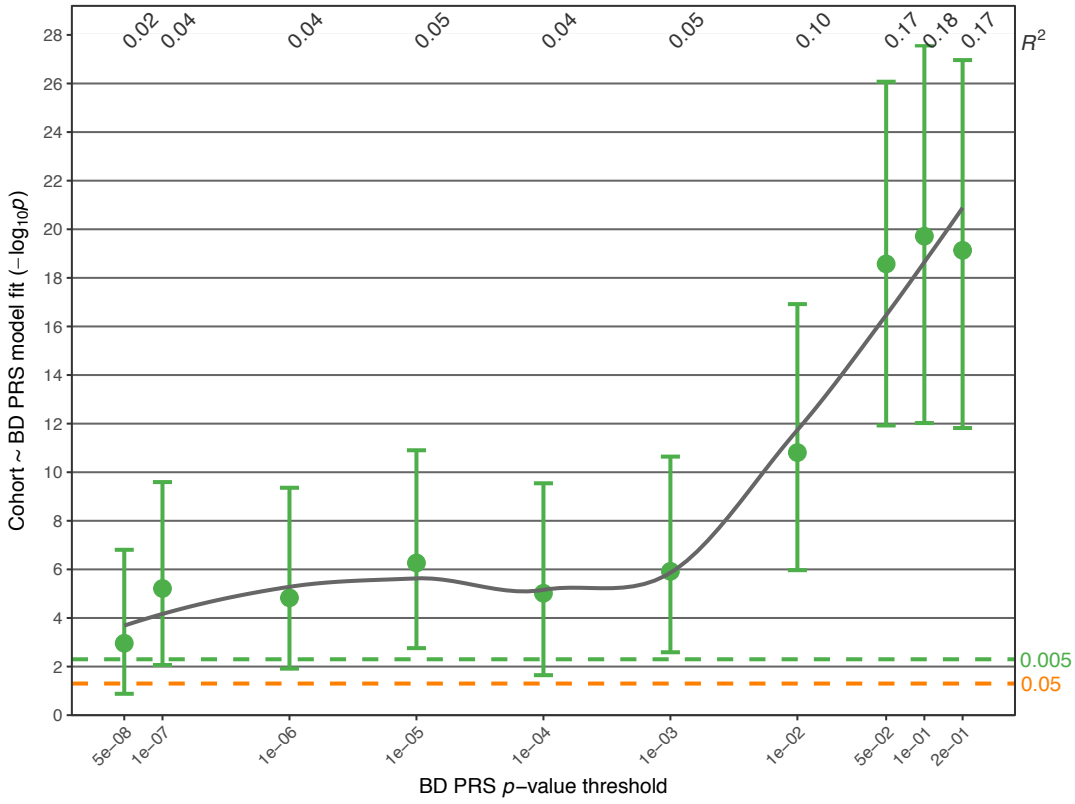


Supplementary Fig. S1I: Boxplots of the LOAD (Alzheimer) PRS.

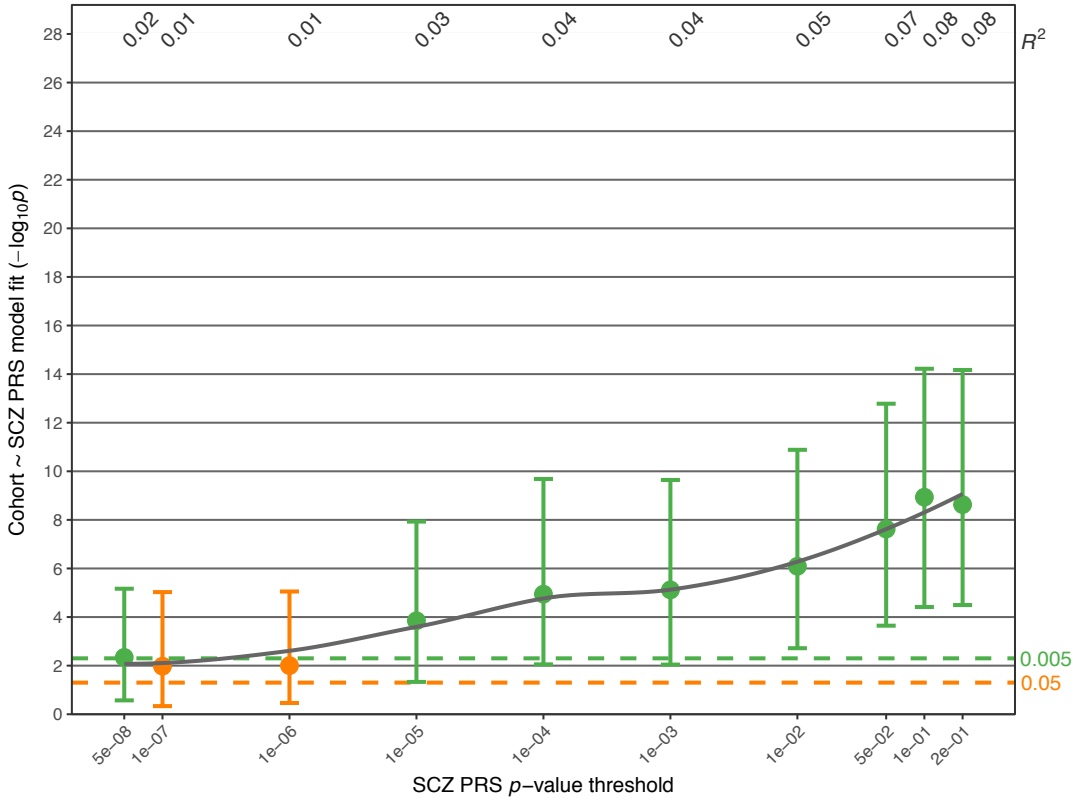


Supplementary Fig. S2: Association analysis comparing PRS in FAM_{BD} cases and $CC_{controls}$. Further details of the plots are described in the legend for Fig. 1. Full association test statistics are shown in Supplementary Table S2.

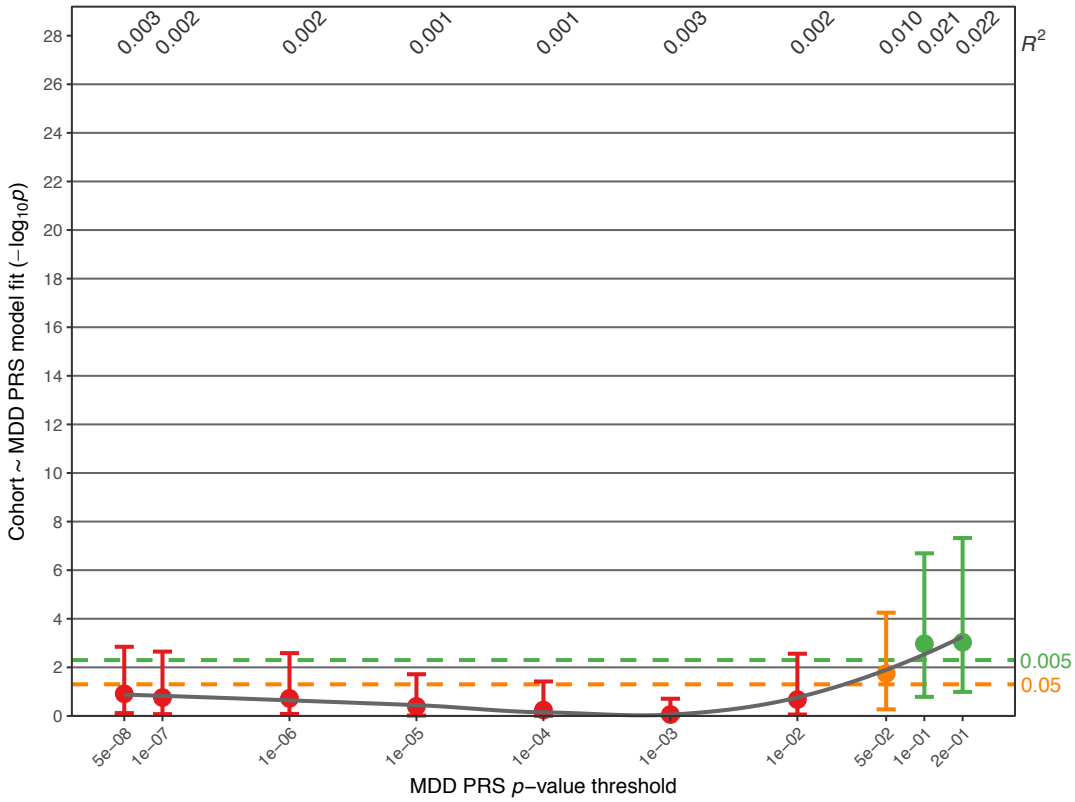
Supplementary Fig. S2A: Association of the BD PRS (data is identical to Fig. 1A).



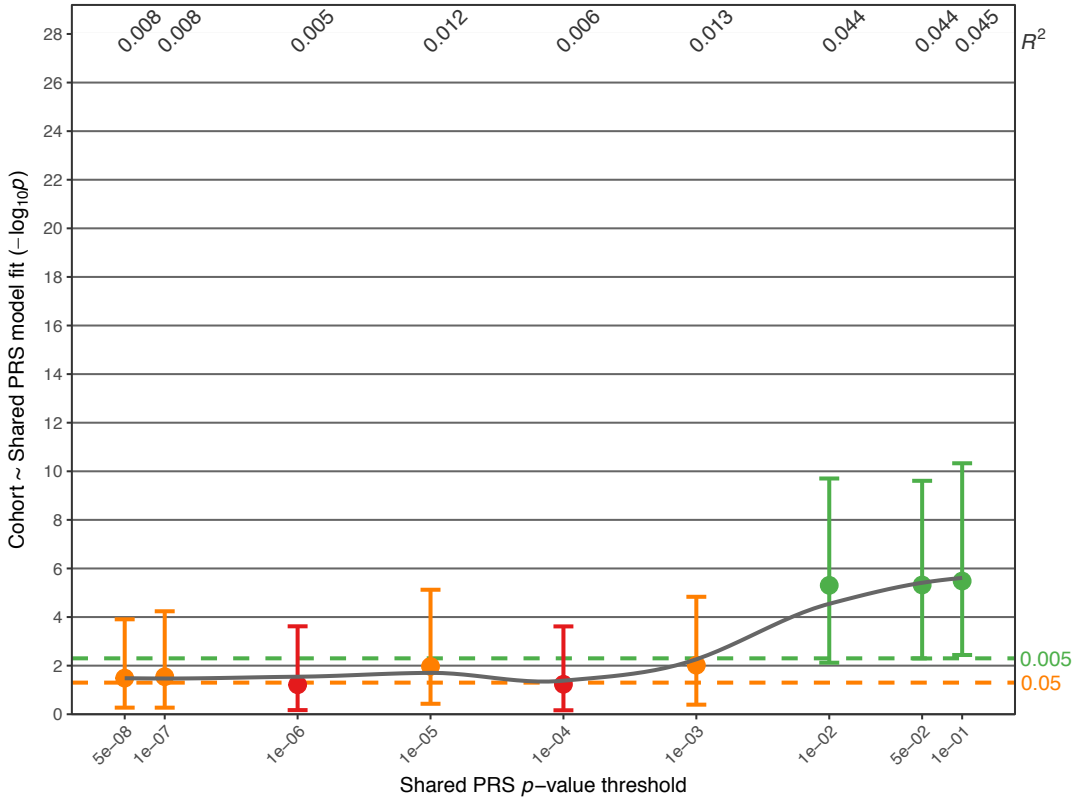
Supplementary Fig. S2B: Association of the SCZ PRS.



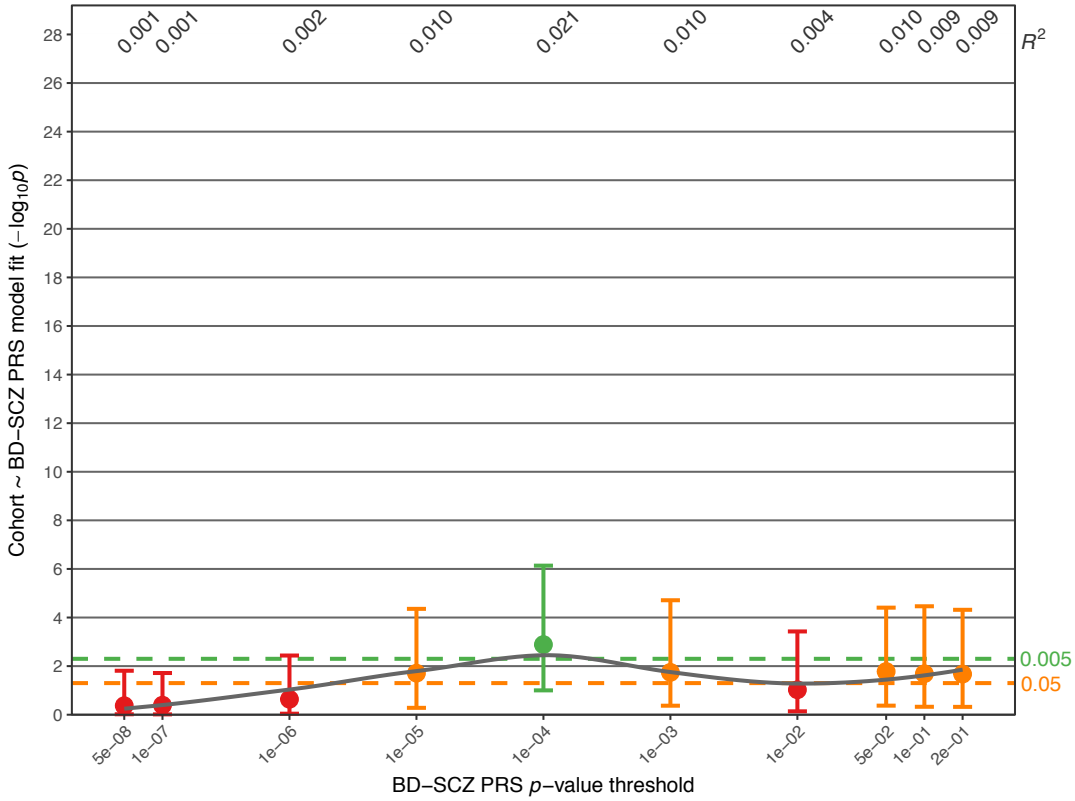
Supplementary Fig. S2C: Association of the MDD PRS.



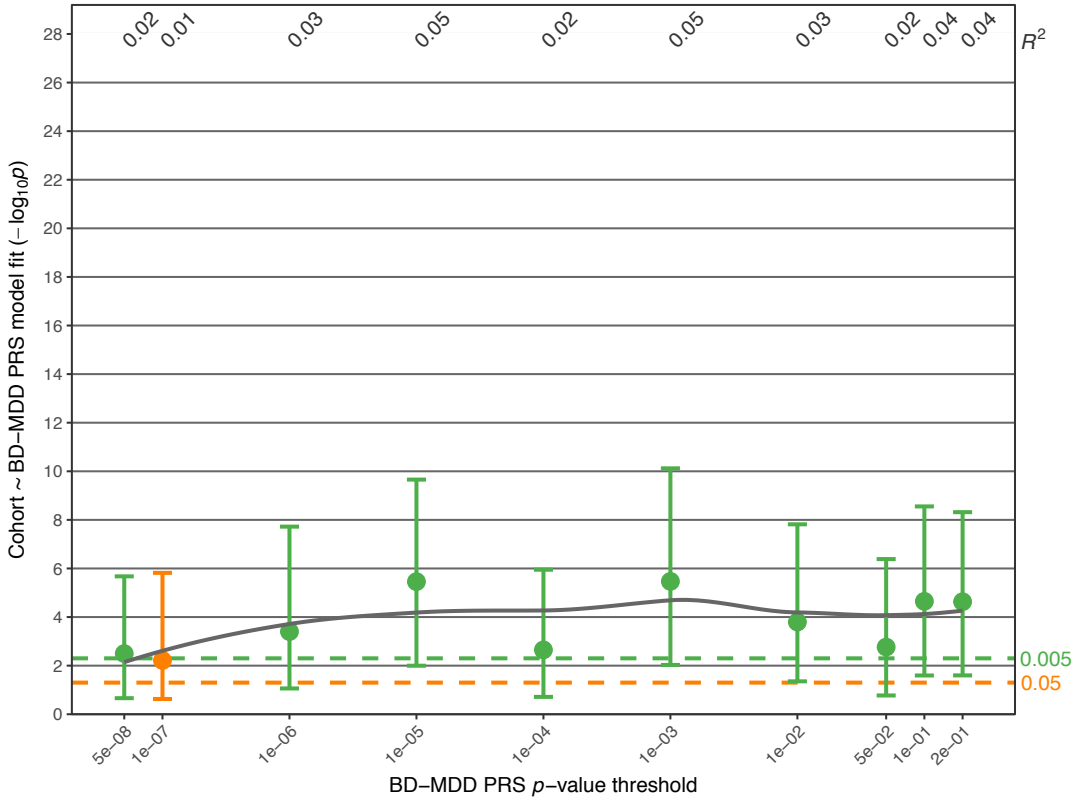
Supplementary Fig. S2D: Association of the *Shared* PRS.



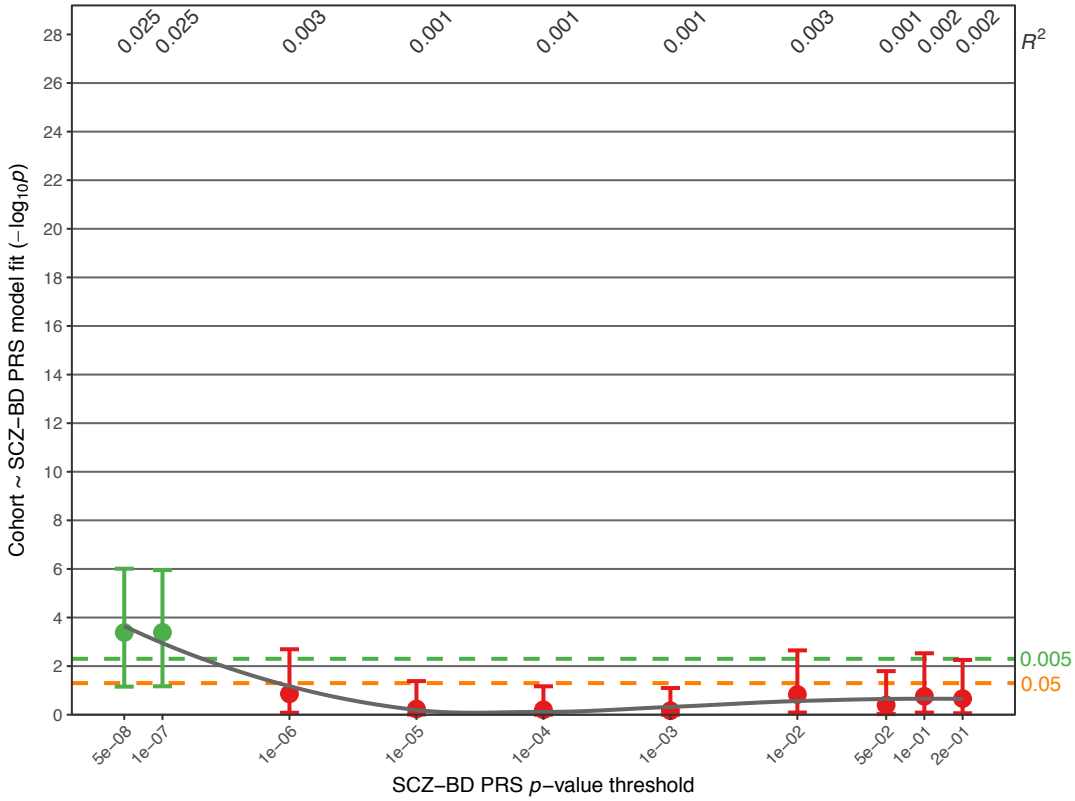
Supplementary Fig. S2E: Association of the BD-SCZ GWIS PRS.



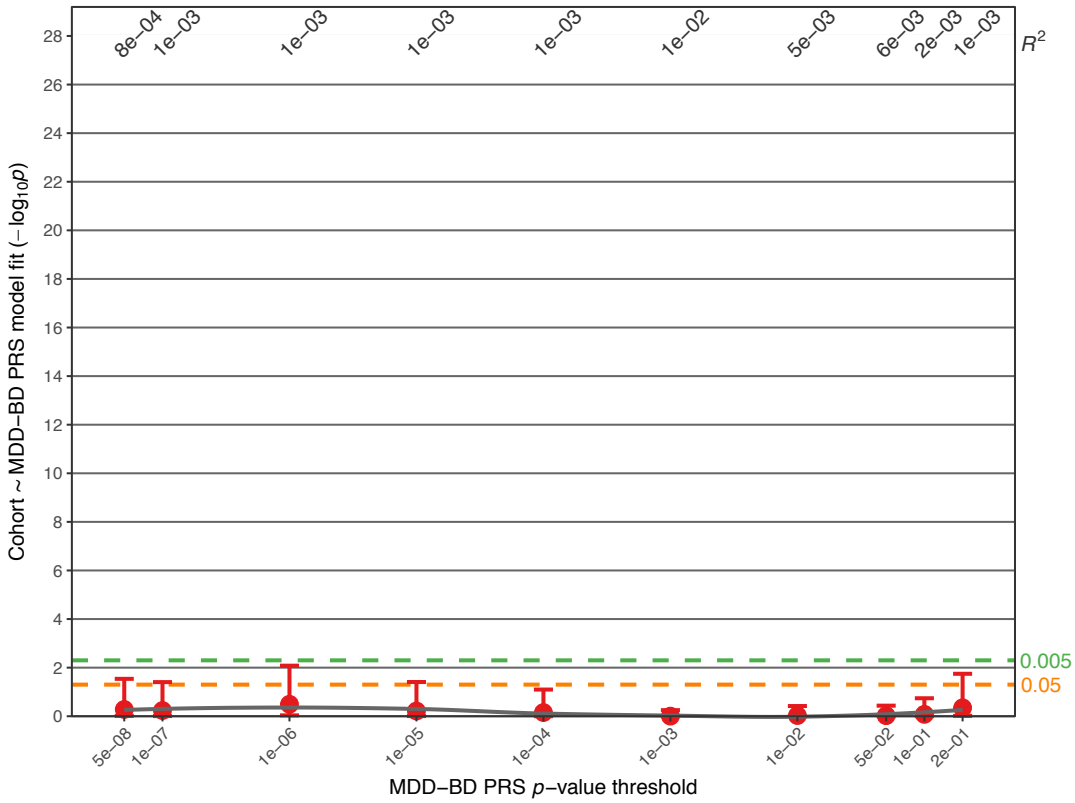
Supplementary Fig. S2F: Association of the BD-MDD GWIS PRS.



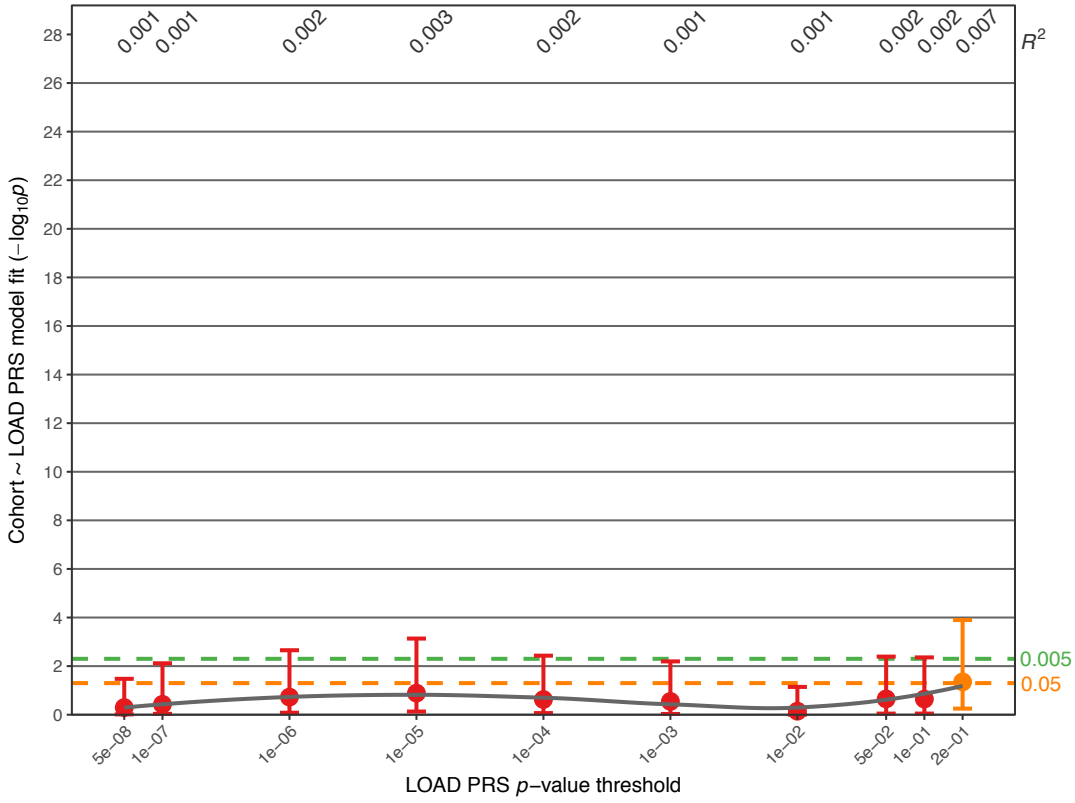
Supplementary Fig. S2G: Association of the SCZ-BD GWIS PRS.



Supplementary Fig. S2H: Association of the MDD-BD GWIS PRS.

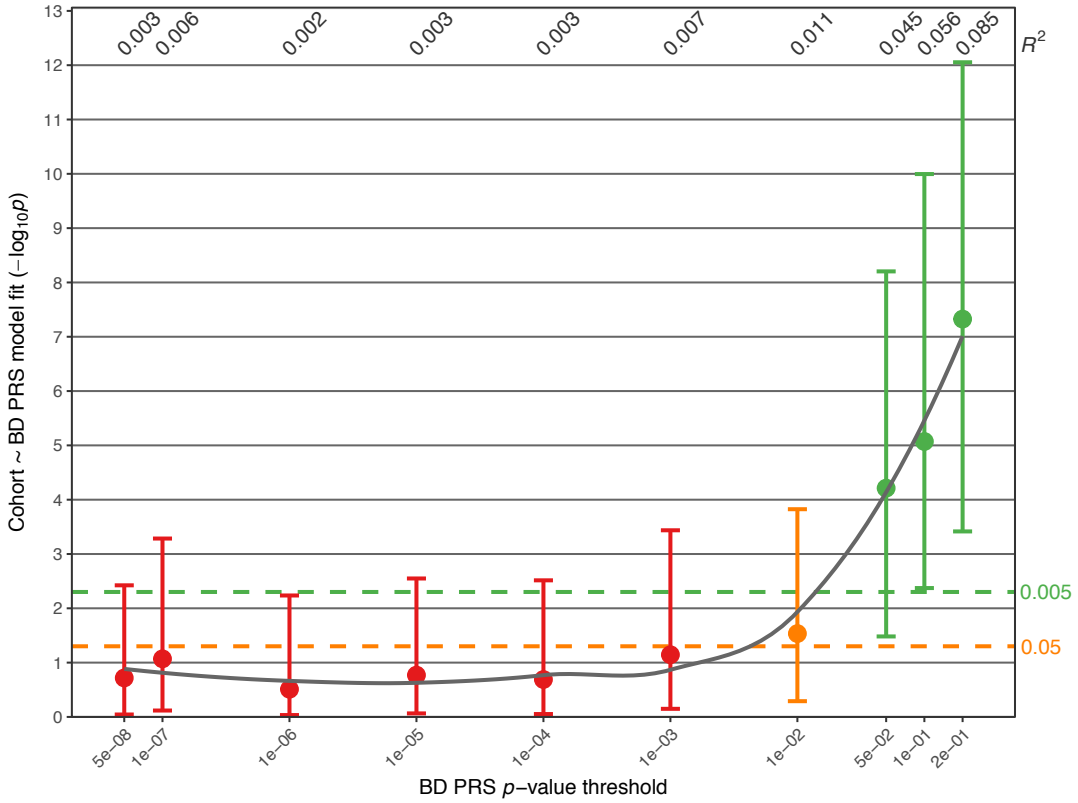


Supplementary Fig. S2I: Association of the LOAD PRS.

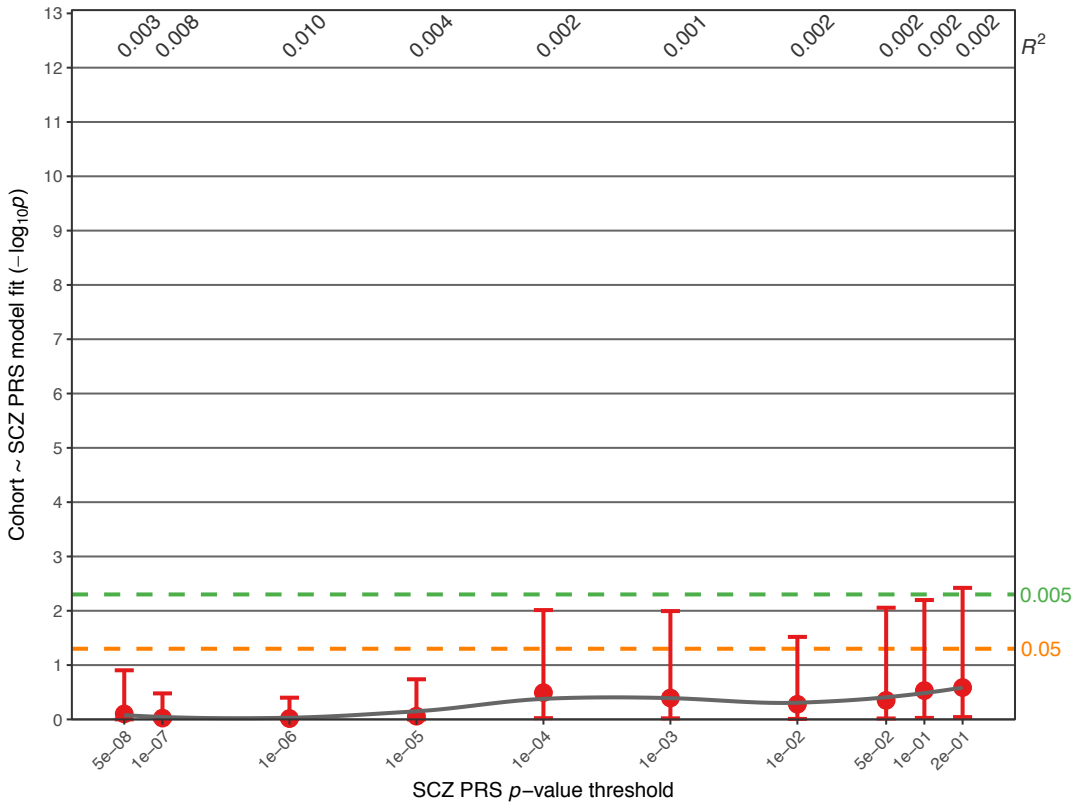


Supplementary Fig. S3: Association analysis comparing PRS in FAM_{BD} cases and sporadic CC_{BD} cases. Further details of the plots are described in the legend for Fig. 1. Full association test statistics are shown in Supplementary Table S3.

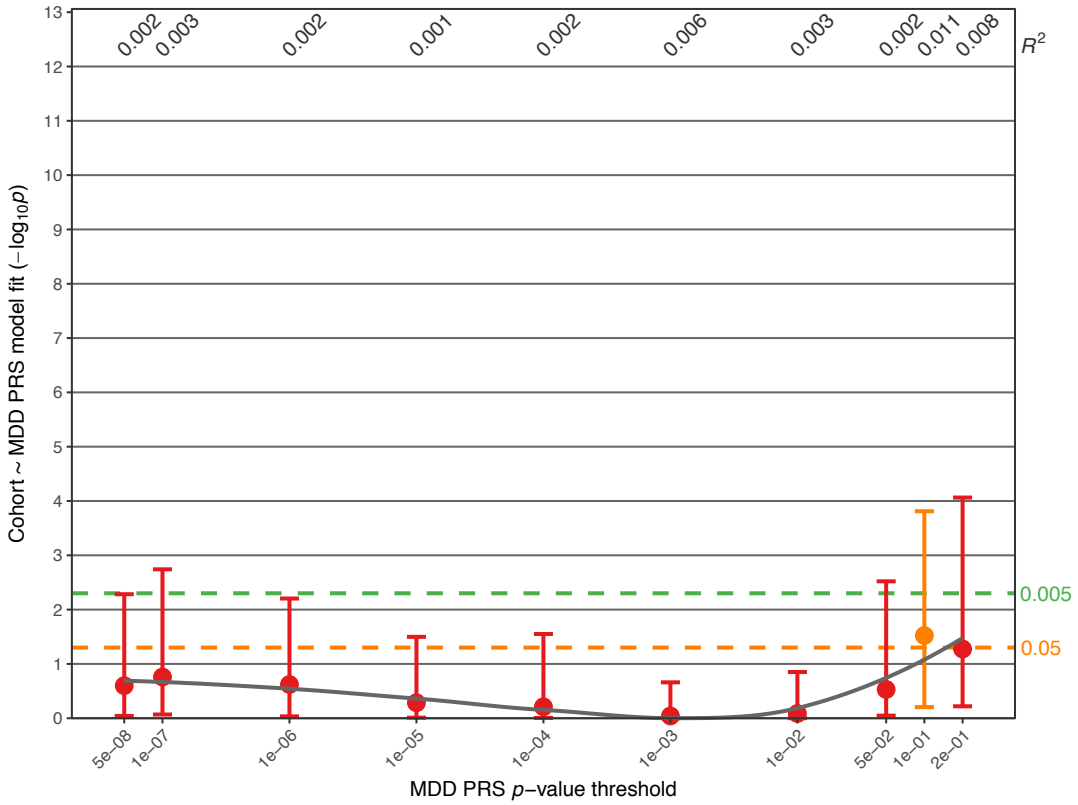
Supplementary Fig. S3A: Association of the BD PRS (data is identical to Fig. 1C).



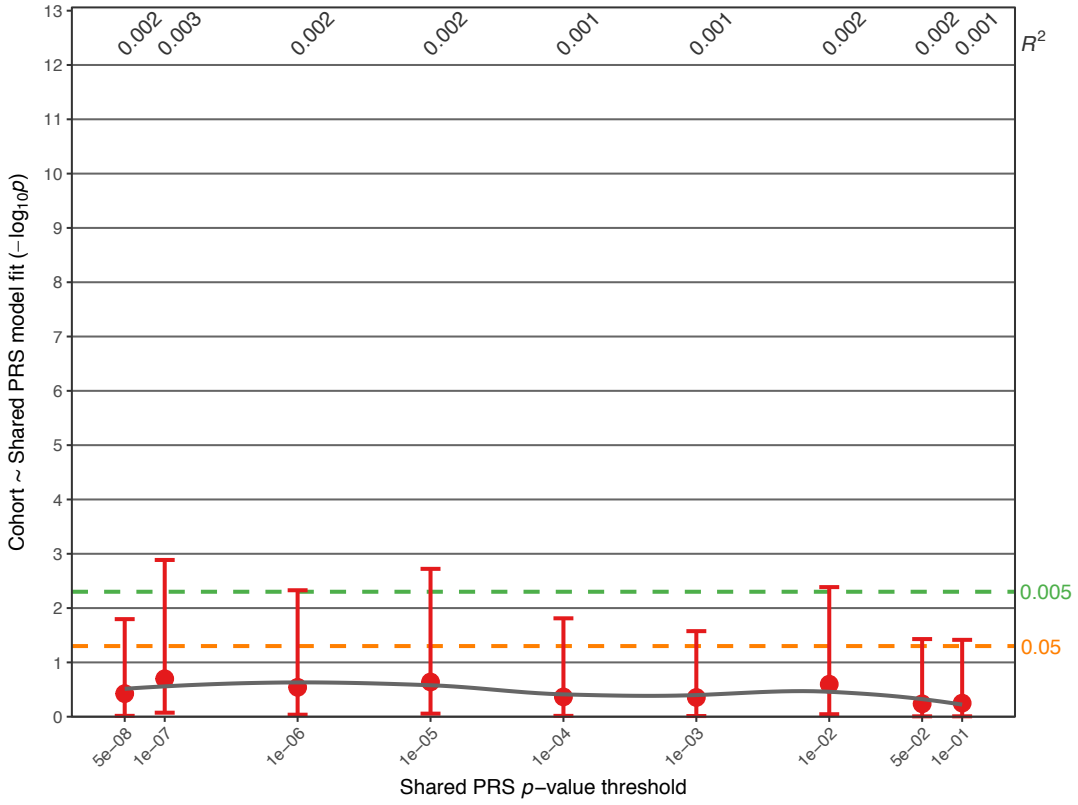
Supplementary Fig. S3B: Association of the SCZ PRS.



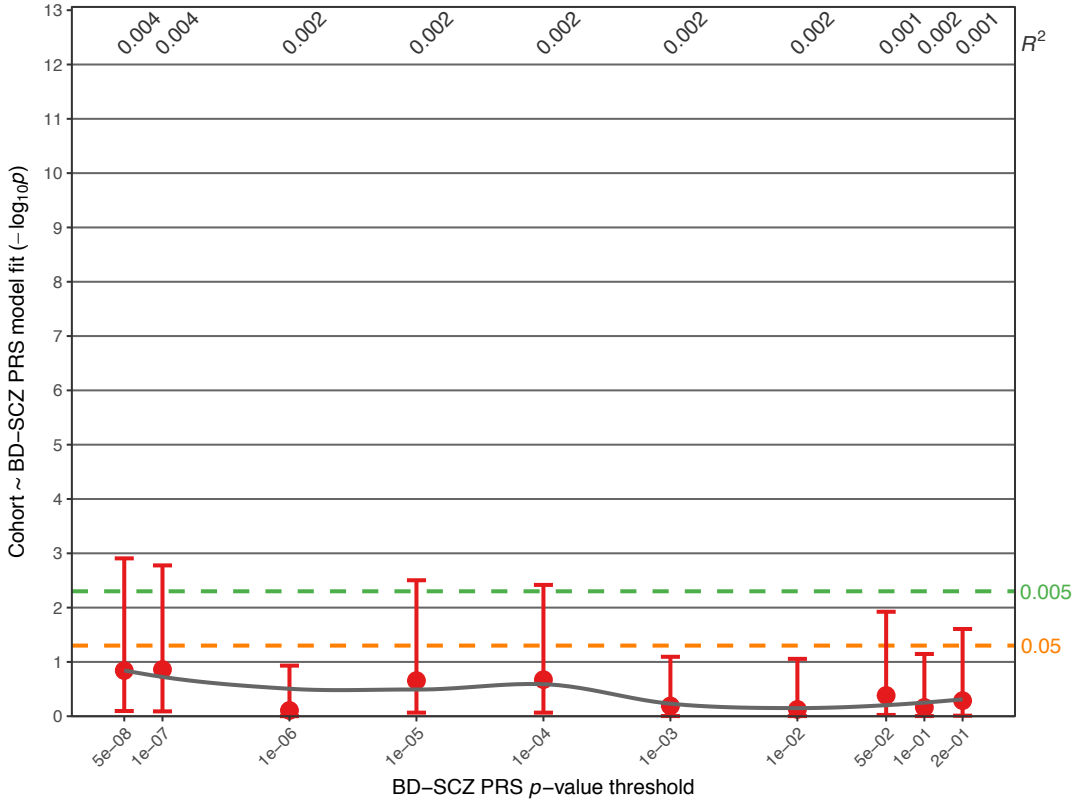
Supplementary Fig. S3C: Association of the MDD PRS.



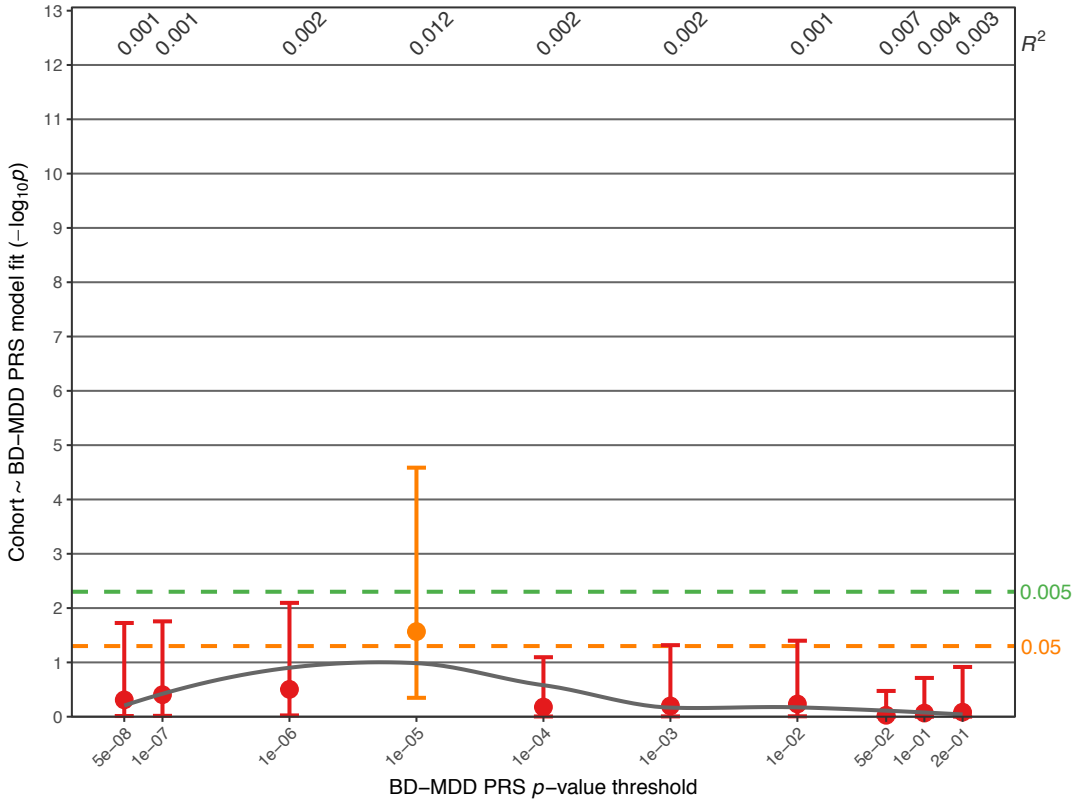
Supplementary Fig. S3D: Association of the *Shared* PRS.



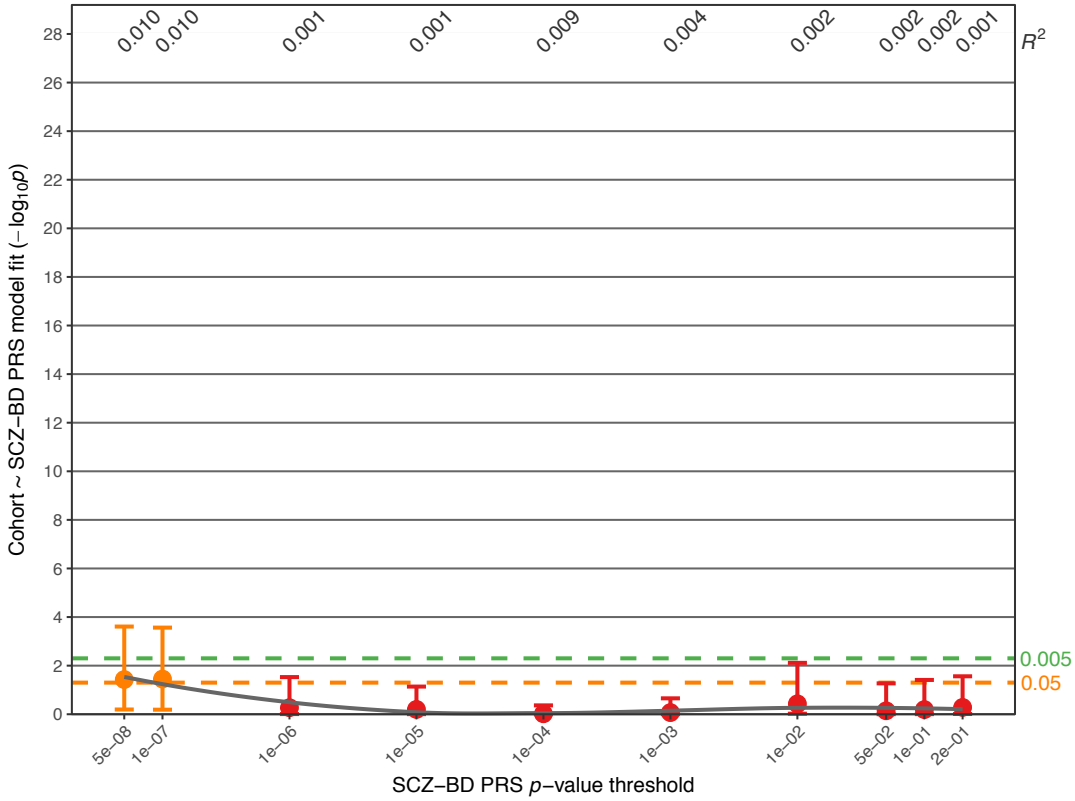
Supplementary Fig. S3E: Association of the BD-SCZ GWIS PRS.



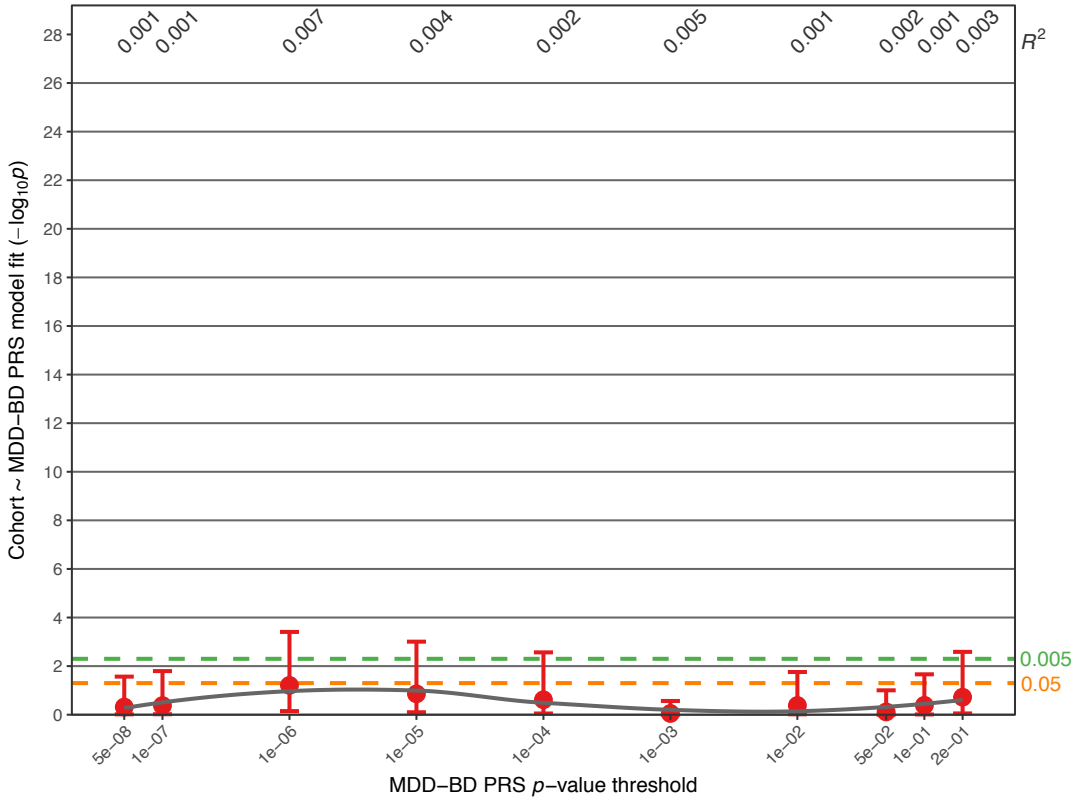
Supplementary Fig. S3F: Association of the BD-MDD GWIS PRS.



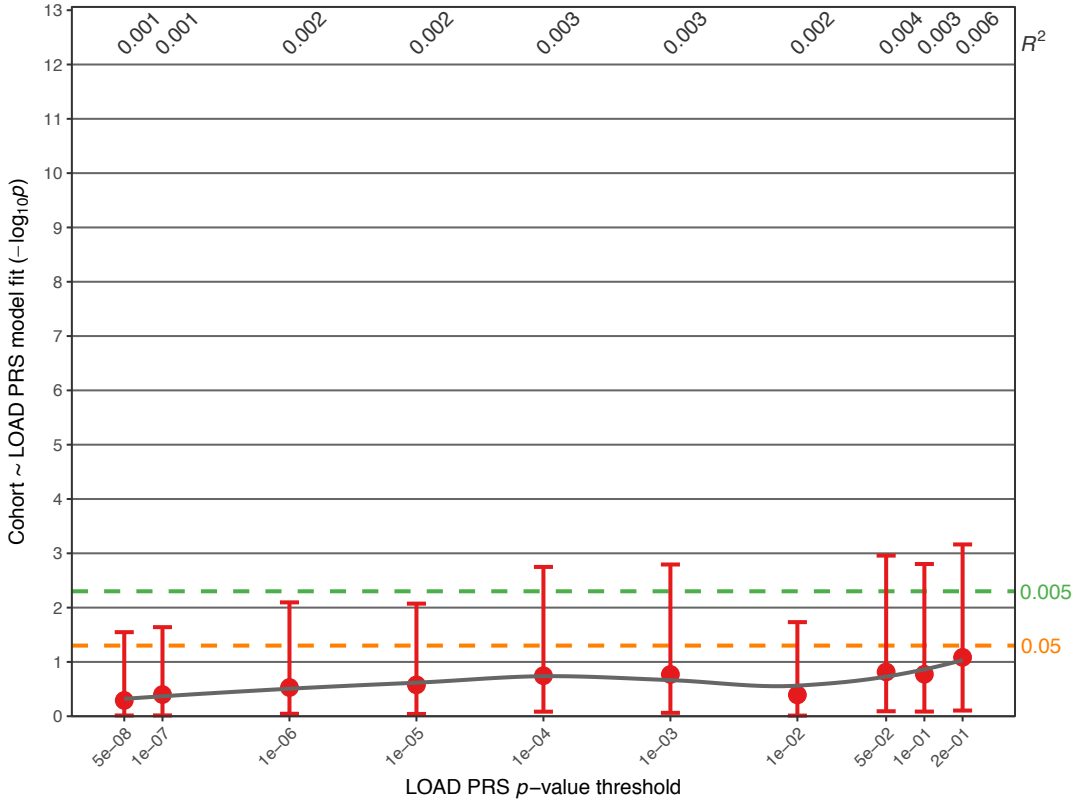
Supplementary Fig. S3G: Association of the SCZ-BD GWIS PRS.



Supplementary Fig. S3H: Association of the MDD-BD GWIS PRS.

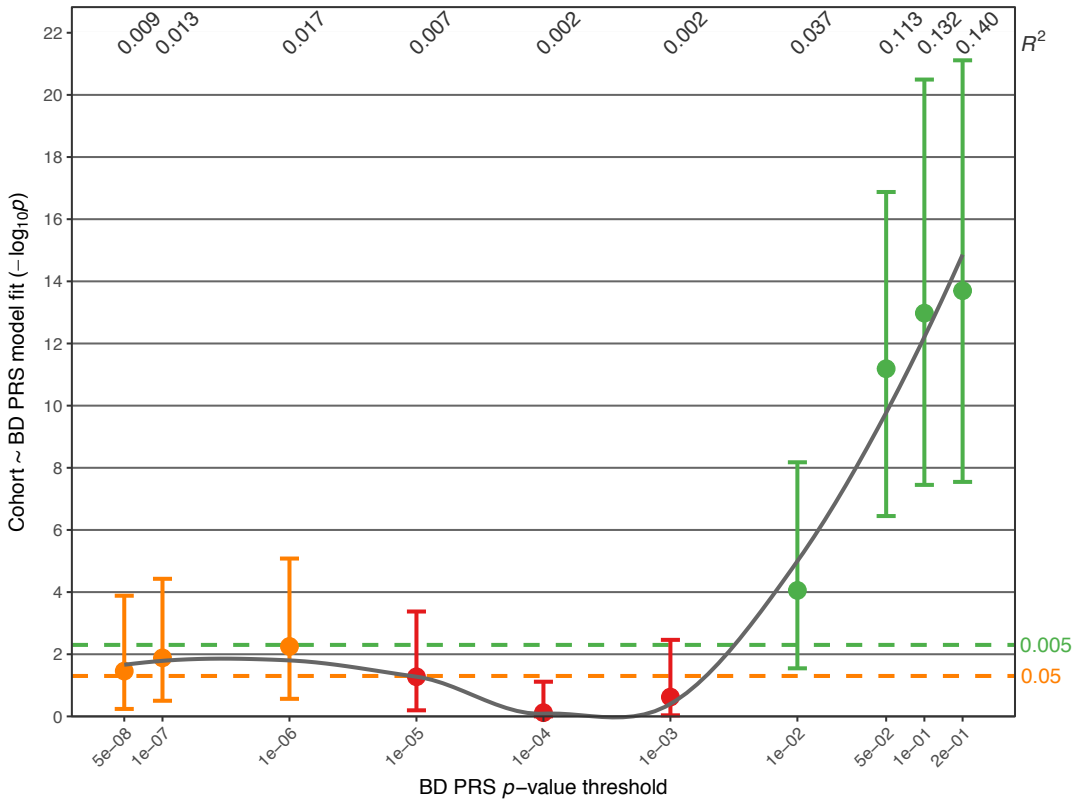


Supplementary Fig. S3I: Association of the LOAD PRS.

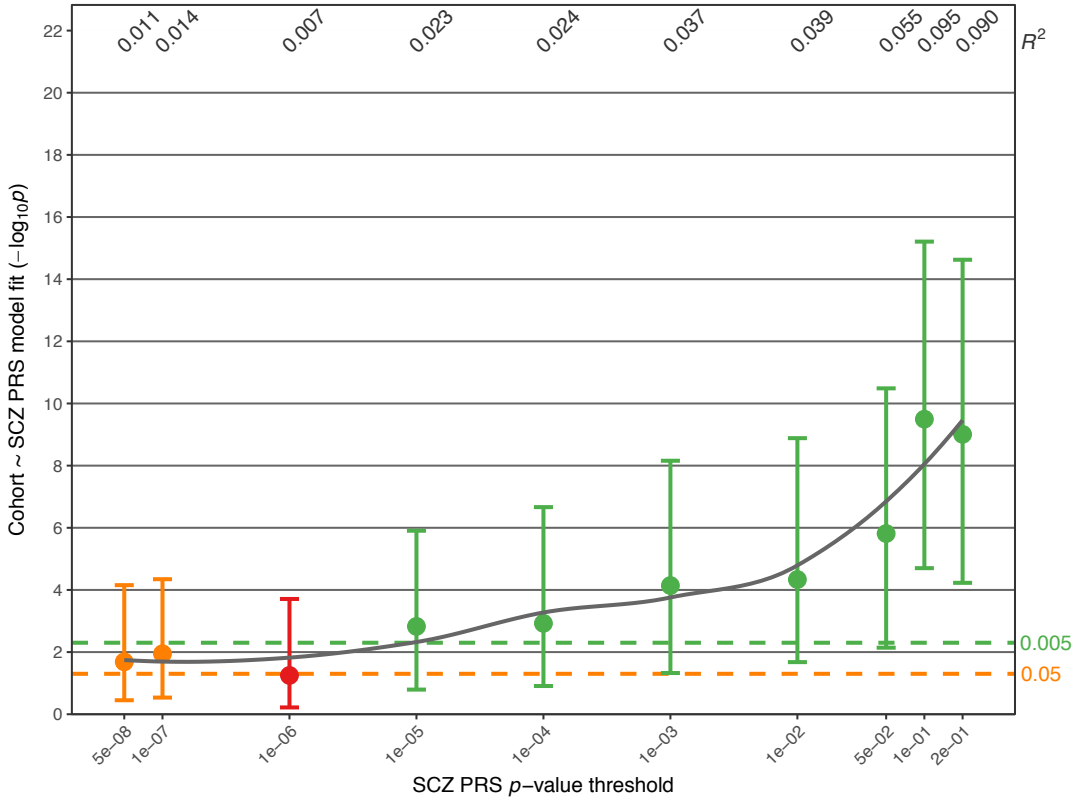


Supplementary Fig. S4: Association analysis comparing PRS in $FAM_{unaffected}$ and $CC_{controls}$. Further details of the plots are described in the legend for Fig. 1. Full association test statistics are shown in Supplementary Table S4.

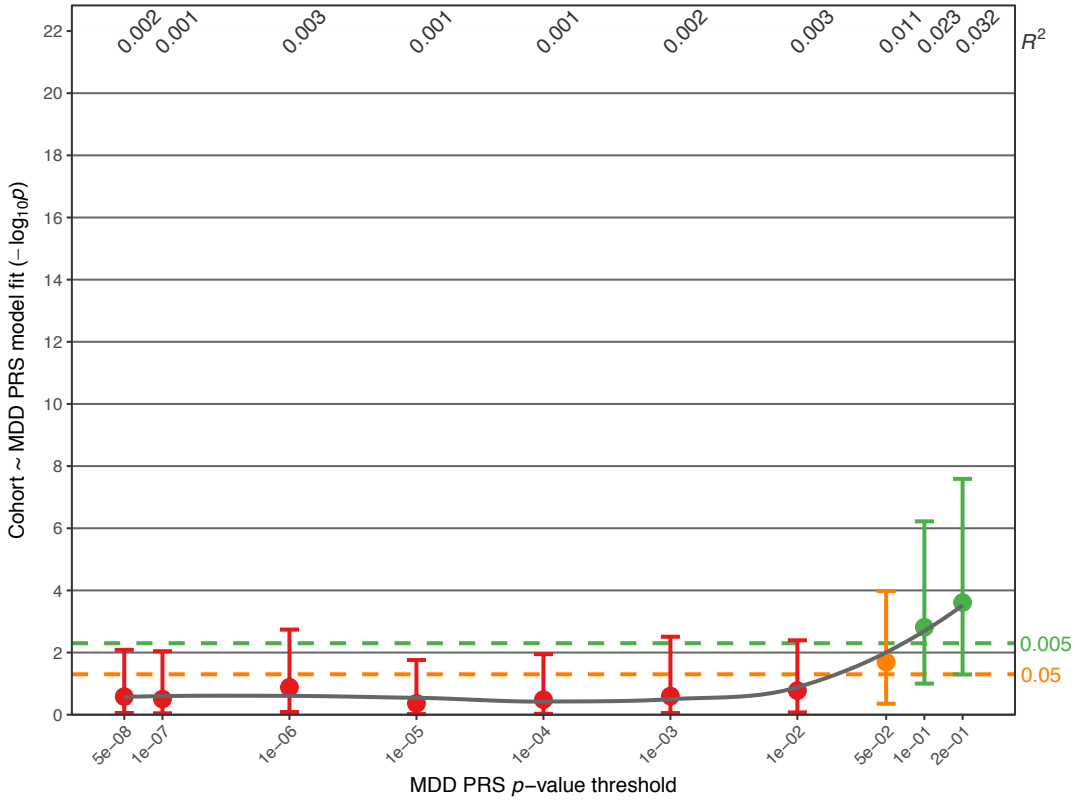
Supplementary Fig. S4A: Association of the BD PRS (data is identical to Fig. 1E).



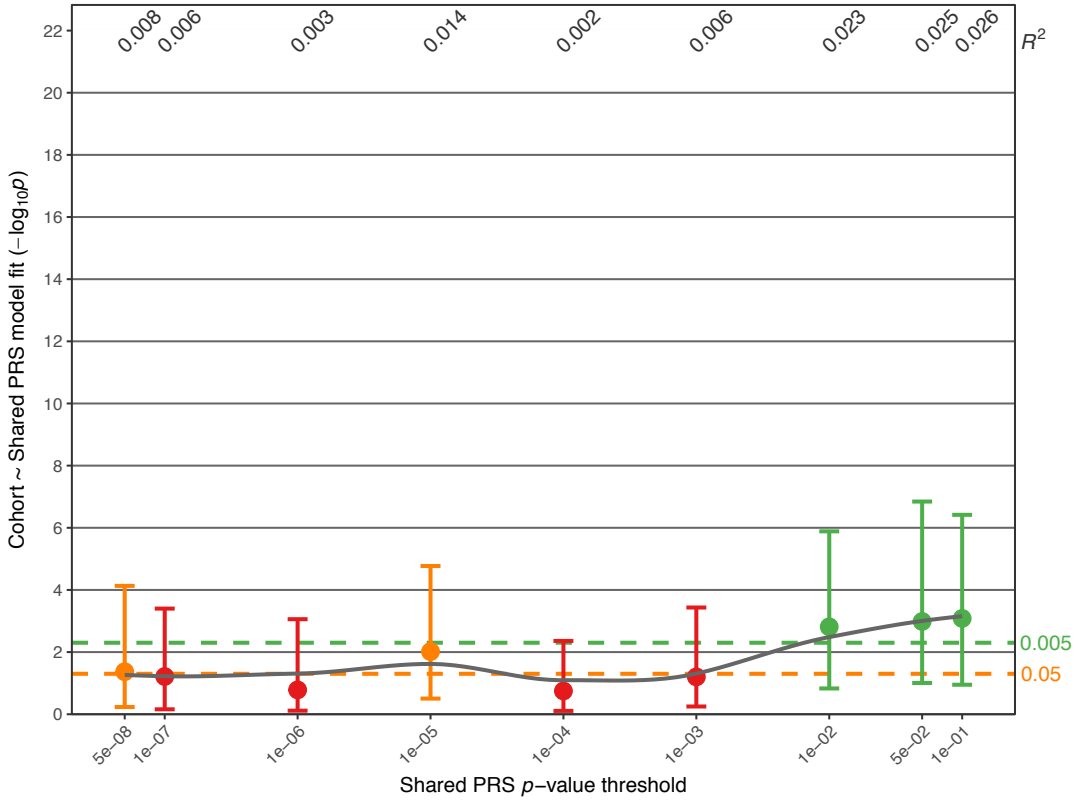
Supplementary Fig. S4B: Association of the SCZ PRS.



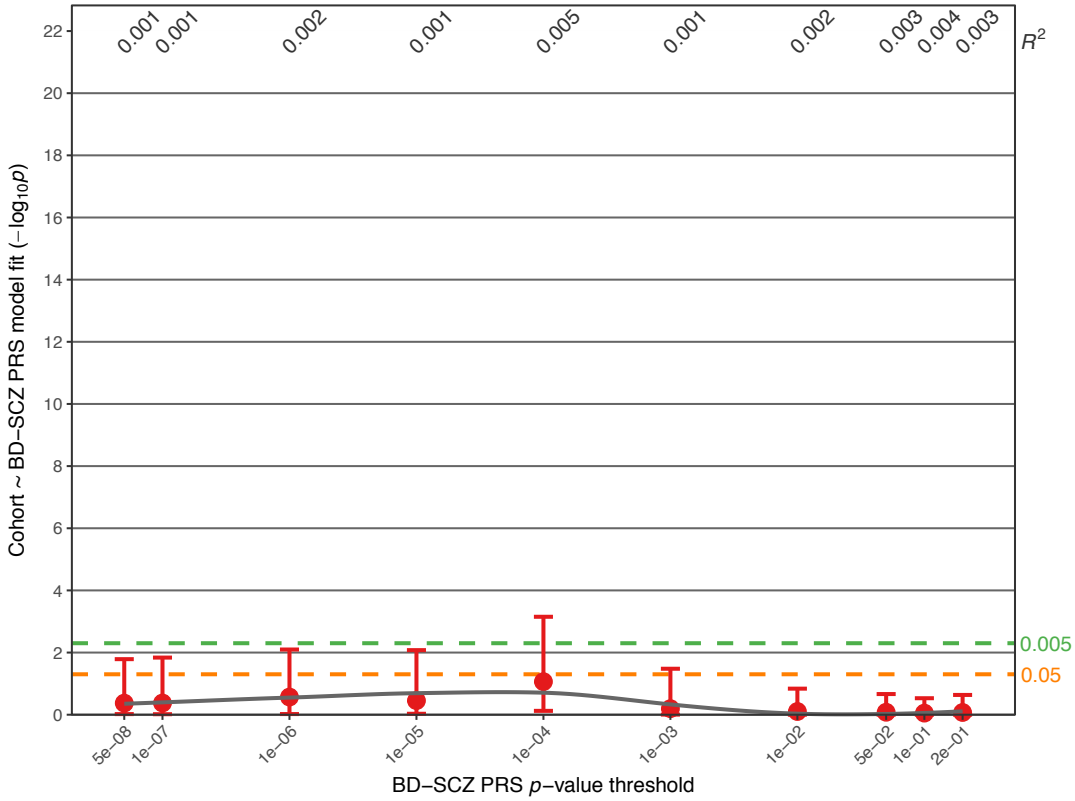
Supplementary Fig. S4C: Association of the MDD PRS.



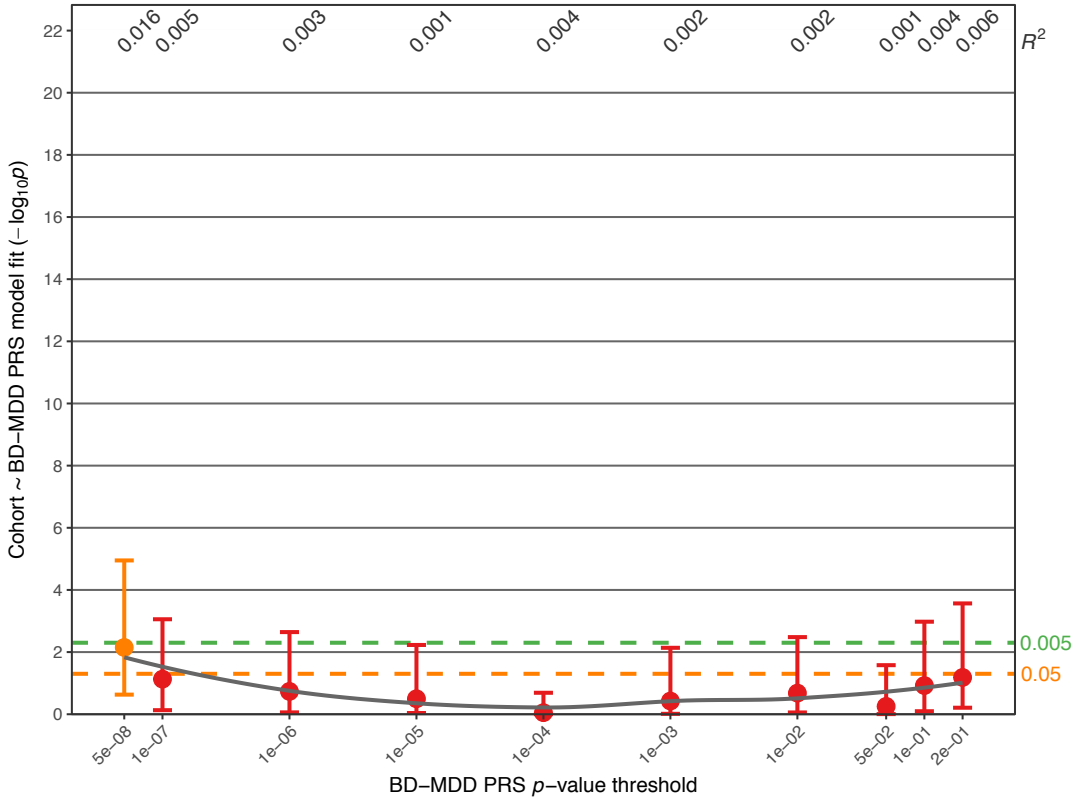
Supplementary Fig. S4D: Association of the *Shared* PRS.



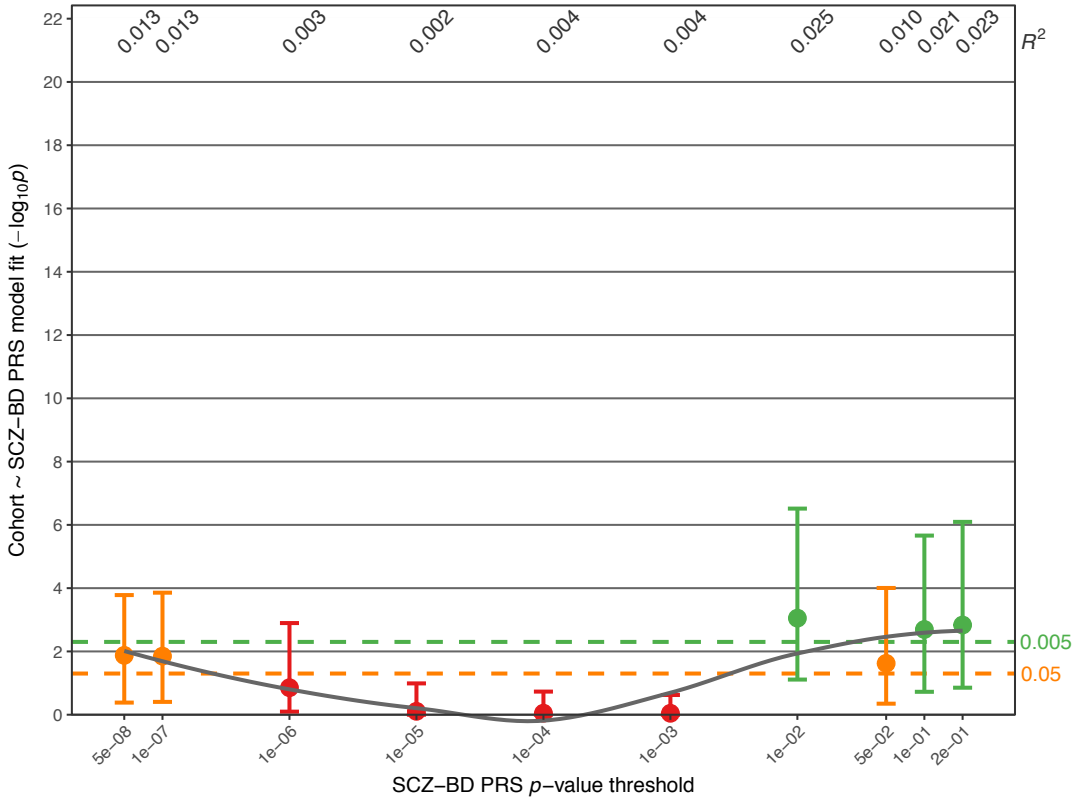
Supplementary Fig. S4E: Association of the BD-SCZ GWIS PRS.



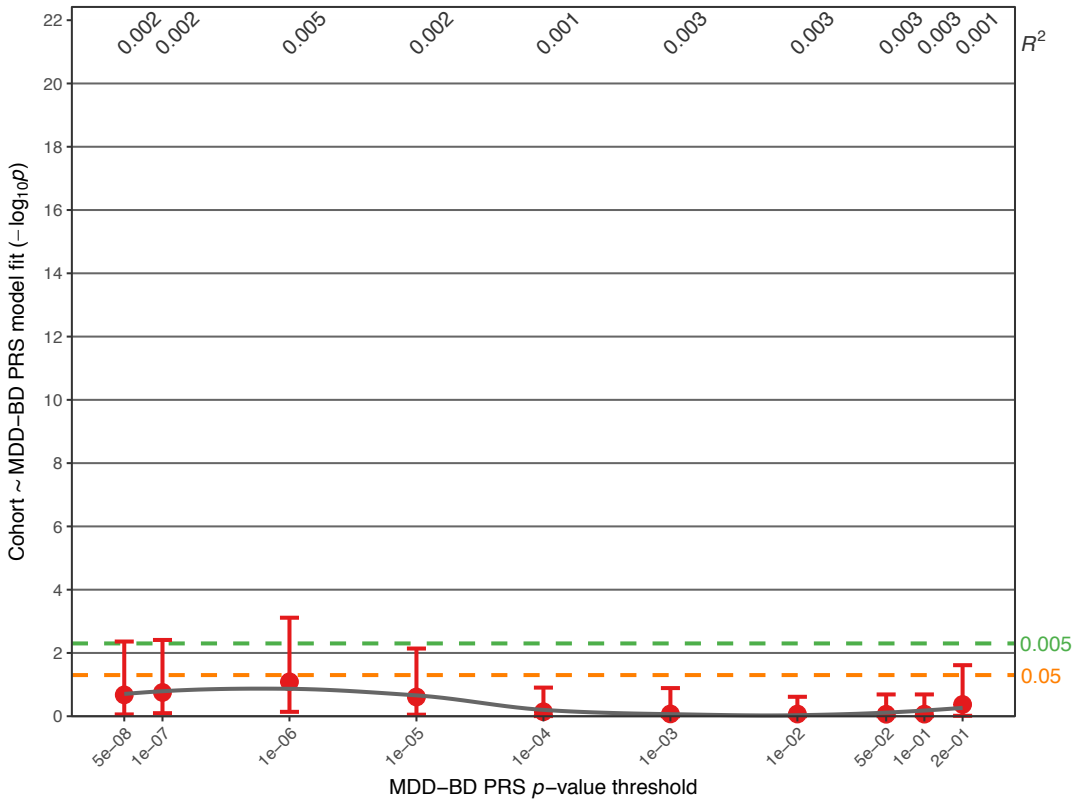
Supplementary Fig. S4F: Association of the BD-MDD GWIS PRS.



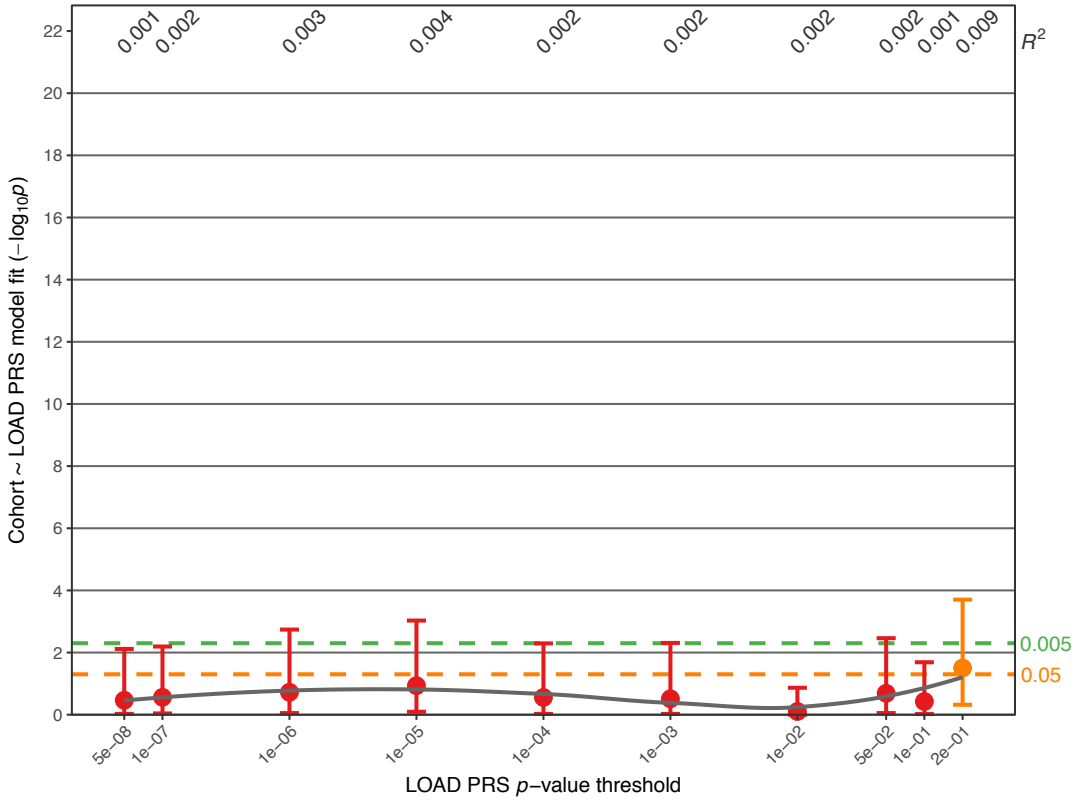
Supplementary Fig. S4G: Association of the SCZ-BD GWIS PRS.



Supplementary Fig. S4H: Association of the MDD-BD GWIS PRS.

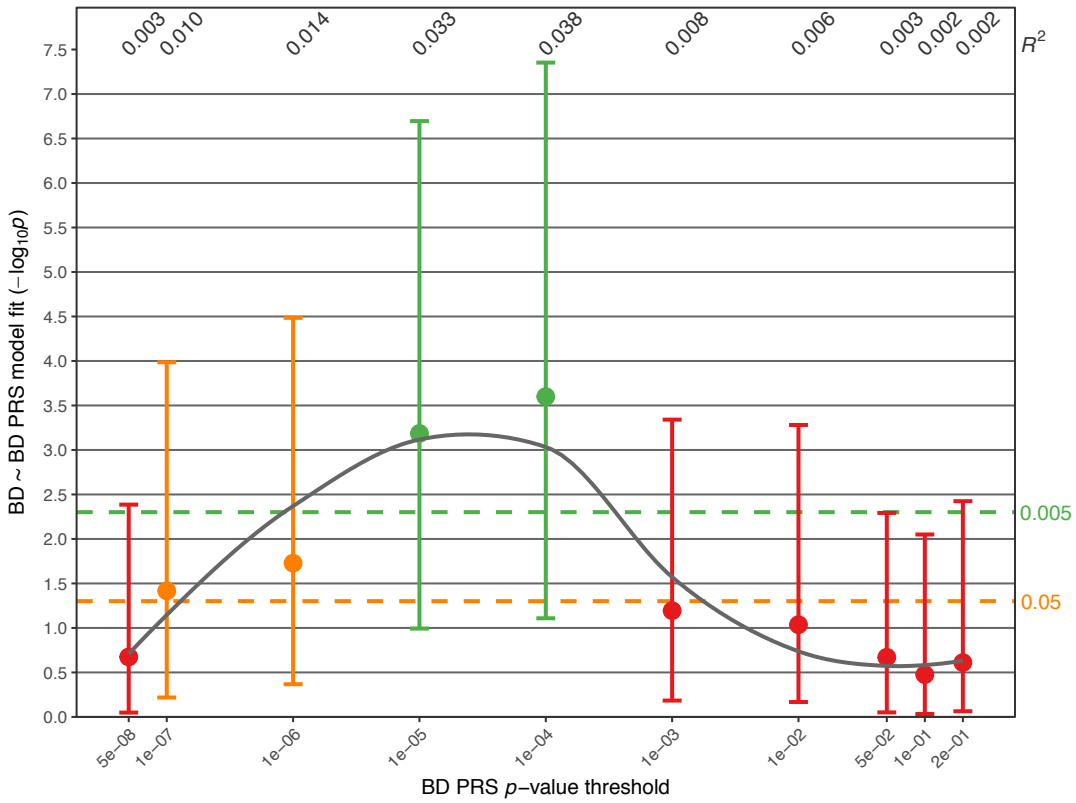


Supplementary Fig. S4I: Association of the LOAD PRS.

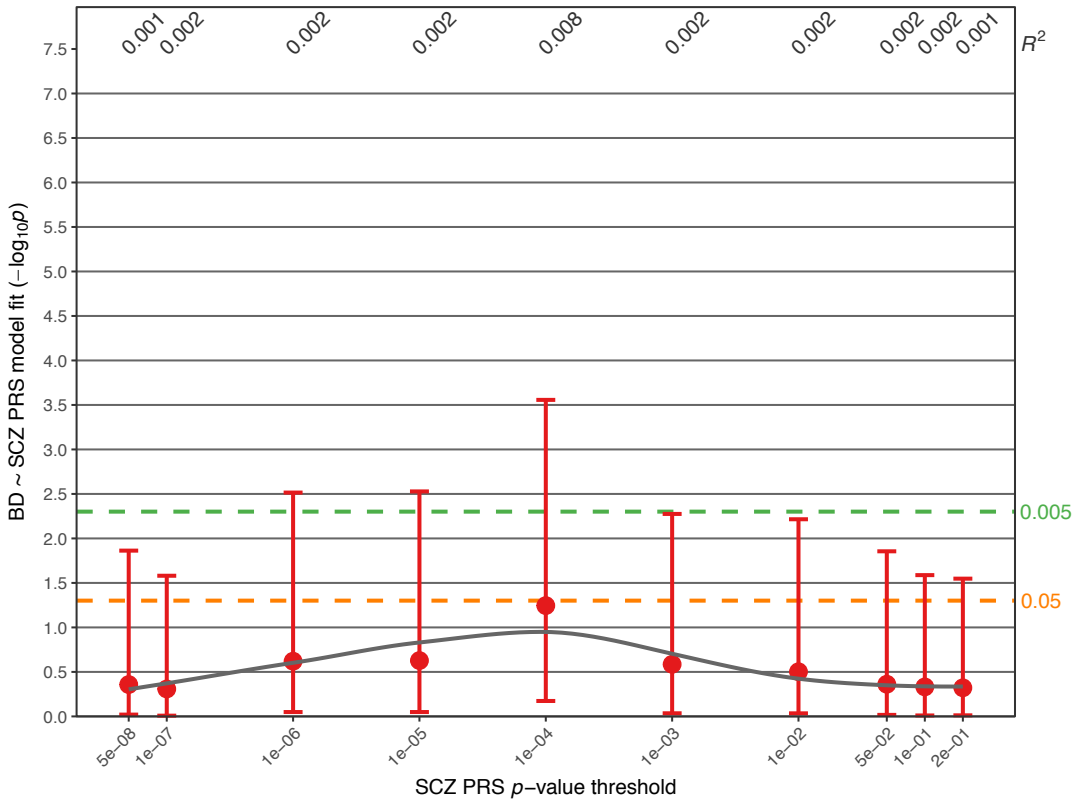


Supplementary Fig. S5: Association analysis comparing PRS in FAM_{BD} cases and $FAM_{unaffected}$. Further details of the plots are described in the legends for Figs. 1 and 2. Full association test statistics are shown in Supplementary Table S5.

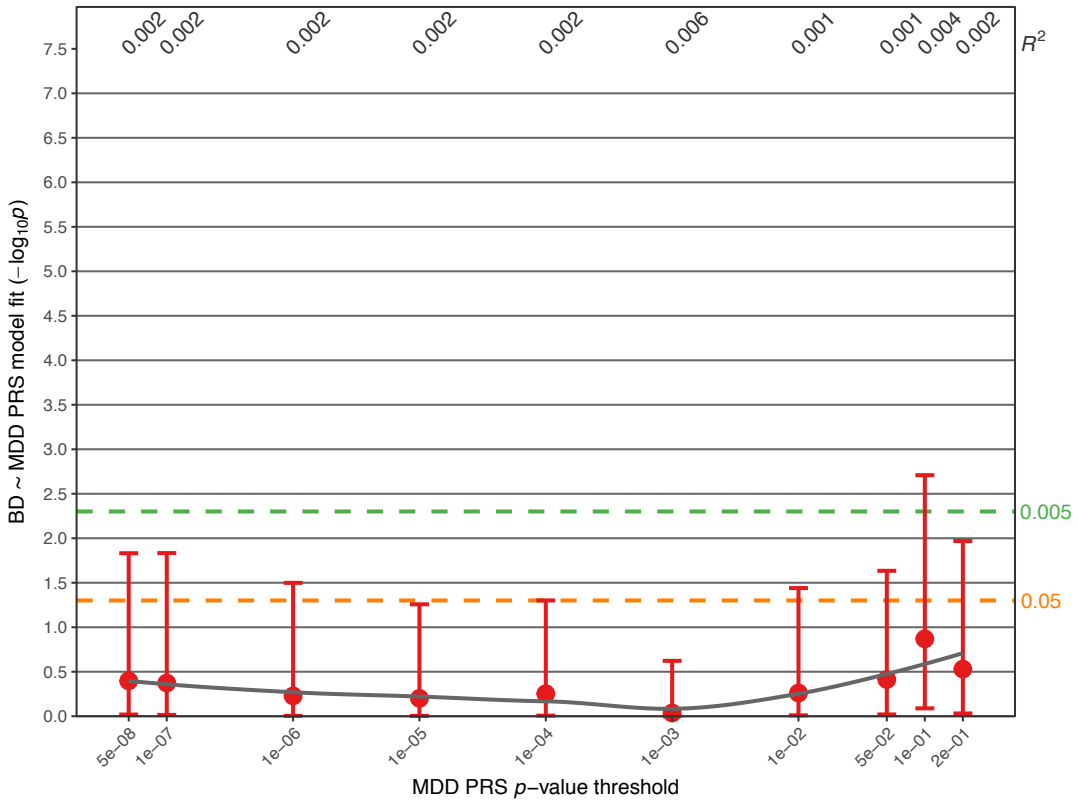
Supplementary Fig. S5A: Association of the BD PRS (data is identical to Fig. 2A).



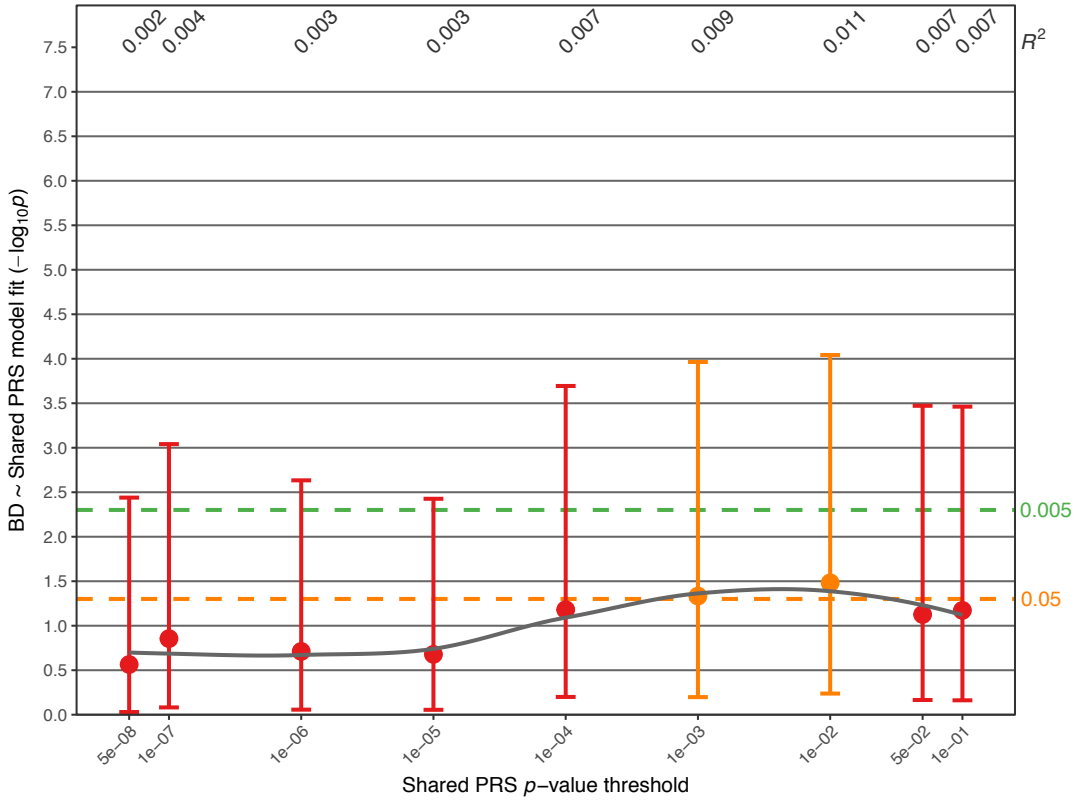
Supplementary Fig. S5B: Association of the SCZ PRS.



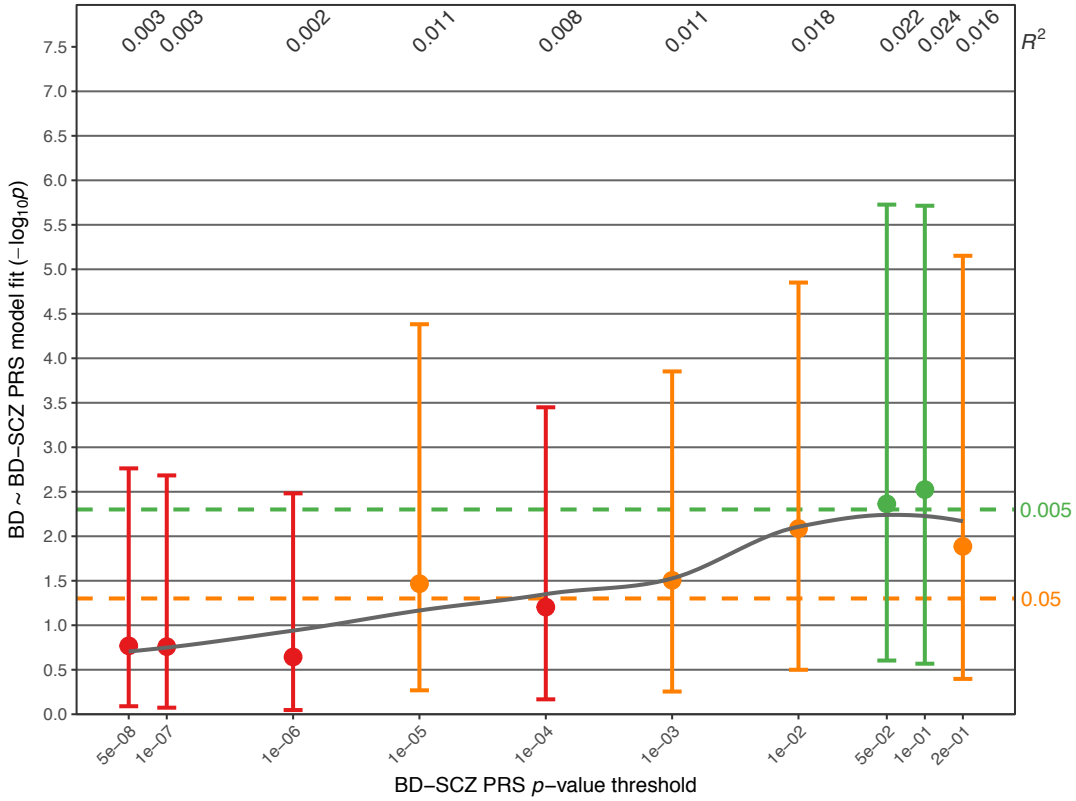
Supplementary Fig. S5C: Association of the MDD PRS.



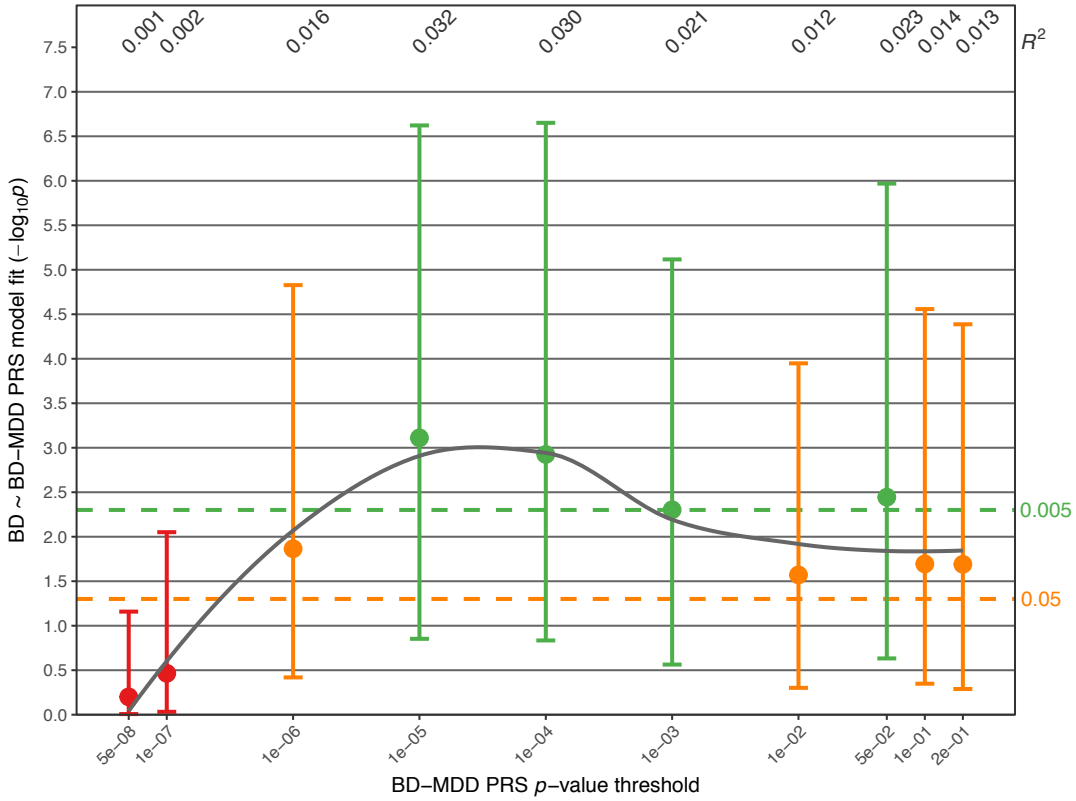
Supplementary Fig. S5D: Association of the *Shared* PRS.



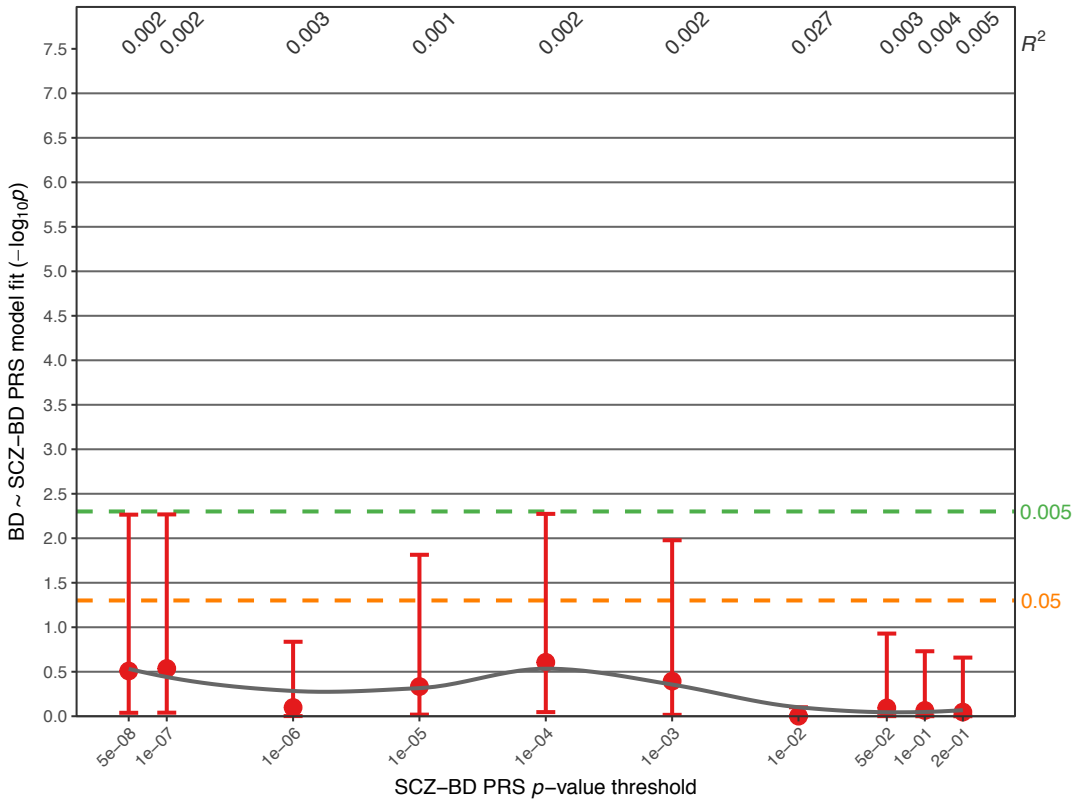
Supplementary Fig. S5E: Association of the BD-SCZ GWIS PRS.



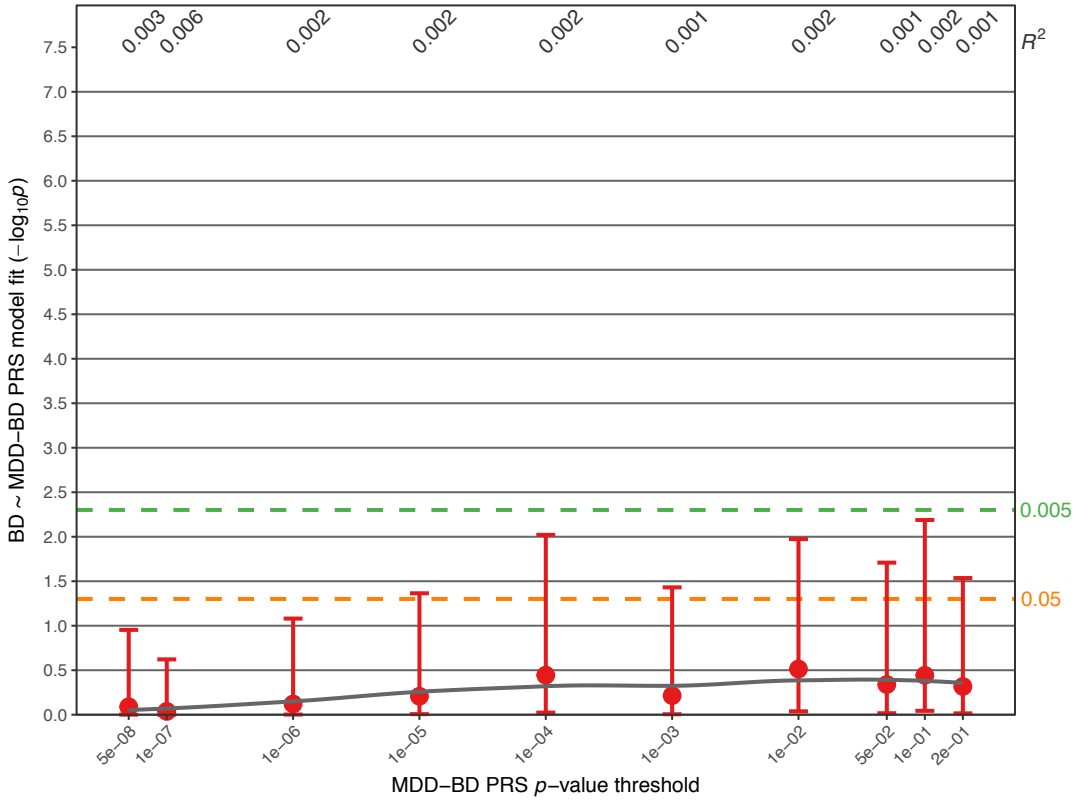
Supplementary Fig. S5F: Association of the BD-MDD GWIS PRS.



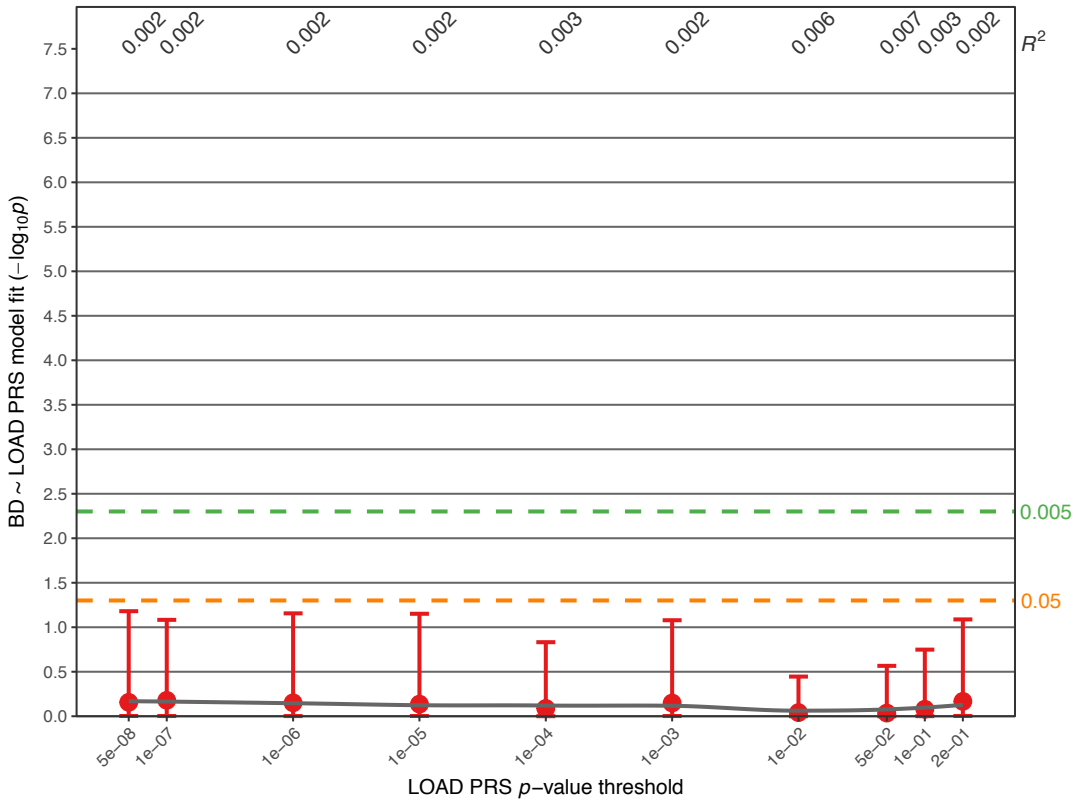
Supplementary Fig. S5G: Association of the SCZ-BD GWIS PRS.



Supplementary Fig. S5H: Association of the MDD-BD GWIS PRS.

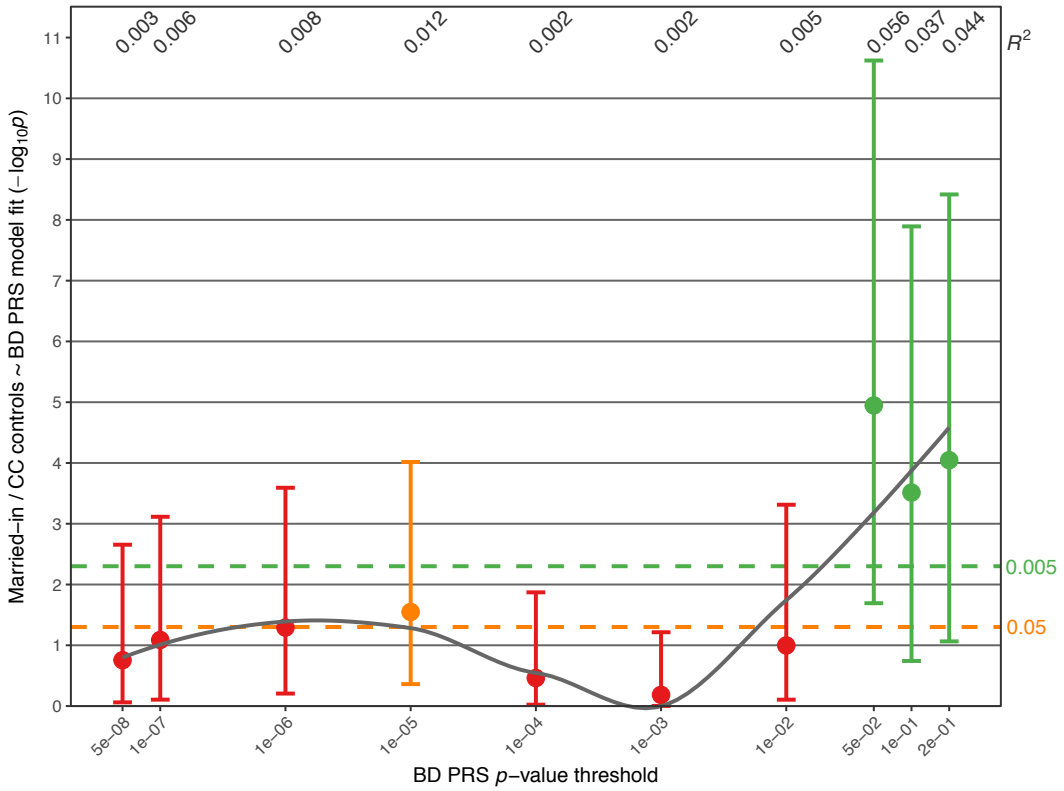


Supplementary Fig. S5l: Association of the LOAD PRS.

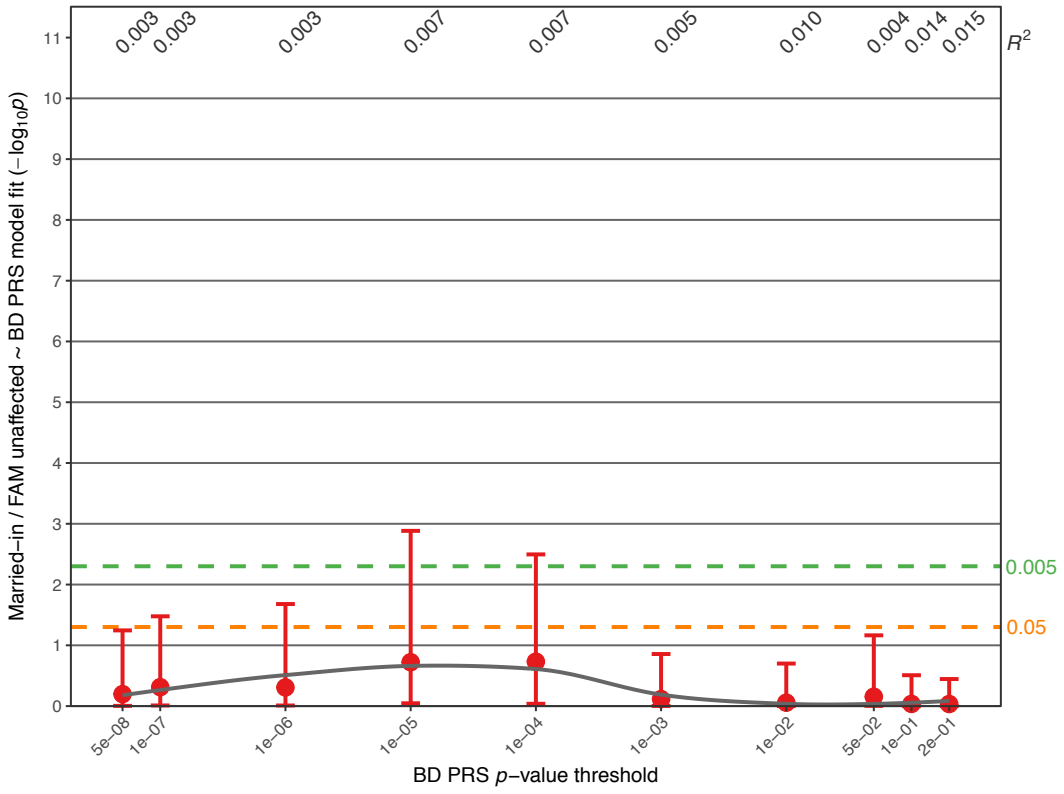


Supplementary Fig. S6: Analysis of assortative mating. Further details regarding the analysis and plots are described in the legend for Fig. 2C. Full association test statistics are shown in Supplementary Table S6.

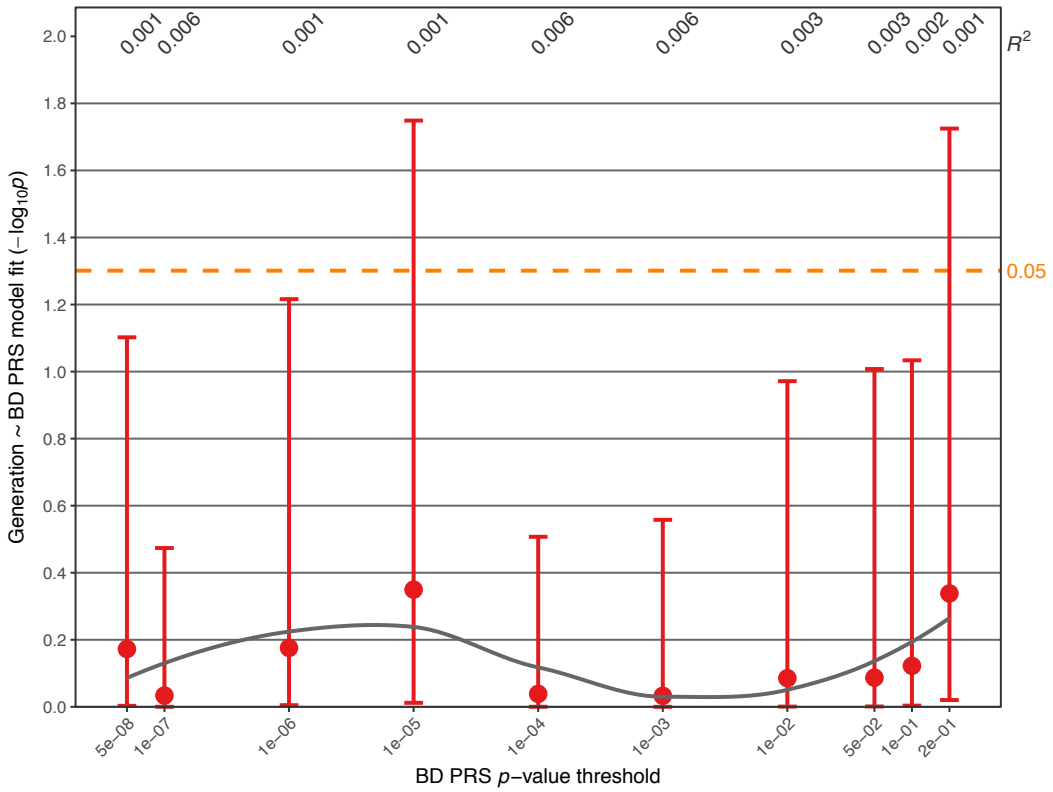
Supplementary Fig. S6A: Association analysis comparing the BD PRS in unaffected married-in family members and $CC_{controls}$.



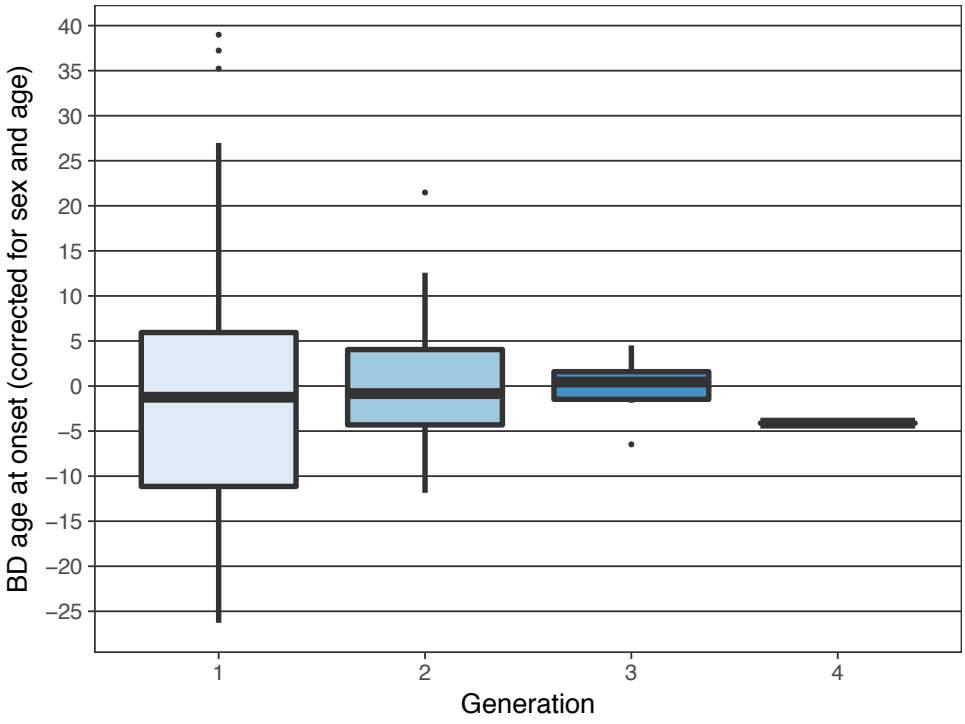
Supplementary Fig. S6B: Association analysis comparing the BD PRS in unaffected married-in family members to $FAM_{unaffected}$.



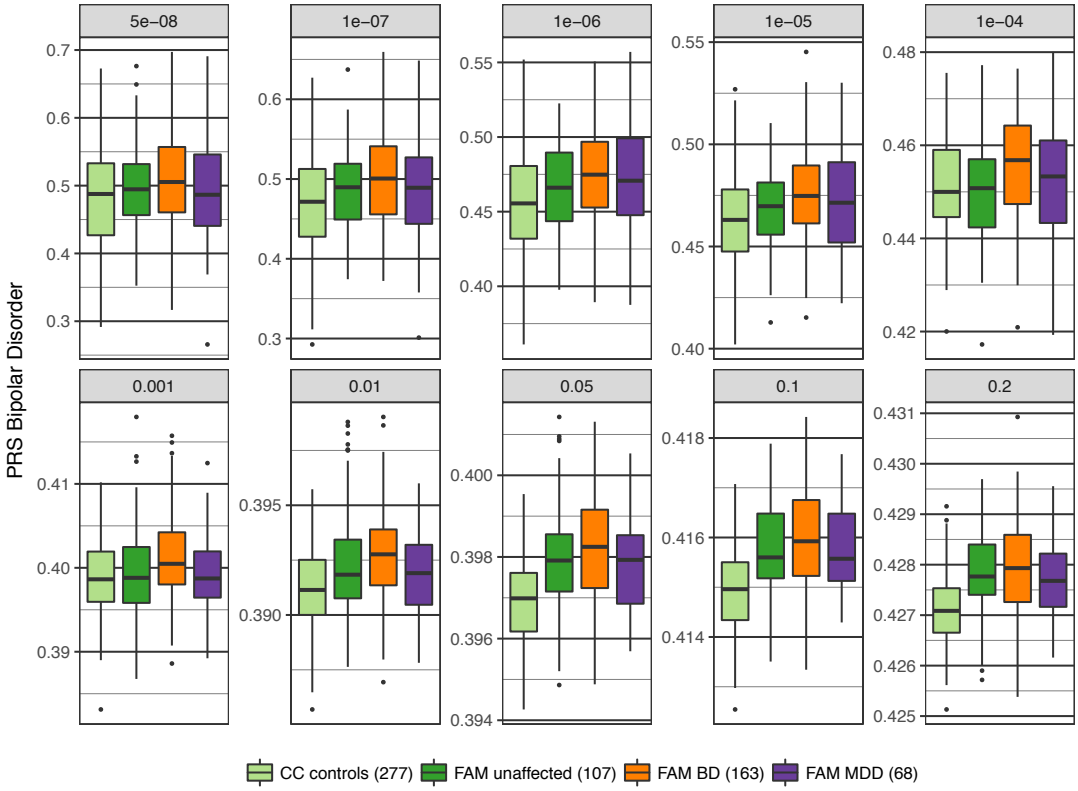
Supplementary Fig. S7: Analysis of anticipation in the FAM sample. Further details regarding the analysis and plots are described in the legend for Fig. 2D. Full association test statistics are shown in Supplementary Table S7.
Supplementary Fig. S7A: Association of the BD PRS with generation.



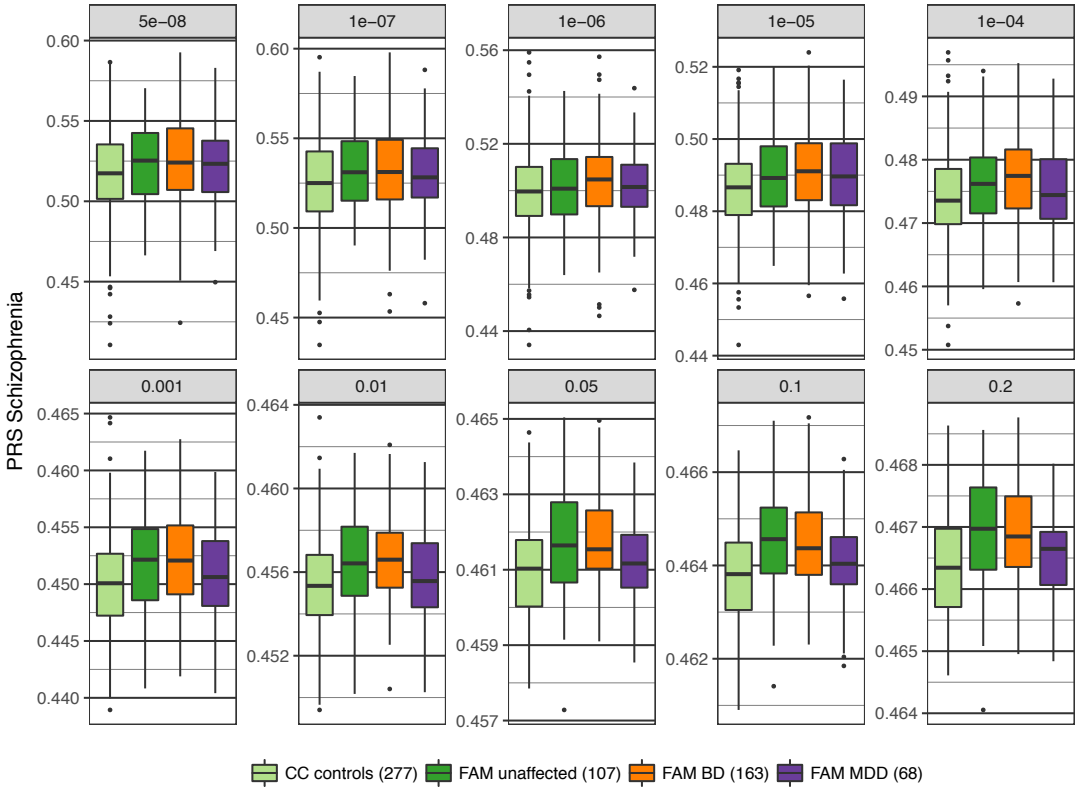
Supplementary Fig. S7B: Association analysis comparing the age at onset for BD across generations. The age at onset did not decrease over generations (p=0.54, Supplementary Table S7). Covariates were sex and age. One-sided p-values were calculated, following the hypothesis that the age at onset decreases across generations. The y-axis shows the residuals from the linear model.



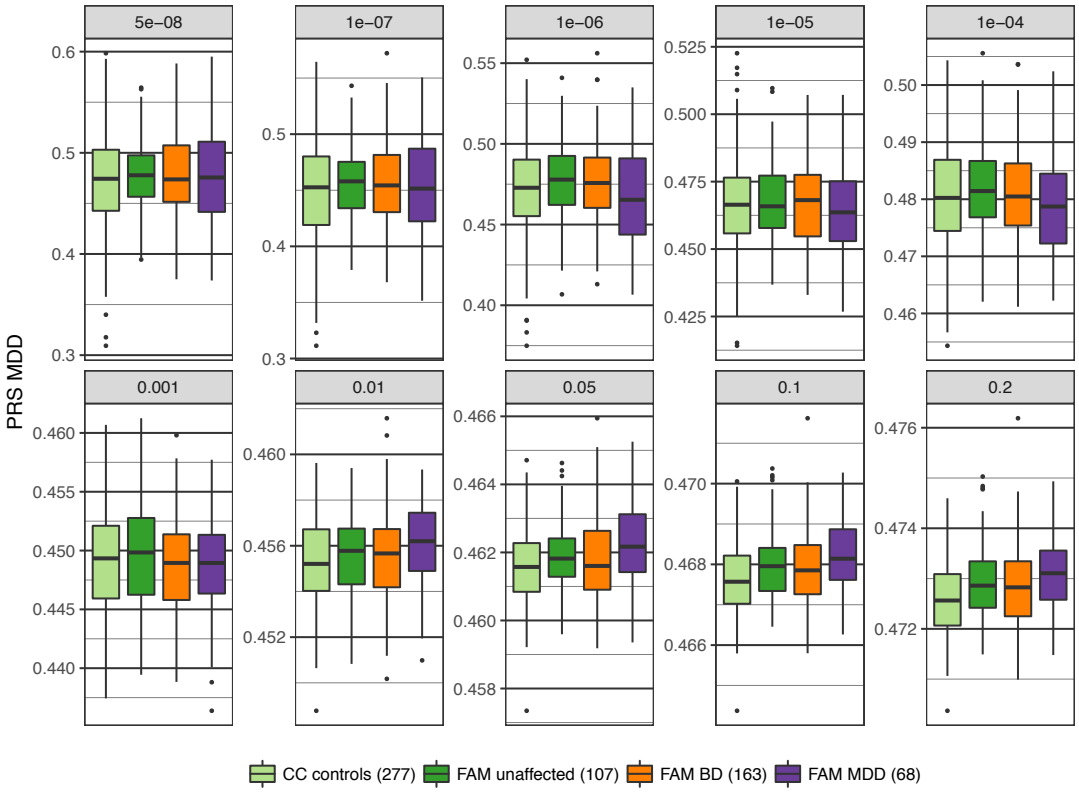
Supplementary Fig. S8: Boxplots of PRS at different *p*-value thresholds, including FAM_{MDD} cases. The following indiduals are not shown in these plots: Family members with a history of substance abuse, married-in family members, and CC_{BD} cases.
Supplementary Fig. S8A: Boxplots of BD PRS.



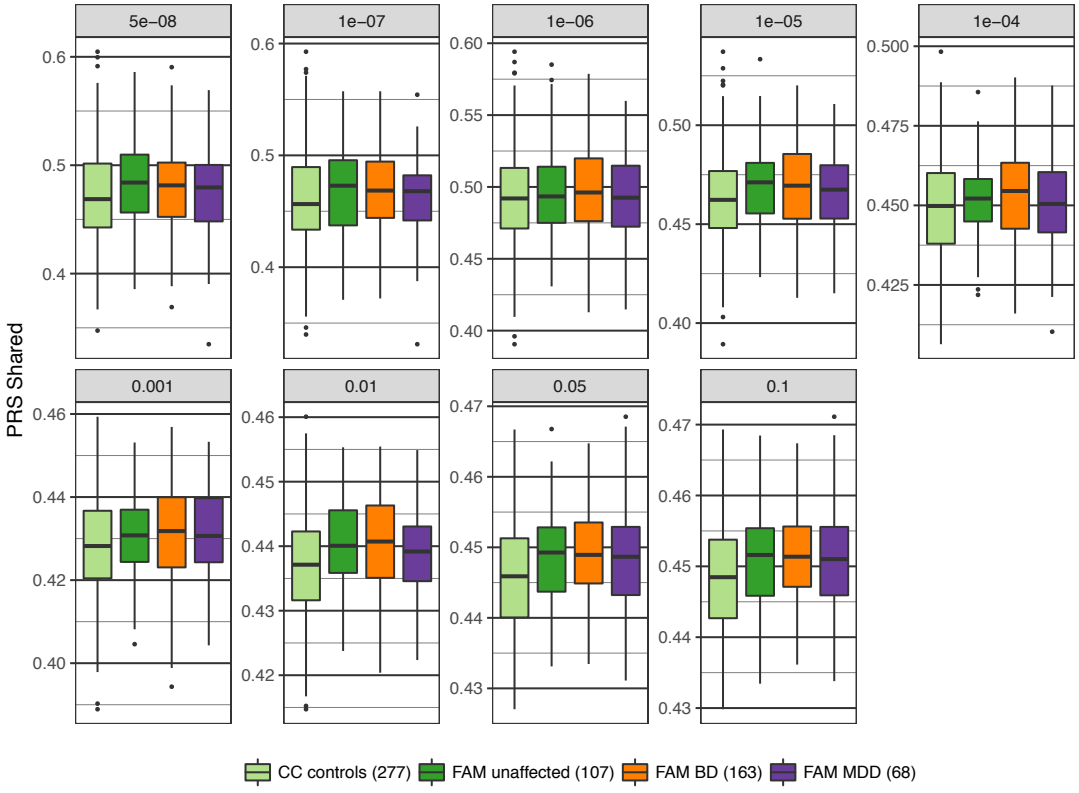
Supplementary Fig. S8B: Boxplots of SCZ PRS.



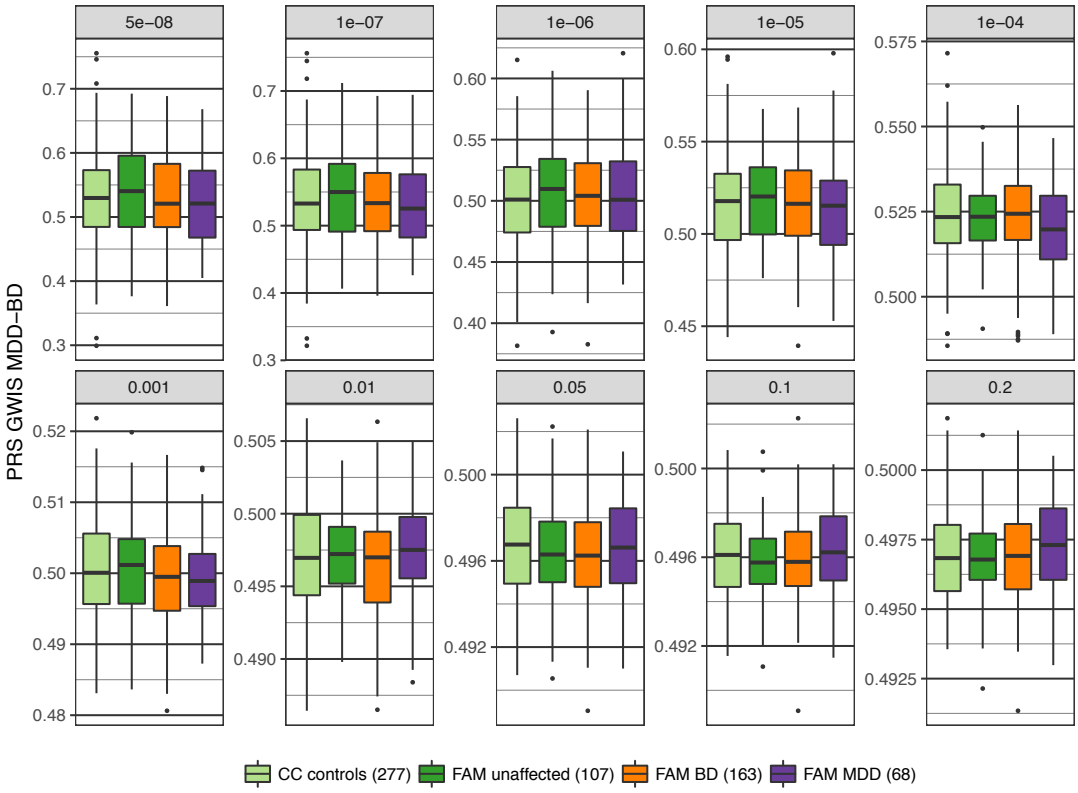
Supplementary Fig. S8C: Boxplots of MDD PRS.



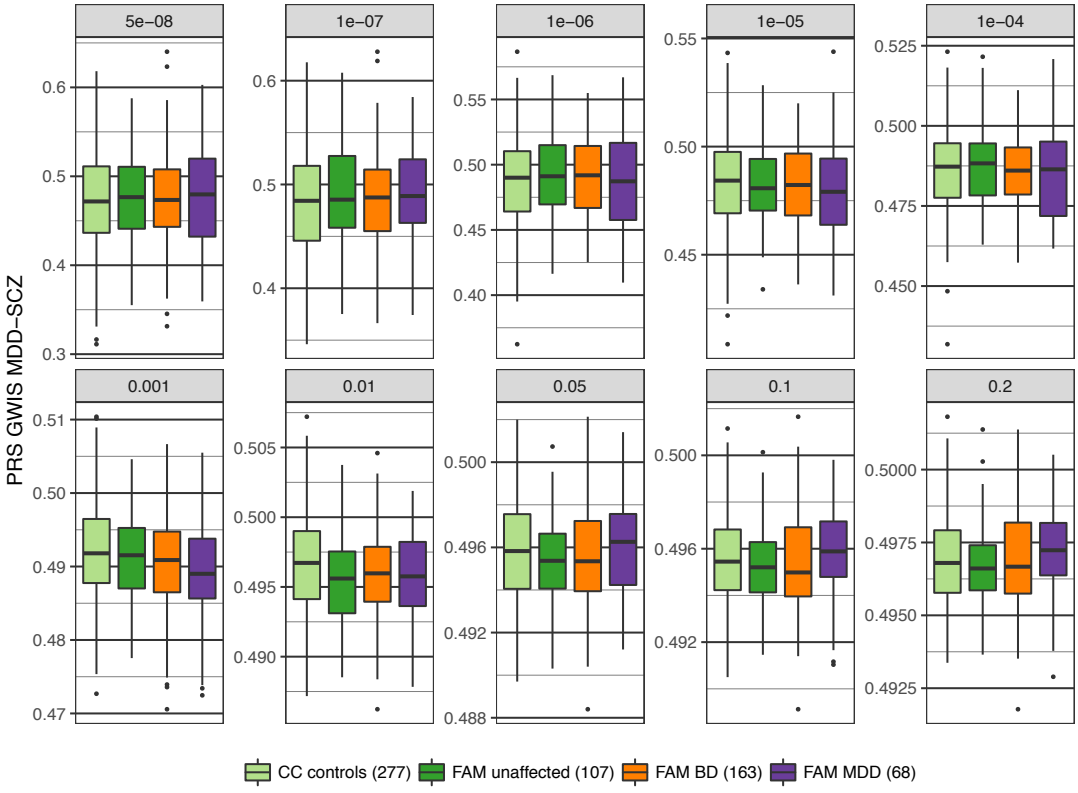
Supplementary Fig. S8D: Boxplots of the BD+SCZ+MDD *Shared* PRS.



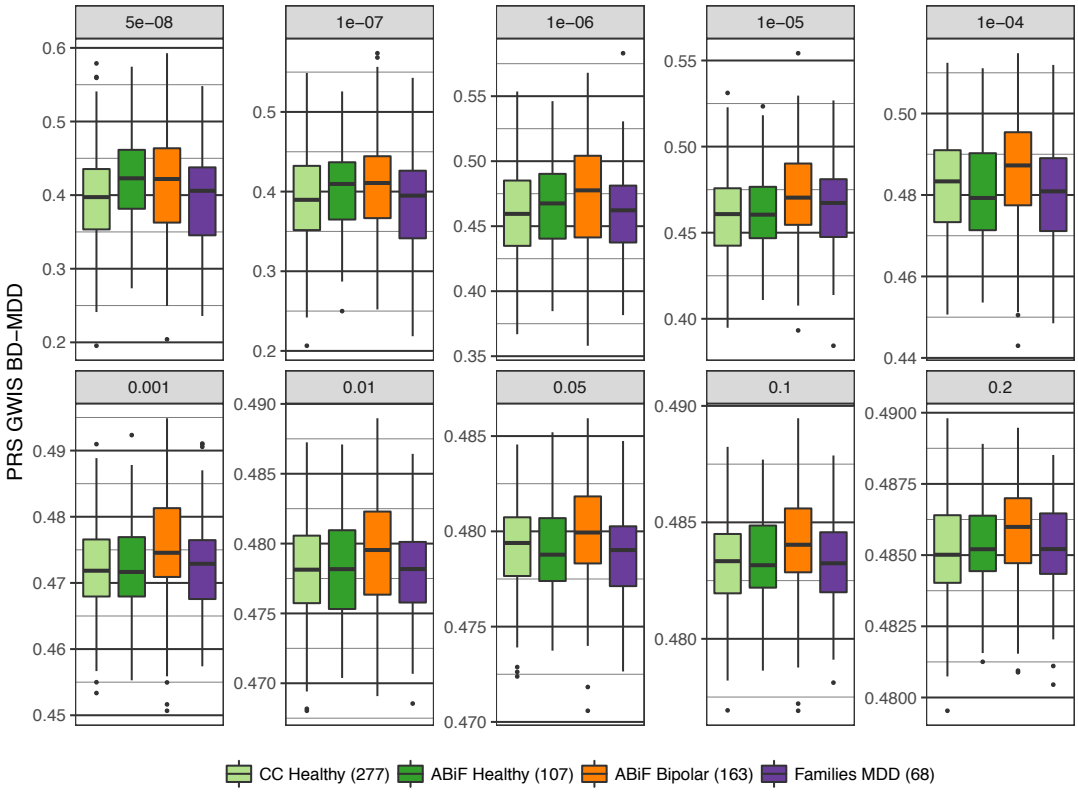
Supplementary Fig. S8E: Boxplots of the MDD-BD GWIS PRS.



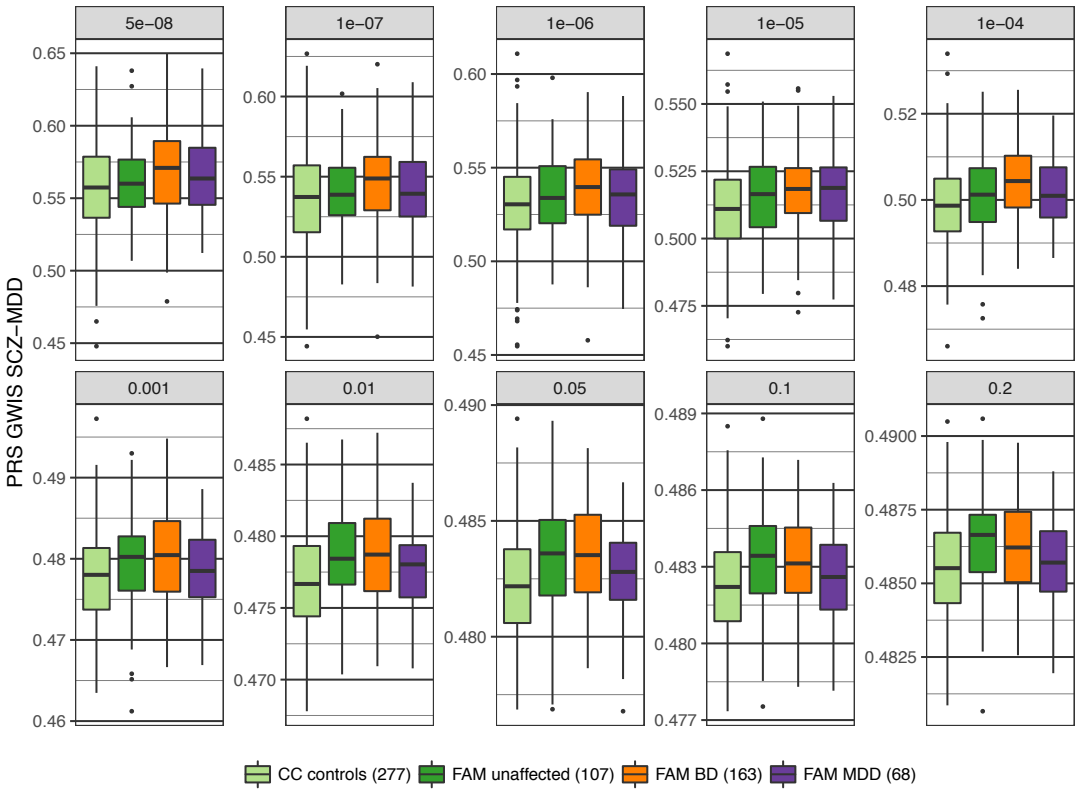
Supplementary Fig. S8F: Boxplots of the MDD-SCZ GWIS PRS.



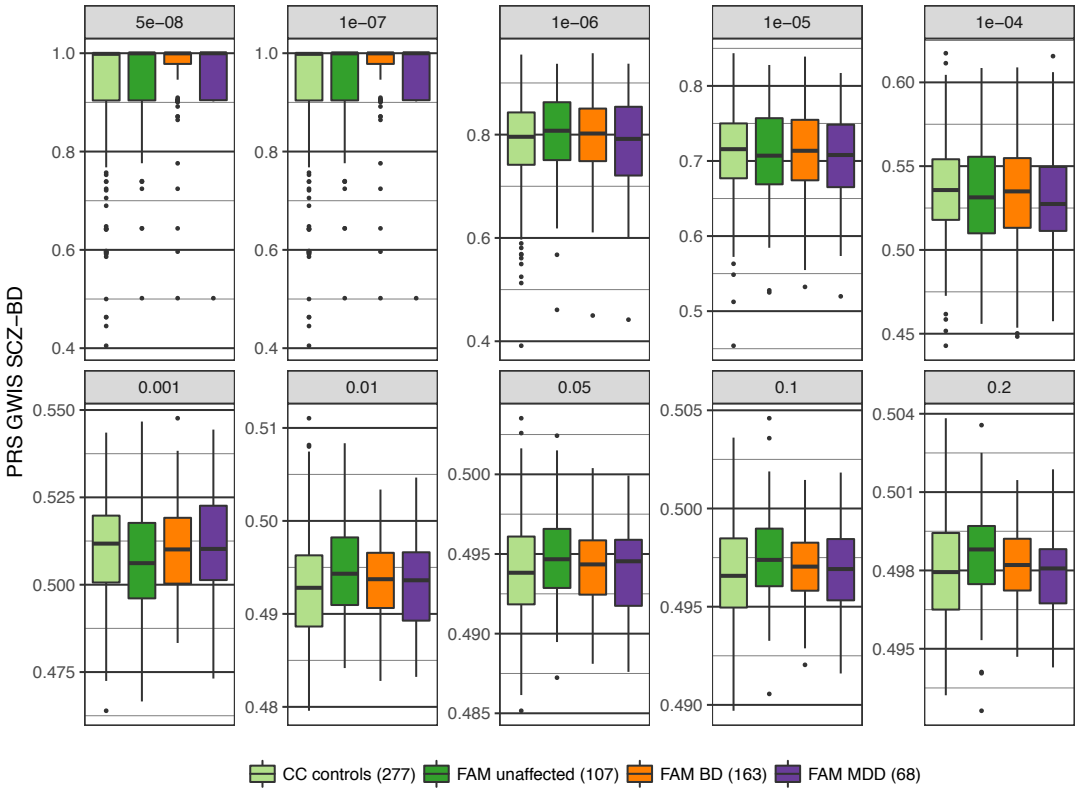
Supplementary Fig. S8G: Boxplots of the BD-MDD GWIS PRS.



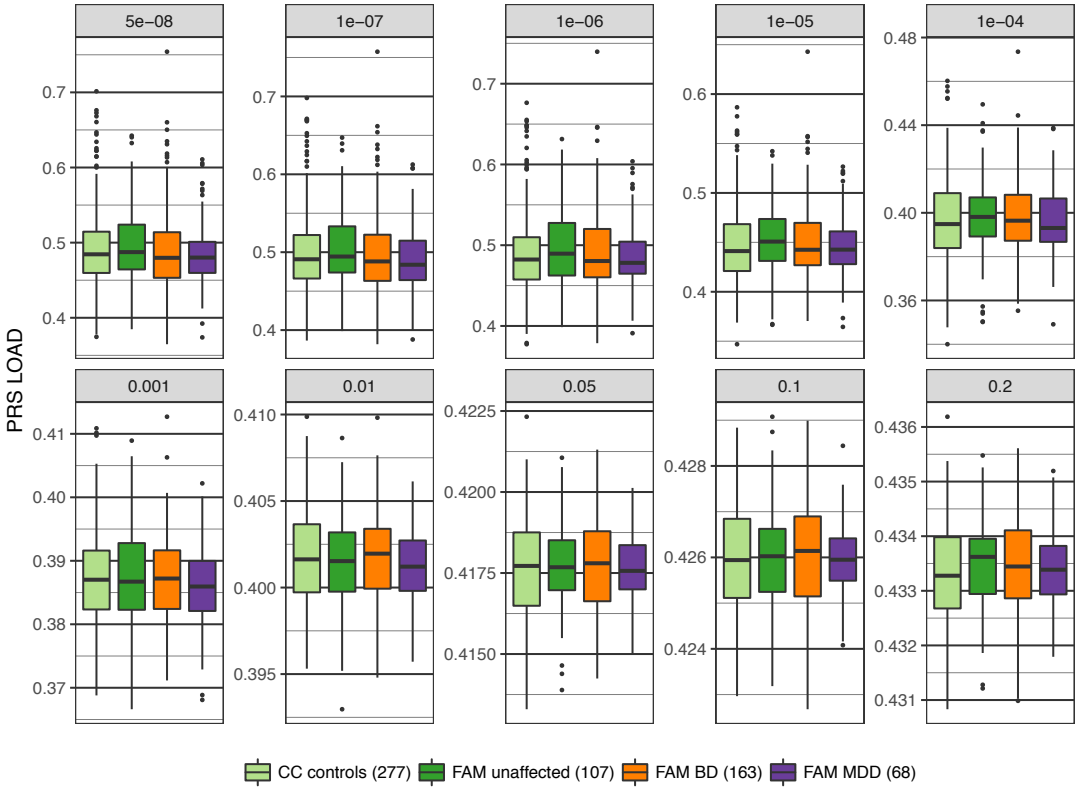
Supplementary Fig. S8H: Boxplots of the SCZ-MDD GWIS PRS.



Supplementary Fig. S8I: Boxplots of the SCZ-BD GWIS PRS.

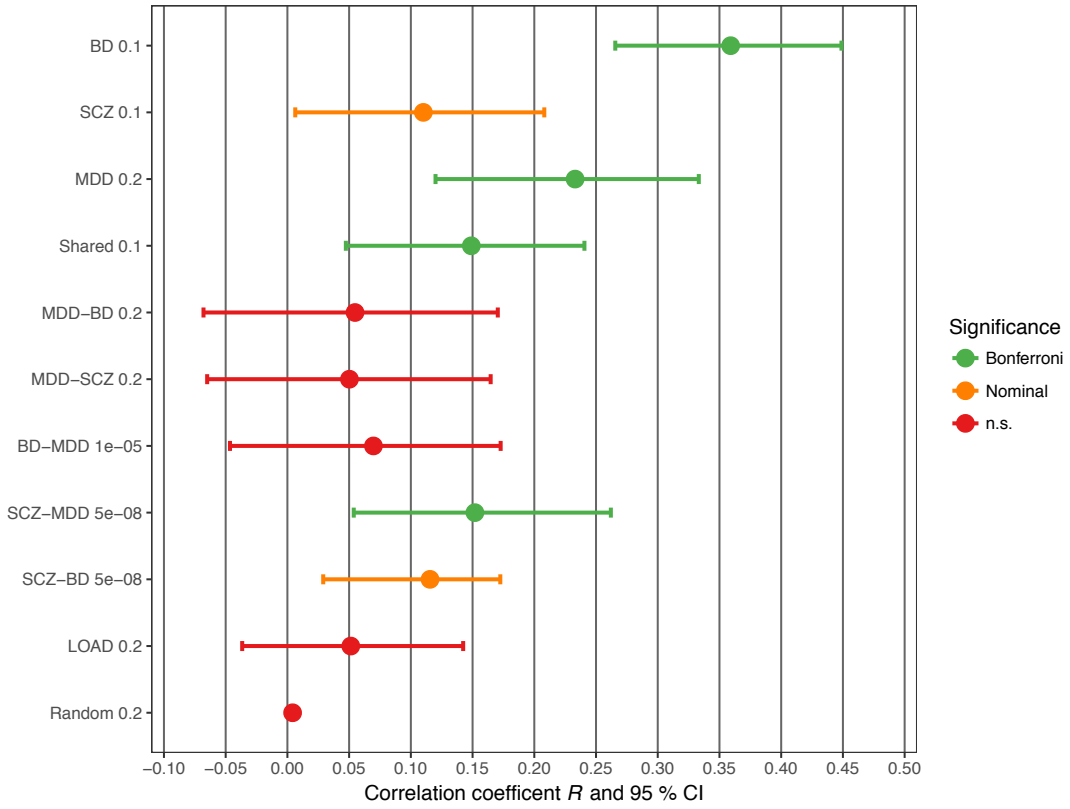


Supplementary Fig. S8J: Boxplots of the LOAD (Alzheimer) PRS.

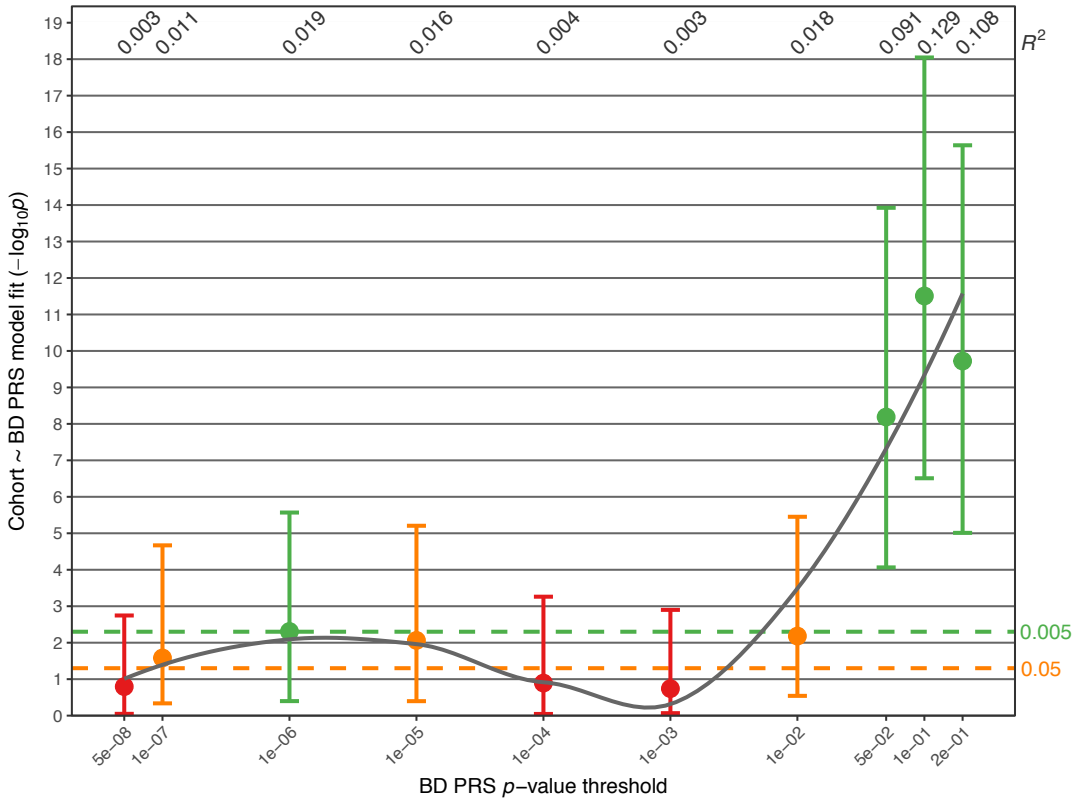


Supplementary Fig. S9: Association analysis comparing PRS in FAM_{MDD} cases and $CC_{controls}$. Further details of the plots are described in the legend for Fig. 1. Full association test statistics are shown in Supplementary Table S8.

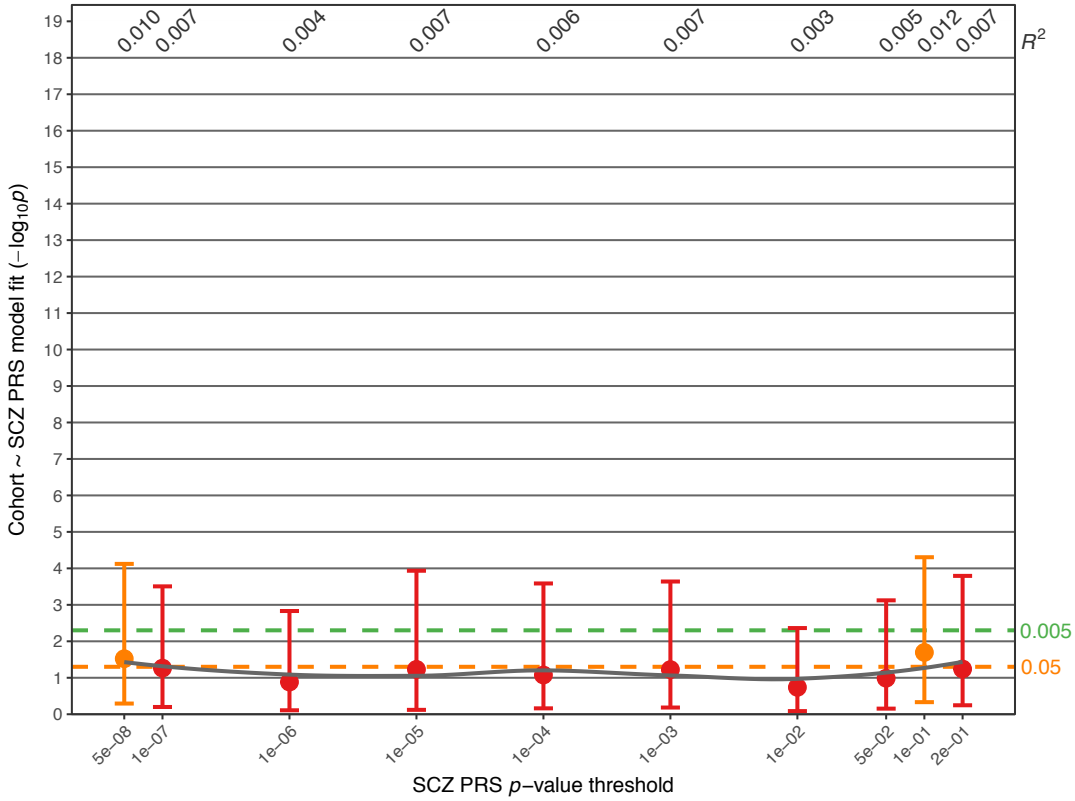
Supplementary Fig. S9A: Top-associated *p*-value thresholds for the tested PRS. The column to the left shows PRS and p_{PRS} thresholds.



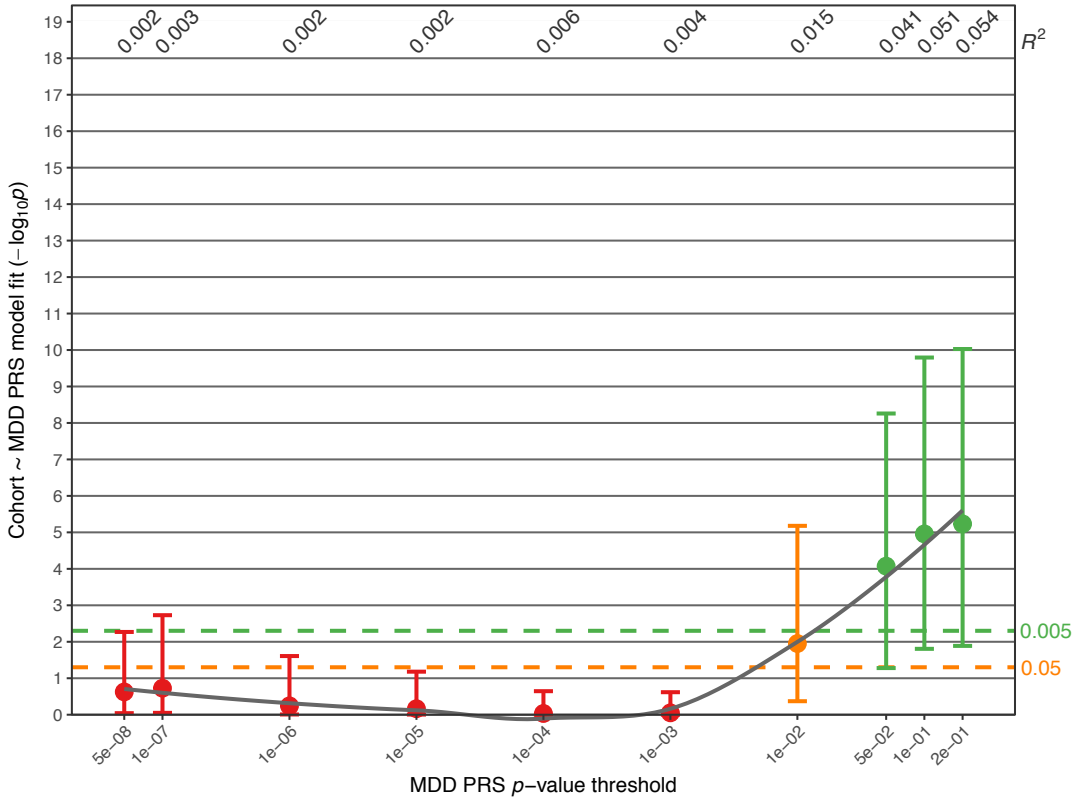
Supplementary Fig. S9B: Association of the BD PRS (all *p*-value thresholds).



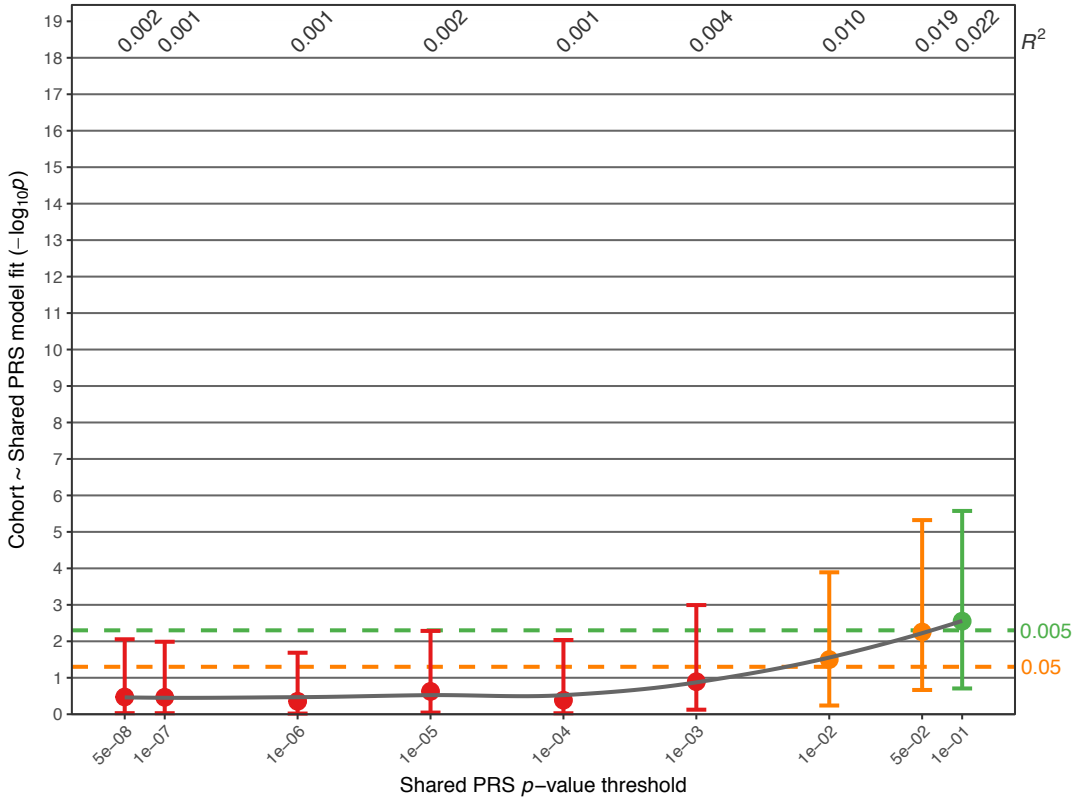
Supplementary Fig. S9C: Association of the SCZ PRS.



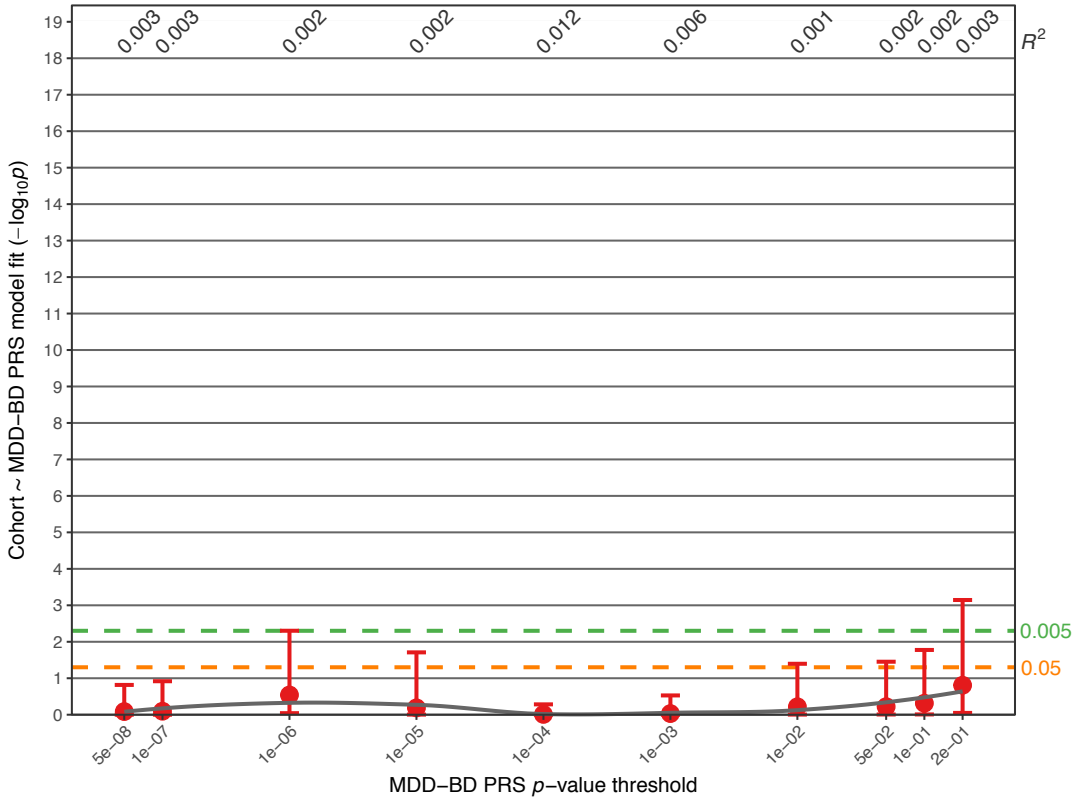
Supplementary Fig. S9D: Association of the MDD PRS.



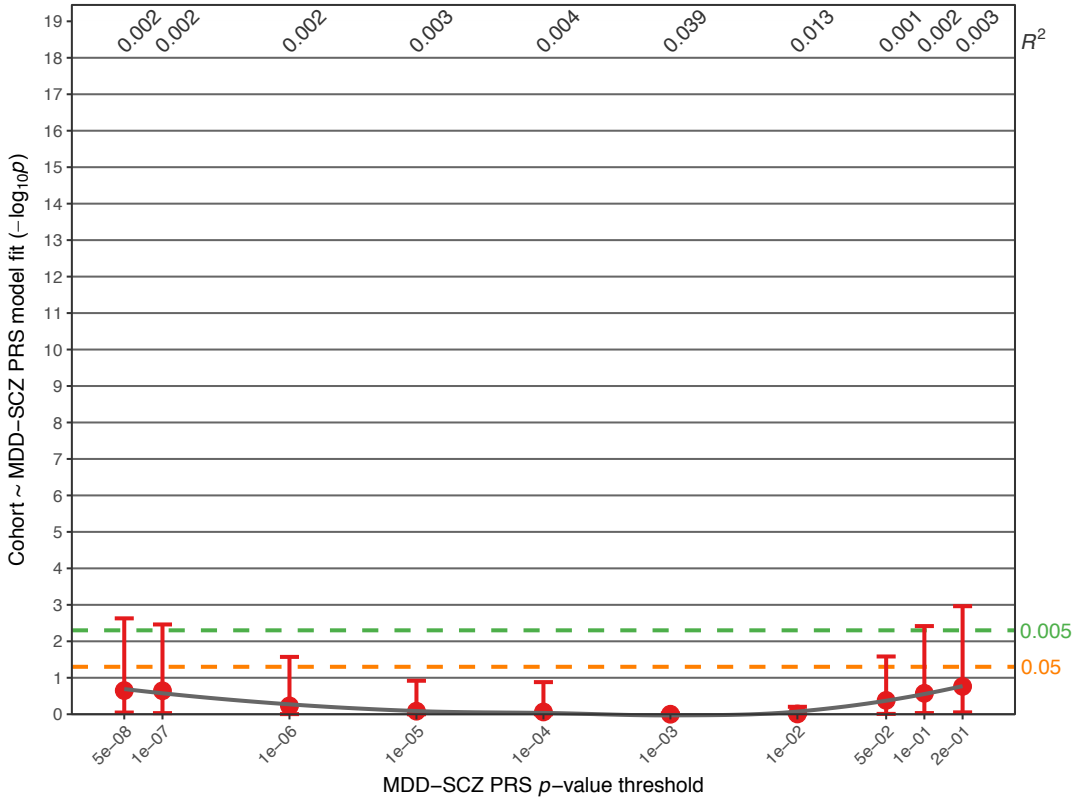
Supplementary Fig. S9E: Association of the *Shared* PRS.



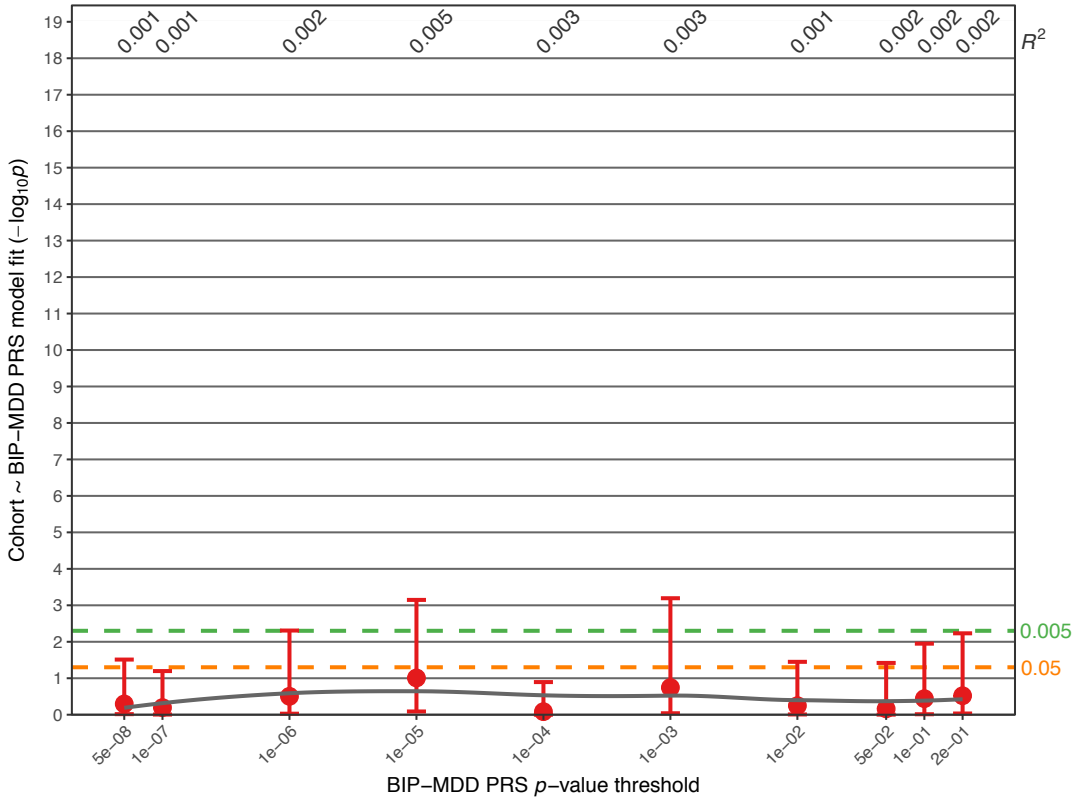
Supplementary Fig. S9F: Association of the MDD-BD GWIS PRS.



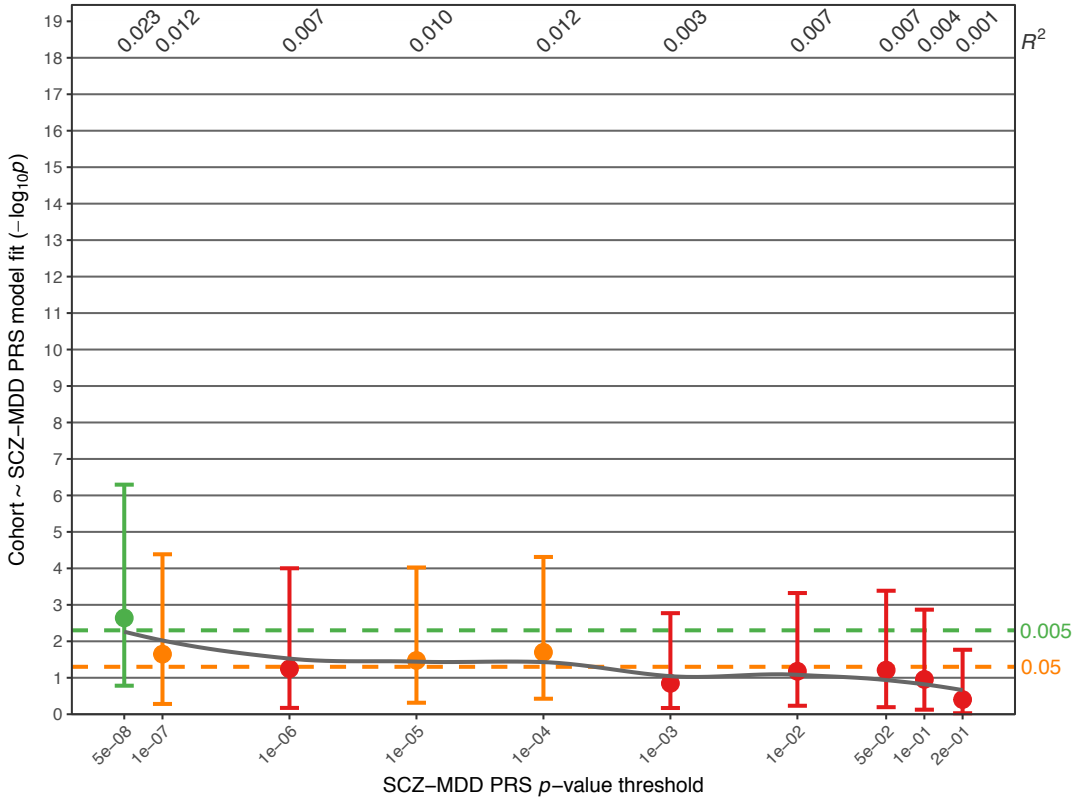
Supplementary Fig. S9G: Association of the MDD-SCZ GWIS PRS.



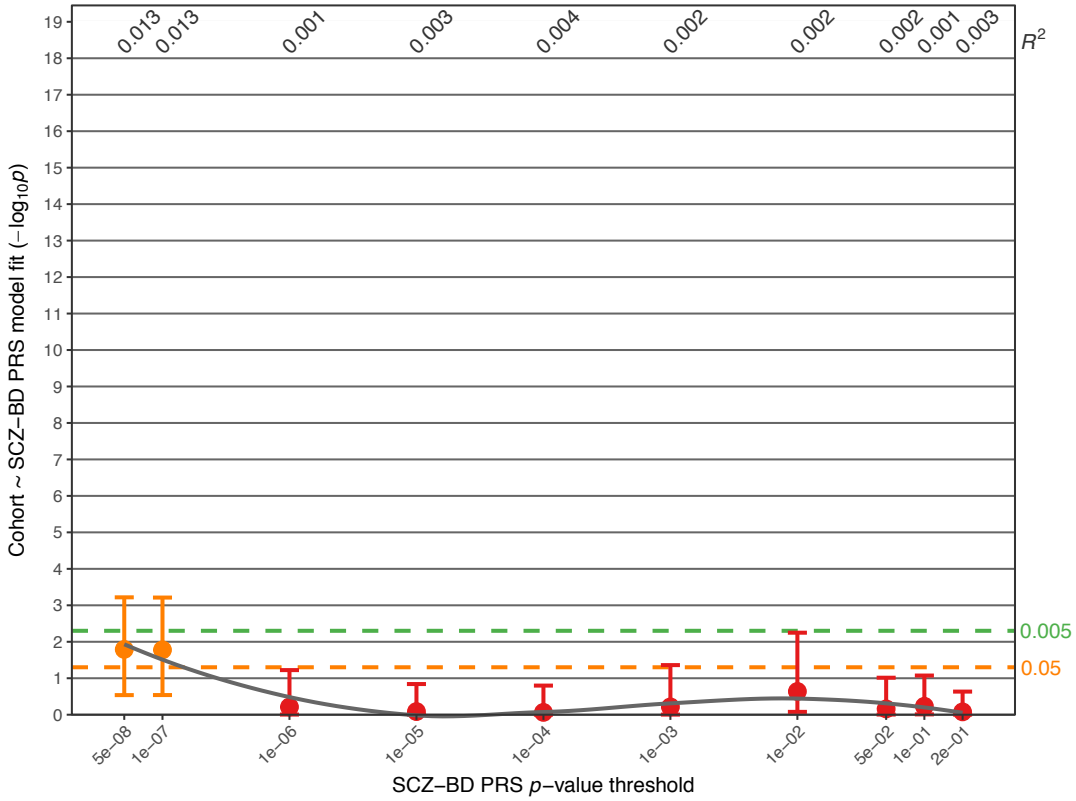
Supplementary Fig. S9H: Association of the BD-MDD GWIS PRS.



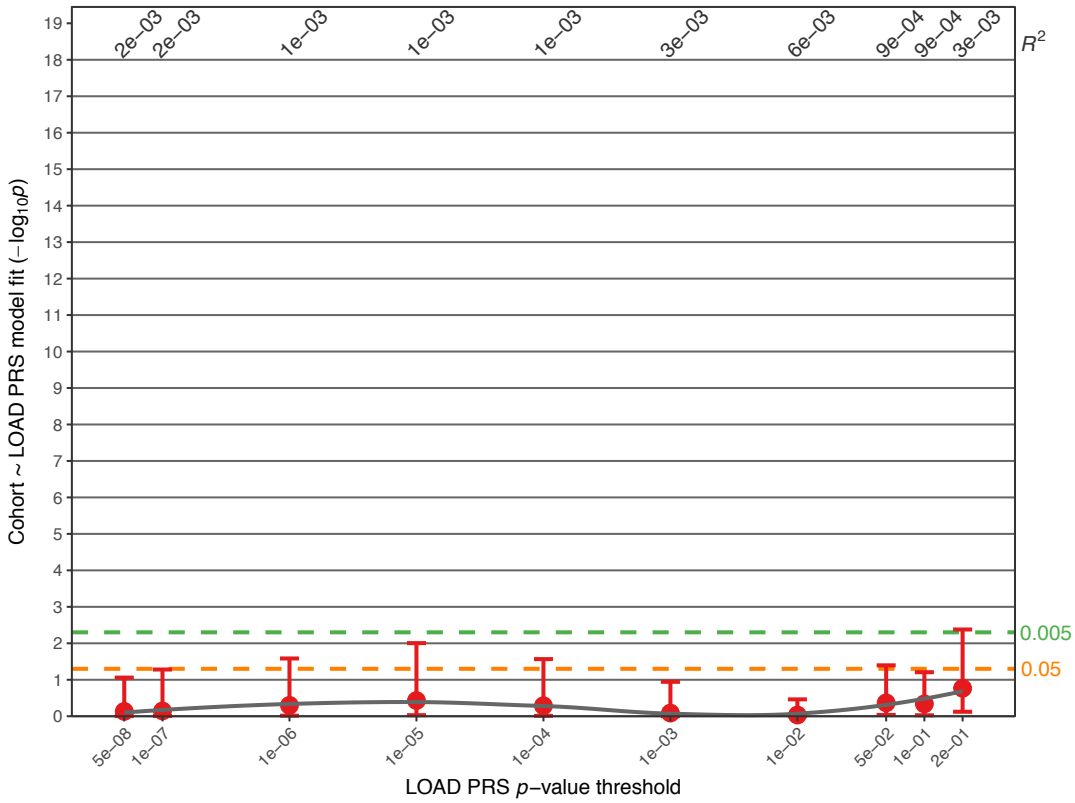
Supplementary Fig. S9I: Association of the SCZ-MDD GWIS PRS.



Supplementary Fig. S9J: Association of the SCZ-BD GWIS PRS.

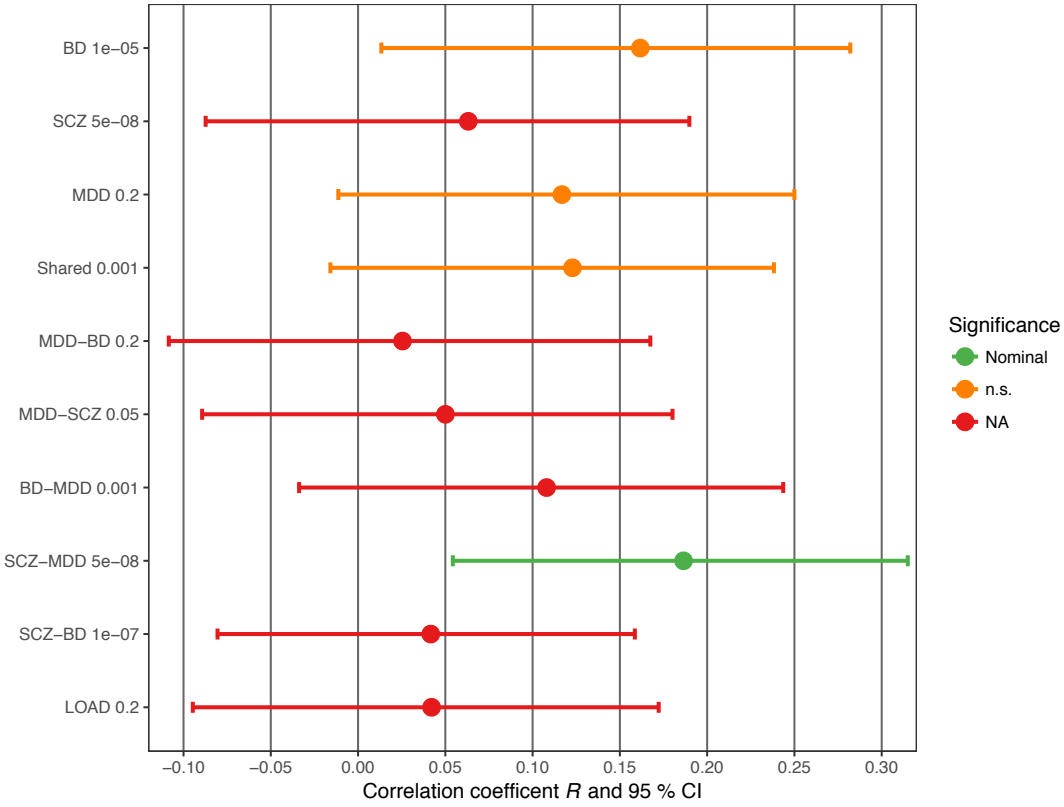


Supplementary Fig. S9K: Association of the LOAD PRS.

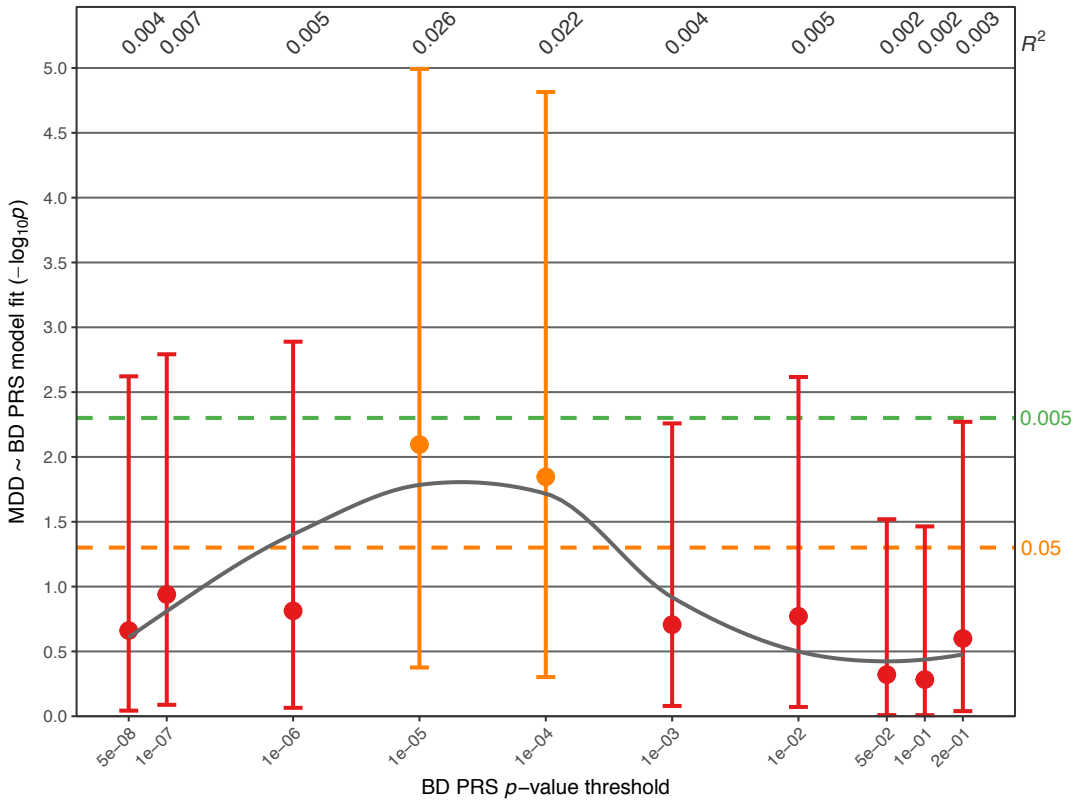


Supplementary Fig. S10: Association analysis comparing PRS in FAM_{MDD} cases and $FAM_{unaffected}$. Further details of the plots are described in the legends for Figs. 1 and 2. Full association test statistics are shown in Supplementary Table S9.

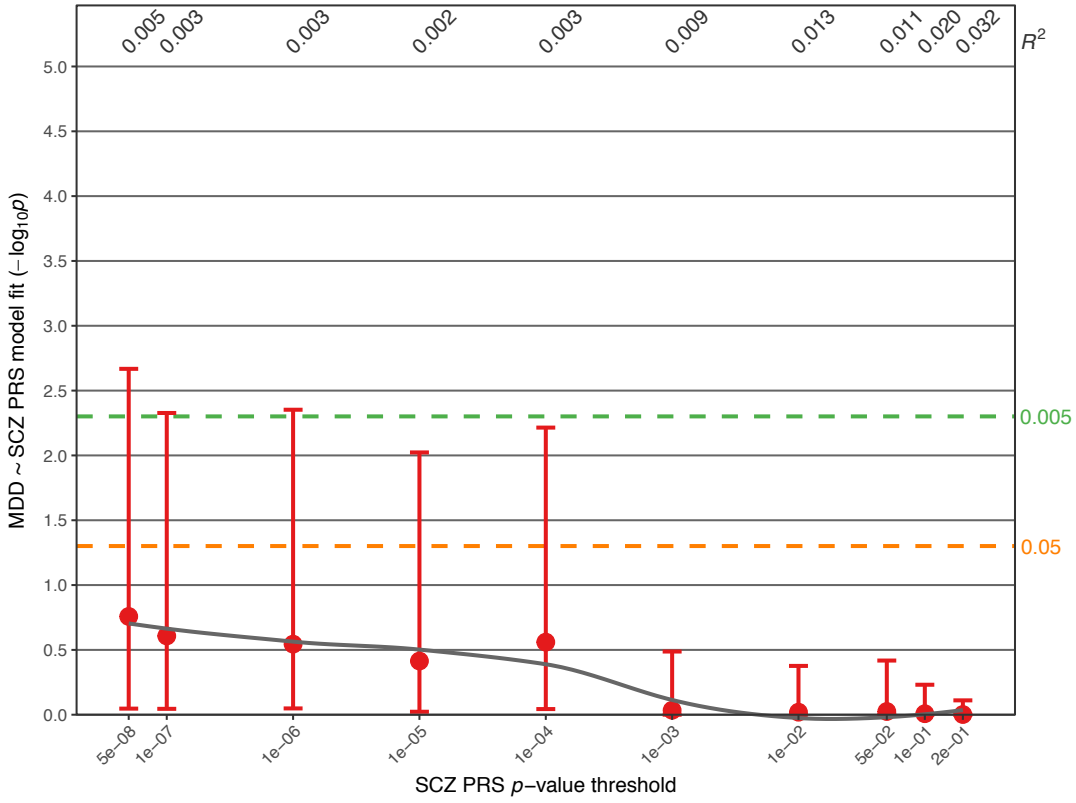
Supplementary Fig. S10A: Top-associated p_{PRS} thresholds for the tested PRS. The column to the left shows PRS and p_{PRS} thresholds.



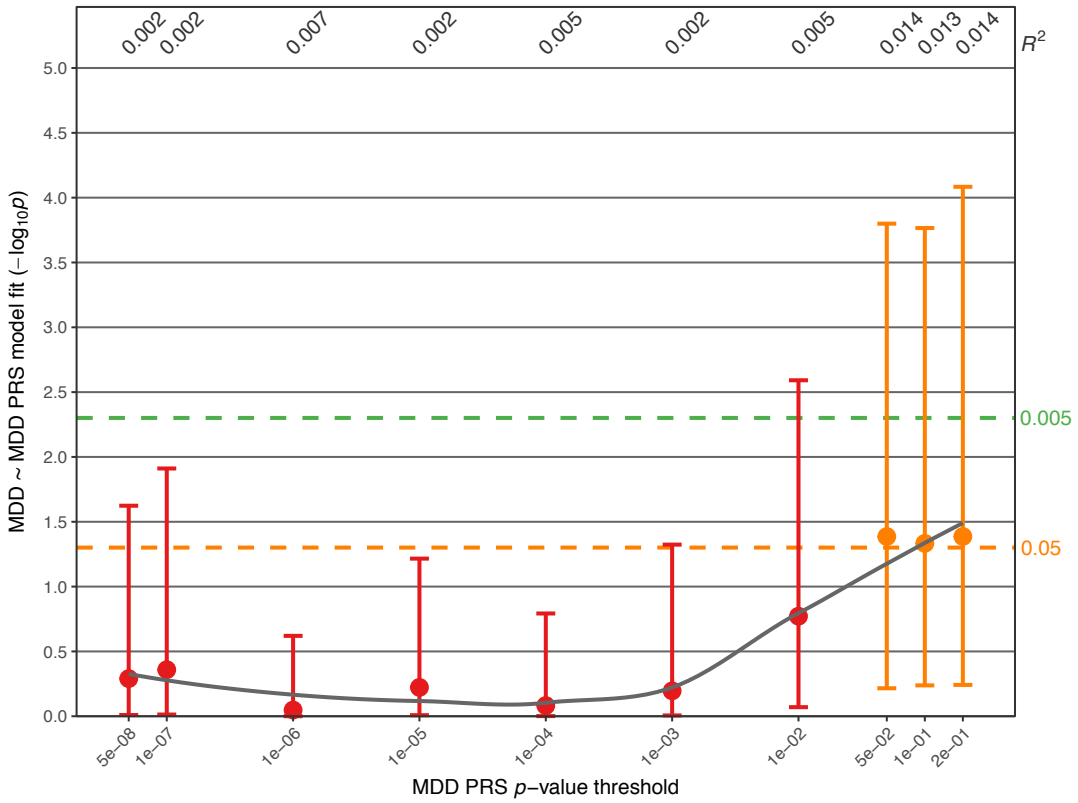
Supplementary Fig. S10B: Association of the BD PRS (all *p*-value thresholds).



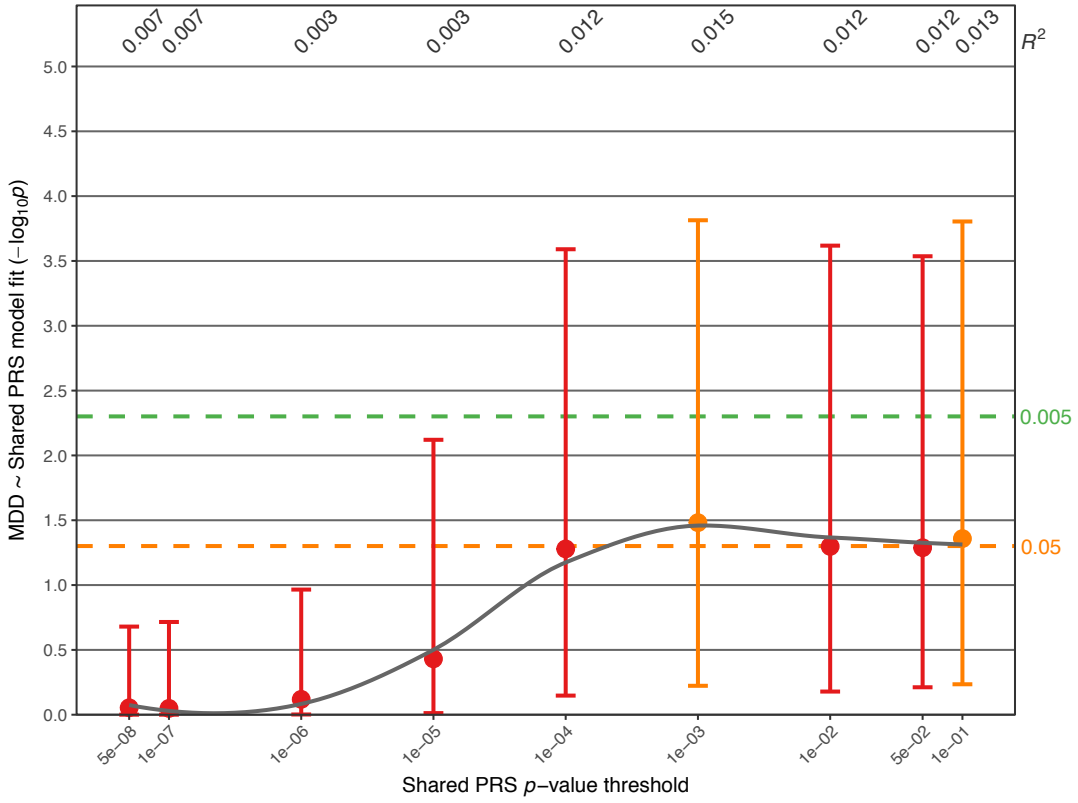
Supplementary Fig. S10C: Association of the SCZ PRS.



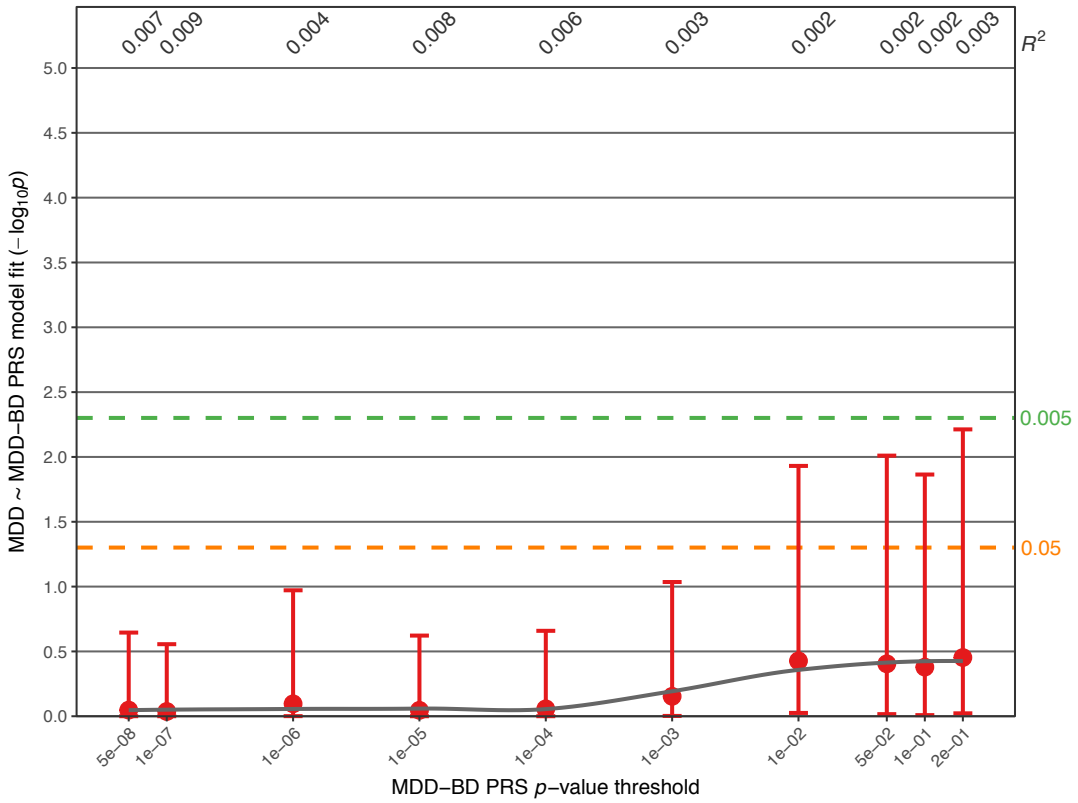
Supplementary Fig. S10D: Association of the MDD PRS.



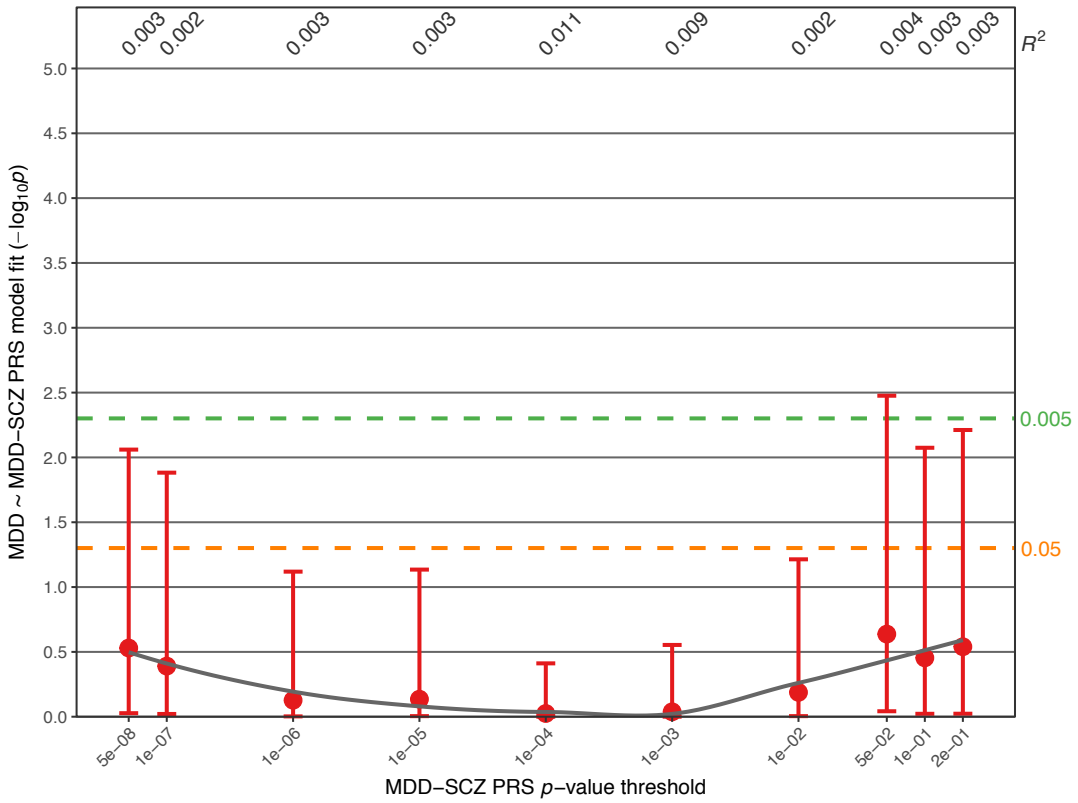
Supplementary Fig. S10E: Association of the *Shared* PRS.



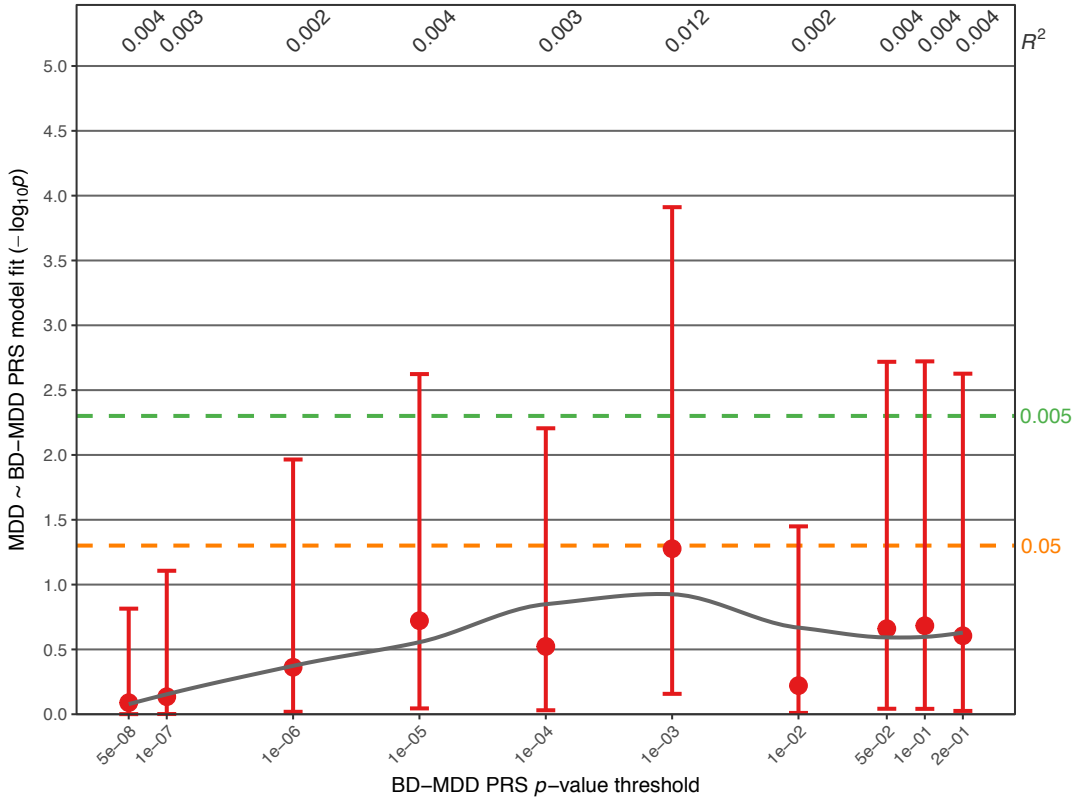
Supplementary Fig. S10F: Association of the MDD-BD GWIS PRS.



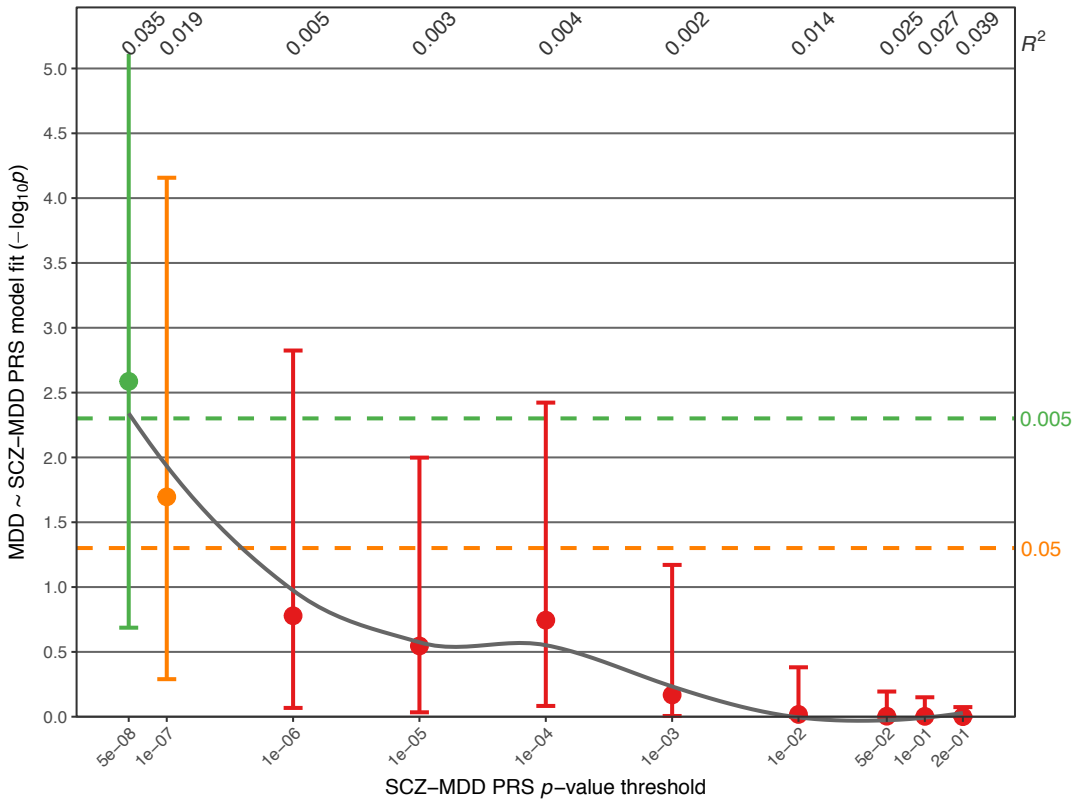
Supplementary Fig. S10G: Association of the MDD-SCZ GWIS PRS.



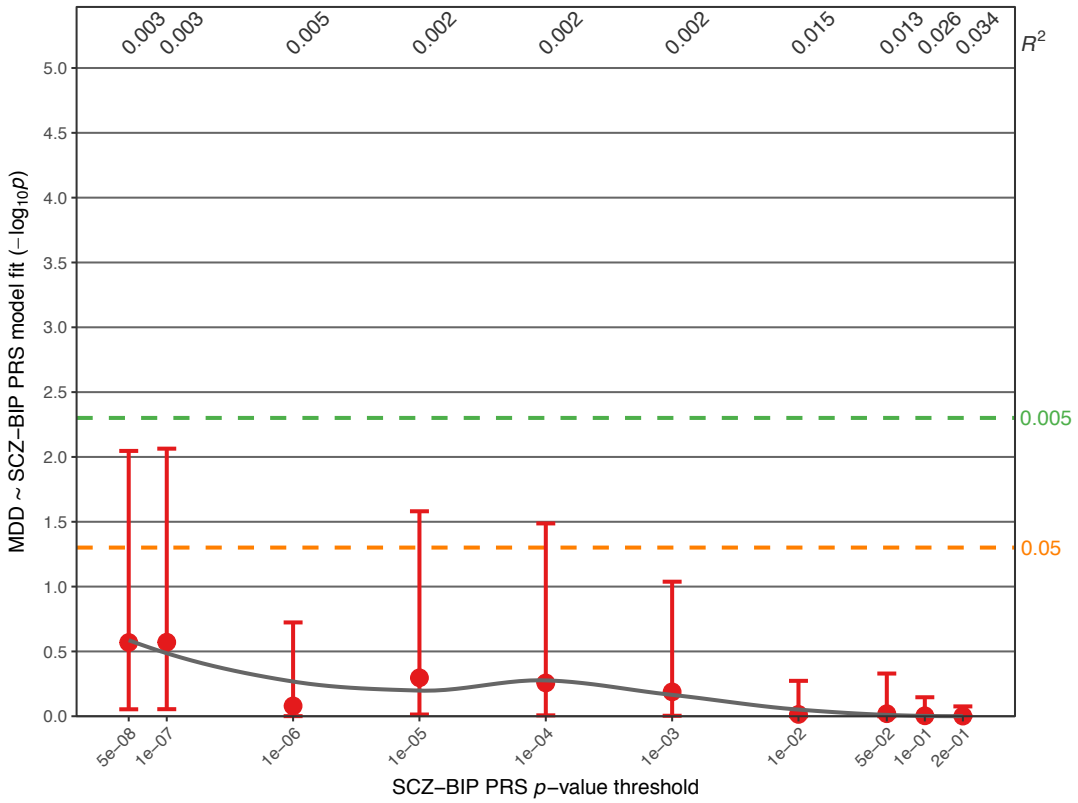
Supplementary Fig. S10H: Association of the BD-MDD GWIS PRS.



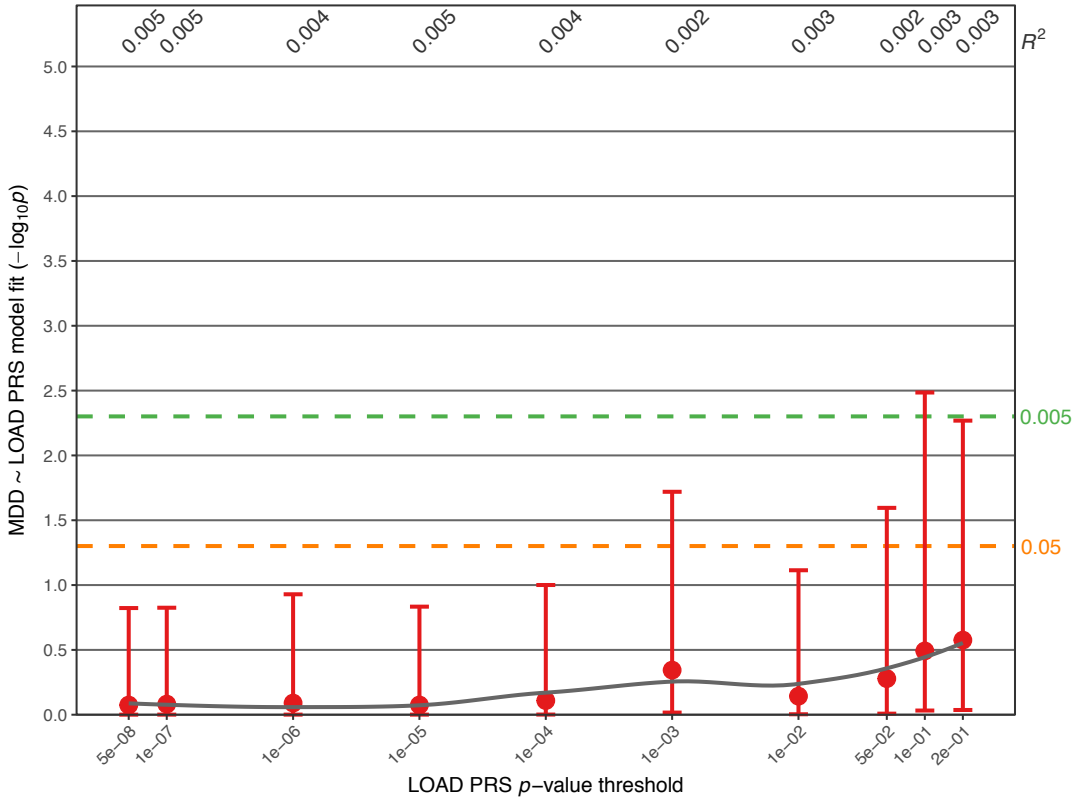
Supplementary Fig. S10I: Association of the SCZ-MDD GWIS PRS.



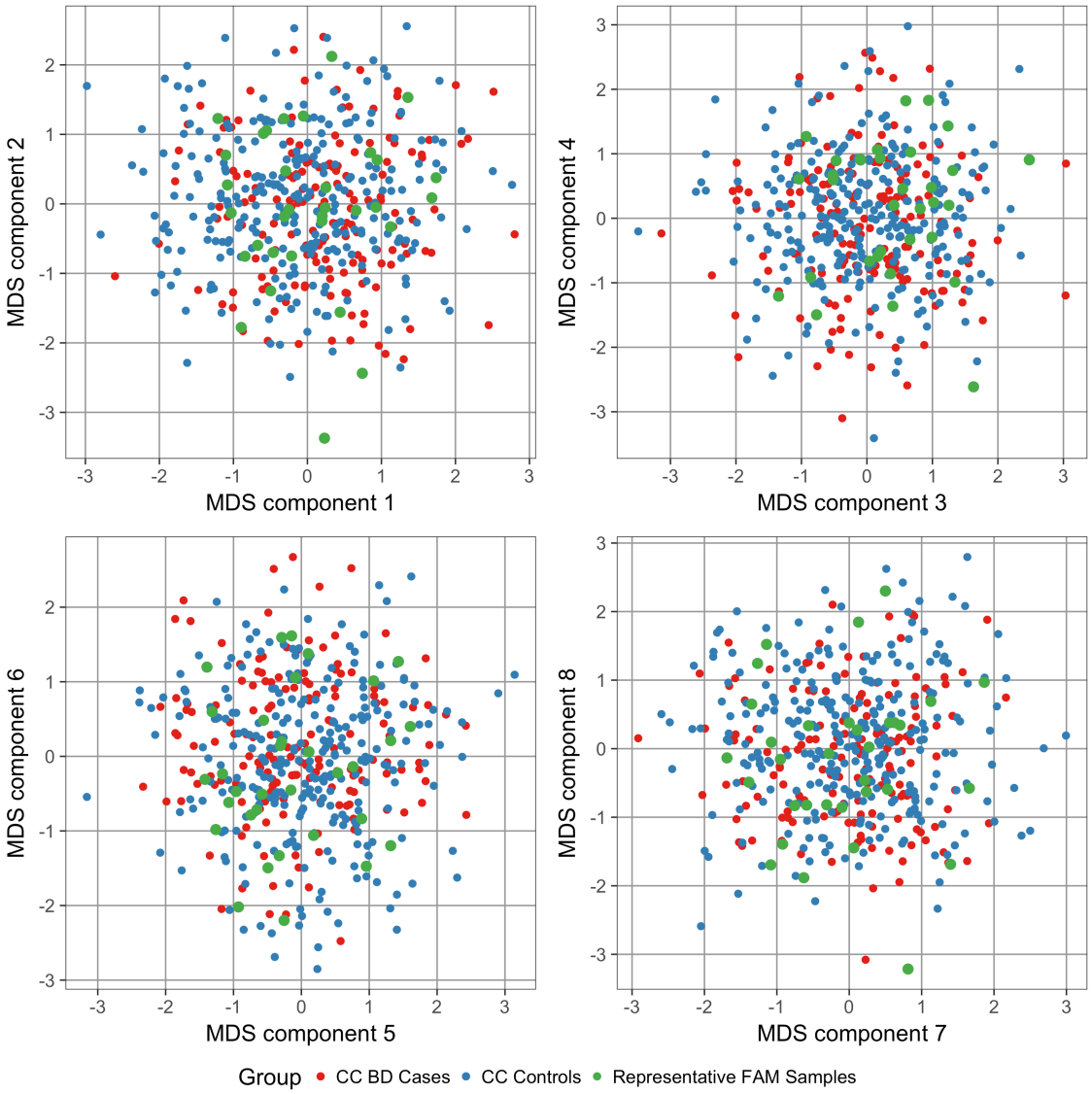
Supplementary Fig. S10J: Association of the SCZ-BD GWIS PRS.



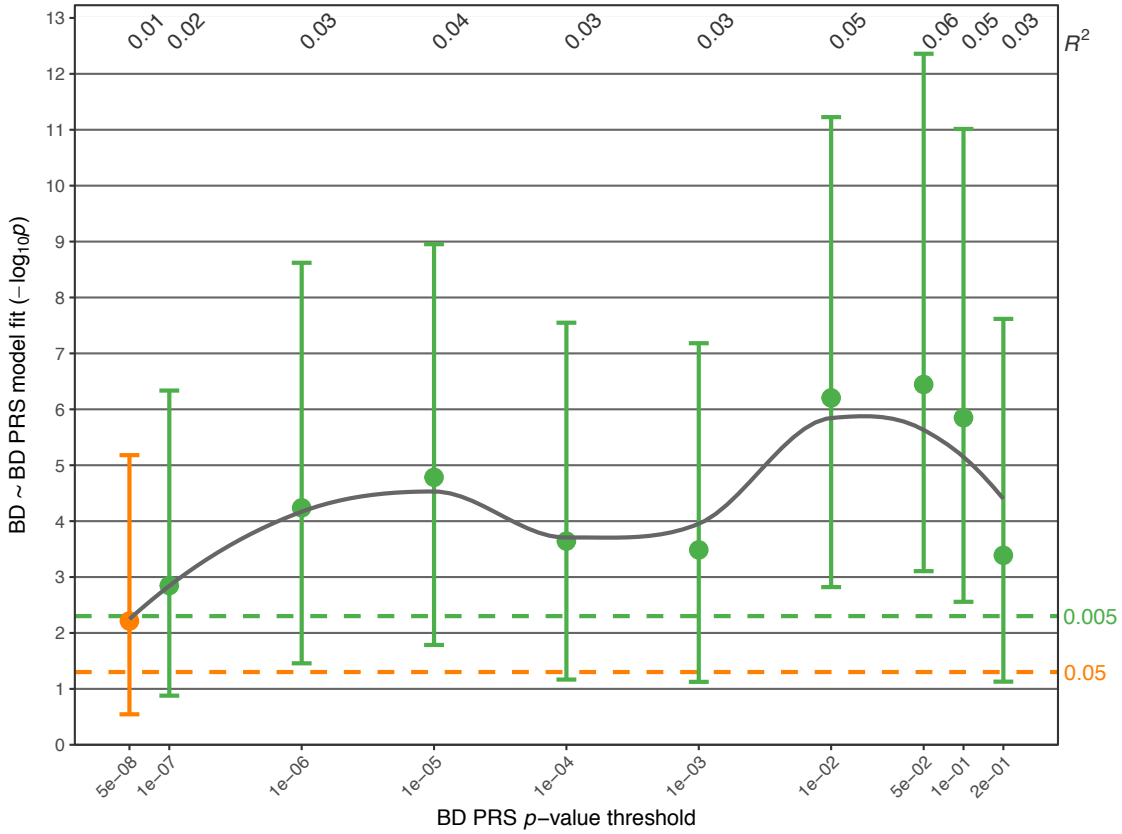
Supplementary Fig. S10K: Association of the LOAD PRS.



Supplementary Fig. S11: Population substructure analysis. Details regarding the generation of MDS components and the population substructure analysis are described above in the Supplementary Methods. The axes have been scaled to show standard deviations.



Supplementary Fig. S12: Association analysis comparing BD PRS in sporadic CC_{BD} cases and $CC_{controls}$. Details of the plot are described in the legend for Fig. 1. Covariate used: Sex. Full association test statistics including *p*-values are shown in Supplementary Table S10.



IGAP Supplementary Methods and Acknowledgments

IGAP Methods for the LOAD GWAS

International Genomics of Alzheimer's Project (IGAP) is a large two-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP used genotyped and imputed data on 7,055,881 single nucleotide polymorphisms (SNPs) to meta-analyse four previously-published GWAS datasets consisting of 17,008 Alzheimer's disease cases and 37,154 controls (The European Alzheimer's disease Initiative – EADI the Alzheimer Disease Genetics Consortium – ADGC The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium – CHARGE The Genetic and Environmental Risk in AD consortium – GERAD). In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,572 Alzheimer's disease cases and 11,312 controls. Finally, a meta-analysis was performed combining results from stages 1 & 2.
The present study used GWAS summary statistics from stage 1 for the calculation of PRS.

IGAP Acknowledgments

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