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Supplemental information

The shared genetic landscape of blood cell traits and risk of neurological and psychiatric disorders

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Supplemental Figures

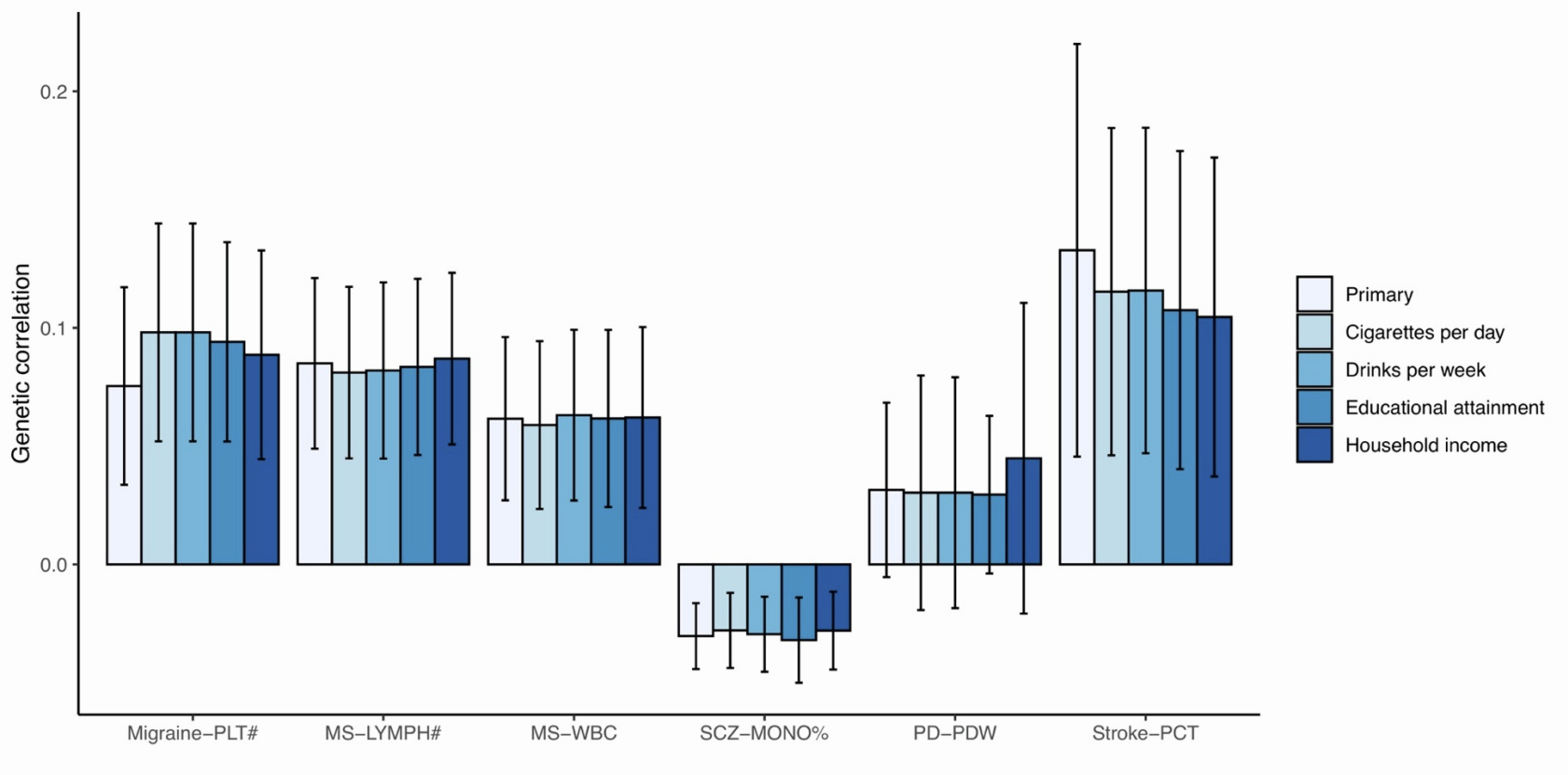

Figure S1. Summary of genetic correlations for specific BCT–NPD pairs estimated by primary HDL and HDL after conditioning GWAS summary data of specific BCTs and NPDs on the GWAS of cigarettes per day, drinks per week, educational attainment, and household income, respectively; related to Figure 2 and STAR Methods. BCT–NPD pairs were included if they had a Bonferroni- or FDR-significant genetic correlation (i.e., MS and LYMPH#, MS and WBC, SCZ and MONO%, migraine and PLT#) or a putative causal relationship (i.e., stroke and PCT, PD and PDW). Error bars represent the 95% CIs for the estimated genetic correlations.

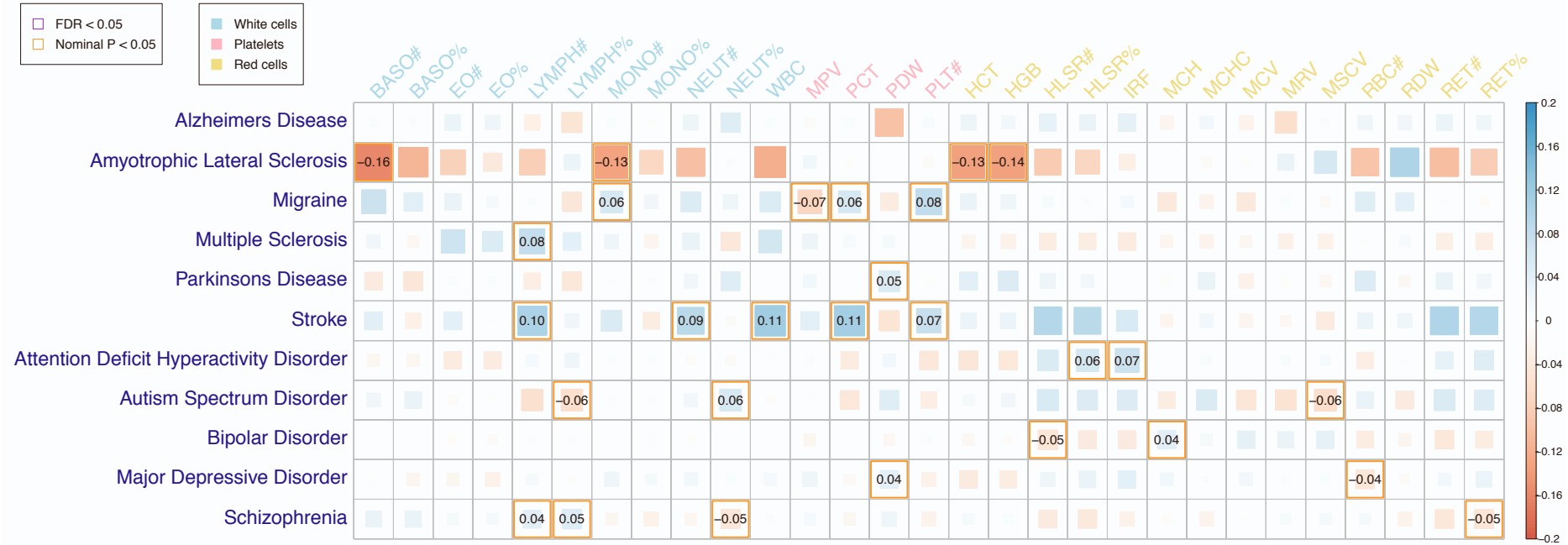

Figure S2. Estimated genetic correlations between BCTs and NPDs using the LDSC model, related to Figure 2 and STAR Methods. Significant genetic correlations (with estimates provided) are highlighted by red, purple, or orange boxes if they were Bonferroni-significant, FDR-significant, or nominally significant, respectively.

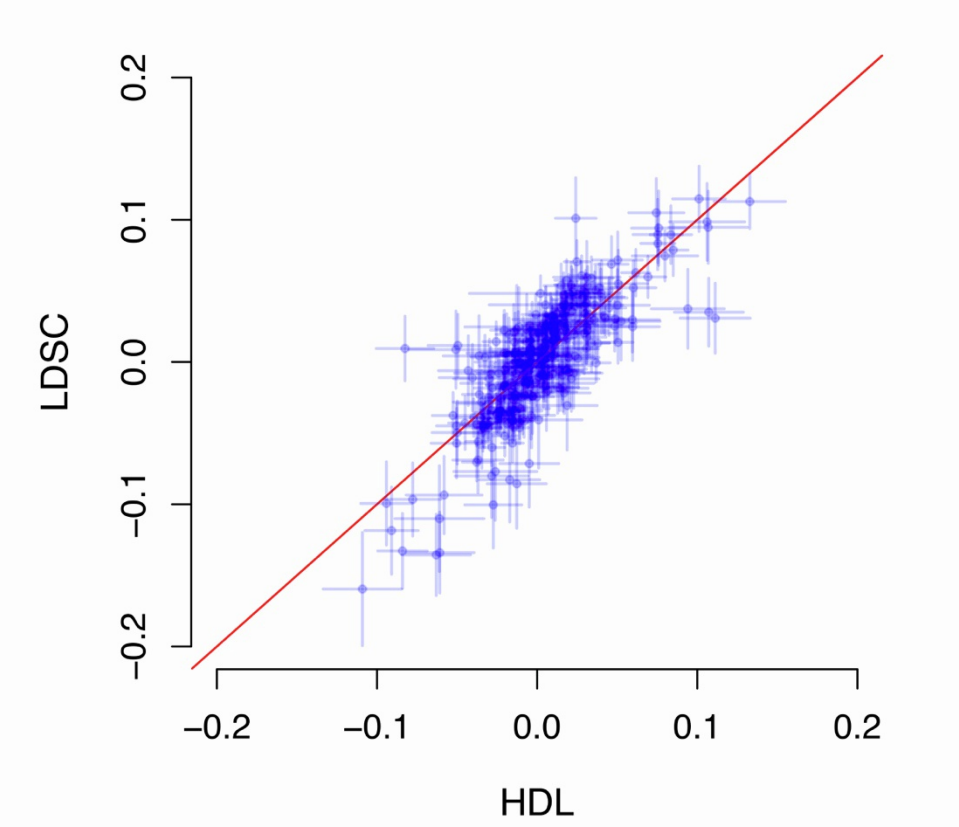

Figure S3. Comparison of genetic correlations estimated by HDL and LDSC, related to Figure 2 and STAR Methods. The estimated correlation = 0.81 (95% CI = 0.76-0.84) between genetic correlations for BCT–NPD pairs estimated by HDL and LDSC.

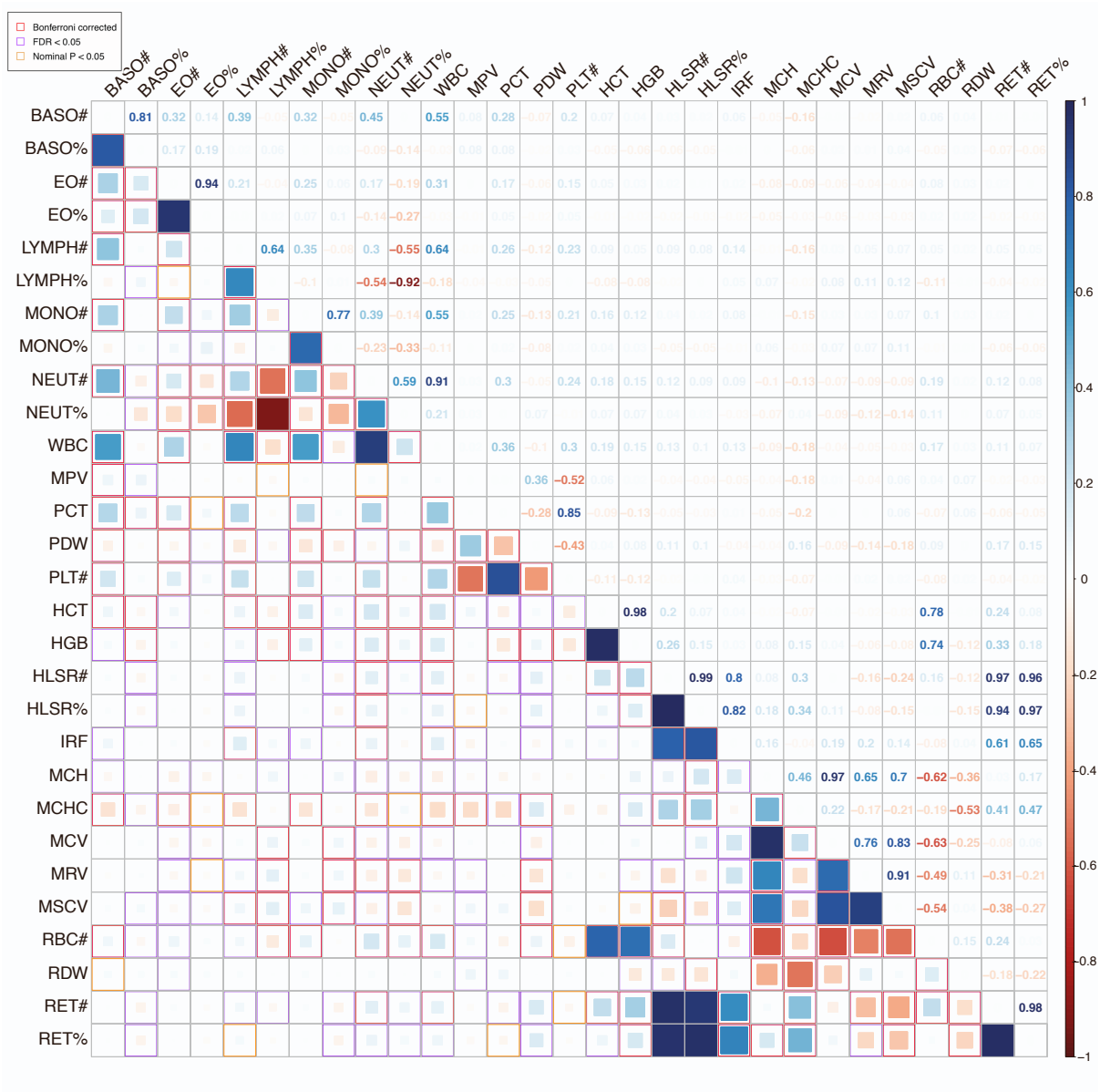

Figure S4. Estimated genetic correlations among BCTs using the HDL model, related to STAR Methods. Significant genetic correlations (in lower triangular heatmap) are highlighted by red, purple, or orange boxes if they were Bonferroni-significant, FDR-significant, or nominally significant, respectively. Estimated genetic correlations are shown in the upper triangular heatmap.

Figure S5. Estimated genetic correlations among BCTs using the LDSC model, related to STAR Methods. Significant genetic correlations (in lower triangular heatmap) are highlighted by red, purple, or orange boxes if they were Bonferroni-significant, FDR-significant, or nominally significant, respectively. Estimated genetic correlations are shown in the upper triangular heatmap.

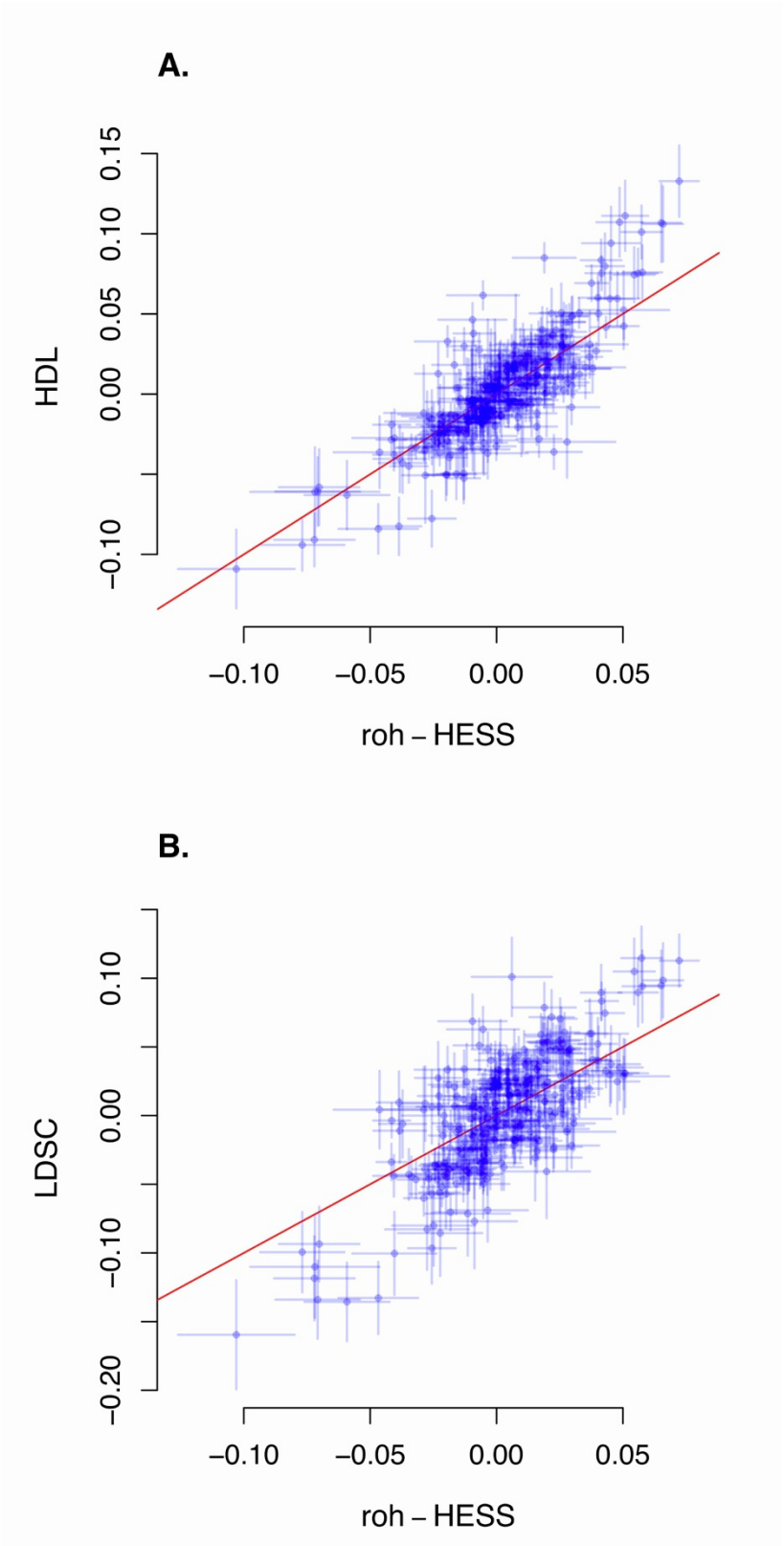

Figure S6. Comparison of genetic correlations for BCT–NPD pairs estimated by ρ-HESS and HDL (A) or LDSC (B), related to Figure 2 and STAR Methods. The estimated correlation = 0.83 (95% CI = 0.79-0.86) for ρ-HESS and HDL; and 0.74 (95% CI = 0.68-0.79) for ρ-HESS and LDSC.

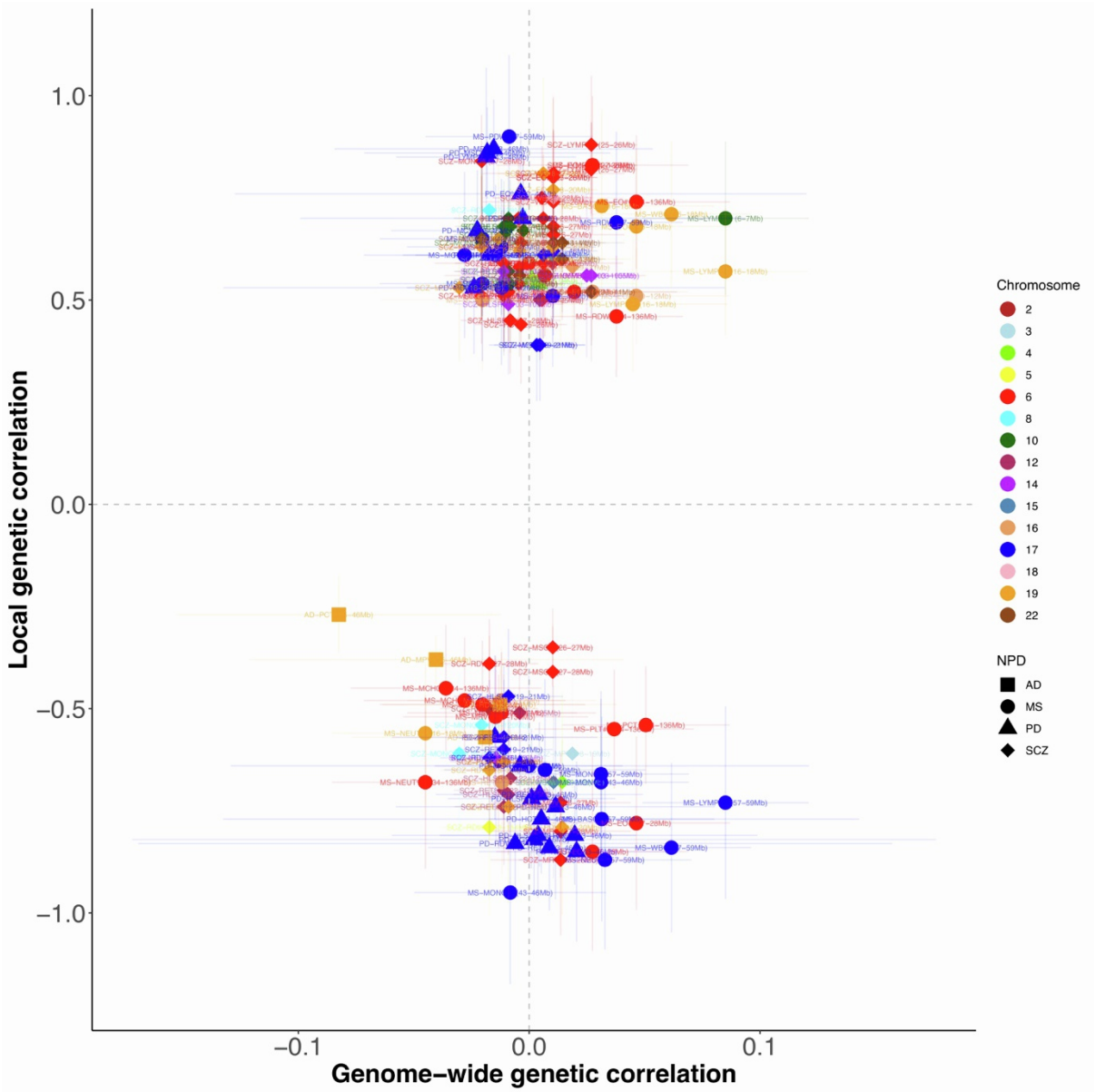

Figure S7. Comparison of genome-wide genetic correlations estimated by HDL (x-axis) and local genetic correlations estimated by ρ-HESS (y-axis) for specific pairs of BCTs and NPDs with Bonferroni-significant local heritability and local genetic correlations, related to STAR Methods. Error bars represent the 95% CIs for the estimated (local) genetic correlations.

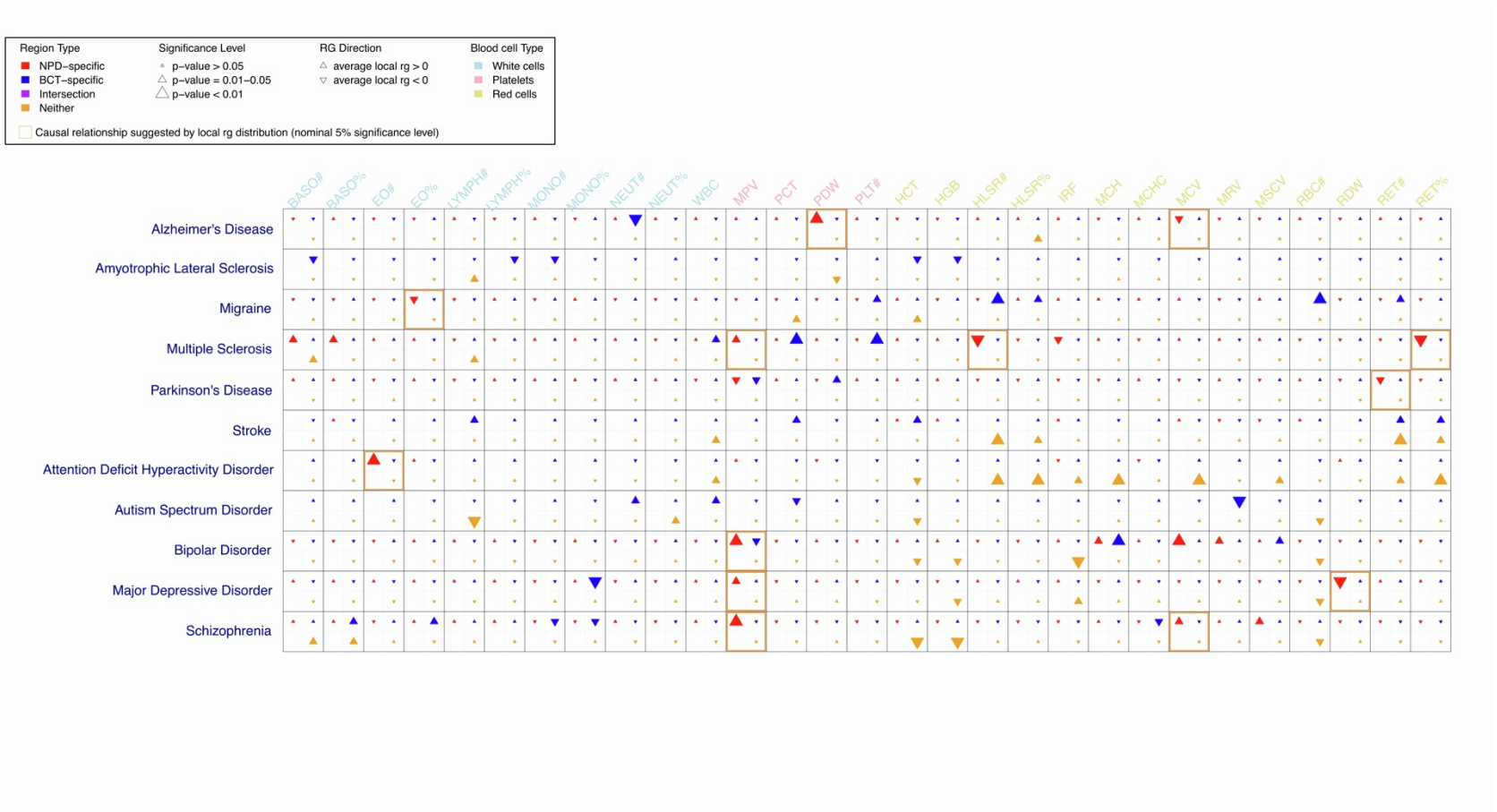

Figure S8. Summary of average local genetic correlations between BCTs and NPDs across trait-specific regions using ρ-HESS, related to STAR Methods. Trait-specific SNPs with GWAS p-value < 5×10^{-8} were used for classifying trait-associated genomic regions and to investigate differences in average local genetic correlation between traits. Significant associations are bordered by orange boxes if (i) the average local genetic correlation in regions harbouring BCT-specific SNPs was significantly different from that in "Intersection" regions, "Neither" regions, and regions harbouring the NPD-specific SNPs; and (ii) at least one of the average local genetic correlations estimated from regions harbouring either BCT- or NPD-specific SNPs was significantly non-zero ($p < 0.05$). See Table S19 for complete details of the ρ-HESS estimates.

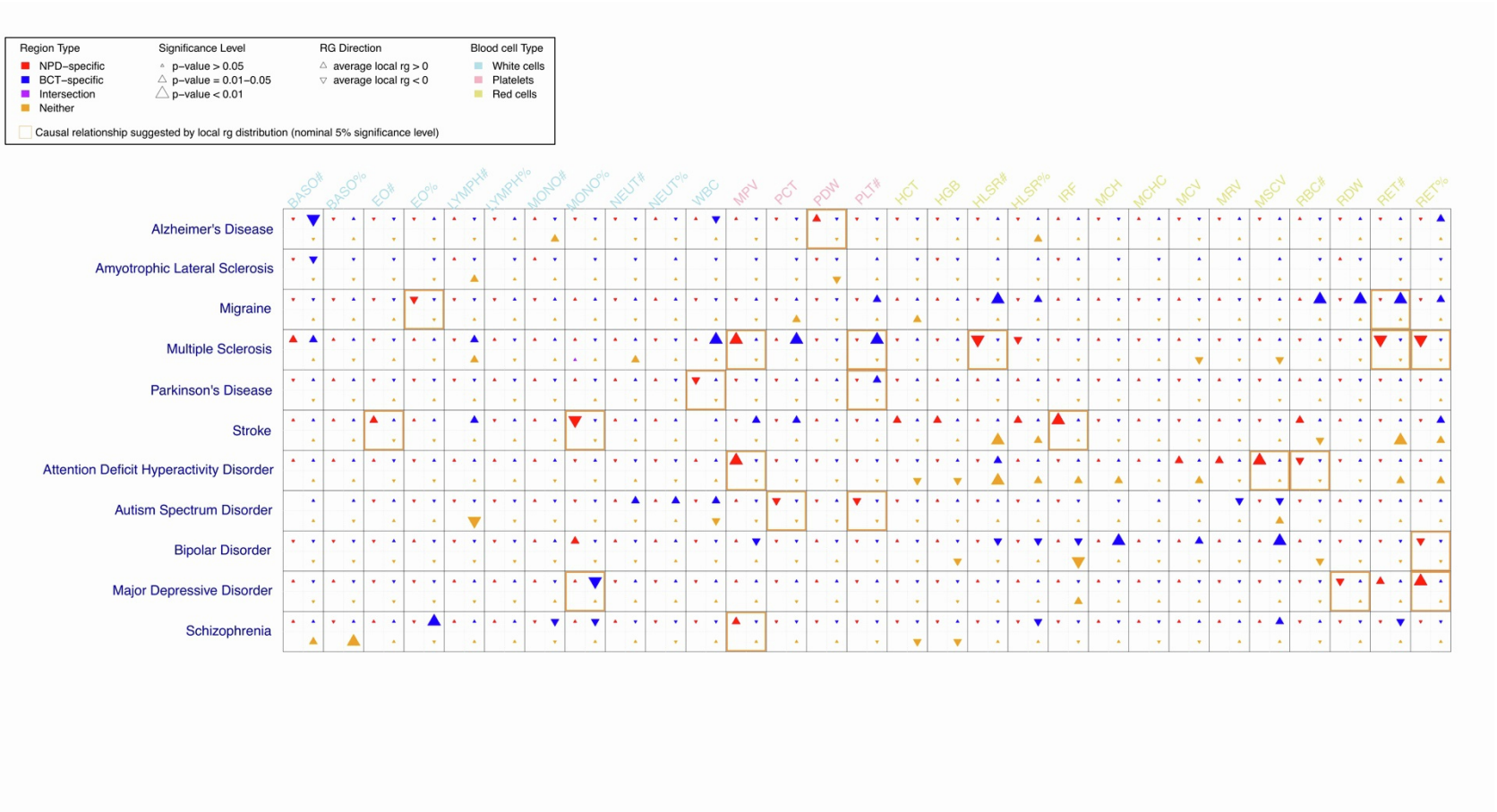

Figure S9. Summary of average local genetic correlations between BCTs and NPDs across trait-specific regions using ρ-HESS, related to STAR Methods. Trait-specific SNPs with GWAS p-value < 1×10^{-6} were used for classifying trait-associated genomic regions and to investigate differences in average local genetic correlation between traits. Significant associations are bordered by orange boxes if (i) the average local genetic correlation in regions harbouring BCT-specific SNPs was significantly different from that in "Intersection" regions, "Neither" regions, and regions harbouring the NPD-specific SNPs; and (ii) at least one of the average local genetic correlations estimated from regions harbouring either BCT- or NPD-specific SNPs was significantly non-zero ($p < 0.05$). See Table S20 for complete details of the ρ-HESS estimates.

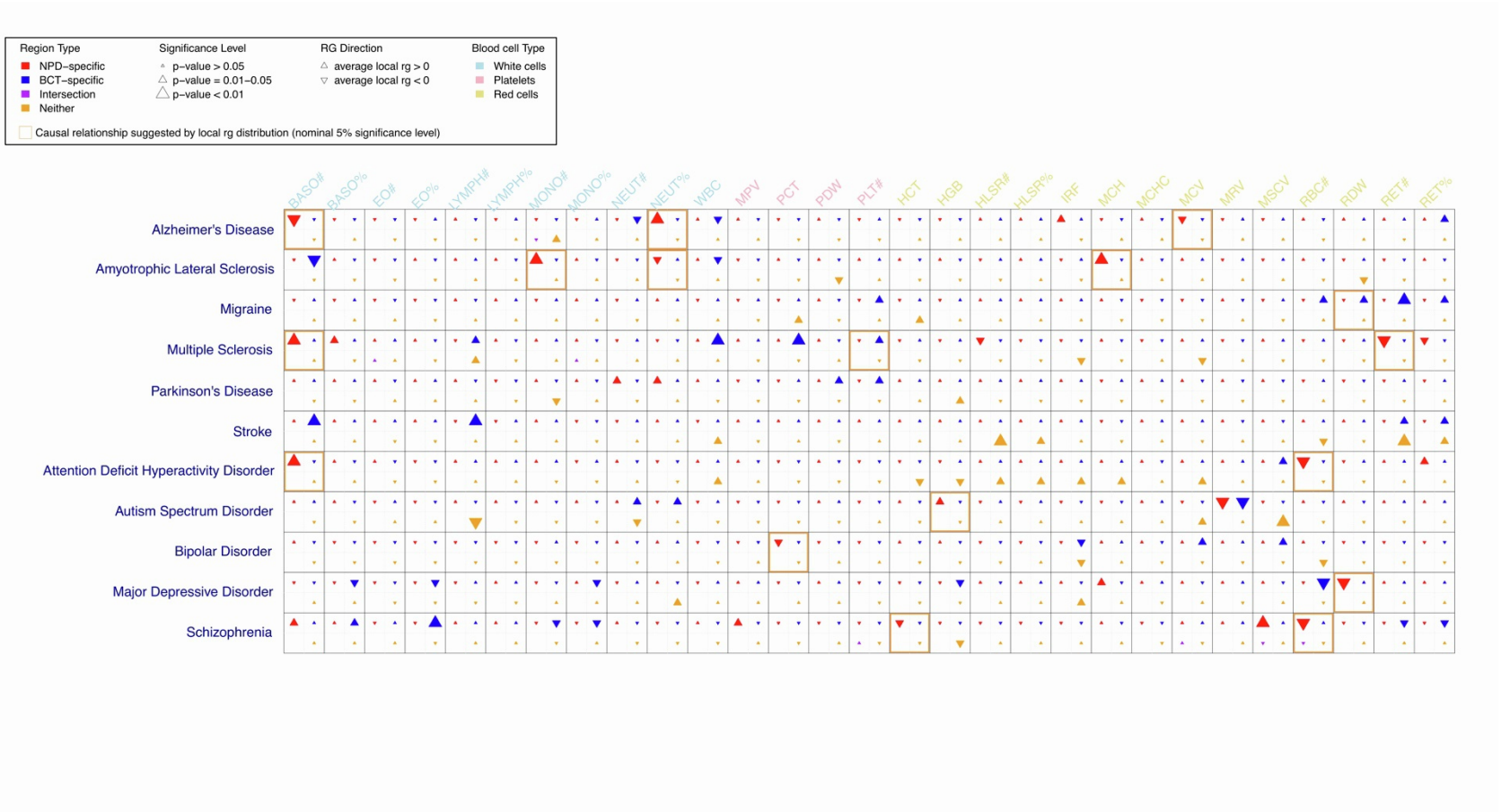

Figure S10. Summary of average local genetic correlations between BCTs and NPDs across trait-specific regions using ρ-HESS, related to STAR Methods. Trait-specific SNPs with GWAS p-value < 1×10^{-5} were used for classifying trait-associated genomic regions and to investigate differences in average local genetic correlation between traits. Significant associations are bordered by orange boxes if (i) the average local genetic correlation in regions harbouring BCT-specific SNPs was significantly different from that in "Intersection" regions, "Neither" regions, and regions harbouring the NPD-specific SNPs; and (ii) at least one of the average local genetic correlations estimated from regions harbouring either BCT- or NPD-specific SNPs was significantly non-zero ($p < 0.05$). See Table S21 for complete details of the ρ-HESS estimates.

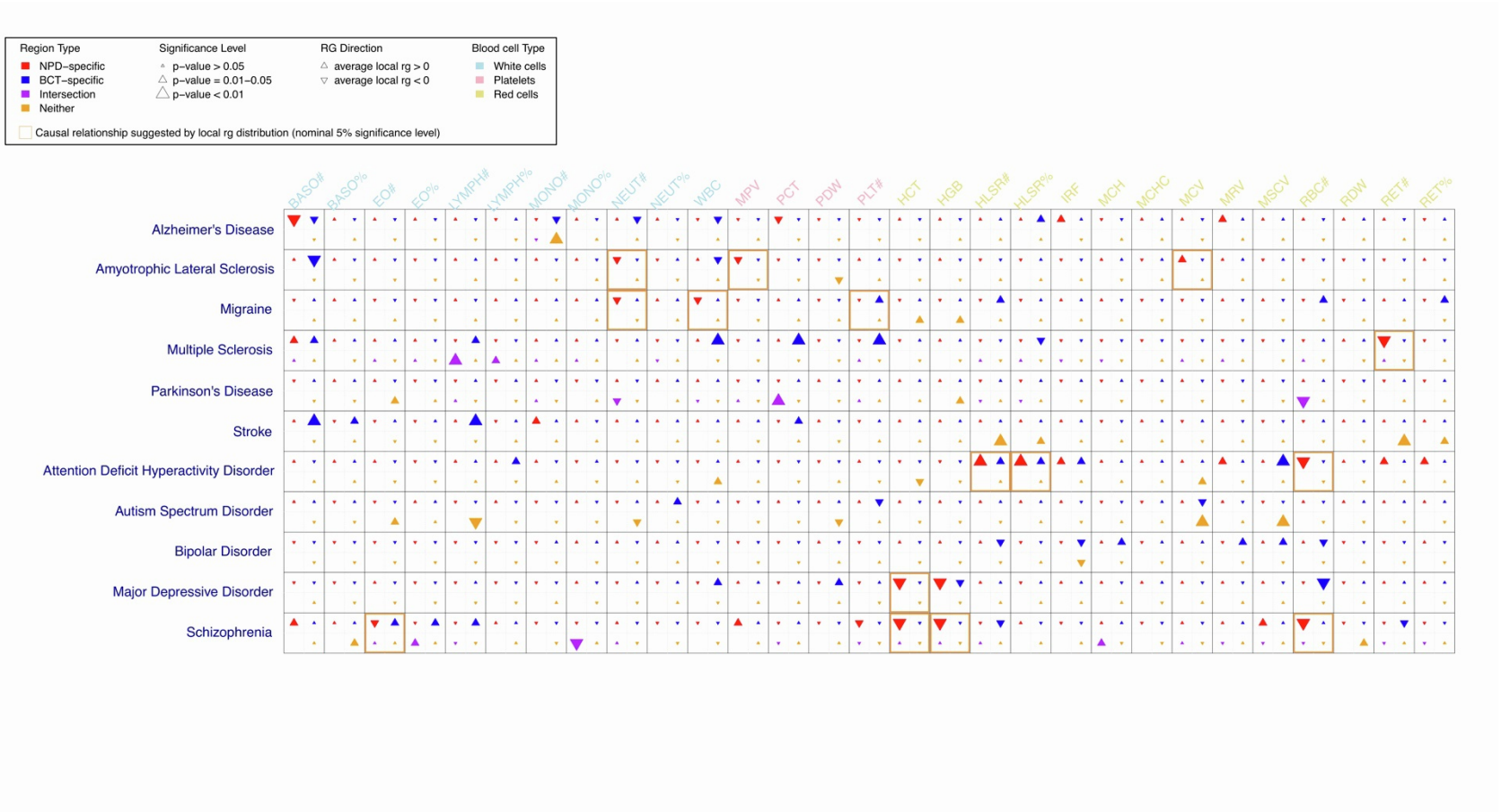

Figure S11. Summary of average local genetic correlations between BCTs and NPDs across trait-specific regions using ρ-HESS, related to STAR Methods. Trait-specific SNPs with GWAS p-value < 1×10^{-4} were used for classifying trait-associated genomic regions and to investigate differences in average local genetic correlation between traits. Significant associations are bordered by orange boxes if (i) the average local genetic correlation in regions harbouring BCT-specific SNPs was significantly different from that in "Intersection" regions, "Neither" regions, and regions harbouring the NPD-specific SNPs; and (ii) at least one of the average local genetic correlations estimated from regions harbouring either BCT- or NPD-specific SNPs was significantly non-zero ($p < 0.05$). See Table S22 for complete details of the ρ-HESS estimates.

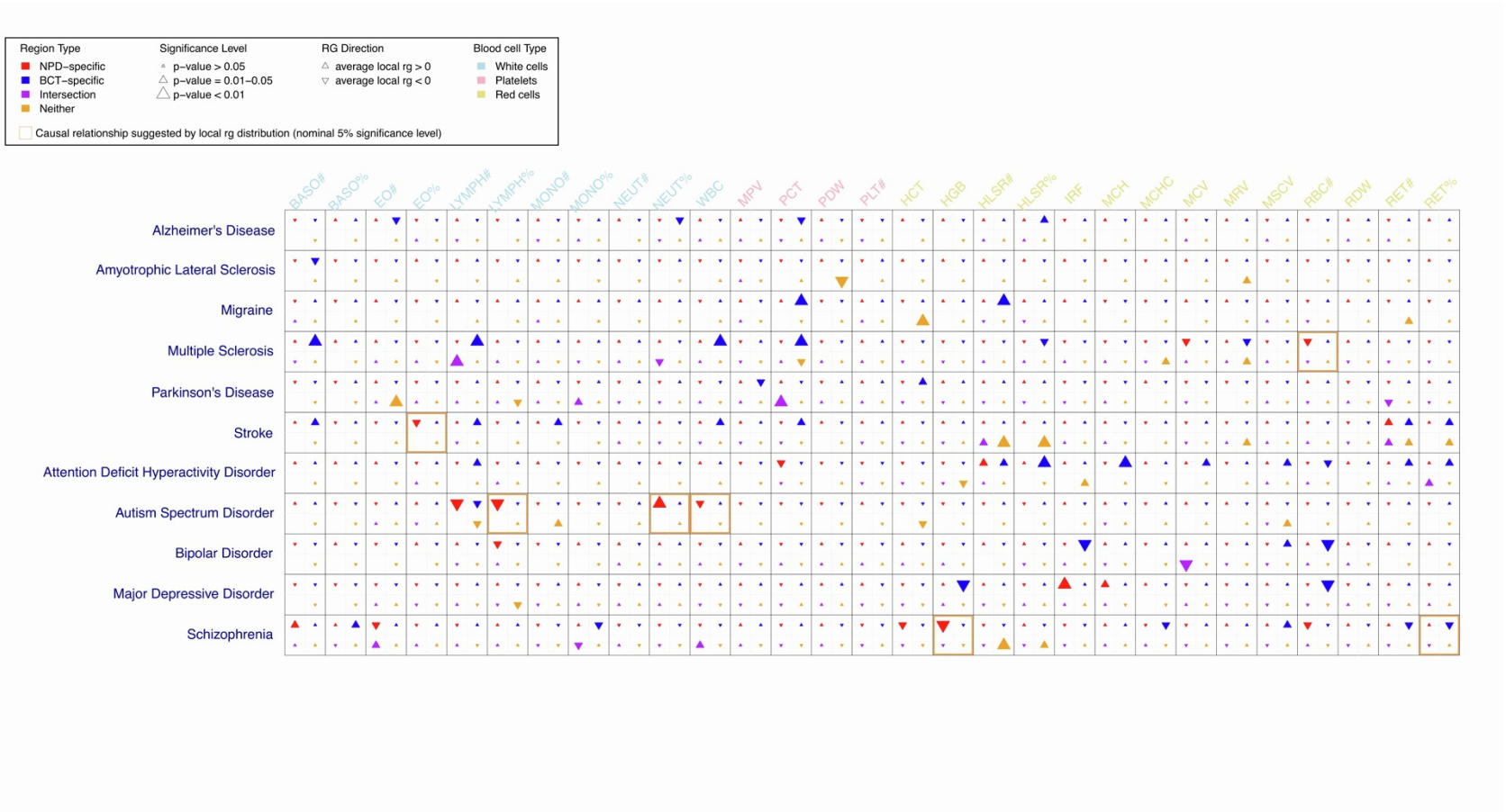

Figure S12. Summary of average local genetic correlations between BCTs and NPDs across trait-specific regions using ρ-HESS, related to STAR Methods. Trait-specific SNPs with GWAS p-value < 1×10^{-3} were used for classifying trait-associated genomic regions and to investigate differences in average local genetic correlation between traits. Significant associations are bordered by orange boxes if (i) the average local genetic correlation in regions harbouring BCT-specific SNPs was significantly different from that in "Intersection" regions, "Neither" regions, and regions harbouring the NPD-specific SNPs; and (ii) at least one of the average local genetic correlations estimated from regions harbouring either BCT- or NPD-specific SNPs was significantly non-zero ($p < 0.05$). See Table S23 for complete details of the ρ-HESS estimates.

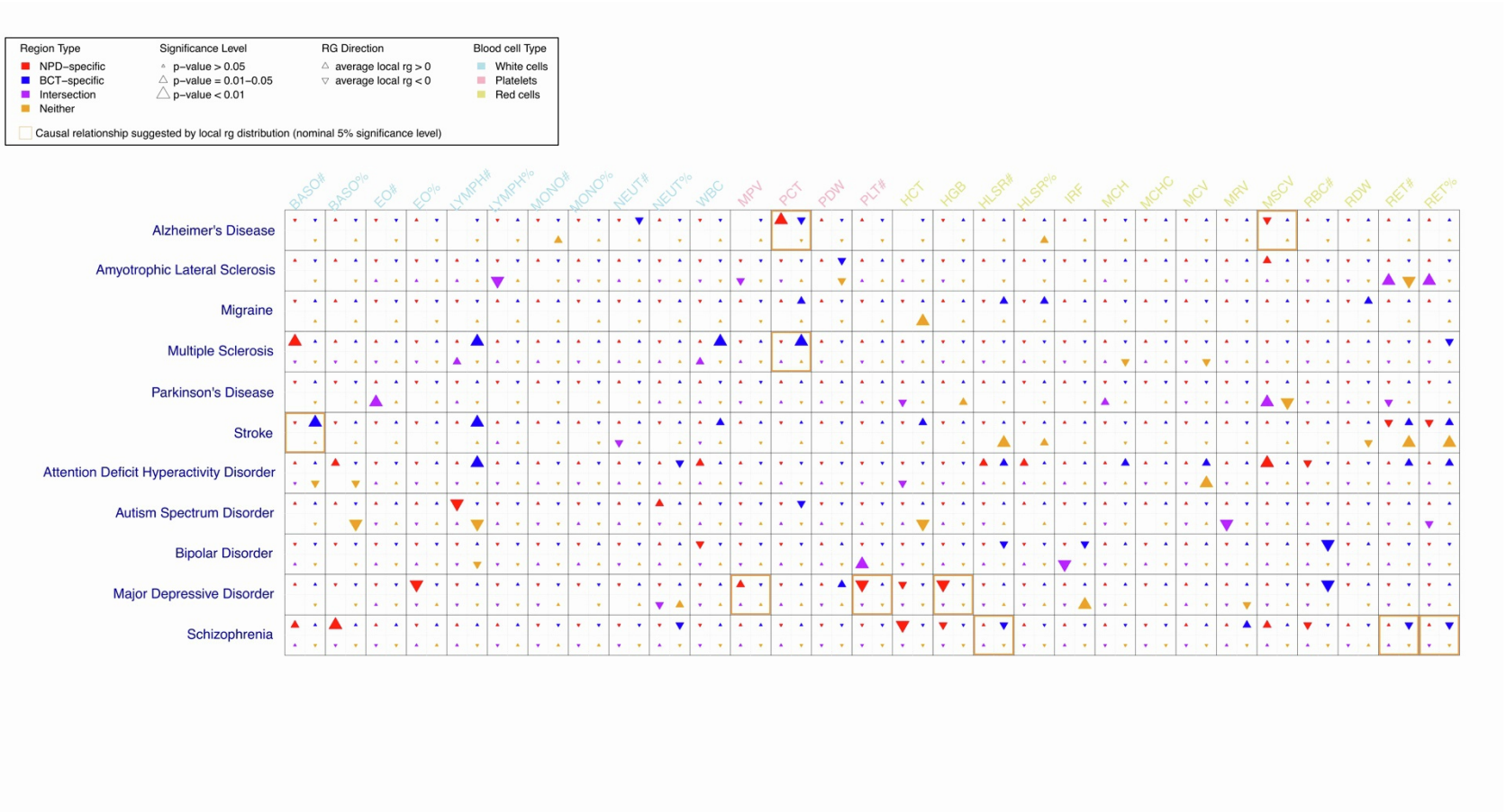

Figure S13. Summary of average local genetic correlations between BCTs and NPDs across trait-specific regions using ρ-HESS, related to STAR Methods. Specific SNPs were selected using the SBayesR method[1] and used for classifying trait-associated genomic regions and to investigate differences in average local genetic correlation between traits. Significant associations are bordered by orange boxes if (i) the average local genetic correlation in regions harbouring BCT-specific SNPs was significantly different from that in "Intersection" regions, "Neither" regions, and regions harbouring the NPD-specific SNPs; and (ii) at least one of the average local genetic correlations estimated from regions harbouring either BCT- or NPD-specific SNPs was significantly non-zero ($p < 0.05$). See Table S24 for complete details of the ρ-HESS estimates.

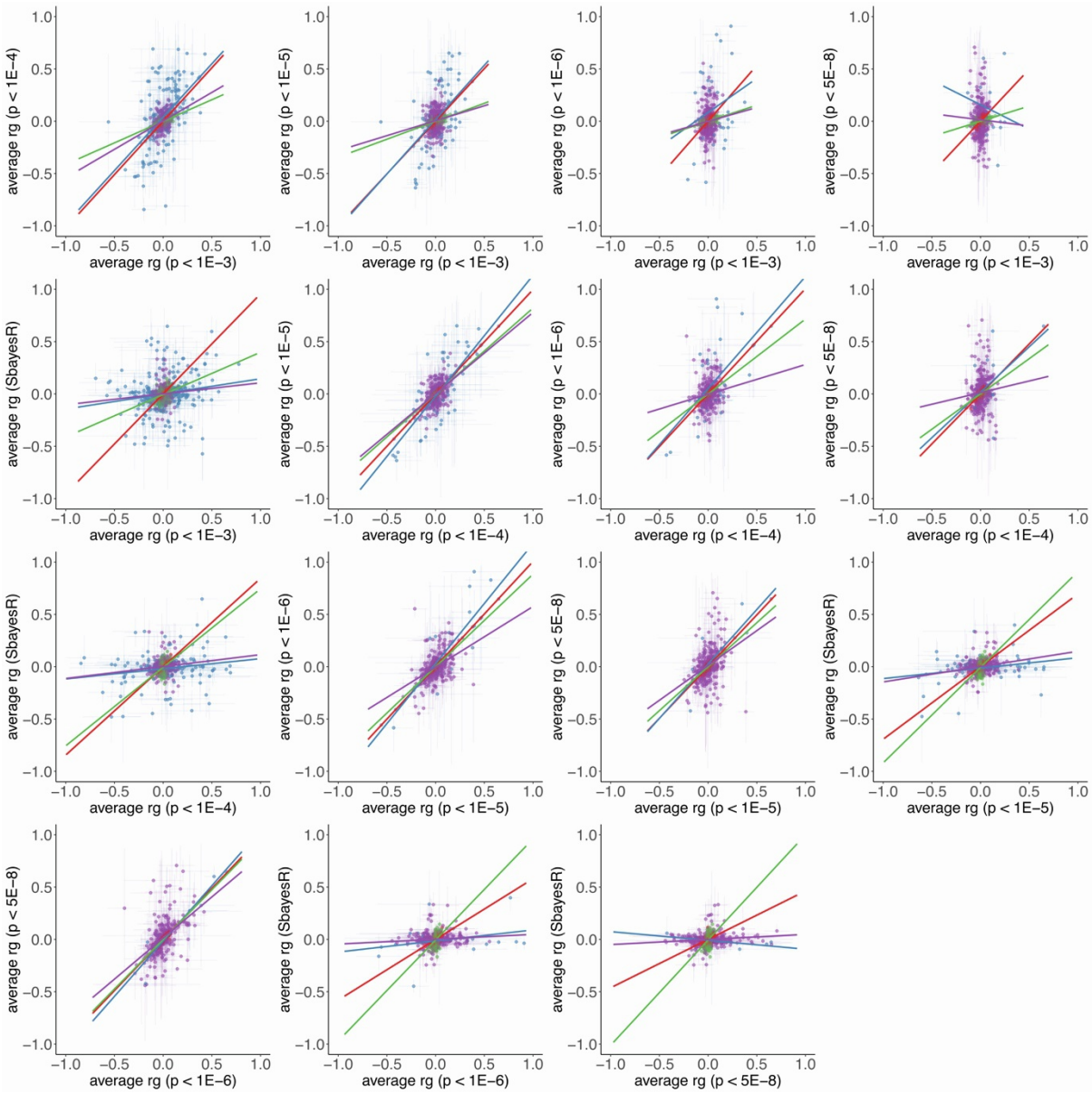

Figure S14. Comparison of average local genetic correlations between n = 319 BCT-NPD trait pairs from analyses performed using different p-value thresholds to define trait-specific regions, related to STAR Methods. Dots in red, green, purple and blue represent the estimated average local genetic correlations from the "BCT-specific" regions, "Neither" regions, "NPD-specific" regions, and "Intersection" regions, respectively, with estimated regression lines displayed in the corresponding colours. Error bars represent the standard errors of the estimated average local genetic correlations.

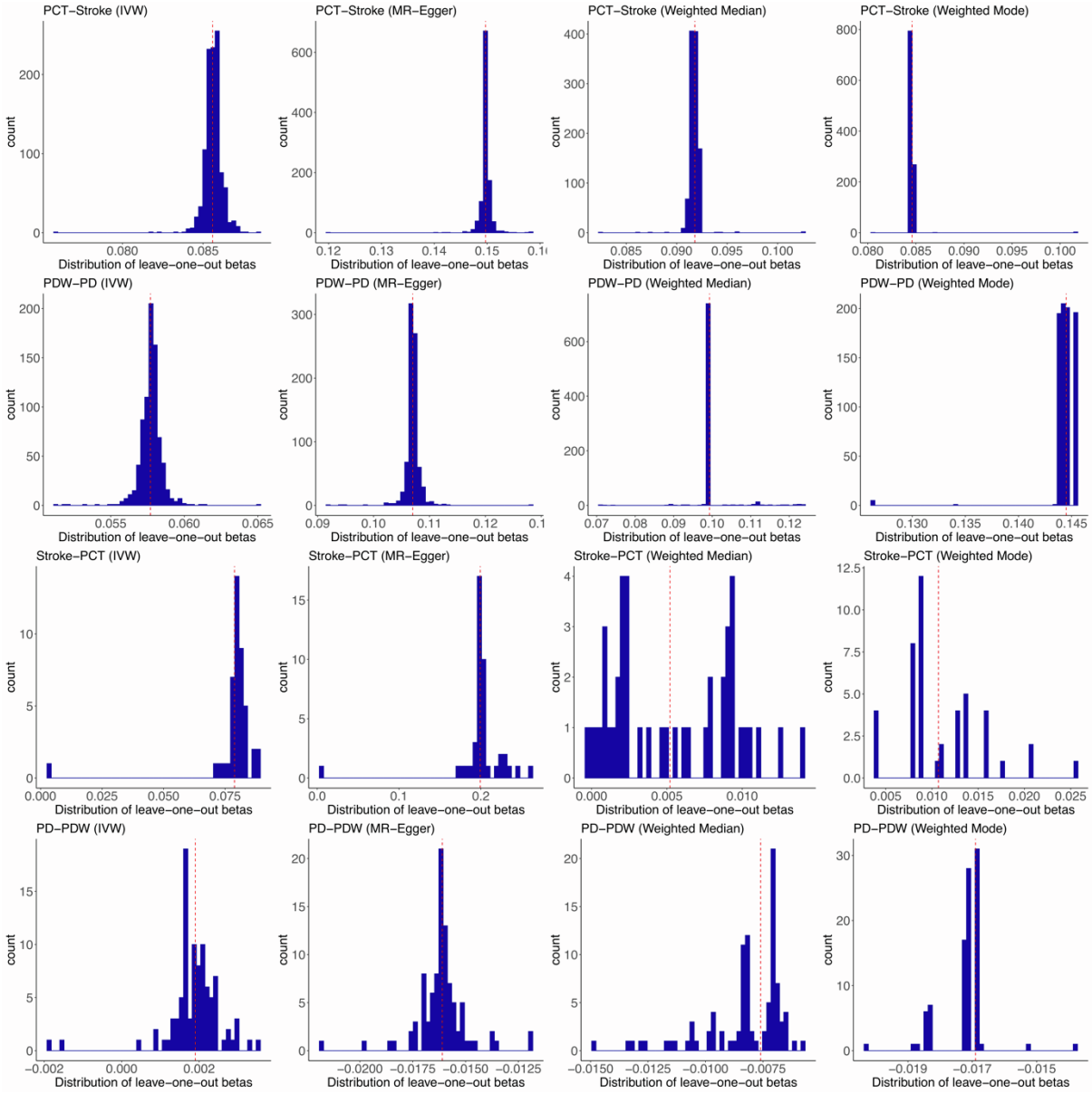

Figure S15. Histograms for estimated beta values from leave-one-out analyses assessing the impact of each instrumental SNP on the putative causal relationships between PCT-stroke and PDW-PD, using IVW, MR-Egger, weighted median, and weighted mode models, respectively, related to Figure 3 and STAR Methods. Plots are also shown for the reverse analyses (i.e., stroke-PCT and PD-PDW). Red dashed lines represent the estimated beta values from the original analyses based on all instrumental SNPs.

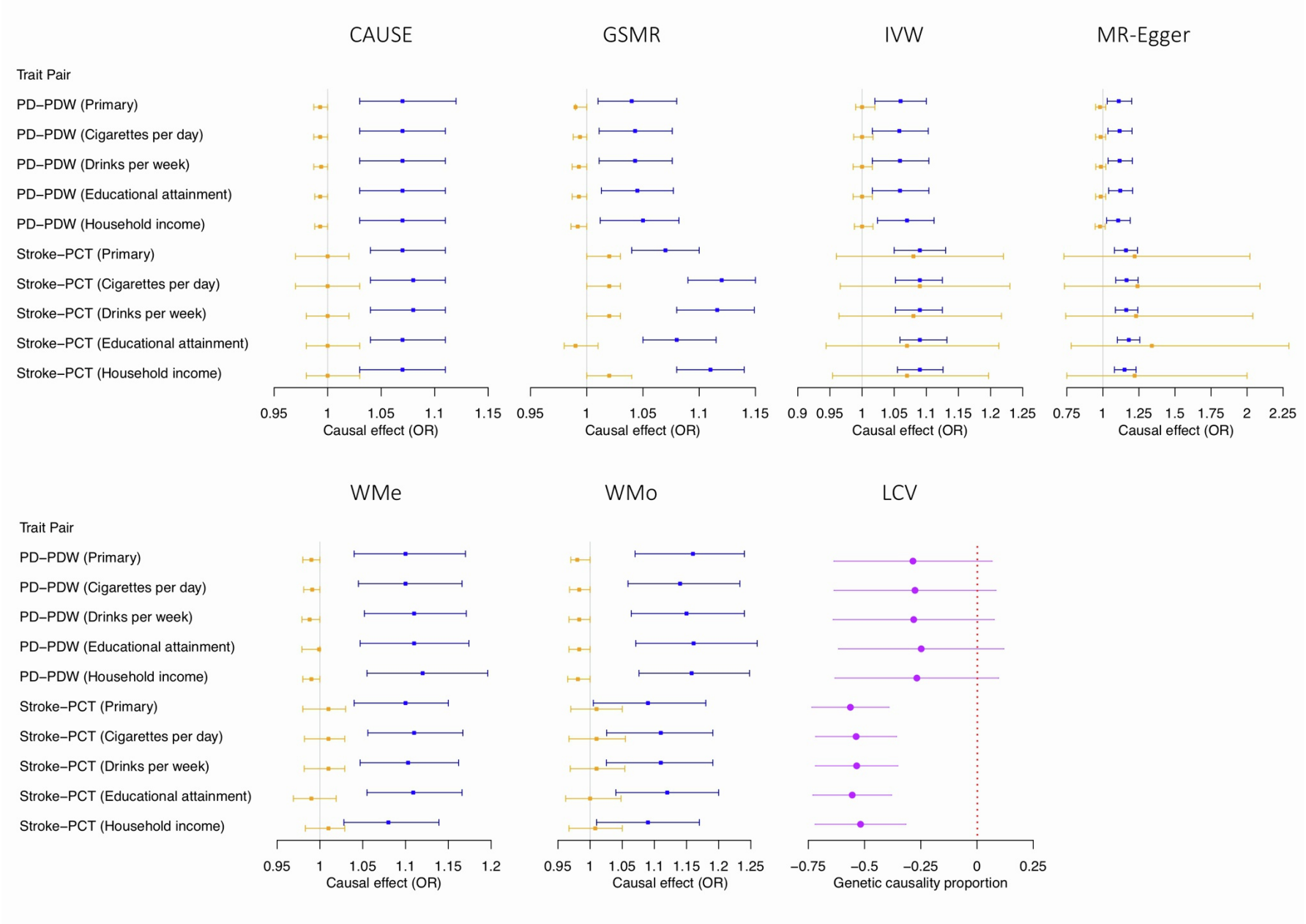
CAUSE
GSMR
IVW
MR-Egger
Trait Pair
PD–PDW (Primary)
PD–PDW (Cigarettes per day)
PD–PDW (Drinks per week)
PD–PDW (Educational attainment)
PD–PDW (Household income)
Stroke–PCT (Primary)
Stroke–PCT (Cigarettes per day)
Stroke–PCT (Drinks per week)
Stroke–PCT (Educational attainment)
Stroke–PCT (Household income)
0.95 1 1.05 1.1 1.15
0.95 1 1.05 1.1 1.15
0.9 0.95 1 1.05 1.1 1.15 1.2 1.25
0.75 1 1.25 1.5 1.75 2 2.25
Causal effect (OR)
WMe
WMo
LCV
Trait Pair
PD–PDW (Primary)
PD–PDW (Cigarettes per day)
PD–PDW (Drinks per week)
PD–PDW (Educational attainment)
PD–PDW (Household income)
Stroke–PCT (Primary)
Stroke–PCT (Cigarettes per day)
Stroke–PCT (Drinks per week)
Stroke–PCT (Educational attainment)
Stroke–PCT (Household income)
0.95 1 1.05 1.1 1.15 1.2
0.95 1 1.05 1.1 1.15 1.2 1.25
−0.75 −0.5 −0.25 0 0.25
Causal effect (OR)
Genetic causality proportion

Figure S16. Summary of the putative causal relationships between PDW and PD as well as between PCT and stroke after adjusting for the effects of cigarettes per day, drinks per week, educational attainment and household income, respectively, related to Figure 3 and STAR Methods. Results coloured in blue represent the estimated causal effect of BCTs on NPDs, while results coloured in orange represent the estimated causal effect of NPDs on BCTs. Error bars for MR methods represent 95% CIs and those for LCV-based GCP point estimates represent standard errors. For LCV, a negative GCP indicates a causal effect of BCT on NPD, and *vice versa*. See Table S34 for complete details of the estimates.

Supplemental Tables

Table S2. Summary of HDL-based genetic correlations adjusted by smoking, drinking, educational attainment and household income individually, related to Figure 2 and STAR Methods.

Risk factor	Trait 1 (NPD)	Trait 2 (BCT)	h^2 (Trait 1)	h^2 se (Trait 1)	h^2 (Trait 2)	h^2 se (Trait 2)	genetic covariance	r_g	r_g se	p-value (r_g)
Cigarettes per day	Migraine	Platelet count	0.0299	0.0022	0.3169	0.0249	0.0096	0.0981	0.0235	3.01×10^{-5}
	Multiple sclerosis	Lymphocyte count	0.3398	0.0227	0.2411	0.0168	0.0232	0.0811	0.0185	1.17×10^{-5}
	Multiple sclerosis	White blood cell count	0.3398	0.0227	0.2317	0.0152	0.0165	0.0589	0.0181	1.11×10^{-3}
	Parkinson's disease	Platelet distribution width	0.0159	0.0016	0.2214	0.0201	0.0018	0.0303	0.0253	0.23
	Schizophrenia	Monocyte percentage of white cells	0.3666	0.0096	0.2451	0.0258	-0.0084	-0.0279	0.0081	5.50×10^{-4}
	Stroke	Plateletcrit	0.0128	0.0021	0.2748	0.0258	0.0068	0.1153	0.0353	1.10×10^{-3}
Drinks per week	Migraine	Platelet count	0.0290	0.0021	0.3166	0.0248	0.0094	0.0981	0.0235	2.93×10^{-5}
	Multiple sclerosis	Lymphocyte count	0.3400	0.0226	0.2404	0.0168	0.0235	0.0820	0.0190	1.55×10^{-5}
	Multiple sclerosis	White blood cell count	0.3400	0.0226	0.2320	0.0152	0.0177	0.0631	0.0184	6.09×10^{-4}
	Parkinson's disease	Platelet distribution width	0.0159	0.0015	0.2215	0.0200	0.0018	0.0303	0.0249	0.22
	Schizophrenia	Monocyte percentage of white cells	0.3803	0.0097	0.2449	0.0258	-0.0090	-0.0295	0.0081	2.69×10^{-4}
	Stroke	Plateletcrit	0.0131	0.0021	0.2748	0.0257	0.0070	0.1158	0.0351	9.64×10^{-4}
Educational attainment	Migraine	Platelet count	0.0329	0.0022	0.3184	0.0246	0.0096	0.0941	0.0215	1.26×10^{-5}
	Multiple sclerosis	Lymphocyte count	0.3396	0.0216	0.2363	0.0153	0.0236	0.0835	0.0190	1.17×10^{-5}
	Multiple sclerosis	White blood cell count	0.3396	0.0216	0.2242	0.0139	0.0170	0.0617	0.0191	1.24×10^{-3}
	Parkinson's disease	Platelet distribution width	0.0167	0.0016	0.2258	0.0200	0.0018	0.0295	0.0170	0.082
	Schizophrenia	Monocyte percentage of white cells	0.3718	0.0098	0.2373	0.0254	-0.0095	-0.0320	0.0092	4.78×10^{-4}
	Stroke	Plateletcrit	0.0129	0.0020	0.2792	0.0261	0.0065	0.1075	0.0343	1.72×10^{-3}
Household income	Migraine	Platelet count	0.0304	0.0022	0.3138	0.0245	0.0087	0.0886	0.0225	8.13×10^{-5}
	Multiple sclerosis	Lymphocyte count	0.3416	0.0225	0.2358	0.0162	0.0247	0.0870	0.0185	2.46×10^{-6}
	Multiple sclerosis	White blood cell count	0.3416	0.0225	0.2215	0.0145	0.0171	0.0621	0.0195	1.42×10^{-3}
	Parkinson's disease	Platelet distribution width	0.0156	0.0015	0.2223	0.0201	0.0026	0.0449	0.0335	0.18
	Schizophrenia	Monocyte percentage of white cells	0.3361	0.0090	0.2395	0.0251	-0.0080	-0.0280	0.0084	9.03×10^{-4}
	Stroke	Plateletcrit	0.0129	0.0020	0.2747	0.0258	0.0062	0.1046	0.0344	2.35×10^{-3}

BCT: blood cell trait. NPD: neurological and psychiatric disorder. h^2: heritability. r_g: genetic correlation. se: standard error. HDL: high-definition likelihood.

Table S25. Comparison of average local genetic correlation between BCTs and NPDs per trait-specific region among different SNP sets for classification of trait-associated regions, related to STAR Methods.

Comparison	Group	Correlation (95% CI)	*p*-value
$p < 1\times10^{-3}$ vs $p < 1\times10^{-4}$	NPD-specific	0.38 (0.28,0.47)	3.02×10^{-12}
$p < 1\times10^{-3}$ vs $p < 1\times10^{-4}$	BCT-specific	0.88 (0.85,0.90)	3.82×10^{-105}
$p < 1\times10^{-3}$ vs $p < 1\times10^{-4}$	Neither	0.67 (0.60,0.73)	7.80×10^{-43}
$p < 1\times10^{-3}$ vs $p < 1\times10^{-4}$	Intersection	0.55 (0.42,0.65)	2.33×10^{-12}
$p < 1\times10^{-3}$ vs $p < 1\times10^{-5}$	NPD-specific	0.13 (0.02,0.24)	0.017
$p < 1\times10^{-3}$ vs $p < 1\times10^{-5}$	BCT-specific	0.79 (0.74,0.82)	4.19×10^{-68}
$p < 1\times10^{-3}$ vs $p < 1\times10^{-5}$	Neither	0.61 (0.54,0.68)	2.52×10^{-34}
$p < 1\times10^{-3}$ vs $p < 1\times10^{-5}$	Intersection	0.52 (0.32,0.67)	4.12×10^{-6}
$p < 1\times10^{-3}$ vs $p < 1\times10^{-6}$	NPD-specific	0.09 (-0.02,0.20)	0.091
$p < 1\times10^{-3}$ vs $p < 1\times10^{-6}$	BCT-specific	0.76 (0.71,0.80)	4.76×10^{-61}
$p < 1\times10^{-3}$ vs $p < 1\times10^{-6}$	Neither	0.60 (0.52,0.66)	3.94×10^{-32}
$p < 1\times10^{-3}$ vs $p < 1\times10^{-6}$	Intersection	0.23 (-0.14,0.54)	0.22
$p < 1\times10^{-3}$ vs $p < 5\times10^{-8}$	NPD-specific	-0.03 (-0.15,0.09)	0.63
$p < 1\times10^{-3}$ vs $p < 5\times10^{-8}$	BCT-specific	0.66 (0.59,0.72)	4.53×10^{-41}
$p < 1\times10^{-3}$ vs $p < 5\times10^{-8}$	Neither	0.57 (0.50,0.64)	2.48×10^{-29}
$p < 1\times10^{-3}$ vs $p < 5\times10^{-8}$	Intersection	-0.18 (-0.67,0.41)	0.55
$p < 1\times10^{-4}$ vs $p < 1\times10^{-5}$	NPD-specific	0.52 (0.44,0.60)	1.43×10^{-23}
$p < 1\times10^{-4}$ vs $p < 1\times10^{-5}$	BCT-specific	0.90 (0.88,0.92)	3.40×10^{-118}
$p < 1\times10^{-4}$ vs $p < 1\times10^{-5}$	Neither	0.90 (0.88,0.92)	3.55×10^{-118}
$p < 1\times10^{-4}$ vs $p < 1\times10^{-5}$	Intersection	0.82 (0.73,0.89)	1.92×10^{-18}
$p < 1\times10^{-4}$ vs $p < 1\times10^{-6}$	NPD-specific	0.15 (0.04,0.25)	9.31×10^{-3}
$p < 1\times10^{-4}$ vs $p < 1\times10^{-6}$	BCT-specific	0.83 (0.79,0.86)	4.89×10^{-83}
$p < 1\times10^{-4}$ vs $p < 1\times10^{-6}$	Neither	0.85 (0.82,0.88)	1.08×10^{-90}
$p < 1\times10^{-4}$ vs $p < 1\times10^{-6}$	Intersection	0.64 (0.37,0.81)	1.13×10^{-4}
$p < 1\times10^{-4}$ vs $p < 5\times10^{-8}$	NPD-specific	0.08 (-0.04,0.20)	0.18
$p < 1\times10^{-4}$ vs $p < 5\times10^{-8}$	BCT-specific	0.73 (0.68,0.78)	2.81×10^{-55}
$p < 1\times10^{-4}$ vs $p < 5\times10^{-8}$	Neither	0.82 (0.78,0.85)	5.49×10^{-78}
$p < 1\times10^{-4}$ vs $p < 5\times10^{-8}$	Intersection	0.51 (-0.06,0.83)	0.076
$p < 1\times10^{-5}$ vs $p < 1\times10^{-6}$	NPD-specific	0.44 (0.35,0.53)	8.25×10^{-17}
$p < 1\times10^{-5}$ vs $p < 1\times10^{-6}$	BCT-specific	0.92 (0.90,0.93)	1.84×10^{-129}
$p < 1\times10^{-5}$ vs $p < 1\times10^{-6}$	Neither	0.96 (0.95,0.96)	6.83×10^{-171}
$p < 1\times10^{-5}$ vs $p < 1\times10^{-6}$	Intersection	0.90 (0.80,0.95)	4.50×10^{-12}
$p < 1\times10^{-5}$ vs $p < 5\times10^{-8}$	NPD-specific	0.34 (0.23,0.44)	7.77×10^{-9}
$p < 1\times10^{-5}$ vs $p < 5\times10^{-8}$	BCT-specific	0.84 (0.80,0.87)	7.12×10^{-86}
$p < 1\times10^{-5}$ vs $p < 5\times10^{-8}$	Neither	0.93 (0.91,0.94)	7.69×10^{-136}
$p < 1\times10^{-5}$ vs $p < 5\times10^{-8}$	Intersection	0.88 (0.64,0.96)	6.89×10^{-5}
$p < 1\times10^{-6}$ vs $p < 5\times10^{-8}$	NPD-specific	0.50 (0.41,0.59)	2.22×10^{-19}
$p < 1\times10^{-6}$ vs $p < 5\times10^{-8}$	BCT-specific	0.91 (0.89,0.92)	5.84×10^{-121}
$p < 1\times10^{-6}$ vs $p < 5\times10^{-8}$	Neither	0.97 (0.96,0.97)	1.41×10^{-190}
$p < 1\times10^{-6}$ vs $p < 5\times10^{-8}$	Intersection	0.96 (0.87,0.99)	1.86×10^{-7}
$p < 1\times10^{-3}$ vs $p <$ SbayesR	NPD-specific	0.07 (-0.04,0.18)	0.19
$p < 1\times10^{-3}$ vs $p <$ SbayesR	BCT-specific	0.81 (0.77,0.85)	1.46×10^{-76}
$p < 1\times10^{-3}$ vs $p <$ SbayesR	Neither	0.40 (0.30,0.48)	1.98×10^{-13}
$p < 1\times10^{-3}$ vs $p <$ SbayesR	Intersection	0.17 (0.05,0.29)	7.84×10^{-3}
$p < 1\times10^{-4}$ vs $p <$ SbayesR	NPD-specific	0.12 (0.01,0.22)	0.038
$p < 1\times10^{-4}$ vs $p <$ SbayesR	BCT-specific	0.83 (0.79,0.86)	4.87×10^{-83}
$p < 1\times10^{-4}$ vs $p <$ SbayesR	Neither	0.45 (0.36,0.54)	1.72×10^{-17}
$p < 1\times10^{-4}$ vs $p <$ SbayesR	Intersection	0.18 (0.01,0.35)	0.041
$p < 1\times10^{-5}$ vs $p <$ SbayesR	NPD-specific	0.22 (0.12,0.33)	5.75×10^{-5}
$p < 1\times10^{-5}$ vs $p <$ SbayesR	BCT-specific	0.76 (0.70,0.80)	2.45×10^{-60}
$p < 1\times10^{-5}$ vs $p <$ SbayesR	Neither	0.50 (0.41,0.58)	1.14×10^{-21}
$p < 1\times10^{-5}$ vs $p <$ SbayesR	Intersection	0.25 (-0.01,0.48)	0.060
$p < 1\times10^{-6}$ vs $p <$ SbayesR	NPD-specific	0.09 (-0.02,0.20)	0.099

$p < 1\times10^{-6}$ vs $p <$ SbayesR	BCT-specific	0.69 (0.63,0.74)	1.59×10^{-46}
$p < 1\times10^{-6}$ vs $p <$ SbayesR	Neither	0.49 (0.40,0.57)	1.18×10^{-20}
$p < 1\times10^{-6}$ vs $p <$ SbayesR	Intersection	0.29 (-0.14,0.62)	0.19
$p < 5\times10^{-8}$ vs $p <$ SbayesR	NPD-specific	0.13 (0.01,0.24)	0.033
$p < 5\times10^{-8}$ vs $p <$ SbayesR	BCT-specific	0.59 (0.52,0.66)	1.17×10^{-31}
$p < 5\times10^{-8}$ vs $p <$ SbayesR	Neither	0.50 (0.41,0.58)	1.33×10^{-21}
$p < 5\times10^{-8}$ vs $p <$ SbayesR	Intersection	-0.54 (-0.92,0.35)	0.21

BCT: blood cell trait. NPD: neurological and psychiatric disorder. SNP: single nucleotide polymorphism. CI: confidence interval.

Table S27. Summary of MR sensitivity analyses, related to Figure 3 and STAR Methods.					
LCV					
Trait 1	Trait 2	n of SNPs	GCP*	GCP se	*p*-value
Autism spectrum disorder	Mean spheric corpuscular volume	1149387	-0.07	0.32	0.46
Multiple sclerosis	Lymphocyte count	1162211	-0.19	0.13	0.25
Multiple sclerosis	Plateletcrit	1162184	0.01	0.58	0.98
Multiple sclerosis	White blood cell count	1162194	0.08	0.37	0.99
Parkinson's disease	Platelet distribution width	1056850	-0.35	0.43	0.17
Stroke	Plateletcrit	1145599	-0.69	0.21	4.43×10^{-23}
GSMR					
Exposure	Outcome	n of SNPs (n after HEIDI-outlier test)	Beta (95% CI)	OR	*p*-value
Autism spectrum disorder**	Mean spheric corpuscular volume	34 (30)	-0.01 (-0.0222, 0.0002)	0.99	0.054
Mean spheric corpuscular volume	Autism spectrum disorder	1172 (1104)	-0.07 (-0.1073, -0.0299)	0.93	5.17×10^{-4}
Multiple sclerosis	Lymphocyte count	70 (29)	0.01 (0.0007, 0.0146)	1.01	0.030
Lymphocyte count	Multiple sclerosis	790 (635)	0.07 (-0.0084, 0.1411)	1.07	0.082
Multiple sclerosis	Plateletcrit	70 (44)	0.00 (-0.0081, 0.0031)	1.00	0.38
Plateletcrit	Multiple sclerosis	1003 (867)	0.11 (0.05600, 0.1669)	1.12	8.19×10^{-5}
Multiple sclerosis	White blood cell count	70 (41)	0.01 (0.0058, 0.0176)	1.01	1.01×10^{-4}
White blood cell count	Multiple sclerosis	802 (662)	0.11 (0.0396, 0.1828)	1.12	2.33×10^{-3}
Parkinson's disease	Platelet distribution width	95 (84)	-0.01 (-0.0123, -0.0004)	0.99	0.036
Platelet distribution width	Parkinson's disease	804 (719)	0.04 (0.0114, 0.0732)	1.04	7.26×10^{-3}
Stroke**	Plateletcrit	44 (32)	0.02 (0.0007, 0.0327)	1.02	0.041
Plateletcrit	Stroke	1067 (984)	0.07 (0.0385, 0.0972)	1.07	5.83×10^{-6}
IVW					
Exposure	Outcome	n of SNPs	Beta (95% CI)	OR	*p*-value
Autism spectrum disorder**	Mean spheric corpuscular volume	34	-0.04 (-0.0812, 0.0093)	0.96	0.12
Mean spheric corpuscular volume	Autism spectrum disorder	1172	-0.08 (-0.1190, -0.0354)	0.93	2.94×10^{-4}
Multiple sclerosis	Lymphocyte count	70	0.02 (-0.0112, 0.0448)	1.02	0.24
Lymphocyte count	Multiple sclerosis	790	0.25 (0.1413, 0.3612)	1.29	7.45×10^{-6}
Multiple sclerosis	Plateletcrit	70	-0.01 (-0.0363, 0.0086)	0.99	0.23
Plateletcrit	Multiple sclerosis	1003	0.09 (0.0080, 0.1702)	1.09	0.031
Multiple sclerosis	White blood cell count	70	0.00 (-0.0177, 0.0214)	1.00	0.85
White blood cell count	Multiple sclerosis	802	0.12 (0.0181, 0.2279)	1.13	0.022
Parkinson's disease	Platelet distribution width	95	0.00 (-0.0128, 0.0165)	1.00	0.80
Platelet distribution width	Parkinson's disease	804	0.06 (0.0164, 0.0990)	1.06	6.13×10^{-3}
Stroke**	Plateletcrit	44	0.08 (-0.0380, 0.1956)	1.08	0.19

Plateletcrit	Stroke	1067	0.09 (0.0519, 0.1193)	1.09	6.32×10^{-7}
MR-Egger					
Exposure	Outcome	n of SNPs	Beta (95% CI)	OR	*p*-value
Autism spectrum disorder**	Mean spheric corpuscular volume	34	-0.06 (-0.3282, 0.2110)	0.94	0.67
Mean spheric corpuscular volume	Autism spectrum disorder	1172	-0.06 (-0.1375, 0.0170)	0.94	0.13
Multiple sclerosis	Lymphocyte count	70	-0.04 (-0.1713, 0.0909)	0.96	0.55
Lymphocyte count	Multiple sclerosis	790	0.59 (0.3429, 0.8434)	1.81	3.97×10^{-6}
Multiple sclerosis	Plateletcrit	70	-0.04 (-0.1456, 0.0660)	0.96	0.46
Plateletcrit	Multiple sclerosis	1003	0.21 (0.0425, 0.3773)	1.23	0.014
Multiple sclerosis	White blood cell count	70	-0.01 (-0.1038, 0.0805)	0.99	0.81
White blood cell count	Multiple sclerosis	802	0.08 (-0.1726, 0.3365)	1.09	0.53
Parkinson's disease	Platelet distribution width	95	-0.02 (-0.0513, 0.0191)	0.98	0.37
Platelet distribution width	Parkinson's disease	804	0.11 (0.0321, 0.1819)	1.11	5.23×10^{-3}
Stroke**	Plateletcrit	44	0.20 (-0.3047, 0.7034)	1.22	0.44
Plateletcrit	Stroke	1067	0.15 (0.0813, 0.2181)	1.16	1.96×10^{-5}
Weighted Median					
Exposure	Outcome	n of SNPs	Beta (95% CI)	OR	*p*-value
Autism spectrum disorder**	Mean spheric corpuscular volume	34	-0.01 (-0.0261, 0.0068)	0.99	0.25
Mean spheric corpuscular volume	Autism spectrum disorder	1172	-0.05 (-0.1262, 0.0177)	0.95	0.14
Multiple sclerosis	Lymphocyte count	70	-0.01 (-0.0191, 0.0027)	0.99	0.14
Lymphocyte count	Multiple sclerosis	790	0.33 (0.2056, 0.4519)	1.39	1.69×10^{-7}
Multiple sclerosis	Plateletcrit	70	0.00 (-0.0126, 0.0055)	1.00	0.44
Plateletcrit	Multiple sclerosis	1003	0.10 (-0.0113, 0.2041)	1.10	0.079
Multiple sclerosis	White blood cell count	70	0.01 (-0.0015, 0.0176)	1.01	0.099
White blood cell count	Multiple sclerosis	802	0.15 (0.0302, 0.2730)	1.16	0.014
Parkinson's disease	Platelet distribution width	95	-0.01 (-0.0175, 0.0023)	0.99	0.12
Platelet distribution width	Parkinson's disease	804	0.10 (0.0426, 0.1560)	1.10	7.08×10^{-4}
Stroke**	Plateletcrit	44	0.01 (-0.0187, 0.0292)	1.01	0.68
Plateletcrit	Stroke	1067	0.09 (0.0406, 0.1429)	1.10	5.28×10^{-4}
Weighted Mode					
Exposure	Outcome	n of SNPs	Beta (95% CI)	OR	*p*-value
Autism spectrum disorder**	Mean spheric corpuscular volume	34	0.00 (-0.0359, 0.0275)	1.00	0.80
Mean spheric corpuscular volume	Autism spectrum disorder	1172	-0.08 (-0.1749, 0.0118)	0.92	0.087
Multiple sclerosis	Lymphocyte count	70	-0.02 (-0.0346, -0.0002)	0.98	0.051
Lymphocyte count	Multiple sclerosis	790	0.71 (0.4183, 1.0041)	2.04	2.31×10^{-6}
Multiple sclerosis	Plateletcrit	70	0.00 (-0.0180, 0.0087)	1.00	0.50
Plateletcrit	Multiple sclerosis	1003	0.13 (-0.0234, 0.2895)	1.14	0.096

Multiple sclerosis	White blood cell count	70	0.00 (-0.0115, 0.0215)	1.00	0.56
White blood cell count	Multiple sclerosis	802	0.13 (-0.1263, 0.3828)	1.14	0.32
Parkinson's disease	Platelet distribution width	95	-0.02 (-0.0320, -0.0018)	0.98	0.020
Platelet distribution width	Parkinson's disease	804	0.14 (0.0641, 0.2250)	1.16	1.87×10^{-4}
Stroke**	Plateletcrit	44	0.01 (-0.0310, 0.0523)	1.01	0.64
Plateletcrit	Stroke	1067	0.08 (0.0045, 0.1646)	1.09	0.049

*Positive GCP suggests the causal effect of NPD on BCT, and *vice versa*. **MR models utilised instrumental SNPs with $p < 1\times10^{-5}$. BCT: blood cell trait. NPD: neurological and psychiatric disorder. OR: odds ratio. SNP: single nucleotide polymorphism. MR: Mendelian randomisation. LCV: latent causal variable model. GSMR: generalised summary-data-based Mendelian randomisation. IVW: inverse variance weighting. GCP: genetic causal proportion. se: standard error.

Table S28. Phenotypic correlations between LYMPH# and MS, PCT and stroke, and PDW and PD in the UK Biobank, related to Figure 3 and STAR Methods.

Neurological and psychiatric disorder UK Biobank code (field code)		Trait Pair		
		LYMPH# - MS	PCT - Stroke	PDW - PD
		MS (41270 [G35])	Stroke (42007+42009+41270 [I64]; exclude self-report only)	PD (41270 [G20])
Full sample	Sample size (MS/Stroke/PD cases)	347898 (1238)	347898 (5288)	347898 (1323)
	Correlation	-0.0010	0.0042	0.0057
	p-value	0.55	0.014	8.44×10^{-4}
proportion of cases at 1%	Sample size (MS/Stroke/PD cases)	123800 (1238)	-	132300 (1323)
	Correlation	-0.0016	-	0.0055
	p-value	0.57	-	0.071
proportion of cases at 2%	Sample size (MS/Stroke/PD cases)	61900 (1238)	-	66150 (1323)
	Correlation	-0.0025	-	0.0077
	p-value	0.54	-	0.051
proportion of cases at 5%	Sample size (MS/Stroke/PD cases)	24760 (1238)	105760 (5288)	26460 (1323)
	Correlation	-0.0021	0.0131	0.0123
	p-value	0.75	2.86×10^{-5}	0.049
proportion of cases at 10%	Sample size (MS/Stroke/PD cases)	-	52880 (5288)	-
	Correlation	-	0.0097	-
	p-value	-	0.029	-

Controls randomly selected from the 'control' individuals (matched by age [+/- 2 year] and sex per case) to match the proportion of cases (i.e., 1%, 2%, 5% and 10%). More details are provided in the Supplementary Note. LYMPH#: lymphocyte count. MS: multiple sclerosis. PCT: plateletcrit. PDW: platelet distribution width. PD: Parkinson's disease.

Table S29. Summary of intercept term tests (in MR-Egger regression) and heterogeneity analyses (in IVW and MR-Egger regression), related to Figure 3 and STAR Methods.

MR-Egger Intercept test				
Exposure	Outcome	Intercept	Intercept se	*p*-value
Plateletcrit	Stroke	-0.0018	0.0008	0.035
Stroke	Plateletcrit	-0.0069	0.0142	0.63
Platelet distribution width	Parkinson's disease	-0.0017	0.0011	0.12
Parkinson's disease	Platelet distribution width	0.0018	0.0016	0.27
Heterogeneity analysis (IVW)				
Exposure	Outcome	Cochran's *Q*	Cochran's I^2	Cochran's *Q* *p*-value
Plateletcrit	Stroke	1550.99	0.31	1.15×10^{-20}
Stroke	Plateletcrit	3292.04	0.99	0.00
Platelet distribution width	Parkinson's disease	1542.76	0.48	3.58×10^{-49}
Parkinson's disease	Platelet distribution width	607.26	0.85	4.51×10^{-76}
Heterogeneity analysis (IVW, removal of pleiotropic SNPs identified by GSMR)				
Exposure	Outcome	Cochran's *Q*	Cochran's I^2	Cochran's *Q* *p*-value
Plateletcrit	Stroke	855.88	0.00	1
Stroke	Plateletcrit	39.52	0.22	0.14
Platelet distribution width	Parkinson's disease	732.97	0.03	0.29
Parkinson's disease	Platelet distribution width	109.41	0.27	0.016
Heterogeneity analysis (MR-Egger)				
Exposure	Outcome	Cochran's *Q*	Cochran's I^2	Cochran's *Q* *p*-value
Plateletcrit	Stroke	1544.56	0.31	2.62×10^{-20}
Stroke	Plateletcrit	3273.92	0.99	0
Platelet distribution width	Parkinson's disease	1538.18	0.48	7.76×10^{-49}
Parkinson's disease	Platelet distribution width	599.43	0.84	4.88×10^{-75}
Heterogeneity analysis (MR-Egger, removal of pleiotropic SNPs identified by GSMR)				
Exposure	Outcome	Cochran's *Q*	Cochran's I^2	Cochran's *Q* *p*-value
Plateletcrit	Stroke	854.92	0.00	1
Stroke	Plateletcrit	38.19	0.21	0.15
Platelet distribution width	Parkinson's disease	728.55	0.02	0.32
Parkinson's disease	Platelet distribution width	106.18	0.26	0.022
Estimated causal effects using IVW after the removal of pleiotropic SNPs identified by GSMR				
Exposure	Outcome	Beta	Beta se	*p*-value
Plateletcrit	Stroke	0.0687	0.0150	4.38×10^{-6}
Stroke	Plateletcrit	0.0167	0.0092	0.069

Platelet distribution width	Parkinson's disease	0.0455	0.0161	4.85×10^{-3}
Parkinson's disease	Platelet distribution width	-0.0065	0.0037	0.083
Estimated causal effects using MR-Egger after the removal of pleiotropic SNPs identified by GSMR				
Exposure	Outcome	Beta	Beta se	*p*-value
Plateletcrit	Stroke	0.0951	0.0308	2.06×10^{-3}
Stroke	Plateletcrit	-0.0179	0.0352	0.61
Platelet distribution width	Parkinson's disease	0.0956	0.0290	1.03×10^{-3}
Parkinson's disease	Platelet distribution width	-0.0198	0.0094	0.038
Estimated causal effects using Weighted Median after the removal of pleiotropic SNPs identified by GSMR				
Exposure	Outcome	Beta	Beta se	*p*-value
Plateletcrit	Stroke	0.0788	0.0260	2.42×10^{-3}
Stroke	Plateletcrit	0.0177	0.0117	0.13
Platelet distribution width	Parkinson's disease	0.0729	0.0296	0.014
Parkinson's disease	Platelet distribution width	-0.0156	0.0050	1.91×10^{-3}
Estimated causal effects using Weighted Mode after the removal of pleiotropic SNPs identified by GSMR				
Exposure	Outcome	Beta	Beta se	*p*-value
Plateletcrit	Stroke	0.0865	0.0423	0.041
Stroke	Plateletcrit	-0.0071	0.0266	0.79
Platelet distribution width	Parkinson's disease	0.1382	0.0384	3.47×10^{-4}
Parkinson's disease	Platelet distribution width	-0.0209	0.0084	0.014

MR: Mendelian randomisation. IVW: inverse variance weighting. SNP: single nucleotide polymorphism. GSMR: generalised summary-data-based Mendelian randomisation. se: standard error.

Table S30. Summary of the leave-one-out analysis for the causal effect of PD on PDW, related to Figure 3 and STAR Methods.

Exposure	Outcome	SNP	IVW			MR-Egger			Weighted Median			Weighted Mode		
			Beta	Beta se	*p*-value	Beta	Beta se	*p*-value	Beta	Beta se	*p*-value	Beta	Beta se	*p*-value
PD	PDW	rs10134885	0.0023	0.0075	0.76	-0.0165	0.0180	0.36	-0.0071	0.0052	0.17	-0.0168	0.0077	0.03
		rs10495249	0.0030	0.0075	0.69	-0.0160	0.0178	0.37	-0.0070	0.0052	0.18	-0.0183	0.0077	0.02
		rs10502915	0.0018	0.0075	0.81	-0.0161	0.0181	0.38	-0.0083	0.0051	0.11	-0.0172	0.0080	0.03
		rs10513789	0.0011	0.0076	0.88	-0.0185	0.0183	0.31	-0.0132	0.0049	7.03×10^{-3}	-0.0171	0.0074	0.02
		rs10516850	0.0023	0.0076	0.76	-0.0153	0.0185	0.41	-0.0065	0.0052	0.21	-0.0169	0.0083	0.04
		rs10810834	0.0021	0.0076	0.78	-0.0160	0.0180	0.38	-0.0069	0.0050	0.17	-0.0169	0.0083	0.05
		rs10878247	0.0013	0.0075	0.86	-0.0161	0.0180	0.37	-0.0096	0.0051	0.06	-0.0171	0.0074	0.02
		rs10913578	0.0004	0.0073	0.95	-0.0138	0.0175	0.43	-0.0079	0.0051	0.12	-0.0171	0.0080	0.03
		rs11060180	0.0009	0.0076	0.90	-0.0173	0.0180	0.34	-0.0127	0.0052	0.01	-0.0171	0.0079	0.03
		rs11150601	0.0026	0.0076	0.73	-0.0157	0.0180	0.38	-0.0067	0.0052	0.19	-0.0168	0.0079	0.04
		rs11174631	0.0019	0.0076	0.80	-0.0163	0.0183	0.38	-0.0106	0.0051	0.04	-0.0172	0.0082	0.04
		rs11175655	0.0024	0.0076	0.75	-0.0152	0.0181	0.40	-0.0068	0.0050	0.17	-0.0169	0.0085	0.05
		rs11683001	0.0021	0.0075	0.78	-0.0164	0.0180	0.37	-0.0070	0.0051	0.17	-0.0169	0.0079	0.03
		rs11726508	0.0017	0.0076	0.83	-0.0166	0.0181	0.36	-0.0106	0.0052	0.04	-0.0172	0.0080	0.03
		rs11950533	0.0021	0.0075	0.78	-0.0160	0.0180	0.38	-0.0071	0.0048	0.13	-0.0169	0.0077	0.03
		rs12147950	0.0015	0.0075	0.84	-0.0152	0.0181	0.40	-0.0081	0.0050	0.11	-0.0171	0.0078	0.03
		rs12287601	0.0020	0.0075	0.79	-0.0164	0.0181	0.37	-0.0070	0.0051	0.17	-0.0184	0.0076	0.02
		rs12497850	0.0015	0.0075	0.84	-0.0156	0.0180	0.39	-0.0083	0.0050	0.09	-0.0171	0.0082	0.04
		rs12503997	0.0016	0.0075	0.84	-0.0161	0.0180	0.37	-0.0085	0.0052	0.10	-0.0171	0.0079	0.03
		rs12505194	0.0016	0.0075	0.83	-0.0158	0.0181	0.38	-0.0088	0.0051	0.09	-0.0171	0.0079	0.03
		rs12505231	0.0023	0.0075	0.76	-0.0148	0.0181	0.41	-0.0071	0.0048	0.14	-0.0183	0.0080	0.02
		rs12726330	0.0016	0.0077	0.83	-0.0219	0.0202	0.28	-0.0149	0.0053	4.99×10^{-3}	-0.0203	0.0080	0.01
		rs1293298	-0.0015	0.0069	0.83	-0.0184	0.0164	0.27	-0.0081	0.0051	0.12	-0.0171	0.0082	0.04
		rs12942703	0.0019	0.0075	0.80	-0.0161	0.0180	0.37	-0.0083	0.0049	0.09	-0.0172	0.0078	0.03
		rs13078687	0.0021	0.0075	0.78	-0.0161	0.0180	0.37	-0.0072	0.0050	0.15	-0.0168	0.0084	0.05
		rs13294100	0.0021	0.0076	0.78	-0.0160	0.0180	0.38	-0.0068	0.0049	0.17	-0.0169	0.0081	0.04
		rs1441904	0.0021	0.0076	0.78	-0.0160	0.0180	0.38	-0.0068	0.0052	0.19	-0.0169	0.0083	0.05
		rs1450522	0.0017	0.0075	0.82	-0.0159	0.0181	0.38	-0.0084	0.0050	0.09	-0.0171	0.0079	0.03
		rs1461809	0.0017	0.0075	0.82	-0.0159	0.0181	0.38	-0.0083	0.0051	0.11	-0.0171	0.0079	0.03
		rs1530297	0.0017	0.0075	0.82	-0.0158	0.0181	0.39	-0.0081	0.0050	0.10	-0.0171	0.0077	0.03
		rs1624451	0.0022	0.0076	0.77	-0.0158	0.0181	0.39	-0.0066	0.0051	0.20	-0.0184	0.0081	0.02
		rs16857578	0.0015	0.0076	0.85	-0.0168	0.0181	0.36	-0.0099	0.0051	0.05	-0.0171	0.0083	0.04
		rs17015738	0.0020	0.0075	0.79	-0.0164	0.0181	0.37	-0.0070	0.0050	0.16	-0.0169	0.0078	0.03
		rs17201246	0.0015	0.0075	0.84	-0.0162	0.0180	0.37	-0.0084	0.0051	0.10	-0.0171	0.0074	0.02
		rs17698151	0.0029	0.0074	0.70	-0.0162	0.0177	0.36	-0.0073	0.0050	0.14	-0.0183	0.0078	0.02
		rs17810668	0.0021	0.0076	0.78	-0.0156	0.0182	0.39	-0.0069	0.0051	0.18	-0.0169	0.0081	0.04
		rs1801274	0.0024	0.0075	0.75	-0.0170	0.0180	0.35	-0.0070	0.0051	0.17	-0.0168	0.0081	0.04
		rs1866996	0.0016	0.0076	0.83	-0.0174	0.0182	0.34	-0.0096	0.0050	0.06	-0.0172	0.0080	0.03
		rs199449	0.0035	0.0077	0.65	-0.0120	0.0192	0.53	-0.0058	0.0051	0.25	-0.0138	0.0090	0.13
		rs2243453	0.0016	0.0076	0.84	-0.0167	0.0181	0.36	-0.0107	0.0051	0.04	-0.0172	0.0072	0.02
		rs2245801	0.0030	0.0077	0.69	-0.0135	0.0189	0.48	-0.0061	0.0053	0.26	-0.0153	0.0087	0.08
		rs2269905	0.0020	0.0075	0.79	-0.0165	0.0181	0.36	-0.0071	0.0052	0.17	-0.0169	0.0078	0.03

		rs2280104	0.0020	0.0075	0.79	-0.0167	0.0181	0.36	-0.0071	0.0050	0.16	-0.0169	0.0076	0.03
		rs2295545	0.0022	0.0075	0.77	-0.0169	0.0180	0.35	-0.0071	0.0050	0.16	-0.0168	0.0086	0.05
		rs2320431	0.0019	0.0075	0.81	-0.0161	0.0180	0.37	-0.0084	0.0052	0.10	-0.0172	0.0081	0.04
		rs26434	0.0013	0.0075	0.86	-0.0151	0.0180	0.40	-0.0081	0.0050	0.11	-0.0171	0.0078	0.03
		rs2835763	0.0033	0.0074	0.65	-0.0174	0.0175	0.32	-0.0072	0.0048	0.13	-0.0183	0.0082	0.03
		rs298616	0.0016	0.0075	0.83	-0.0156	0.0181	0.39	-0.0081	0.0049	0.10	-0.0171	0.0077	0.03
		rs3104767	0.0024	0.0075	0.75	-0.0169	0.0180	0.35	-0.0070	0.0050	0.16	-0.0168	0.0083	0.05
		rs34869253	0.0022	0.0075	0.77	-0.0169	0.0180	0.35	-0.0071	0.0051	0.16	-0.0168	0.0082	0.04
		rs35643925	0.0019	0.0076	0.81	-0.0175	0.0187	0.35	-0.0129	0.0049	8.49×10^{-3}	-0.0188	0.0077	0.02
		rs35902694	0.0020	0.0075	0.79	-0.0166	0.0181	0.36	-0.0071	0.0048	0.14	-0.0169	0.0080	0.04
		rs3744434	0.0019	0.0075	0.80	-0.0161	0.0180	0.37	-0.0084	0.0049	0.09	-0.0184	0.0086	0.04
		rs3768408	0.0024	0.0075	0.74	-0.0161	0.0179	0.37	-0.0072	0.0049	0.14	-0.0183	0.0076	0.02
		rs3802920	0.0019	0.0076	0.81	-0.0161	0.0181	0.37	-0.0113	0.0051	0.03	-0.0172	0.0080	0.03
		rs3857047	0.0019	0.0076	0.80	-0.0161	0.0181	0.38	-0.0097	0.0051	0.05	-0.0172	0.0078	0.03
		rs4122861	0.0023	0.0076	0.76	-0.0151	0.0186	0.42	-0.0066	0.0050	0.18	-0.0169	0.0080	0.04
		rs4130047	0.0020	0.0076	0.79	-0.0160	0.0181	0.38	-0.0117	0.0051	0.02	-0.0187	0.0083	0.03
		rs4690326	0.0021	0.0076	0.78	-0.0159	0.0182	0.38	-0.0133	0.0053	0.01	-0.0184	0.0089	0.04
		rs4698412	0.0024	0.0076	0.75	-0.0155	0.0181	0.39	-0.0065	0.0049	0.18	-0.0169	0.0081	0.04
		rs4771267	0.0017	0.0075	0.83	-0.0158	0.0181	0.38	-0.0081	0.0051	0.12	-0.0171	0.0078	0.03
		rs4785224	0.0021	0.0075	0.78	-0.0169	0.0181	0.35	-0.0071	0.0049	0.15	-0.0169	0.0079	0.04
		rs535283	0.0014	0.0075	0.85	-0.0161	0.0180	0.37	-0.0098	0.0051	0.05	-0.0171	0.0084	0.04
		rs544169	0.0020	0.0075	0.79	-0.0165	0.0181	0.36	-0.0071	0.0050	0.15	-0.0169	0.0078	0.03
		rs5910	-0.0019	0.0062	0.76	-0.0120	0.0149	0.42	-0.0078	0.0048	0.11	-0.0173	0.0077	0.03
		rs6076910	0.0021	0.0075	0.78	-0.0162	0.0180	0.37	-0.0072	0.0050	0.15	-0.0168	0.0077	0.03
		rs6676110	0.0017	0.0075	0.83	-0.0159	0.0181	0.38	-0.0083	0.0049	0.09	-0.0171	0.0080	0.03
		rs6734966	0.0019	0.0075	0.80	-0.0162	0.0180	0.37	-0.0074	0.0049	0.13	-0.0184	0.0079	0.02
		rs6803771	0.0009	0.0075	0.90	-0.0146	0.0179	0.42	-0.0081	0.0050	0.10	-0.0171	0.0083	0.04
		rs6812193	0.0016	0.0076	0.84	-0.0163	0.0180	0.37	-0.0115	0.0052	0.03	-0.0172	0.0081	0.04
		rs6828371	0.0022	0.0076	0.78	-0.0155	0.0182	0.40	-0.0069	0.0051	0.17	-0.0169	0.0077	0.03
		rs6857404	0.0022	0.0075	0.77	-0.0169	0.0180	0.35	-0.0071	0.0050	0.16	-0.0168	0.0084	0.05
		rs6963	0.0012	0.0075	0.87	-0.0151	0.0180	0.40	-0.0081	0.0050	0.11	-0.0171	0.0080	0.04
		rs7075684	0.0019	0.0075	0.80	-0.0163	0.0181	0.37	-0.0082	0.0051	0.10	-0.0172	0.0078	0.03
		rs721579	0.0015	0.0075	0.85	-0.0160	0.0180	0.38	-0.0093	0.0049	0.06	-0.0171	0.0079	0.03
		rs7562413	0.0018	0.0075	0.81	-0.0161	0.0181	0.38	-0.0081	0.0051	0.11	-0.0172	0.0079	0.03
		rs7749147	0.0016	0.0075	0.83	-0.0161	0.0180	0.37	-0.0081	0.0050	0.10	-0.0171	0.0079	0.03
		rs7938782	0.0018	0.0075	0.82	-0.0161	0.0180	0.37	-0.0083	0.0051	0.10	-0.0172	0.0077	0.03
		rs7991335	0.0016	0.0075	0.83	-0.0157	0.0181	0.39	-0.0081	0.0049	0.10	-0.0171	0.0078	0.03
		rs8012377	0.0019	0.0075	0.80	-0.0165	0.0181	0.37	-0.0083	0.0050	0.10	-0.0184	0.0081	0.03
		rs8018800	0.0017	0.0076	0.83	-0.0161	0.0180	0.37	-0.0104	0.0049	0.03	-0.0172	0.0077	0.03
		rs8045689	0.0023	0.0075	0.76	-0.0170	0.0180	0.35	-0.0071	0.0050	0.16	-0.0168	0.0078	0.03
		rs823114	0.0028	0.0076	0.71	-0.0149	0.0180	0.41	-0.0065	0.0052	0.21	-0.0168	0.0077	0.03
		rs823136	0.0020	0.0075	0.79	-0.0158	0.0181	0.39	-0.0071	0.0052	0.17	-0.0169	0.0080	0.04
		rs8327	0.0016	0.0076	0.83	-0.0161	0.0180	0.37	-0.0096	0.0051	0.06	-0.0172	0.0076	0.03
		rs8946	0.0022	0.0075	0.77	-0.0164	0.0180	0.37	-0.0069	0.0048	0.15	-0.0169	0.0077	0.03
		rs896435	0.0016	0.0076	0.83	-0.0160	0.0180	0.38	-0.0093	0.0049	0.06	-0.0171	0.0075	0.03
		rs9217	0.0030	0.0074	0.68	-0.0197	0.0176	0.26	-0.0074	0.0050	0.14	-0.0167	0.0082	0.04

		rs9295746	0.0017	0.0076	0.82	-0.0161	0.0180	0.38	-0.0090	0.0051	0.07	-0.0172	0.0076	0.03
		rs940634	0.0024	0.0075	0.75	-0.0159	0.0180	0.38	-0.0070	0.0050	0.16	-0.0183	0.0082	0.03
		rs9442714	0.0024	0.0075	0.75	-0.0169	0.0180	0.35	-0.0071	0.0049	0.15	-0.0183	0.0077	0.02
		rs970668	0.0013	0.0075	0.87	-0.0163	0.0179	0.37	-0.0080	0.0048	0.10	-0.0171	0.0084	0.04
		rs976080	0.0014	0.0076	0.85	-0.0175	0.0181	0.34	-0.0106	0.0050	0.03	-0.0171	0.0079	0.03
		rs979812	0.0014	0.0075	0.85	-0.0154	0.0181	0.40	-0.0085	0.0049	0.08	-0.0171	0.0083	0.04
		rs9917256	0.0028	0.0076	0.71	-0.0137	0.0183	0.45	-0.0065	0.0050	0.19	-0.0168	0.0076	0.03
		All	0.0019	0.0075	0.80	-0.0161	0.0180	0.37	-0.0076	0.0049	0.12	-0.0169	0.0071	0.02

PDW: platelet distribution width. PD: Parkinson's disease. IVW: inverse variance weighting. SNP: single nucleotide polymorphism. se: standard error.

Table S32. Summary of the leave-one-out analysis for the causal effect of stroke on PCT, related to Figure 3 and STAR Methods.

Exposure	Outcome	SNP	IVW			MR-Egger			Weighted Median			Weighted Mode		
			Beta	Beta se	*p*-value	Beta	Beta se	*p*-value	Beta	Beta se	*p*-value	Beta	Beta se	*p*-value
Stroke	PCT	rs1052053	0.0879	0.0613	0.15	0.2372	0.2630	0.37	0.0125	0.0123	0.31	0.0080	0.0183	0.66
		rs10778417	0.0789	0.0608	0.19	0.2034	0.2644	0.45	0.0022	0.0125	0.86	0.0089	0.0203	0.66
		rs11105439	0.0802	0.0610	0.19	0.1985	0.2603	0.45	0.0010	0.0126	0.94	0.0112	0.0203	0.59
		rs11952498	0.0792	0.0609	0.19	0.2007	0.2632	0.45	0.0018	0.0126	0.89	0.0088	0.0199	0.66
		rs12361415	0.0828	0.0607	0.17	0.1879	0.2610	0.48	0.0078	0.0121	0.52	0.0080	0.0209	0.70
		rs12445022	0.0802	0.0610	0.19	0.1986	0.2603	0.45	0.0006	0.0122	0.96	0.0088	0.0224	0.70
		rs12562305	0.0813	0.0609	0.18	0.2252	0.2676	0.40	0.0093	0.0126	0.46	0.0128	0.0220	0.56
		rs12635936	0.0813	0.0608	0.18	0.2305	0.2696	0.40	0.0088	0.0120	0.46	0.0128	0.0219	0.56
		rs1471859	0.0798	0.0608	0.19	0.1980	0.2634	0.46	0.0018	0.0128	0.89	0.0088	0.0214	0.68
		rs1537375	0.0839	0.0610	0.17	0.1961	0.2597	0.45	0.0101	0.0122	0.41	0.0080	0.0203	0.69
		rs1563788	0.0871	0.0600	0.15	0.1705	0.2588	0.51	0.0061	0.0120	0.61	0.0078	0.0210	0.71
		rs17021459	0.0798	0.0610	0.19	0.2618	0.3031	0.39	0.0009	0.0124	0.94	0.0040	0.0218	0.86
		rs17260983	0.0820	0.0611	0.18	0.2233	0.2665	0.41	0.0110	0.0123	0.37	0.0208	0.0217	0.34
		rs1939214	0.0811	0.0608	0.18	0.2021	0.2602	0.44	0.0090	0.0129	0.49	0.0128	0.0219	0.56
		rs2284665	0.0810	0.0610	0.18	0.2039	0.2608	0.44	0.0104	0.0125	0.41	0.0208	0.0207	0.32
		rs2526619	0.0804	0.0612	0.19	0.2195	0.2698	0.42	-0.0002	0.0124	0.99	0.0040	0.0229	0.86
		rs2585193	0.0806	0.0610	0.19	0.1975	0.2604	0.45	0.0098	0.0125	0.43	0.0160	0.0219	0.47
		rs2723334	0.0832	0.0616	0.18	0.2434	0.2742	0.38	0.0141	0.0130	0.28	0.0256	0.0229	0.27
		rs2742313	0.0886	0.0601	0.14	0.1776	0.2577	0.49	0.0065	0.0122	0.60	0.0080	0.0209	0.70
		rs3176326	0.0779	0.0609	0.20	0.1990	0.2603	0.45	0.0023	0.0119	0.85	0.0137	0.0220	0.54
		rs3790604	0.0784	0.0609	0.20	0.2009	0.2651	0.45	0.0022	0.0119	0.85	0.0089	0.0205	0.67
		rs4132234	0.0796	0.0610	0.19	0.1990	0.2603	0.45	0.0009	0.0125	0.94	0.0040	0.0220	0.86
		rs42039	0.0736	0.0609	0.23	0.1934	0.2596	0.46	0.0033	0.0125	0.79	0.0137	0.0216	0.53
		rs4783296	0.0791	0.0610	0.19	0.1994	0.2603	0.45	0.0013	0.0119	0.92	0.0088	0.0199	0.66
		rs4793588	0.0785	0.0609	0.20	0.1995	0.2603	0.45	0.0021	0.0124	0.87	0.0089	0.0211	0.68
		rs4886564	0.0805	0.0609	0.19	0.2060	0.2616	0.44	0.0092	0.0125	0.46	0.0160	0.0207	0.45
		rs4903725	0.0791	0.0608	0.19	0.1999	0.2605	0.45	0.0022	0.0123	0.86	0.0088	0.0212	0.68
		rs4950915	0.0801	0.0608	0.19	0.1964	0.2634	0.46	0.0054	0.0127	0.67	0.0112	0.0208	0.59
		rs495828	0.0744	0.0607	0.22	0.2011	0.2594	0.44	0.0039	0.0130	0.76	0.0137	0.0209	0.51
		rs564018	0.0797	0.0611	0.19	0.2086	0.2653	0.44	0.0004	0.0123	0.97	0.0040	0.0230	0.86
		rs653178	0.0036	0.0220	0.87	0.0062	0.0938	0.95	0.0051	0.0122	0.68	0.0104	0.0210	0.62
		rs6544653	0.0709	0.0603	0.24	0.2300	0.2588	0.38	0.0046	0.0125	0.72	0.0137	0.0218	0.53
		rs6561321	0.0789	0.0612	0.20	0.2007	0.2619	0.45	-0.0001	0.0128	0.99	0.0089	0.0209	0.67
		rs6584579	0.0770	0.0610	0.21	0.2030	0.2606	0.44	0.0020	0.0125	0.87	0.0137	0.0193	0.48
		rs6596445	0.0789	0.0609	0.19	0.1994	0.2604	0.45	0.0019	0.0117	0.87	0.0089	0.0219	0.69
		rs6825454	0.0828	0.0609	0.17	0.1997	0.2597	0.45	0.0093	0.0121	0.44	0.0080	0.0217	0.71
		rs6838973	0.0828	0.0607	0.17	0.1821	0.2632	0.49	0.0079	0.0121	0.52	0.0080	0.0227	0.73
		rs6872625	0.0807	0.0608	0.18	0.1977	0.2603	0.45	0.0091	0.0123	0.46	0.0160	0.0208	0.45
		rs7488386	0.0792	0.0608	0.19	0.2016	0.2644	0.45	0.0021	0.0126	0.87	0.0088	0.0195	0.65
		rs8064211	0.0812	0.0609	0.18	0.1929	0.2621	0.47	0.0093	0.0124	0.46	0.0176	0.0204	0.39
		rs879324	0.0816	0.0608	0.18	0.2019	0.2600	0.44	0.0087	0.0119	0.46	0.0128	0.0214	0.55
		rs880315	0.0871	0.0606	0.15	0.1953	0.2582	0.45	0.0077	0.0124	0.53	0.0080	0.0214	0.71

		rs9112	0.0788	0.0610	0.20	0.2008	0.2615	0.45	0.0015	0.0123	0.90	0.0089	0.0199	0.66
		rs9305020	0.0809	0.0608	0.18	0.2010	0.2602	0.44	0.0091	0.0125	0.47	0.0160	0.0214	0.46
		All	0.0788	0.0596	0.19	0.1993	0.2572	0.44	0.0052	0.0128	0.68	0.0107	0.0224	0.64

PCT: plateletcrit. IVW: inverse variance weighting. SNP: single nucleotide polymorphism. se: standard error.

Table S35. Summary of MVMR sensitivity analyses adjusting for smoking, drinking, educational attainment and household income concurrently, related to Figure 3 and STAR Methods.

Exposure	Outcome	n of SNPs	OR (95% CI)	*p*-value
Parkinson's disease	Platelet distribution width	87	1.00 (0.98, 1.02)	0.97
Platelet distribution width	Parkinson's disease	798	1.05 (1.01, 1.10)	0.011
Stroke*	Plateletcrit	40	1.12 (0.98, 1.27)	0.093
Plateletcrit	Stroke	1027	1.09 (1.05, 1.13)	3.79×10^{-7}

*MR models utilised instrumental SNPs with stroke GWAS $p < 1\times10^{-5}$. MVMR: multivariate Mendelian randomisation. SNP: single nucleotide polymorphism. OR: odds ratio. CI: confidence interval.

Table S37. FDR-significant (FDR < 0.05) SMR associations between platelet-based gene expression and BCT-NPD trait pairs with evidence for a putative causal relationship, related to Figure 4 and STAR Methods.

Gene	*RHD*		*FXYD5*		*MAP1LC3A*		*SRSF6*	
Probe ID	ENSG00000187010		ENSG00000089327		ENSG00000101460		ENSG00000124193	
Chromosome	1		19		20		20	
Probe position (hg19)	24579435		34629498		32139351		41087450	
top SNP	rs72660908		rs1633915		rs2295444		rs3746532	
Top SNP chromosome	1		19		20		20	
Top SNP position (hg19)	25583610		35649324		33173883		42099331	
effect allele	G		C		T		C	
non-effect allele	C		G		C		A	
effect allele frequency	0.38		0.21		0.49		0.27	
Trait	PD	PDW	PD	PDW	PD	PDW	PD	PDW
Beta (GWAS)	0.05	0.02	-0.04	-0.04	0.03	0.01	-0.04	0.01
Beta se (GWAS)	0.01	0.00	0.01	0.00	0.01	0.00	0.01	0.00
p-value (GWAS)	1.34×10^{-4}	1.30×10^{-27}	5.12×10^{-4}	1.70×10^{-48}	6.05×10^{-4}	8.90×10^{-4}	8.71×10^{-4}	5.60×10^{-3}
Beta (*cis*-eQTL)	0.54	0.54	-0.35	-0.35	-0.19	-0.19	-0.31	-0.31
Beta se (*cis*-eQTL)	0.05	0.05	0.04	0.04	0.02	0.02	0.03	0.03
p-value (*cis*-eQTL)	4.53×10^{-28}	4.53×10^{-28}	1.73×10^{-15}	1.73×10^{-15}	1.63×10^{-15}	1.63×10^{-15}	1.09×10^{-27}	1.09×10^{-27}
Beta (SMR)	0.09	0.04	0.12	0.12	-0.17	-0.04	0.13	-0.02
Beta se (SMR)	0.02	0.01	0.04	0.02	0.05	0.01	0.04	0.01
p-value (SMR)	3.17×10^{-4}	1.06×10^{-14}	1.46×10^{-3}	2.71×10^{-12}	1.58×10^{-3}	2.16×10^{-3}	1.45×10^{-3}	7.28×10^{-3}
FDR (SMR)	0.015	1.05×10^{-12}	0.047	$1.79\text{E}\times10^{-10}$	0.049	0.011	0.047	0.029
p-value (HEIDI)	0.11	0.057	0.078	0.15	0.17	0.062	0.43	0.12
n of SNPs after HEIDI	18	20	10	15	20	20	20	20

BCT: blood cell trait. NPD: neurological and psychiatric disorder. PD: Parkinson's disease. PDW: platelet distribution width. SNP: single nucleotide polymorphism. se: standard error. GWAS: genome-wide association study. *cis*-eQTL: *cis*-expression quantitative trait loci. SMR: Summary-data-based Mendelian randomisation. HEIDI: HEterogeneity In Dependent Instruments. FDR: Benjamini-Hochberg false discovery rate.

Table S38. FDR-significant (FDR < 0.05) SMR associations between brain-based gene expression and Parkinson's disease or stroke (for genes presented in Tables S36-37), related to Figure 4 and STAR Methods.

Gene	*RHD*	*DNAJB4*	*UBXN2A*	*SFXN5*	*GGCX*	*COA5*	*ARL8B*
probe ID	ENSG00000187010	ENSG00000162616	ENSG00000173960	ENSG00000144040	ENSG00000115486	ENSG00000183513	ENSG00000134108
Chromosome	1	1	2	2	2	2	3
Probe position (hg19)	25627910	78464253	24188967	73235956	85781706	99220375	5193250
top SNP	rs72660908	rs7514180	rs12621152	rs73945731	rs6714157	rs72823796	rs6787725
Top SNP chromosome	1	1	2	2	2	2	3
Top SNP position (hg19)	25583610	78460935	24257682	73252335	85763274	99227812	5201054
effect allele	G	G	C	C	G	T	G
non-effect allele	C	A	T	T	A	C	A
effect allele frequency	0.39	0.79	0.83	0.94	0.50	0.27	0.67
Trait	Parkinson's disease	Parkinson's disease	Parkinson's disease	Parkinson's disease	Parkinson's disease	Parkinson's disease	Parkinson's disease
Beta (GWAS)	0.05	-0.05	0.05	0.06	-0.03	0.03	-0.04
Beta se (GWAS)	0.01	0.01	0.01	0.02	0.01	0.01	0.01
p-value (GWAS)	1.34×10^{-4}	8.08×10^{-5}	2.15×10^{-4}	1.79×10^{-3}	2.32×10^{-3}	2.32×10^{-3}	5.75×10^{-4}
Beta (*cis*-eQTL)	-0.93	-0.45	0.30	0.69	0.43	0.45	1.14
Beta se (*cis*-eQTL)	0.08	0.06	0.05	0.08	0.04	0.05	0.03
p-value (*cis*-eQTL)	8.48×10^{-28}	4.39×10^{-14}	2.11×10^{-9}	1.66×10^{-19}	1.88×10^{-29}	1.09×10^{-18}	2.09×10^{-291}
Beta (SMR)	-0.05	0.10	0.17	0.09	-0.07	0.07	-0.03
Beta se (SMR)	0.01	0.03	0.06	0.03	0.02	0.02	0.01
p-value (SMR)	3.20×10^{-4}	4.87×10^{-4}	1.66×10^{-3}	3.13×10^{-3}	3.31×10^{-3}	3.97×10^{-3}	6.14×10^{-4}
FDR (SMR)	6.57×10^{-3}	6.57×10^{-3}	9.98×10^{-3}	0.012	0.012	0.013	6.64×10^{-3}
p-value (HEIDI)	0.18	0.28	0.037	0.19	0.71	0.21	0.073
n of SNPs after HEIDI	16	20	20	10	20	19	20
Gene	*PPM1M*	*GLYCTK*	*PTK2*	*TSPAN4*	*PLA2G4B*	*RANBP10*	*SOX15*
probe ID	ENSG00000164088	ENSG00000168237	ENSG00000169398	ENSG00000214063	ENSG00000243708	ENSG00000141084	ENSG00000129194
Chromosome	3	3	8	11	15	16	17
Probe position (hg19)	52282227	52325188	141840157	854962	42135159	67798780	7492902
top SNP	rs353547	rs7622851	rs7815898	rs9704919	rs28708888	rs9938862	rs12938899
Top SNP chromosome	3	3	8	11	15	16	17
Top SNP position (hg19)	52268866	52333671	141876541	842682	41898885	67723801	7525546
effect allele	C	C	G	G	C	C	C
non-effect allele	T	G	C	A	A	T	T
effect allele frequency	0.58	0.48	0.43	0.67	0.38	0.04	0.82
Trait	Parkinson's disease	Parkinson's disease	Parkinson's disease	Parkinson's disease	Parkinson's disease	Parkinson's disease	Parkinson's disease
Beta (GWAS)	-0.03	-0.04	0.04	0.03	0.04	0.06	-0.04
Beta se (GWAS)	0.01	0.01	0.01	0.01	0.01	0.02	0.01
p-value (GWAS)	8.62×10^{-4}	6.92×10^{-5}	2.71×10^{-4}	1.40×10^{-3}	3.78×10^{-4}	2.34×10^{-3}	9.08×10^{-4}
Beta (*cis*-eQTL)	0.47	0.28	-0.37	-0.42	0.97	-0.84	0.38
Beta se (*cis*-eQTL)	0.04	0.05	0.05	0.05	0.03	0.11	0.06
p-value (*cis*-eQTL)	1.37×10^{-36}	5.57×10^{-9}	4.14×10^{-15}	2.73×10^{-17}	5.79×10^{-261}	1.41×10^{-15}	2.55×10^{-10}
Beta (SMR)	-0.07	-0.13	-0.10	-0.08	0.04	-0.08	-0.10
Beta se (SMR)	0.02	0.04	0.03	0.03	0.01	0.03	0.04

p-value (SMR)	1.32×10^{-3}	1.02×10^{-3}	9.26×10^{-4}	2.83×10^{-3}	3.92×10^{-4}	4.46×10^{-3}	3.42×10^{-3}
FDR (SMR)	8.94×10^{-3}	7.83×10^{-3}	7.83×10^{-3}	0.012	6.57×10^{-3}	0.013	0.012
p-value (HEIDI)	0.08	0.032	0.96	0.44	0.15	0.69	0.25
n of SNPs after HEIDI	20	20	20	20	20	20	20
Gene	*PDCD5*	*FXYD5*	*MGAT3*	*CLBA1*	*IVD*	*RMC1*	
probe ID	ENSG00000105185	ENSG00000089327	ENSG00000128268	ENSG00000140104	ENSG00000128928	ENSG00000141452	
Chromosome	19	19	22	14	15	18	
Probe position (hg19)	33075166	35653209	39870774	105464465	40712916	21097609	
top SNP	rs8182578	rs9807816	rs5750828	rs2033932	rs7165012	rs1618725	
Top SNP chromosome	19	19	22	14	15	18	
Top SNP position (hg19)	33056477	35684944	39835083	105447075	40654038	21126952	
effect allele	A	G	C	C	G	T	
non-effect allele	G	T	T	T	A	C	
effect allele frequency	0.40	0.79	0.70	0.79	0.53	0.47	
Trait	Parkinson's disease	Parkinson's disease	Parkinson's disease	Stroke	Stroke	Stroke	
Beta (GWAS)	-0.04	0.04	-0.03	-0.04	-0.03	-0.02	
Beta se (GWAS)	0.01	0.01	0.01	0.01	0.01	0.01	
p-value (GWAS)	4.73×10^{-5}	2.24×10^{-3}	3.83×10^{-3}	3.11×10^{-3}	2.59×10^{-3}	0.012	
Beta (*cis*-eQTL)	1.02	-0.42	0.33	-1.27	0.48	0.47	
Beta se (*cis*-eQTL)	0.03	0.06	0.05	0.03	0.04	0.04	
p-value (*cis*-eQTL)	1.03×10^{-288}	4.88×10^{-13}	4.45×10^{-11}	5.73×10^{-305}	6.18×10^{-40}	3.83×10^{-36}	
Beta (SMR)	-0.04	-0.09	-0.10	0.03	-0.06	-0.05	
Beta se (SMR)	0.01	0.03	0.04	0.01	0.02	0.02	
p-value (SMR)	5.06×10^{-5}	4.88×10^{-3}	8.22×10^{-3}	3.26×10^{-3}	3.44×10^{-3}	0.014	
FDR (SMR)	2.73×10^{-3}	0.014	0.019	0.012	0.012	0.031	
p-value (HEIDI)	0.94	0.65	0.11	0.75	0.13	0.68	
n of SNPs after HEIDI	20	11	18	20	20	20	

SNP: single nucleotide polymorphism. se: standard error. GWAS: genome-wide association study. *cis*-eQTL: *cis*-expression quantitative trait loci. SMR: Summary-data-based Mendelian randomisation. HEIDI: HEterogeneity In Dependent Instruments. FDR: Benjamini-Hochberg false discovery rate.

Table S45. Bonferroni-significant SMR associations between brain-based gene expression and specific NPDs shown in Tables S43-44, related to Figure 5 and STAR Methods.

Gene	*GNL3*	*AC100854.1*	*OGFOD2*	*GATAD2A*
probe ID	ENSG00000163938	ENSG00000254352	ENSG00000111325	ENSG00000167491
Chromosome	3	8	12	19
Listed table	S36	S35	S35 & S36	S35 & S36
Probe position (hg19)	52721840	79636201	123461858	19558189
top SNP	rs7646741	rs2717538	rs1727309	rs8101499
Top SNP chromosome	3	8	12	19
Top SNP position (hg19)	52785238	79633149	123658258	19476984
effect allele	A	A	G	A
non-effect allele	G	G	A	G
effect allele frequency	0.48	0.29	0.78	0.33
Trait	Schizophrenia	Multiple sclerosis	Schizophrenia	Schizophrenia
Beta (GWAS)	0.08	0.10	-0.07	0.07
Beta se (GWAS)	0.01	0.02	0.01	0.01
p-value (GWAS)	2.19×10^{-17}	1.46×10^{-8}	5.53×10^{-11}	4.57×10^{-15}
Beta (*cis*-eQTL)	0.58	-0.68	-0.38	-0.31
Beta se (*cis*-eQTL)	0.05	0.08	0.05	0.04
p-value (*cis*-eQTL)	1.70×10^{-36}	7.39×10^{-16}	4.11×10^{-13}	2.08×10^{-16}
Beta (SMR)	0.13	-0.15	0.19	-0.24
Beta se (SMR)	0.02	0.03	0.04	0.04
p-value (SMR)	2.11×10^{-12}	3.55×10^{-6}	1.10×10^{-6}	1.51×10^{-8}
p-value (HEIDI)	0.43	0.38	0.053	0.40
n of SNPs after HEIDI	20	16	20	20

NPD: neurological and psychiatric disorder. SNP: single nucleotide polymorphism. se: standard error. GWAS: genome-wide association study. *cis*-eQTL: *cis*-expression quantitative trait loci. SMR: Summary-data-based Mendelian randomisation. HEIDI: HEterogeneity In Dependent Instruments.

Table S46. Bonferroni-significant SMR associations between brain-based DNA methylation and gene expression for genes shown in Table S45, related to Figure 5 and STAR Methods.

Exp ID (mQTL)	cg14845053	cg02792780	cg07148594	cg16977858	cg17372223	cg05564831
Exp chromosome	3	3	3	3	3	3
Exp probe position (hg19)	52276132	52529341	52565909	52567510	52568218	52568323
Out ID (eQTL)	ENSG00000163938	ENSG00000163938	ENSG00000163938	ENSG00000163938	ENSG00000163938	ENSG00000163938
Out Chromosome	3	3	3	3	3	3
Out Gene	*GNL3*	*GNL3*	*GNL3*	*GNL3*	*GNL3*	*GNL3*
Out probe position (hg19)	52721840	52721840	52721840	52721840	52721840	52721840
Top SNP	rs610060	rs1570	rs4282054	rs7639267	rs12489828	rs12489828
Top SNP chromosome	3	3	3	3	3	3
Top SNP position (hg19)	52273421	52586682	52566065	52568805	52567014	52567014
effect allele	A	T	T	G	G	G
non-effect allele	G	A	C	T	T	T
effect allele frequency	0.48	0.57	0.44	0.43	0.45	0.45
Beta (*cis*-eQTL)	0.46	0.49	0.49	0.50	0.43	0.43
Beta se (*cis*-eQTL)	0.05	0.05	0.05	0.05	0.05	0.05
p-value (*cis*-eQTL)	7.02×10^{-22}	2.27×10^{-24}	7.77×10^{-25}	3.08×10^{-26}	5.48×10^{-19}	5.48×10^{-19}
Beta (mQTL)	0.40	0.36	0.59	0.37	-0.40	-0.51
Beta se (mQTL)	0.06	0.06	0.04	0.04	0.04	0.04
p-value (mQTL)	3.80×10^{-11}	7.14×10^{-9}	3.25×10^{-47}	4.05×10^{-17}	9.53×10^{-21}	2.18×10^{-35}
Beta (SMR)	1.14	1.34	0.83	1.38	-1.07	-0.83
Beta se (SMR)	0.21	0.27	0.10	0.21	0.17	0.11
p-value (SMR)	5.11×10^{-8}	4.85×10^{-7}	5.35×10^{-17}	4.45×10^{-11}	1.16×10^{-10}	4.68×10^{-13}
p-value (HEIDI)	0.12	0.26	0.019	0.091	0.040	0.019
n of SNPs after HEIDI	14	14	20	14	12	20
Exp ID (mQTL)	cg24629711	cg23815702	cg17117718	cg22694191	cg14449575	cg13364410
Exp chromosome	3	3	17	19	19	19
Exp probe position (hg19)	52869263	52869738	43663208	19373575	19373743	19373755
Out ID (eQTL)	ENSG00000163938	ENSG00000163938	ENSG00000264070	ENSG00000167491	ENSG00000167491	ENSG00000167491
Out Chromosome	3	3	17	19	19	19
Out Gene	*GNL3*	*GNL3*	*DND1P1*	*GATAD2A*	*GATAD2A*	*GATAD2A*
Out probe position (hg19)	52721840	52721840	43663766	19558189	19558189	19558189
Top SNP	rs2256332	rs6445541	rs1724390	rs10426780	rs2074295	rs2074295
Top SNP chromosome	3	3	17	19	19	19
Top SNP position (hg19)	52855865	52880128	43663247	19375883	19369435	19369435
effect allele	G	G	A	C	A	A
non-effect allele	A	T	C	T	G	G
effect allele frequency	0.61	0.60	0.24	0.32	0.79	0.79
Beta (*cis*-eQTL)	0.39	0.42	0.60	-0.29	0.27	0.27
Beta se (*cis*-eQTL)	0.05	0.05	0.11	0.04	0.04	0.04
p-value (*cis*-eQTL)	3.76×10^{-15}	2.86×10^{-17}	3.60×10^{-8}	1.00×10^{-14}	1.75×10^{-10}	1.75×10^{-10}
Beta (mQTL)	-0.57	-0.36	1.40	-0.31	0.50	0.44
Beta se (mQTL)	0.06	0.04	0.05	0.04	0.05	0.05

p-value (mQTL)	1.91×10^{-23}	1.90×10^{-16}	1.08×10^{-203}	2.76×10^{-12}	1.11×10^{-25}	4.47×10^{-20}
Beta (SMR)	-0.68	-1.15	0.43	0.94	0.54	0.61
Beta se (SMR)	0.11	0.20	0.08	0.18	0.10	0.12
p-value (SMR)	6.59×10^{-10}	3.73×10^{-9}	5.92×10^{-8}	2.14×10^{-7}	5.03×10^{-8}	1.61×10^{-7}
p-value (HEIDI)	0.079	0.11	0.046	0.031	0.028	0.14
n of SNPs after HEIDI	12	20	16	19	20	15
Exp ID (mQTL)	cg14021871	cg01262667	cg17414380	cg26162025	cg26732615	
Exp chromosome	19	19	19	19	19	
Exp probe position (hg19)	19384381	19385393	19431394	19616502	19648335	
Out ID (eQTL)	ENSG00000167491	ENSG00000167491	ENSG00000167491	ENSG00000167491	ENSG00000167491	
Out Chromosome	19	19	19	19	19	
Out Gene	*GATAD2A*	*GATAD2A*	*GATAD2A*	*GATAD2A*	*GATAD2A*	
Out probe position (hg19)	19558189	19558189	19558189	19558189	19558189	
Top SNP	rs2905425	rs2074303	rs7247309	rs4808198	rs4808208	
Top SNP chromosome	19	19	19	19	19	
Top SNP position (hg19)	19475717	19381755	19439631	19533630	19650096	
effect allele	G	T	A	C	G	
non-effect allele	C	C	T	T	A	
effect allele frequency	0.32	0.32	0.33	0.33	0.32	
Beta (*cis*-eQTL)	-0.30	-0.29	-0.29	-0.29	-0.28	
Beta se (*cis*-eQTL)	0.04	0.04	0.04	0.04	0.04	
p-value (*cis*-eQTL)	4.23×10^{-15}	2.00×10^{-14}	2.02×10^{-14}	8.08×10^{-15}	1.66×10^{-13}	
Beta (mQTL)	-0.56	1.16	0.42	0.70	0.74	
Beta se (mQTL)	0.06	0.03	0.04	0.06	0.04	
p-value (mQTL)	4.84×10^{-19}	0	3.51×10^{-22}	9.86×10^{-32}	3.90×10^{-81}	
Beta (SMR)	0.53	-0.25	-0.68	-0.42	-0.37	
Beta se (SMR)	0.09	0.03	0.11	0.06	0.05	
p-value (SMR)	3.84×10^{-9}	5.45×10^{-14}	1.94×10^{-9}	9.53×10^{-11}	6.07×10^{-12}	
p-value (HEIDI)	0.24	0.025	0.13	0.029	0.21	
n of SNPs after HEIDI	20	20	17	19	20	

SNP: single nucleotide polymorphism. se: standard error. GWAS: genome-wide association study. *cis*-eQTL: *cis*-expression quantitative trait loci. mQTL: DNA methylation quantitative trait loci. SMR: Summary-data-based Mendelian randomisation. HEIDI: HEterogeneity In Dependent Instruments.

Table S47. Bonferroni-significant SMR associations between brain-based DNA methylation (shown in Table S46) and specific NPDs (shown in Table S45), related to Figure 5 and STAR Methods.

probe ID	cg07148594	cg16977858	cg17372223	cg05564831	cg24629711	cg14449575	cg13364410	cg14021871	cg17414380	cg26162025	cg26732615
Chromosome	3	3	3	3	3	19	19	19	19	19	19
Probe position (hg19)	52565909	52567510	52568218	52568323	52869263	19373743	19373755	19384381	19431394	19616502	19648335
Top SNP chromosome	rs4282054	rs7639267	rs12489828	rs12489828	rs2256332	rs2074295	rs2074295	rs2905425	rs7247309	rs4808198	rs4808208
Top SNP chromosome	3	3	3	3	3	19	19	19	19	19	19
Top SNP position (hg19)	52566065	52568805	52567014	52567014	52855865	19369435	19369435	19475717	19439631	19533630	19650096
effect allele	T	G	G	G	G	A	A	G	A	C	G
non-effect allele	C	T	T	T	A	G	G	C	T	T	A
effect allele frequency	0.44	0.43	0.45	0.45	0.61	0.79	0.79	0.32	0.33	0.33	0.32
Trait	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia
Beta (GWAS)	0.06	0.07	0.07	0.07	0.07	-0.06	-0.06	0.07	0.07	0.07	0.07
Beta se (GWAS)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
p-value (GWAS)	3.94×10^{-13}	2.47×10^{-13}	2.51×10^{-13}	2.51×10^{-13}	4.53×10^{-16}	1.02×10^{-9}	1.02×10^{-9}	4.78×10^{-15}	1.47×10^{-13}	1.43×10^{-15}	2.36×10^{-14}
Beta (mQTL)	0.59	0.37	-0.40	-0.51	-0.57	0.50	0.44	-0.56	0.42	0.70	0.74
Beta se (mQTL)	0.04	0.04	0.04	0.04	0.06	0.05	0.05	0.06	0.04	0.06	0.04
p-value (mQTL)	3.25×10^{-47}	4.05×10^{-17}	9.53×10^{-21}	2.18×10^{-35}	1.91×10^{-23}	1.11×10^{-25}	4.47×10^{-20}	4.84×10^{-19}	3.51×10^{-22}	9.86×10^{-32}	3.90×10^{-81}
Beta (SMR)	0.11	0.18	-0.16	-0.13	-0.13	-0.13	-0.15	-0.13	0.16	0.11	0.10
Beta se (SMR)	0.02	0.03	0.03	0.02	0.02	0.02	0.03	0.02	0.03	0.02	0.01
p-value (SMR)	9.37×10^{-11}	3.49×10^{-8}	8.74×10^{-19}	3.08×10^{-10}	3.22×10^{-10}	1.21×10^{-7}	3.43×10^{-7}	4.37×10^{-9}	4.56×10^{-9}	4.78×10^{-11}	1.77×10^{-12}
p-value (HEIDI)	0.064	0.23	0.034	0.033	0.25	0.019	0.16	0.26	0.33	0.012	0.19
n of SNPs after HEIDI	20	14	12	20	12	20	15	20	17	19	20

NPD: neurological and psychiatric disorder. SNP: single nucleotide polymorphism. se: standard error. GWAS: genome-wide association study. mQTL: DNA methylation quantitative trait loci. SMR: Summary-data-based Mendelian randomisation. HEIDI: HEterogeneity In Dependent Instruments.

Table S48. Estimated correlations among significant brain-based DNA methylation probes shown in Table S47, related to Figure 5 and STAR Methods.

correlation	cg07148594	cg16977858	cg17372223	cg05564831	cg24629711	cg14449575	cg13364410	cg14021871	cg17414380	cg26162025	cg26732615
cg07148594	1.00	1.00	-0.96	-0.96	-0.85	-	-	-	-	-	-
cg16977858	1.00	1.00	-0.96	-0.96	-0.84	-	-	-	-	-	-
cg17372223	-0.96	-0.96	1.00	1.00	0.88	-	-	-	-	-	-
cg05564831	-0.96	-0.96	1.00	1.00	0.88	-	-	-	-	-	-
cg24629711	-0.85	-0.84	0.88	0.88	1.00	-	-	-	-	-	-
cg14449575	-	-	-	-	-	1.00	1.00	0.79	-0.81	-0.77	-0.82
cg13364410	-	-	-	-	-	1.00	1.00	0.80	-0.81	-0.77	-0.82
cg14021871	-	-	-	-	-	0.79	0.80	1.00	-0.98	-0.97	-0.97
cg17414380	-	-	-	-	-	-0.81	-0.81	-0.98	1.00	0.97	0.97
cg26162025	-	-	-	-	-	-0.77	-0.77	-0.97	0.97	1.00	0.99
cg26732615	-	-	-	-	-	-0.82	-0.82	-0.97	0.97	0.99	1.00

Table S49. Candidate gene lists for specific pairs of traits used in gene set enrichment analysis, related to Figure 5 and STAR Methods.	
Trait Pair	Gene list
Multiple sclerosis - Eosinophil count	*CD5 FCRL2 FCRL3 MYO19 PRXL2B ZNHIT3*
Multiple sclerosis - Lymphocyte count	*ABCB9 AC100854.1 BACH2 BANF1 GPR25 TNFSF14 ZMIZ1*
Multiple sclerosis - Neutrophil percentage of white cells	*ABCB9 AC100854.1 AHI1 BACH2 SCO2 ZC2HC1A ZMIZ1*
Multiple sclerosis - Red cell distribution width	*BANF1 GGNBP2 MAST3 MYO19 TYMP ZNHIT3*
Schizophrenia - Eosinophil count/Eosinophil percentage of white cells	*AC005829.1 AC091132.1 GATAD2A MAPK8IP1P1 MAPK8IP1P2*
Schizophrenia - Lymphocyte count	*ABCB9 AL360001.33 DDHD2 KANSL1-AS1 LRRC37A2 MAPK8IP1P1 RABEP1 WHSC1L1 ZNF664*
Schizophrenia - Lymphocyte percentage of white cells	*AC005829.1 AC091132.16 DDHD2 DND1P1 KANSL1-AS1 MAPK8IP1P1 MAPK8IP1P2 PPP2R3C*
Schizophrenia - Monocyte percentage of white cells	*AC005829.1 EP300 GATAD2A MAP1A STRCP1*
Schizophrenia - Neutrophil percentage of white cells	*ABCB9 AC005829.1 AC091132.16 MAPK3 MAPK8IP1P1 MAPK8IP1P2*
Schizophrenia - Reticulocyte count	*ABCB9 ARL6IP4 GATAD2A OGFOD2 ZNF664*
Schizophrenia - Reticulocyte fraction of red cells	*ABCB9 AC091132.1 AC091132.16 ARL6IP4 GATAD2A INO80E LRRC37A2 MAPK8IP1P1 MAPK8IP1P2 OGFOD2 ZNF664*

Table S50. Summary of significant pathways identified in the gene set enrichment analysis using ShinyGO, related to Figure 5 and STAR Methods.

Trait Pair	Pathway database	Pathway	Enrichment FDR	n of Genes	n of Pathway Genes	Enrichment Fold	Involved Genes
Schizophrenia - Monocyte percentage of white cells	GO: Molecular Function	Tau protein binding	4.68×10^{-4}	2	45	337.72	*EP300 MAP1A*
Schizophrenia - Reticulocyte fraction of red cells	GO: Cellular Component	SWI/SNF superfamily-type complex	5.87×10^{-3}	2	94	69.29	*GATAD2A INO80E*
Schizophrenia - Reticulocyte fraction of red cells	GO: Cellular Component	ATPase complex	5.87×10^{-3}	2	95	68.56	*GATAD2A INO80E*
Schizophrenia - Lymphocyte count	GO: Cellular Component	Centrosome	6.52×10^{-3}	2	658	34.64	*DDHD2 PPP2R3C*
Schizophrenia - Lymphocyte count	GO: Cellular Component	Microtubule organizing center	6.52×10^{-3}	2	868	26.26	*DDHD2 PPP2R3C*
Schizophrenia - Monocyte percentage of white cells	GO: Molecular Function	Protein-macromolecule adaptor activity	8.48×10^{-3}	2	283	53.70	*MAP1A GATAD2A*
Schizophrenia - Monocyte percentage of white cells	GO: Molecular Function	Molecular adaptor activity	8.48×10^{-3}	2	353	43.05	*MAP1A GATAD2A*
Schizophrenia - Lymphocyte count	GO: Cellular Component	Microtubule cytoskeleton	0.011	2	1391	16.39	*DDHD2 PPP2R3C*
Schizophrenia - Neutrophil percentage of white cells	GO: Molecular Function	ATP binding	0.014	2	1662	13.72	*MAPK3 ABCB9*
Schizophrenia - Neutrophil percentage of white cells	GO: Molecular Function	Adenyl nucleotide binding	0.014	2	1743	13.08	*MAPK3 ABCB9*
Schizophrenia - Neutrophil percentage of white cells	GO: Molecular Function	Adenyl ribonucleotide binding	0.014	2	1730	13.18	*MAPK3 ABCB9*
Schizophrenia - Lymphocyte count	GO: Cellular Component	Golgi apparatus	0.014	2	1812	12.58	*DDHD2 PPP2R3C*
Schizophrenia - Monocyte percentage of white cells	GO: Cellular Component	Transcription regulator complex	0.016	2	465	32.68	*EP300 GATAD2A*
Schizophrenia - Monocyte percentage of white cells	GO: Molecular Function	Zinc ion binding	0.016	2	942	16.13	*EP300 GATAD2A*
Schizophrenia - Monocyte percentage of white cells	GO: Molecular Function	Cytoskeletal protein binding	0.017	2	1050	14.47	*EP300 MAP1A*
Schizophrenia - Monocyte percentage of white cells	GO: Molecular Function	Transition metal ion binding	0.019	2	1238	12.28	*EP300 GATAD2A*
Multiple sclerosis - Eosinophil count	GO: Cellular Component	Cell surface	0.020	3	960	11.87	*CD5 FCRL2 FCRL3*
Multiple sclerosis - Eosinophil count	GO: Molecular Function	Phosphatase binding	0.023	2	224	33.92	*FCRL2 FCRL3*
Multiple sclerosis - Eosinophil count	GO: Molecular Function	Protein phosphatase binding	0.023	2	170	44.70	*FCRL2 FCRL3*
Schizophrenia - Monocyte percentage of white cells	GO: Cellular Component	Nuclear protein-containing complex	0.031	2	1379	11.02	*EP300 GATAD2A*
Schizophrenia - Monocyte percentage of white cells	GO: Cellular Component	Catalytic complex	0.031	2	1540	9.87	*EP300 GATAD2A*
Schizophrenia - Lymphocyte count	GO: Biological Process	Positive regulation of developmental process	0.032	2	1373	16.60	*DDHD2 PPP2R3C*
Multiple sclerosis - Red cell distribution width	GO: Biological Process	Mitochondrion organization	0.040	2	605	12.56	*TYMP MYO19*
Multiple sclerosis - Red cell distribution width	GO: Biological Process	Organelle fission	0.040	2	584	13.01	*BANF1 MYO19*
Schizophrenia - Reticulocyte fraction of red cells	GO: Cellular Component	Nuclear speck	0.041	2	481	13.54	*GATAD2A ARL6IP4*
Schizophrenia - Monocyte percentage of white cells	GO: Biological Process	Learning or memory	0.041	2	273	55.67	*EP300 MAP1A*
Schizophrenia - Monocyte percentage of white cells	GO: Biological Process	Cognition	0.041	2	327	46.48	*EP300 MAP1A*
Schizophrenia - Reticulocyte count	GO: Cellular Component	Nuclear speck	0.043	2	481	18.96	*GATAD2A ARL6IP4*
Schizophrenia - Monocyte percentage of white cells	GO: Cellular Component	Chromosome	0.044	2	1918	7.92	*EP300 GATAD2A*
Multiple sclerosis - Eosinophil count	GO: Cellular Component	Integral component of plasma membrane	0.045	3	1881	6.06	*CD5 FCRL2 FCRL3*
Multiple sclerosis - Eosinophil count	GO: Cellular Component	Intrinsic component of plasma membrane	0.045	3	1965	5.80	*CD5 FCRL2 FCRL3*

Table S51. Drug targets identified for shared candidate genes (listed in Tables S36-37) underlying PDW - PD and PCT - stroke, respectively, related to Figure 4 and STAR Methods.

Trait Pair	Gene	Drug	Sources*
PDW - PD	*CTNNB1*	TEMSIROLIMUS	JAX-CKB
PDW - PD	*CTNNB1*	CYCLOPHOSPHAMIDE	PharmGKB
PDW - PD	*CTNNB1*	LENALIDOMIDE	PharmGKB
PDW - PD	*CTNNB1*	LETROZOLE	CGI
PDW - PD	*CTNNB1*	EVEROLIMUS	CGI
PDW - PD	*CTNNB1*	EOSIN_Y	DTC
PDW - PD	*CTNNB1*	THALIDOMIDE	PharmGKB
PDW - PD	*CTNNB1*	VANTICTUMAB	JAX-CKB
PDW - PD	*CTNNB1*	CELECOXIB	PharmGKB
PDW - PD	*CTNNB1*	CHEMBL410484	DTC
PDW - PD	*CTNNB1*	DEXAMETHASONE	PharmGKB
PDW - PD	*CTNNB1*	IMATINIB	JAX-CKB
PDW - PD	*CTNNB1*	FLUORESCEIN SODIUM	DTC
PDW - PD	*CTNNB1*	DITHIAZANINE IODIDE	DTC
PDW - PD	*CTNNB1*	CHEMBL2172378	DTC
PDW - PD	*CTNNB1*	TRICIRIBINE	JAX-CKB
PDW - PD	*CTNNB1*	CHEMBL533293	DTC
PDW - PD	*CTNNB1*	TRAMETINIB	JAX-CKB
PDW - PD	*CTNNB1*	CHEMBL91638	DTC
PDW - PD	*FXR2*	METHYLPHENIDATE	PharmGKB
PDW - PD	*GGCX*	PHYTONADIONE	TdgClinicalTrial|TEND|TTD
PDW - PD	*GGCX*	ANISINDIONE	TdgClinicalTrial|TEND|GuideToPharmacology
PDW - PD	*GGCX*	MENADIONE	TdgClinicalTrial|TEND
PDW - PD	*GGCX*	ACENOCOUMAROL	PharmGKB
PCT - Stroke	*KCNK5*	QUINIDINE	GuideToPharmacology
PCT - Stroke	*KCNK5*	HALOTHANE	GuideToPharmacology
PDW - PD	*MAP3K5*	HYDROXYUREA	PharmGKB
PDW - PD	*MAP3K5*	SELONSERTIB	ChemblInteractions|GuideToPharmacology|TTD
PDW - PD	*PRKD1*	QUERCETIN	MyCancerGenome
PDW - PD	*PRKD1*	GSK-690693	ChemblInteractions
PDW - PD	*PRKD1*	MIDOSTAURIN	ChemblInteractions
PDW - PD	*PRKD1*	UCN-01	ChemblInteractions
PDW - PD	*PRKD1*	SOTRASTAURIN	ChemblInteractions
PDW - PD	*PRKD1*	CEP-2563	ChemblInteractions
PDW - PD	*PRKD1*	BRYOSTATIN	TdgClinicalTrial
PDW - PD	*PRKD1*	VASOPRESSIN	NCI
PDW - PD	*PRKD1*	RESVERATROL	NCI
PDW - PD	*PSMB10*	BORTEZOMIB	DTC|MyCancerGenome|ChemblInteractions
PDW - PD	*PSMB10*	OPROZOMIB	ChemblInteractions
PDW - PD	*PSMB10*	IXAZOMIB CITRATE	ChemblInteractions
PDW - PD	*PSMB10*	CARFILZOMIB	DTC|MyCancerGenome|ChemblInteractions
PDW - PD	*PSMB10*	MARIZOMIB	ChemblInteractions
PDW - PD	*PTK2*	PF-00562271	TALC|DTC|ChemblInteractions|GuideToPharmacology|TTD
PDW - PD	*PTK2*	GSK-2256098	ChemblInteractions|TTD
PDW - PD	*PTK2*	VS-4718	ChemblInteractions|GuideToPharmacology|TTD
PDW - PD	*PTK2*	CEP-37440	ChemblInteractions|GuideToPharmacology|TTD
PDW - PD	*PTK2*	ENMD-2076	TdgClinicalTrial|GuideToPharmacology
PDW - PD	*PTK2*	DEFACTINIB	TdgClinicalTrial|ChemblInteractions
PDW - PD	*PTK2*	HESPERADIN	DTC
PDW - PD	*PTK2*	BI-853520	ChemblInteractions|TTD
PDW - PD	*PTK2*	MASITINIB	MyCancerGenome
PDW - PD	*PTK2*	SNS-314	DTC
PDW - PD	*PTK2*	CHEMBL456559	DTC
PDW - PD	*PTK2*	LINIFANIB	DTC
PDW - PD	*PTK2*	GW843682X	DTC
PDW - PD	*PTK2*	CHEMBL2333445	DTC
PDW - PD	*PTK2*	PD-0166285	DTC
PDW - PD	*PTK2*	ALISERTIB	DTC
PDW - PD	*PTK2*	RG-1530	DTC
PDW - PD	*PTK2*	DEFACTINIB HYDROCHLORIDE	TTD
PDW - PD	*PTK2*	ENTRECTINIB	DTC
PDW - PD	*PTK2*	PAZOPANIB	DTC
PDW - PD	*PTK2*	ADAVOSERTIB	DTC
PDW - PD	*PTK2*	ILORASERTIB	DTC
PDW - PD	*PTK2*	R-406	DTC

PDW - PD	*PTK2*	CHEMBL1997335	DTC
PDW - PD	*PTK2*	CHLORPYRAMIN HYDROCHLORIDE	DTC
PDW - PD	*PTK2*	MLN-8054	DTC
PCT - Stroke	*PXN*	CHEMBL456559	DTC
PCT - Stroke	*PXN*	LOVASTATIN	NCI
PDW - PD	*RHD*	ROZROLIMUPAB	ChemblInteractions
PDW - PD	*RHD*	ROLEDUMAB	ChemblInteractions|TTD
PDW - PD	*RHD*	ATOROLIMUMAB	ChemblInteractions
PDW - PD	*SENP3*	METHYLPHENIDATE	PharmGKB
PDW - PD	*SREBF1*	INSULIN	NCI
PDW - PD	*SREBF1*	FLUVASTATIN	PharmGKB
PDW - PD	*SYK*	CERDULATINIB	ChemblInteractions|GuideToPharmacology|TTD
PDW - PD	*SYK*	APITOLISIB	GuideToPharmacology
PDW - PD	*SYK*	FOSTAMATINIB	MyCancerGenome|TdgClinicalTrial|ChemblInteractions|TTD
PDW - PD	*SYK*	R-343	ChemblInteractions
PDW - PD	*SYK*	ENTOSPLETINIB	ChemblInteractions|GuideToPharmacology|TTD
PDW - PD	*SYK*	R-112	ChemblInteractions
PDW - PD	*SYK*	R-406	DTC|ChemblInteractions
PDW - PD	*SYK*	LANRAPLENIB	GuideToPharmacology
PDW - PD	*SYK*	PRT-2607	ChemblInteractions|GuideToPharmacology|TTD
PDW - PD	*SYK*	HMPL-523	ChemblInteractions
PDW - PD	*SYK*	R-348	ChemblInteractions
PDW - PD	*SYK*	TAK-659	ChemblInteractions|TTD
PDW - PD	*SYK*	R-333	ChemblInteractions
PDW - PD	*SYK*	ENTRECTINIB	DTC
PDW - PD	*SYK*	CEDIRANIB	DTC
PDW - PD	*SYK*	ERLOTINIB	DTC
PDW - PD	*SYK*	SP-600125	DTC
PDW - PD	*SYK*	CHEMBL535331	DTC
PDW - PD	*SYK*	PD-0166285	DTC
PDW - PD	*SYK*	RG-1530	DTC
PDW - PD	*SYK*	ILORASERTIB	DTC
PDW - PD	*SYK*	ADAVOSERTIB	DTC
PDW - PD	*SYK*	IMATINIB MESYLATE	TTD
PDW - PD	*SYK*	GW441756X	DTC
PDW - PD	*SYK*	TAE-684	DTC
PDW - PD	*SYK*	PACLITAXEL	CIViC
PDW - PD	*SYK*	CYC-116	DTC
PDW - PD	*SYK*	CENISERTIB	DTC
PDW - PD	*SYK*	DASATINIB	DTC
PDW - PD	*SYK*	CHEMBL379975	DTC

*Sources are based on the drug-gene interaction database (DGIdb; https://www.dgidb.org/). PCT: plateletcrit. PDW: platelet distribution width. PD: Parkinson's disease.

Supplemental Data

Data S1. Phenotypic correlations for BCT-NPD trait pairs with putative causal relationships, related to STAR Methods.

Using individual-level data from the UK Biobank (UKB) cohort, we estimated phenotypic correlations for the three blood cell trait (BCT)-neurological and psychiatric disorder (NPD) pairs found to have a putative or suggestive causal relationship on the basis of Mendelian randomisation (MR): plateletcrit ("PCT") and stroke, platelet distribution width ("PDW") and Parkinson's disease (PD), and lymphocyte count (LYMPH#) and multiple sclerosis (MS). After restricting to unrelated Europeans (genetic relatedness < 0.05) and removing individuals with missing data on sex and age at recruitment, nearly 348K individuals remained. Individuals were coded with information on PCT (UKB field ID: 30090), PDW (UKB field ID: 30110), LYMPH# (UKB field ID: 30120), stroke-related variables (UKB field ID: 42007 [hospital admission, exclude self-report only], 42009 [hospital admission, exclude self-report only], 41270-I64 [10th revision of the International Statistical Classification of Diseases (ICD10)-based stroke status]), PD status (UKB field ID: 41270-G20 [ICD10-based PD status]), and MS status (UKB field ID: 41270-G35 [ICD10-based MS status]).

We defined stroke cases (hospital admission and ICD10-based stroke, n = 5,288, UKB field ID: 42007 + 42009 + 41270-I64), PD cases (ICD10-based PD, n = 1,323, UKB field ID: 41270-G20), and MS cases (ICD10-based MS, n = 1,238, UKB field ID: 41270-G35). For each diagnostic group (i.e., stroke, PD or MS cases, respectively), we randomly selected healthy controls from individuals without the respective diagnosis (i.e., non-stroke, non-PD or non-MS), matching by sex and age (+/- 2 years). We then evaluated the phenotypic correlations (r_P) for these three pairs of traits, using the full sample and lists of sub-samples at an assumed prevalence of 1% (for PD and MS), 2% (for PD and MS), 5% (for all three diseases) and 10% (for stroke only), respectively. We observed significant phenotypic correlations between PCT and stroke, regardless of the definition used to define the prevalence, with estimated r_P at around 0.01 ($p < 0.05$; Table S28). We also observed marginally significant phenotypic correlations between PDW and PD ($r_P \sim 0.01$, $p < 0.07$; Table S28). Conversely, we failed to observe any evidence for a significant phenotypic correlation between LYMPH# and MS, potentially due to the modest number of MS cases in the UKB (Table S28).

Data S2. Investigating the role of inflammatory response in mediating the causal relationship between platelet distribution width and Parkinson's disease, related to STAR Methods.

Published studies[2-6] support a critical role for the inflammatory response on both PD and platelet hyperactivity. On the basis of these findings, we hypothesised that C-reactive protein (CRP, used as a 'proxy' of inflammatory response) might be relevant to the putative causal effect of PDW on PD.

We investigated the role of CRP using a conditional MR approach. First, we utilised multi-trait-based conditional & joint analysis (mtCOJO)[7] to condition genome-wide association study (GWAS) summary data of PDW and PD on the GWAS of CRP[8], based on the in-house UKB genotype reference of unrelated Europeans. Here, we used summary data from the GWAS of CRP by Ligthart et al.[8], which was generated from 204,402 individuals of European ancestry using fixed-effect inverse-variance-weighted meta-analysis. Second, we re-estimated the causal relationship between PD and PDW on the basis of the conditional GWAS summary statistics using CAUSE[9]. Notably, the results from these conditional CAUSE analyses were highly consistent with the original analyses, both with PDW as an exposure for PD (odds ratio [OR_{CAUSE}] = 1.07, 95% confidence interval [CI] = 1.02-1.12, $p_{OR} = 1.37\times10^{-3}$; $p = 0.04$ for testing if the causal model is a better fit than the sharing model or null model) and PD as an exposure for PDW ($OR_{CAUSE} = 0.99$, 95% CI = 0.98-1.00, $p_{OR} = 0.06$; $p = 0.27$) (Table S26). This suggests a limited contribution of the inflammatory response on the putative causality of PDW on risk of PD. This conclusion is also supported by the absence of support for a significant genome-wide genetic correlation (estimated by linkage disequilibrium score regression[10]) between CRP and PDW ($r_g = 0.07$, se = 0.06, $p = 0.11$), or between CRP and PD ($r_g = -0.06$, se = 0.05, $p = 0.10$).

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