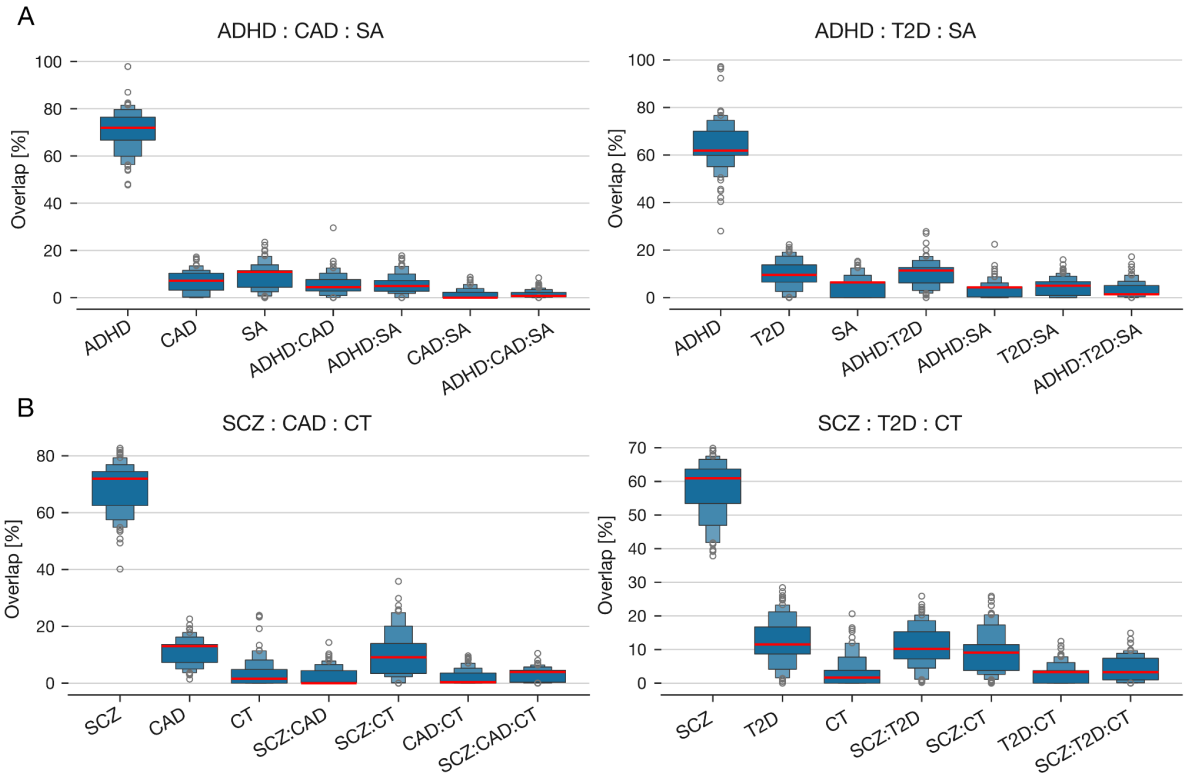
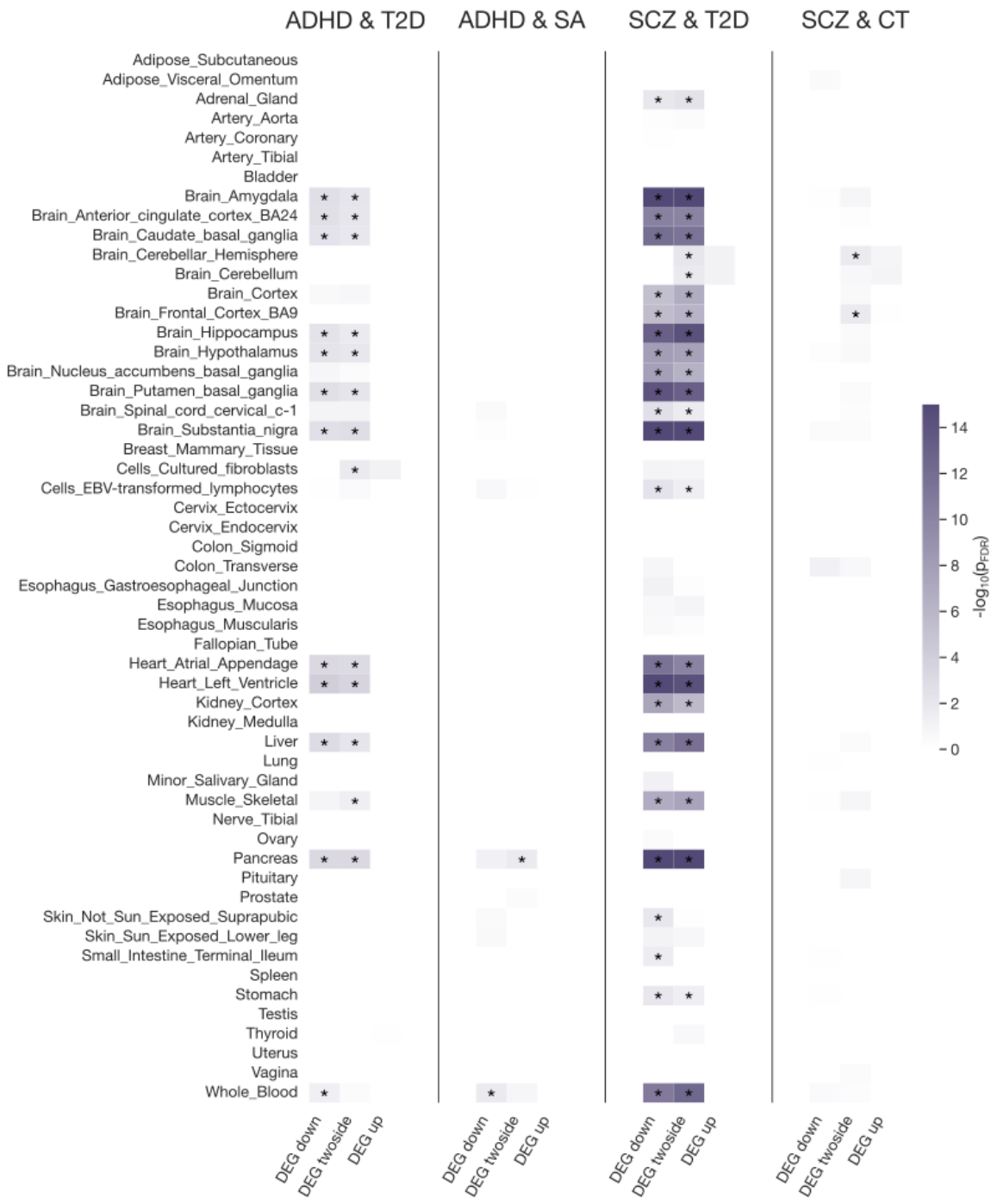
Supplementary Material

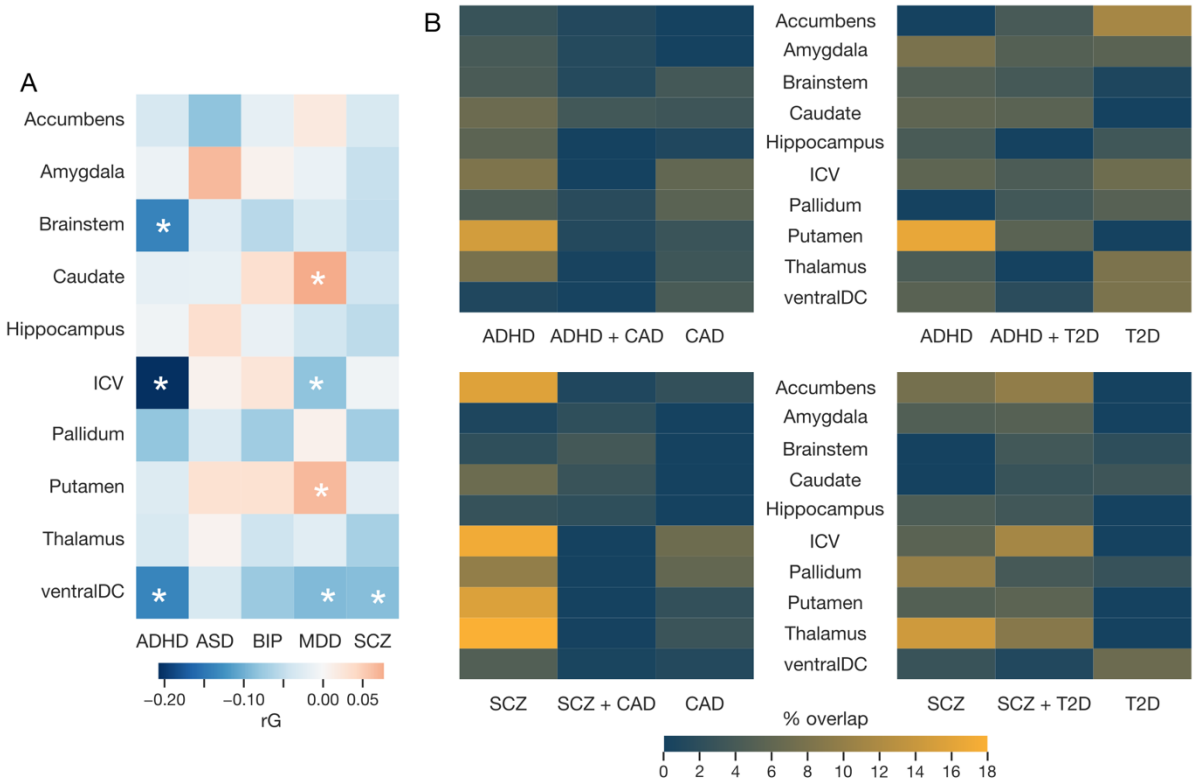
Supplementary Figures



Supplementary Figure 1: Stability of trivariate MiXeR model estimates
The trivariate MiXeR results presented in the main text reflect optimal estimates derived from 100 independent optimization runs. For each polygenicity parameter, the median value across runs was computed, and the final result was selected as the run with the smallest deviation from the median overlap pattern. Each panel displays boxen plots of polygenicity and pairwise overlap estimates derived from 100 independent model fits (**A** for ADHD, **B** for SCZ). Boxen plots depict multiple nested quantile ranges (e.g., deciles), enabling a high-resolution view of the distribution tails and skewness beyond what standard box plots capture. The optimal run (used in the main text) is highlighted in red.



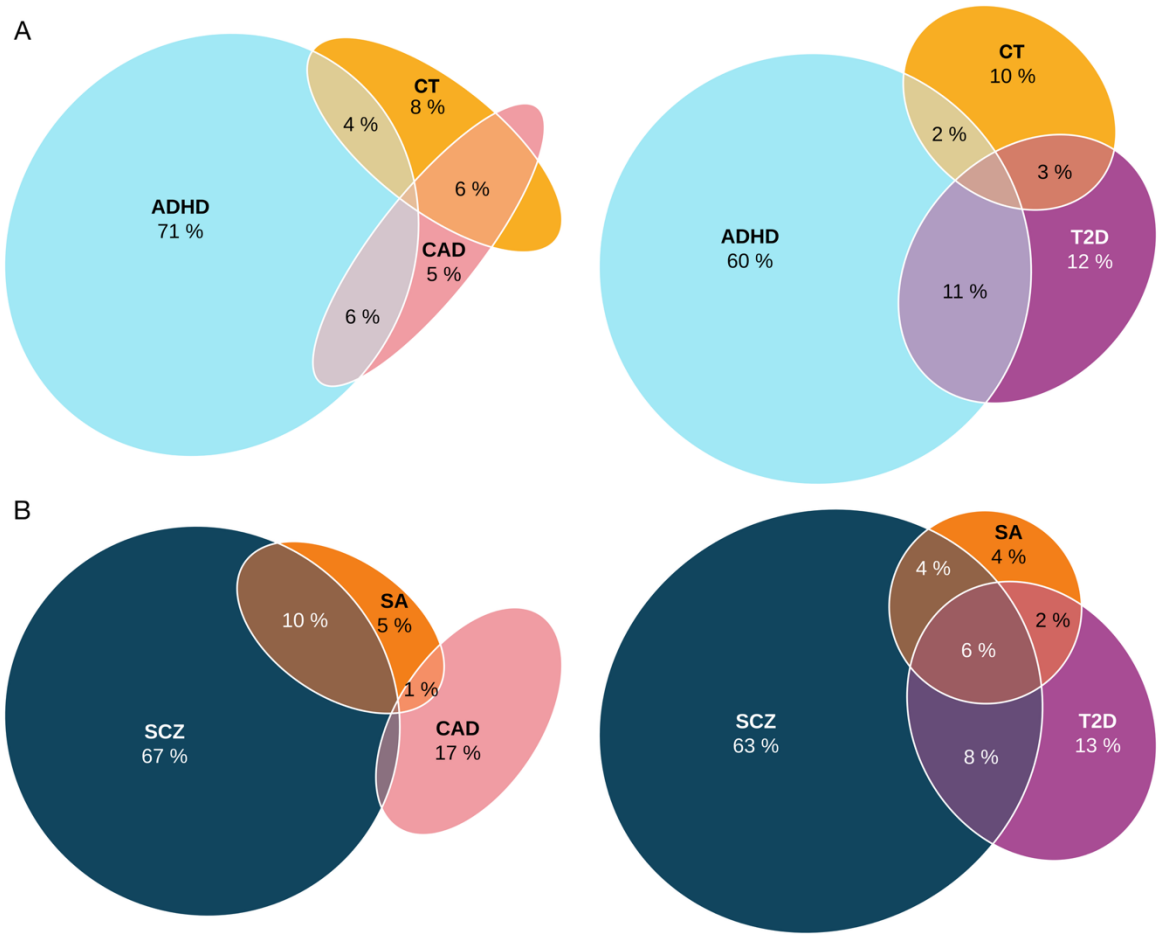
Supplementary Figure 2. Tissue-specific expression enrichment of mapped genes
Heatmap shows $-\log_{10}$(FDR-adjusted p-values) from GTEx v8 differential expression analyses of genes mapped to loci shared between psychiatric, cardiometabolic, and cortical traits (ADHD & T2D, ADHD & SA, SCZ & T2D, SCZ & CT). Rows represent 54 GTEx tissue types, and columns correspond to differentially expressed gene (DEG) categories (downregulated, upregulated, bidirectional). Asterisks indicate significant enrichment at $p_{FDR} < 0.05$.



Supplementary Figure 3: Genetic convergence between subcortical volumes and psychiatric disorders.

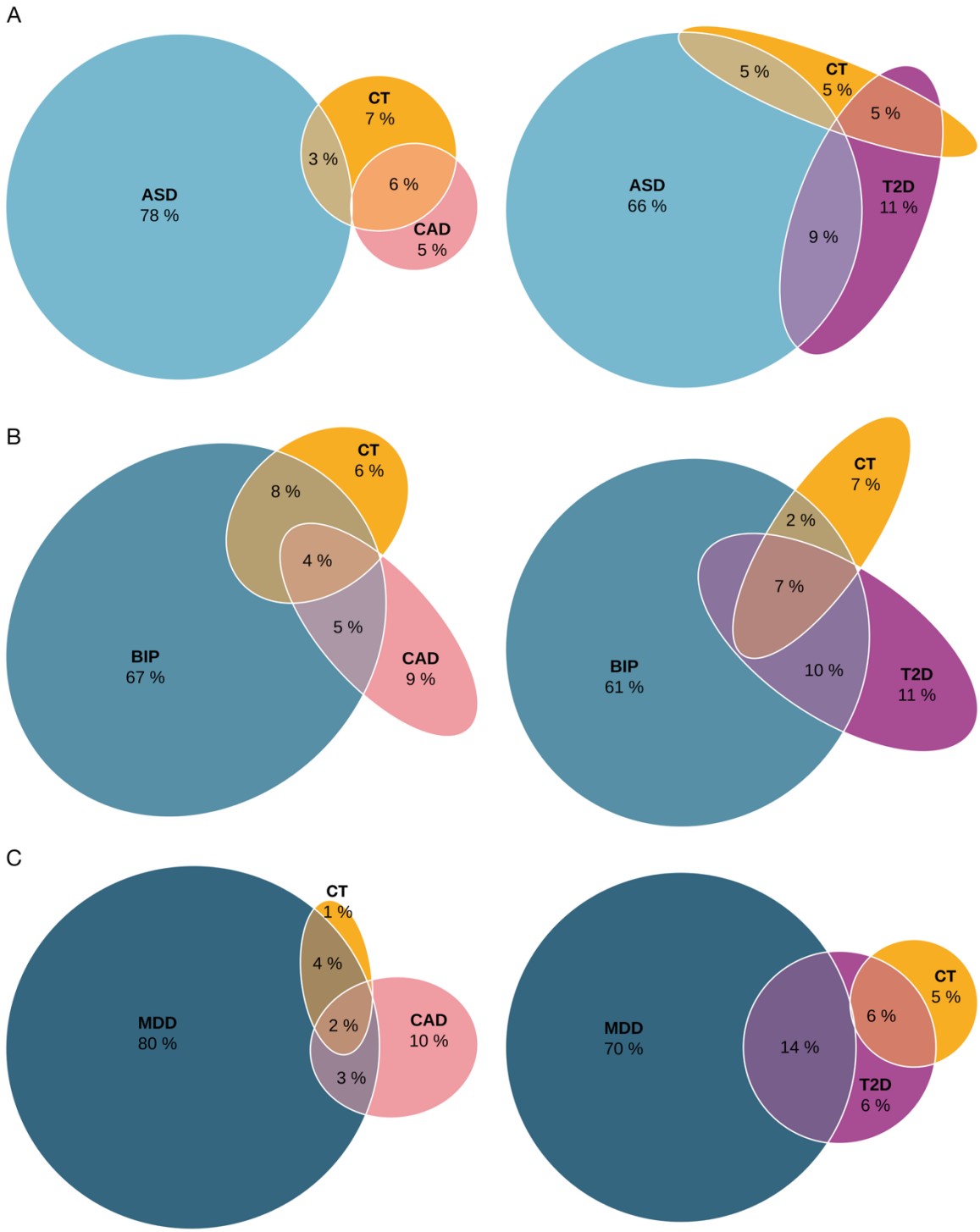
A. Genetic correlation analyses. Genetic correlations (rG) between ten ENIGMA subcortical volume measures (García-Marín et al., 2024) and five psychiatric disorders, estimated using LD Score Regression. The subcortical phenotypes include the brainstem, amygdala, hippocampus, caudate, putamen, pallidum, thalamus, ventral diencephalon (ventralDC), nucleus accumbens, and intracranial volume (ICV). Asterisks (*) denote genetic correlations that remained significant after FDR correction across all tests. Genetic correlations were modest and structure-specific, with significant associations primarily observed for ADHD and MDD, particularly with intracranial volume and select subcortical nuclei. **B.** Trivariate MiXeR estimates of shared polygenic components between subcortical structures, psychiatric disorders (ADHD or SCZ), and cardiometabolic diseases (CAD or T2D). Each heatmap displays: (1) the bivariate overlap between a subcortical measure and the psychiatric disorder (left column), (2) the trivariate overlap jointly shared by the subcortical measure, psychiatric disorder, and cardiometabolic disease (middle column), and (3) the bivariate overlap between the subcortical measure and the cardiometabolic disease (right column). Parallel to CT and SA, subcortical volumes exhibited notable overlap with SCZ and ADHD, yet showed no trivariate component with CAD, with SCZ consistently yielding the strongest trivariate overlap, particularly in combination with T2D.

Ref: García-Marín, L. M. et al. Genomic analysis of intracranial and subcortical brain volumes yields polygenic scores accounting for variation across ancestries. Nat Genet 56, 2333–2344 (2024).



Supplementary Figure 4: Complementary trivariate overlap between psychiatric disorders, cardiometabolic disease and cortical morphology

A. Genetic overlap between ADHD, CT, and cardiometabolic disease. Based on trivariate MiXeR analyses, the Venn diagrams illustrate the extent of genetic overlap between cortical morphology (i.e., CT), ADHD, and cardiometabolic traits (CAD and T2D). Only genetic overlaps exceeding 1% are annotated. **B.** Genetic overlap between SCZ, SA, and cardiometabolic disease. Genetic overlaps between CT, SCZ, and the cardiometabolic traits CAD and T2D are presented using Venn diagrams.

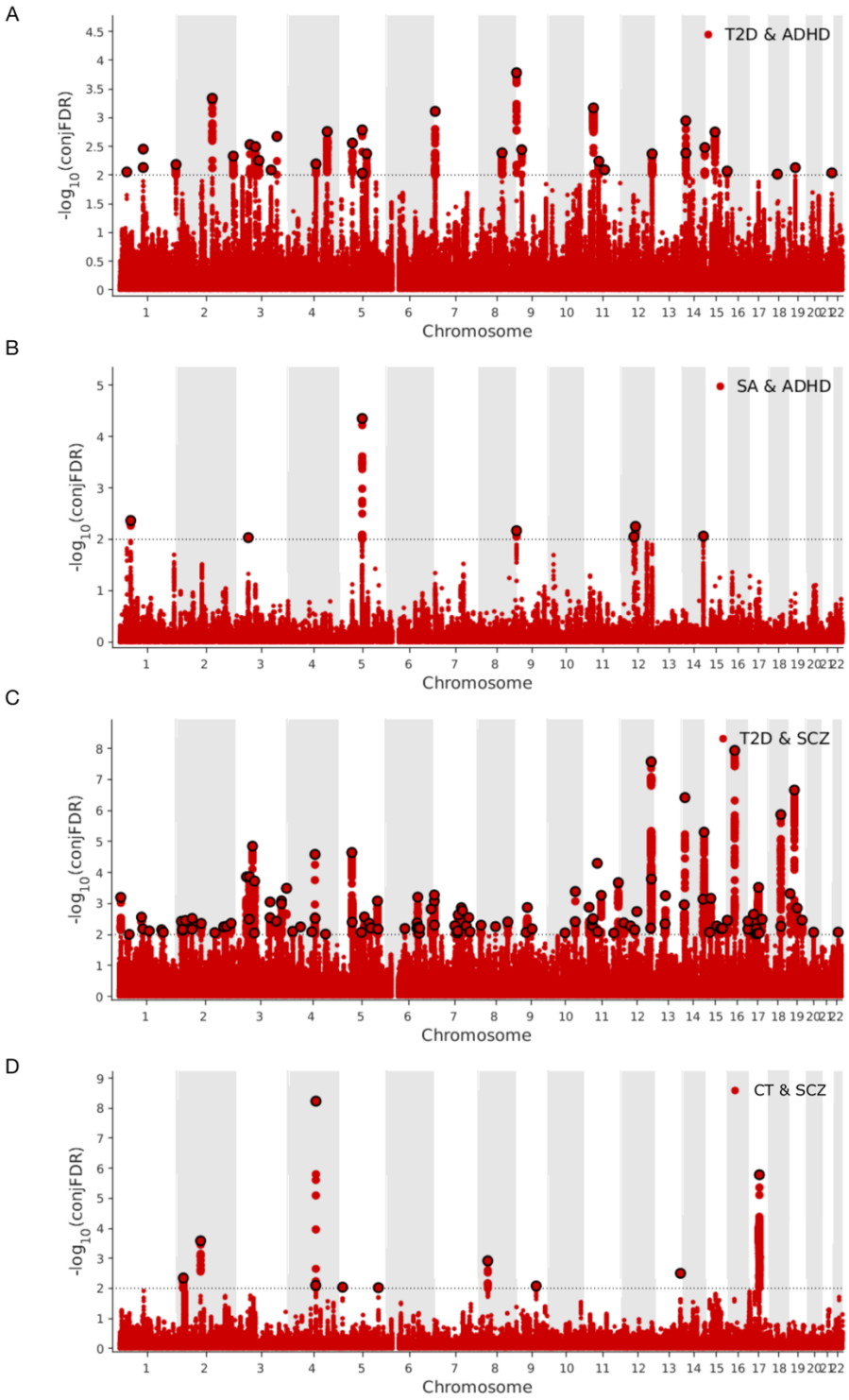


Supplementary Figure 5: Trivariate overlap between remaining psychiatric disorders, cardiometabolic disease and cortical thickness

Genetic overlap between three psychiatric disorders, CT, and cardiometabolic disease. Based on trivariate MiXeR analyses, the Venn diagrams illustrate the extent of genetic overlap between cortical morphology (i.e., CT), psychiatric disorder (i.e., ASD, BIP, MDD), and cardiometabolic traits (CAD and T2D). Only genetic overlaps exceeding 1% are annotated. Results are presented for ASD (**A**), BIP (**B**), and MDD (**C**).

Supplementary Figure 6: Trivariate overlap between remaining psychiatric disorders, cardiometabolic disease and surface area

Genetic overlap between three psychiatric disorders, SA, and cardiometabolic disease. Based on trivariate MiXeR analyses, the Venn diagrams illustrate the extent of genetic overlap between cortical morphology (i.e., SA), psychiatric disorder (i.e., ASD, BIP, MDD), and cardiometabolic traits (CAD and T2D). Only genetic overlaps exceeding 1% are annotated. Results are presented for ASD (**A**), BIP (**B**), and MDD (**C**).



Supplementary Figure 7: Shared loci at conjDFR < 0.01

We searched for SNPs jointly associated between ADHD and SA (**A**), ADHD and T2D (**B**), SCZ and T2D (**C**), as well as SCZ and CT (**D**). For these four analyses, the associated Manhattan plot displays genetic variants shared by the respective two traits. Each Manhattan plot shows the $-\log_{10}$ transformed conjFDR values for each SNP on the y-axis. SNPs with conjFDR < 0.01are shown with enlarged data points. A black circle around the enlarged data points indicates the most significant SNP in each linkage disequilibrium block. The analysis revealed 30, 7, 110, and 9 lead SNPs respectively.

Supplementary Tables

Supplementary Table 1: Mendelian randomization assumption checks

For each exposure–outcome analysis, the table reports the number of instruments (N SNPs), mean, median, and minimum F-statistic, and the proportion of instruments with F > 10 as indicators of instrument strength. Directional horizontal pleiotropy was evaluated using the MR-Egger intercept, with corresponding standard error (SE) and p-value. Heterogeneity was assessed using Cochran's Q statistic and p-value for both IVW and MR-Egger models. Overall, instruments were generally strong (mean F > 10), with limited evidence of directional pleiotropy.

Exposure	Outcome	N SNPs	Mean F	Median F	Min F	% F>10	Egger intercept	Egger SE	Egger p-value	Q (IVW)	Q (IVW) p-value	Q (Egger)	Q (Egger) p-value
ADHD	T2D	25	38,79	34,85	29,85	100	0,014	0,010	0,203	194,1	1,43E-28	180,6	1,95E-26
ADHD	SA	25	38,79	34,85	29,85	100	-0,013	0,008	0,127	50,1	1,37E-03	45,2	3,77E-03
SCZ	T2D	148	43,93	38,65	29,46	100	0,000	0,004	0,909	1059,7	5,45E-138	1059,6	2,10E-138
SCZ	CT	148	43,93	38,65	29,46	100	0,009	0,004	0,041	369,0	4,52E-21	358,6	6,69E-20
T2D	ADHD	423	89,36	52,20	29,40	100	0,005	0,002	0,001	880,9	1,54E-34	860,0	2,48E-32
SA	ADHD	20	54,96	41,70	30,42	100	-0,003	0,009	0,747	36,4	9,36E-03	36,2	6,64E-03
T2D	SCZ	454	89,81	51,28	29,40	100	-0,002	0,002	0,364	1396,9	8,09E-97	1394,4	1,09E-96
CT	SCZ	21	44,31	40,30	29,78	100	-0,007	0,024	0,783	193,7	1,99E-30	192,9	8,80E-31
T2D	CT	455	89,79	51,12	29,40	100	-0,001	0,001	0,338	686,1	1,04E-11	684,7	1,07E-11
T2D	SA	455	89,79	51,12	29,40	100	0,002	0,009	0,850	989,4	7,71E-42	974,8	2,75E-40
CT	T2D	21	44,31	40,30	29,78	100	0,002	0,009	0,850	654,5	5,25E-125	641,5	5,02E-123
SA	T2D	22	52,91	38,25	29,88	100	-0,009	0,015	0,532	654,5	5,45E-138	1059,6	2,10E-138

Supplementary Table 2: Enriched biological pathways shared between ADHD & T2D
The table presents enriched pathways with KEGG pathways highlighted in red and REACTOME pathways in blue. Reported columns include the number of input genes associated with each pathway (Count), the raw p-value from the modified Fisher's exact test, and the fold enrichment. Fold enrichment reflects the ratio between the proportion of genes associated with a given pathway in the input list and the corresponding proportion in the background population. Representative genes are shown for each term.

Term	Count	p-value	Genes (ENSG)	Fold Enrichment
Regulation of TP53 Activity	4	4,4E-03	ENSG00000183955, 00000181929, 00000167491, 00000012048	11,42
Selective autophagy	3	0,02	00000188554, 00000181929, 00000109332	15,16
Macroautophagy	3	0,04	00000188554, 00000181929, 00000109332	9,51
Transcriptional Regulation by TP53	4	0,04	00000183955, 00000181929, 00000167491, 00000012048	5,09
Autophagy	3	0,04	00000188554, 00000181929, 00000109332	8,62
SUMOylation	3	0,06	00000079387, 00000172262, 00000012048	7,38

Supplementary Table 3: Enriched biological pathways shared between ADHD and SA

The table is formatted identically to Table S2.

Term	Count	p-value	Genes (ENSG)	Fold Enrichment
Regulation of TP53 Activity	3	3,9E-03	00000183955, 00000117020, 00000181929	26,77
Alcoholic liver disease	3	0,01	00000117020, 00000168036, 00000181929	19,75
VEGFR2 mediated vascular permeability	2	0,02	00000117020, 00000168036	99,09
Transcriptional Regulation by TP53	3	0,02	00000183955, 00000117020, 00000181929	11,94
Salmonella infection	3	0,02	00000117020, 00000168036, 00000111540	11,33
Infectious disease	4	0,02	00000117020, 00000168036, 00000126091, 00000111540	5,25
Generic Transcription Pathway	4	0,03	00000183955, 00000117020, 00000168036, 00000181929	4,54
Transcriptional and post-translational regulation of MITF-M exp. and act.	2	0,04	00000117020, 00000168036	46,35
RNA Polymerase II Transcription	4	0,04	00000183955, 00000117020, 00000168036, 00000181929	4,13
TP53 Regulates Metabolic Genes	2	0,05	00000117020, 00000181929	34,62
RAB GEFs exchange GTP for GDP on RABs	2	0,05	00000117020, 00000111540	31,93
Endometrial cancer	2	0,05	00000117020, 00000168036	32,14
Membrane Trafficking	3	0,06	00000117020, 00000181929, 00000111540	6,65
Longevity regulating pathway - multiple species	2	0,06	00000117020, 00000181929	30,59
VEGFA-VEGFR2 Pathway	2	0,06	00000117020, 00000168036	29,62
Gene expression (Transcription)	4	0,06	00000183955, 00000117020, 00000168036, 00000181929	3,56
Adipocytokine signaling pathway	2	0,06	00000117020, 00000181929	27,09
Signaling by VEGF	2	0,06	00000117020, 00000168036	26,61
Vesicle-mediated transport	3	0,07	00000117020, 00000181929, 00000111540	5,73
Rab regulation of trafficking	2	0,07	00000117020, 00000111540	22,99
Colorectal cancer	2	0,08	00000117020, 00000168036	21,80
Longevity regulating pathway	2	0,08	00000117020, 00000181929	21,07
Prostate cancer	2	0,09	00000117020, 00000168036	19,35
MITF-M-regulated melanocyte development	2	0,09	00000117020, 00000168036	18,54
Glucagon signaling pathway	2	0,10	00000117020, 00000181929	17,72
Apoptosis	2	0,10	00000117020, 00000168036	17,31
Disease	4	0,10	00000117020, 00000168036, 00000126091, 00000111540	2,98
Insulin resistance	2	0,10	00000117020, 00000181929	17,40
Viral Infection Pathways	3	0,10	00000117020, 00000126091, 00000111540	4,82

Supplementary Table 4: Enriched biological pathways shared between SCZ and T2D
The table is formatted identically to Table S2.

Term	Count	p-value	Genes (ENSG)	Fold Enrichment
Parkinson disease	8	0,02	00000168653, 00000159199, 00000164305, 00000108671, 00000186868, 00000126214, 00000132388, 00000145335	3,04
Notch signaling pathway	4	0,02	00000162736, 00000159692, 00000196498, 00000078747	6,63
Chromatin organization	8	0,03	00000183955, 00000170291, 00000172977, 00000120071, 00000196498, 00000070061, 00000167491, 00000127663	2,74
Chromatin modifying enzymes	8	0,03	00000183955, 00000170291, 00000172977, 00000120071, 00000196498, 00000070061, 00000167491, 00000127663	2,74
Alzheimer disease	9	0,03	00000168653, 00000159593, 00000162736, 00000159199, 00000164305, 00000108671, 00000186868, 00000126214, 00000145335	2,37
Antigen processing: Ubiquitination & Proteasome degradation	8	0,04	00000164068, 00000153827, 00000108671, 00000109332, 00000159202, 00000078747, 00000154359, 00000132388	2,55
Pathways of neurodegeneration - multiple diseases	10	0,04	00000101460, 00000168653, 00000159199, 00000197653, 00000164305, 00000108671, 00000186868, 00000126214, 00000132388, 00000145335	2,13
Class I MHC mediated antigen processing & presentation	9	0,04	00000170458, 00000164068, 00000153827, 00000108671, 00000109332, 00000159202, 00000078747, 00000154359, 00000132388	2,29
Synthesis of active ubiquitin: roles of E1 and E2 enzymes	3	0,04	00000109332, 00000159202, 00000132388	8,83
Ubiquitin mediated proteolysis	5	0,05	00000153827, 00000109332, 00000159202, 00000078747, 00000132388	3,62
Signaling by MST1	2	0,05	00000164078, 00000173531	37,69
Programmed Cell Death	6	0,06	00000170458, 00000164305, 00000108671, 00000078747, 00000186868, 00000088808	2,84
Amyotrophic lateral sclerosis	8	0,07	00000101460, 00000108559, 00000168653, 00000159199, 00000197653, 00000164305, 00000108671, 00000126214	2,22
Signaling by Rho GTPases, Miro GTPases and RHOBTB3	13	0,08	00000002822, 00000242247, 00000047932, 00000159314, 00000089639, 00000172757, 00000151725, 00000166165, 00000123329, 00000126777, 00000103415, 00000126214, 00000278259	1,67
CDC42 GTPase cycle	5	0,08	00000089639, 00000242247, 00000123329, 00000126777, 00000159314	3,00
Apoptosis	5	0,10	00000170458, 00000164305, 00000108671, 00000186868, 00000088808	2,84

Supplementary Table 5: Enriched biological pathways between SCZ and CT

The table is formatted identically to Table S2.

Term	Count	p-value	Genes (ENSG)	Fold Enrichment
Fructose and mannose metabolism	2	0,05	00000138030, 00000178802	35,86
Tryptophan metabolism	2	0,06	00000119689, 00000171097	29,03
Asparagine N-linked glycosylation	3	0,09	00000238083, 00000140506, 00000178802	5,46