nature portfolio

Peer Review File

Mapping genetic convergence across brain structure, mental health, and cardiometabolic disease

Corresponding Author: Dr Jakub Kopal

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
Thanks for inviting me to review the paper COMMSMED-25-1715-T. The manuscript is interesting and the high number of participants and variety of data included in the study is valuable. Please, see below my comments.
1. From your results related to Figure 1, my understanding is that you aim to report: (1) the genetic differences between SCZ and ADHD (i.e., low genetic correlation), and (2) the different genetic correlations of SCZ and ADHD with cardiometabolic diseases and cortical morphology (positive vs. negative). Therefore, you want to investigate their shared and unique genetic links with cardiometabolic diseases and cortical morphology, respectively. If this is correct, I suggest reorganizing the paragraphs to focus on the findings among SCZ/ADHD, cardiometabolic diseases (T2D and CAD), and cortical morphology (CT and SA), while moving results for other psychiatric disorders to the supplementary materials, as they may overwhelm the main findings. Additionally, you mentioned that 'All phenotypes included in the analysis passed recommended quality control criteria, including adequate polygenicity and heritability to support advanced statistical modeling (Fig. 1D).' in line 137-138. Could you clarify what these recommended quality control criteria are? Specifically, are there any thresholds for polygenicity or heritability when conducting genetic correlation analyses? If so, can you indicate the thresholds in your sentence?
2. Similar to my first comment, your main findings focus on SCZ and ADHD in relation to other cardiometabolic diseases (T2D and CAD) and cortical morphology measures (CT and SA).
3. For your Mendelian randomization analyses, did you check the MR assumptions? Also, did you use individual-level genotype data, or only GWAS summary statistics?
4. Colocalization analysis as implemented in the COLOC R package (https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1004383) can also be used to examine shared genetic variants between two traits. Have you considered applying it to identify shared loci between psychiatric and cardiometabolic phenotypes?

Reviewer #2

(Remarks to the Author)
General comments
This manuscript addresses an important and timely topic, exploring the genetic basis underlying the comorbidity between psychiatric and cardiometabolic disorders through brain morphology. The use of complementary genetic approaches is valuable, and the findings provide novel insights into shared and disorder-specific pathways. However, there are substantial issues in study design, phenotype selection, and methodological transparency that need to be clarified or expanded before the conclusions can be considered robust. I therefore recommend major revision.

Specific comments
1. In the introduction, you mention that schizophrenia is comorbid with cardiovascular and respiratory diseases, while ADHD is comorbid with nervous system disorders (particularly sleep disorders), as well as cardiovascular, respiratory, musculoskeletal, and metabolic diseases. However, in the subsequent analyses you only focused on psychiatric–cardiometabolic comorbidity. Could you clarify the rationale for restricting the analyses to cardiometabolic diseases, rather than including other comorbid disease systems (respiratory, musculoskeletal)?
2. Regarding the choice of imaging phenotypes, only cortical thickness and surface area were included. Other important brain phenotypes, such as subcortical volumes, functional connectivity, and white matter connectivity, which are highly

relevant to psychiatric disorders (especially schizophrenia), were not considered. Please justify this choice and consider providing additional analyses.
3. When performing genetic correlation analyses between diseases, did you apply multiple testing correction? Please report the adjusted P values.
4. Please specify in the Methods section the exact multiple testing correction procedure you used.
5. For mediation analyses using GWAS summary data, you employed a genomic SEM (gSEM) approach rather than the more classical multivariable Mendelian randomization (MVMR) framework. Could you explain the rationale for this choice and discuss the robustness of the two methods?
6. Are the GWAS summary statistics used in this study derived from the largest available European ancestry samples to date? If so, please state this explicitly in the Methods.

Reviewer #3

(Remarks to the Author)
This study explored the shared genetic architecture across psychiatric disorders (ADHD, ASD, MDD, BIP, SCZ), cardiometabolic diseases (CAD, T2D), and brain morphology (cortical thickness [CT], cortical surface area [SA]) using complementary genetic approaches including LDSC, trivariate MiXeR, Mendelian Randomization (MR), mediation analysis, and pathway enrichment. This study demonstrated the genetic basis of the comorbidity between psychiatric and cardiometabolic disorders, as well as the role of brain structure in these relationships. Nevertheless, there are several aspects of the study that, in my opinion, could be enhanced.

1.It is important to evaluate the presence of sample overlap among the included phenotypes, as such overlap could bias the identification of pleiotropic loci and causal associations.
2.The authors should ascertain whether the identified pleiotropic loci are associated with trait specificity, rather than being influenced by confounding factors that could affect the observed pleiotropic associations.
3.The introduction briefly notes that brain structure mediates genetic effects on psychiatric disorders, but it lacks discussion on regional specificity in brain morphology–disorder associations. The authors should justify the choice of CT and SA as the primary phenotypes, rather than more detailed regional brain phenotypes.
4.While the pathway enrichment analyses, such as TP53-related pathways in ADHD and neurodevelopmental/immune pathways in SCZ, effectively highlight biological mechanisms, incorporating “tissue-specific enrichment analyses” would further refine the functional context of the identified genes. For instance, verifying if genes shared between psychiatric disorders and brain morphology are highly expressed in neurodevelopmental brain regions could clarify the tissue-specific drivers of comorbidity.
5.While the trivariate MiXeR analysis effectively quantifies genetic overlap across three traits, the manuscript lacks a clear explanation of why trivariate results differ from bivariate analyses.
6.Although the mediation analysis identifies SA as a partial mediator of the ADHD-T2D genetic link, the manuscript does not adequately discuss the clinical relevance of this modest mediation effect. The authors should explicitly acknowledge this limitation. Additionally, the need for longitudinal clinical studies to validate whether targeting SA-related pathways could meaningfully reduce T2D risk in ADHD patients should also be emphasized.

Reviewer #4

(Remarks to the Author)
Kopal et al. investigated the genetic factors underlying psychiatric disorders, cardiometabolic diseases, and brain morphology using complementary genetic approaches, including LDSC, MR, trivariate MiXeR, conjFDR, and pathway enrichment analysis. They found that SCZ was genetically distinct from ADHD. Specifically, SCZ showed substantial polygenic overlap with CT and T2D, whereas ADHD was more genetically correlated with CAD and T2D but exhibited limited overlap with CT. MR results further revealed that T2D has a positive causal effect on ADHD, and SA has a negative causal effect on ADHD, while no causal effects were observed between T2D, CT, and SCZ. Overall, the study is well-designed and executed. Nevertheless, I have several minor suggestions that could further improve the clarity and impact of this work:
1. Figure 1C – Is this intended to be a Manhattan plot for GWAS of SCZ and ADHD? The figure legend might be incorrect. Based on the P values, it appears that the inner ring displays the -log10(p-values) for SCZ. Please clarify.
2. Figure 2 – It is recommended to retain the "percent of genetic overlap" values to one decimal place and to label all numerical values directly within the Venn diagrams for easier interpretation.
3. Figure 2A and 2B – The authors presented MiXeR results for ADHD and SA (Figure 2A) and for SCZ and CT (Figure 2B), while the remaining results were shown in Figure S1. This split presentation is not very intuitive. It would be clearer to integrate all trivariate MiXeR results into the main Figure 2.
4. Figure 2B – From the left panel, SCZ and CT appear to share 4% + 9% = 13% of variants, but from the right panel, they share 9% + 3% = 12%. How should this discrepancy be interpreted?
5. Line 166 – The conclusion that "ADHD exhibits a distinct genetic architecture characterized by smaller trivariate overlaps" seems difficult to support based solely on Figures 2A and 2B. Given that the GWAS of SCZ identified many more significant loci than ADHD, it is expected that ADHD would share fewer variants with traits such as SA or CT. This should be discussed more cautiously.
6. Line 191 – Similarly, it is not straightforward to deduce “potential cardiometabolic contributions to brain-related genetic risk for psychiatric disorders” from the trivariate MiXeR results alone. This conclusion seems better supported by the MR findings and could be reframed accordingly.
7. Is it possible to identify the percentage of shared variants between ADHD & CT and SCZ & CT, ADHD & CAD and SCZ &

CAD, …
8. Lines 200–201 – Odds ratios (ORs) might be more interpretable than β coefficients here.
9. Lines 204–205 – The sentence “In contrast to the findings for ADHD, IVW MR did not reveal any significant causal effect of SCZ on CT or T2D” could be better contextualized by also reporting the causal effects of T2D and SA on SCZ. More broadly, the MR results might be presented in a more coherent structure: first forward MR (ADHD or SCZ → T2D and SA), followed by reverse MR (T2D or SA → ADHD or SCZ). This would also highlight that ADHD has a positive causal effect on T2D.
10. Line 238 – According to Figure 4B, this should refer to ADHD and SA.
11. Regarding conjFDR analyses: for ADHD, the authors conducted conjFDR with T2D and SA, while for SCZ they conducted conjFDR with T2D and CT. Why were the same sets of traits not analyzed across both disorders? This discrepancy should be justified.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The authors have addressed my comments thoroughly and thoughtfully. I have no further comments.

Reviewer #2

(Remarks to the Author)
Thank you for your response. While I appreciate your rationale for initially focusing on cortical thickness (CT) and surface area (SA), I find the current justification insufficient to fully address my original concern. Cortical morphology is undoubtedly fundamental, but psychiatric disorders—particularly schizophrenia—are characterized by widespread alterations not only in cortical structure but also in subcortical volumes, functional connectivity, and white matter integrity. These modalities have substantial genetic underpinnings and are directly relevant to the disease mechanisms you aim to interrogate.

Your response largely emphasizes the conceptual clarity of starting with CT and SA, as well as the methodological heterogeneity of other modalities. However, this reasoning does not preclude at least sensitivity or complementary analyses to demonstrate whether the genetic convergence you report is specific to cortical morphology or generalizable to other major brain phenotypes.

I strongly encourage you to consider adding at least exploratory analyses using publicly available GWAS summary statistics for subcortical volumes or white matter connectivity, which are well-characterized (e.g., ENIGMA, UK Biobank).

Reviewer #3

(Remarks to the Author)
All my concerns have been addressed.

Reviewer #4

(Remarks to the Author)
The authors have addressed all my concerns. I have no further questions.

Version 2:

Reviewer comments:

Reviewer #2

(Remarks to the Author)
I agree with the author's revisions and support publication.

Revision COMMSMED-25-1715-T

Reviewer #1 (Remarks to the Author):
Thanks for inviting me to review the paper COMMSMED-25-1715-T. The manuscript is interesting and the high number of participants and variety of data included in the study is valuable. Please, see below my comments.

We thank the reviewer for the positive assessment of our work. We here provide point-by-point answers to all raised comments. Deleted parts of the original text are highlighted in ~~red~~, and added parts in blue below. A complete set of edits is available in the attached manuscript with full track changes.

1. From your results related to Figure 1, my understanding is that you aim to report: (1) the genetic differences between SCZ and ADHD (i.e., low genetic correlation), and (2) the different genetic correlations of SCZ and ADHD with cardiometabolic diseases and cortical morphology (positive vs. negative). Therefore, you want to investigate their shared and unique genetic links with cardiometabolic diseases and cortical morphology, respectively. If this is correct, I suggest reorganizing the paragraphs to focus on the findings among SCZ/ADHD, cardiometabolic diseases (T2D and CAD), and cortical morphology (CT and SA), while moving results for other psychiatric disorders to the supplementary materials, as they may overwhelm the main findings.

We thank the reviewer for this constructive suggestion and agree with the interpretation. We have revised the Results section to highlight SCZ and ADHD as the primary focus of our analyses, emphasizing their divergent genetic correlations with cortical morphology and cardiometabolic disease. At the same time, we have retained the genetic correlation estimates for other psychiatric disorders in the main figure, as they provide an essential reference frame and context for interpreting the comparatively low correlation between SCZ and ADHD. To avoid overwhelming the reader, we now present these additional results more briefly in the text, while keeping SCZ and ADHD at the center of the narrative. Furthermore, although we let the SCZ–ADHD focus emerge from the Results, we added an anticipatory phrase in the Introduction to signal this analytical emphasis.

Line 111:
We employed a comprehensive suite of genetic tools ranging from genetic correlation and polygenic overlap to causal inference, mediation analysis, and pathway enrichment. Notably, the novel trivariate MiXeR tool allowed us to deconstruct the patterns of polygenic overlap among three complex phenotypes that could not be deduced from bivariate methods[46]. This integrative framework provides a systematic means to delineate shared and disorder-specific genetic links across psychiatric, cardiometabolic, and brain phenotypes, and to highlight instances where particular disorders, such as SCZ and ADHD, exhibit especially distinct patterns. ~~Our results reveal both common and distinct genetic patterns across psychiatric disorders, emphasizing the heterogeneous genetic architecture that shapes their links to cardiometabolic health and brain structure.~~

Line 130:
We systematically analyzed the genetic overlap among psychiatric disorders, cardiometabolic diseases, and cortical morphology. To this end, we utilized respective

GWAS summary statistics to quantify shared genetic architecture across these traits (Table 1). We begin by revisiting previous findings from our and other groups[16,40], where LD score regression (LDSC) analysis revealed notable genetic distinctions among psychiatric disorders, laying the foundation for the current study. Specifically, ADHD and SCZ displayed the lowest genetic correlation among the investigated psychiatric disorders (r_G = 0.20, $p_{FDR} < 1 \times 10^{-16}$; Fig. 1A). Furthermore, we observed striking differences in the genetic correlation of ADHD and SCZ ~~major mental disorders~~ with cardiometabolic diseases represented by CAD and T2D (Fig. 1B). ~~While ADHD and MDD displayed positive genetic correlations with CAD (ADHD: r_G = 0.30; MDD: r_G = 0.25), ASD, BIP, and SCZ showed correlations close to zero (ASD: r_G = -0.01; BIP: r_G = 0.03; SCZ: r_G = -0.03). A similar pattern of associations was observed for T2D (Fig. 1B).~~ ADHD showed a robust positive correlation with both CAD (r_G = 0.30, $p_{FDR} < 1 \times 10^{-16}$) and T2D ($r_G$ = 0.29, $p_{FDR} < 1 \times 10^{-16}$), whereas SCZ displayed correlations close to zero (CAD: r_G = -0.03, p_{FDR} = 0.36; T2D: r_G = -0.06, p_{FDR} = 0.003). For comparison, MDD also correlated positively with CAD (r_G = 0.25, $p_{FDR} < 1 \times 10^{-16}$), while ASD and BIP showed estimates near zero (Fig. 1B). In addition, SCZ and ADHD ~~psychiatric disorders~~ differed in their associations with cortical morphology represented by CT and SA. While all psychiatric disorders ~~of them~~ showed minimal genetic correlation with CT, ADHD and MDD exhibited negative correlations with SA (ADHD: r_G = -0.19, $p_{FDR} < 1 \times 10^{-16}$: MDD: r_G = -0.10, p_{FDR} = 0.01). The relatively low genetic similarity between SCZ and ADHD, coupled with their divergent associations with CAD and T2D, highlights differences in their genetic architecture and suggests that these disorders may be linked to cardiometabolic disease through distinct biological mechanisms (Fig. 1C). All phenotypes included in the analysis passed recommended quality control criteria, including sufficient SNP-heritability (typically h^2_{SNP}>0.06 for highly polygenic traits with effective sample sizes >100,000) and broadly comparable polygenicity to support advanced statistical modeling (van der Meer, et al. 2025) ~~adequate polygenicity and heritability to support advanced statistical modeling~~ (Fig. 1D). Collectively, ~~these findings indicate that~~ SCZ and ADHD emerge as ~~represent~~ genetically distinct diagnoses, which motivates a closer examination of their shared and unique genetic links with cardiometabolic disease and cortical morphology. ~~that are well suited for further investigation into their shared and unique genetic links with cardiometabolic disease and cortical morphology.~~

Line 157:
We leveraged trivariate MiXeR to directly estimate the genetic overlap between psychiatric disorders, cardiometabolic diseases and cortical morphology (Fig 2a). Given the observed differences in genetic architecture, we focused on SCZ and ADHD, while retaining the other psychiatric disorders as a reference frame for interpreting the relative magnitude of genetic overlap. Notably, the trivariate overlap was less pronounced for ADHD compared to SCZ.

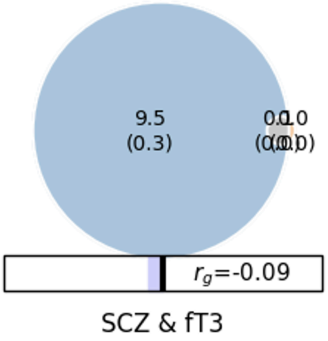
References:
van der Meer, D. et al. Mapping the Genetic Landscape of Psychiatric Disorders With the MiXeR Toolset. Biological Psychiatry 98, 455–465 (2025).

Additionally, you mentioned that 'All phenotypes included in the analysis passed recommended quality control criteria, including adequate polygenicity and heritability to support advanced statistical modeling (Fig. 1D).' in line 137-138. Could you clarify what these recommended quality control criteria are? Specifically, are there any

thresholds for polygenicity or heritability when conducting genetic correlation analyses? If so, can you indicate the thresholds in your sentence?

Our statement refers to the recommended criteria for ensuring robust MiXeR modeling (van der Meer et al., 2025). As noted previously in Hindley, et al. 2022, the additional parameters estimated by MiXeR require well-powered GWAS to ensure reliable results. The statistical power of a GWAS increases with sample size and SNP-heritability, but decreases with trait polygenicity. Simulation studies indicate that for highly polygenic traits, an effective sample size of ~100,000 combined with an SNP-heritability h_{SNP}^2>0.06 generally provides robust results. Lower sample sizes can be sufficient for traits with relatively high discoverability, as shown in applications to neuroimaging traits (van der Meer et al., 2020).

At the same time, there is no universally applicable threshold, as power depends on the research question and the traits being modeled. A useful rule of thumb is that the examined phenotypes should have comparable polygenicity, to avoid scenarios where the standard error of the estimated genetic overlap exceeds the polygenicity of one trait. For instance, in our exemplary analysis of thyroid function (Sterenborg et al., 2024) and schizophrenia, the polygenicity of free and total triiodothyronine (fT3) is several-fold lower than that of schizophrenia, leading to unstable estimates.



The figure shows the genetic overlap between free and total triiodothyronine (fT3), the biologically active thyroid hormone that regulates metabolism, growth, and development, as estimated using the bivariate MiXeR model. Compared to schizophrenia, fT3 shows markedly lower polygenicity, which limits statistical power and prevents reliable quantification of their genetic overlap.

We have clarified this point in the revised text, noting the published simulation guidance and emphasizing that relative polygenicity between phenotypes is as important as absolute thresholds.

Line 149:

All phenotypes included in the analysis passed recommended quality control criteria, including sufficient SNP-heritability (typically h_{SNP}^2>0.06 for highly polygenic traits with effective sample sizes >100,000) and broadly comparable polygenicity to support advanced statistical modeling (van der Meer, et al. 2025) ~~adequate polygenicity and heritability to support advanced statistical modeling~~ (Fig. 1D).

References:

van der Meer, D. et al. Mapping the Genetic Landscape of Psychiatric Disorders With the MiXeR Toolset. Biological Psychiatry 98, 455–465 (2025).
van der Meer, D. et al. Quantifying the Polygenic Architecture of the Human Cerebral Cortex: Extensive Genetic Overlap between Cortical Thickness and Surface Area. Cereb Cortex 30, 5597–5603 (2020).
Hindley, G. et al. Charting the Landscape of Genetic Overlap Between Mental Disorders and Related Traits Beyond Genetic Correlation. Am J Psychiatry 179, 833–843 (2022).
Sterenborg, R. B. T. M. et al. Multi-trait analysis characterizes the genetics of thyroid function and identifies causal associations with clinical implications. Nat Commun 15, 888 (2024).

2. Similar to my first comment, your main findings focus on SCZ and ADHD in relation to other cardiometabolic diseases (T2D and CAD) and cortical morphology measures (CT and SA).

We fully share the reviewer's concern regarding the focus. In line with your suggestion, we have strengthened the focus on SCZ and ADHD throughout the Results, beginning with a clearer framing in the opening paragraphs. The narrative now consistently emphasizes their divergent genetic relationships with cardiometabolic traits (T2D, CAD) and cortical morphology (CT, SA). The genetic analyses for the other psychiatric disorders remain in the figures and tables to provide a necessary reference frame and context for interpreting the comparatively low SCZ–ADHD similarity.

3. For your Mendelian randomization analyses, did you check the MR assumptions? Also, did you use individual-level genotype data, or only GWAS summary statistics?

The reviewer raises an important point. To evaluate the MR assumptions, we systematically assessed instrument strength, horizontal pleiotropy, and heterogeneity. Instrument strength was examined using F-statistics, which were consistently strong across all exposure–outcome pairs (mean F > 10). We also report directional pleiotropy using MR-Egger intercepts and heterogeneity using Cochran's Q.

To increase the robustness and transparency of our MR analyses, we now also report MR-PRESSO diagnostics applied to the IVW estimates, including the Global RSS, Global p-value, and the outlier-corrected PRESSO estimates (b, se, pval) for each exposure–outcome pair. The MR-PRESSO results were consistent with the IVW estimates, supporting the robustness of our findings. Weighted median and weighted mode estimators generally supported the IVW results, providing additional protection against violations of instrumental variable assumptions. As expected, MR-Egger regression was less precise and occasionally diverged from IVW.

We have added details to the Methods and supplementary tables (Sup. Tables 1 and 2) summarizing F-statistics, Egger intercepts, Q statistics, and PRESSO results for each exposure–outcome pair. Finally, we note that our analyses relied exclusively on GWAS summary statistics and did not involve individual-level genotype data.

Line 256:

Our trivariate analyses demonstrated distinct genetic signatures of ADHD and SCZ. To follow up these results of genetic overlaps, we probed causal relationships between cortical morphology, psychiatric disorders and cardiometabolic diseases ~~(Sup. Tab. 1)~~. All MR analyses were accompanied by systematic assumption checks, including F-statistics, MR-Egger intercepts, Cochran's Q, and MR-PRESSO diagnostics (Sup. Tabs. 1–2). Focusing on the trait combinations with the highest genetic overlap, we further investigated

the bidirectional causal relationships between ADHD, T2D, and SA, as well as SCZ, T2D, and CT, using inverse-variance weighted (IVW) Mendelian randomization (MR) (Fig. 3A, Sup. Tab. 2). IVW MR did not provide evidence for a causal effect of ADHD on SA or T2D. Similarly, we found no significant evidence for a causal effect of SCZ on T2D or CT. In contrast, in the reverse direction, higher genetic liability for T2D was associated with increased susceptibility to ADHD ~~found evidence that genetic liability for T2D has a causal effect on ADHD risk, with higher T2D liability associated with increased genetic susceptibility to ADHD~~ (OR = 1.14, β = 0.13, FDR-correct p_{FDR} = 9.5×10^{-11}). ~~In addition, lower SA was associated with increased genetic risk for ADHD~~ Notably, the MR-Egger intercept was significant for this analysis, indicating potential directional pleiotropy; however, the effect remained robust across sensitivity analyses. It remained significant after MR-PRESSO outlier correction and showed consistent direction across MR-Egger, weighted median, and simple mode estimators, with the weighted median also reaching statistical significance. We also found that lower SA exerted a causal effect on increased genetic risk for ADHD (OR = 0.77, β = –0.26, p_{FDR} = 0.0003). ~~In contrast to the findings for ADHD, IVW MR did not reveal any significant causal effect of SCZ on CT or T2D.~~ Finally, we identified a significant negative effect of T2D on CT (β = –0.03, p_{FDR} = 0.03), suggesting that increased genetic liability for T2D may contribute to cortical thinning. ~~These findings suggest that ADHD is embedded in a bidirectional causal network involving SA and T2D risk, whereas SCZ may be indirectly shaped by T2D liability through its effects on CT.~~ In these significant analyses, MR-Egger intercepts were not significant. Overall, the results suggest that ADHD is influenced by both cortical surface area and T2D liability, In contrast, SCZ may be indirectly shaped by T2D liability through its effects on cortical thickness.

Line 712:

All other settings were kept at default. Causal estimates were obtained using the Inverse Variance Weighted (IVW) method. All estimates with associated standard errors and p-values are available in Sup. Tab. 2~~1~~. We also include estimates using weighted median[84], MR-Egger[85], Simple Mode, and Weighted Mode[86] methods ~~(Sup. Tab. 1)~~. In addition, we applied MR-PRESSO to IVW estimates, reporting the Global RSS and Global p-value, as well as outlier-corrected estimates to detect and adjust for potential outlier instruments.

To evaluate the validity of MR assumptions, we quantified instrument strength using per-SNP F-statistics (reporting mean, median, minimum, and the proportion with F>10), harmonized alleles and removed ambiguous palindromic SNPs, and assessed directional pleiotropy using the MR-Egger intercept test. For IVW and MR-Egger, we report Cochran's Q statistics to evaluate heterogeneity. These diagnostics are summarized in Sup. Tab. 1.

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 ~~1~~2: Mendelian Randomization results

The table summarizes Mendelian Randomization (MR) estimates for each exposure–outcome pair tested using different methods implemented in the TwoSampleMR framework. Columns report the exposure and outcome traits, the MR method used, the number of SNPs included as instruments (nsnp), the estimated causal effect (b), its standard error (se), and the corresponding p-value (pval). Results reflect harmonized and clumped datasets based on genome-wide summary statistics. For IVW estimates, additional MR-PRESSO diagnostics are provided, including the Global residual sum of squares (RSS) and Global p-value, as well as the outlier-corrected PRESSO estimates (b, se, pval). All analyses were conducted on harmonized and clumped datasets based on genome-wide summary statistics.

Outcome	Exposure	Method	nsnp	b	se	pval	PRESSO Global RSS	PRESSO Global pval	b PRESSO	se PRESSO	pval PRESSO
T2D	ADHD	MR Egger	25	-0,130	0,158	0,419					
T2D	ADHD	Weighted median	25	0,076	0,024	0,002					
T2D	ADHD	Inverse variance weighted	25	0,072	0,035	0,041	209,1	<1E-04	0,093	0,024	0,001
T2D	ADHD	Simple mode	25	0,027	0,064	0,675					
T2D	ADHD	Weighted mode	25	0,048	0,039	0,228					
T2D	SCZ	MR Egger	148	-0,005	0,065	0,942					
T2D	SCZ	Weighted median	148	-0,020	0,010	0,047					
T2D	SCZ	Inverse variance weighted	148	-0,012	0,014	0,400	0,8	<1E-04	-0,008	0,010	0,391
T2D	SCZ	Simple mode	148	-0,036	0,028	0,202					
T2D	SCZ	Weighted mode	148	-0,033	0,022	0,137					
T2D	CT	MR Egger	21	-0,123	0,174	0,488					
T2D	CT	Weighted median	21	-0,004	0,036	0,907					
T2D	CT	Inverse variance weighted	21	-0,091	0,054	0,090	180,9	<1E-04	-0,093	0,041	0,042
T2D	CT	Simple mode	21	0,032	0,066	0,632					
T2D	CT	Weighted mode	21	0,029	0,045	0,521					
ADHD	T2D	MR Egger	423	0,010	0,041	0,817					
ADHD	T2D	Weighted median	423	0,068	0,022	0,002					
ADHD	T2D	Inverse variance weighted	423	0,128	0,019	1,4E-11	885,4	<1E-04	0,130	0,018	5,14E-12
ADHD	T2D	Simple mode	423	0,089	0,067	0,184					

4. Colocalization analysis as implemented in the COLOC R package (https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1004383) can also be used to examine shared genetic variants between two traits. Have you considered applying it to identify shared loci between psychiatric and cardiometabolic phenotypes?

We thank the reviewer for this suggestion. Our primary goal was to capture genome-wide polygenic sharing, for which we applied the conjunctional false discovery rate (conjFDR) framework that has been widely used to identify shared loci between complex traits. Colocalization approaches such as COLOC address a complementary question —

whether two traits share the same causal variant within a given locus. As our study focuses on genome-wide overlap patterns rather than locus-specific fine-mapping, we did not apply COLOC in the present work. We agree that colocalization analyses represent a valuable next step to characterize the functional architecture of specific loci, and we have highlighted this in the Discussion.

Line 596:
Several considerations and potential limitations should be noted. We focused on genome-wide patterns of genetic convergence and did not perform locus-specific colocalization analyses, which could provide finer resolution of shared loci and help distinguish common from distinct causal mechanisms.

Reviewer #2 (Remarks to the Author):
General comments
This manuscript addresses an important and timely topic, exploring the genetic basis underlying the comorbidity between psychiatric and cardiometabolic disorders through brain morphology. The use of complementary genetic approaches is valuable, and the findings provide novel insights into shared and disorder-specific pathways. However, there are substantial issues in study design, phenotype selection, and methodological transparency that need to be clarified or expanded before the conclusions can be considered robust. I therefore recommend major revision.

We thank the reviewer for their thoughtful evaluation and for recognizing the importance of our study and the novelty of the complementary genetic approaches applied.

Specific comments
1. In the introduction, you mention that schizophrenia is comorbid with cardiovascular and respiratory diseases, while ADHD is comorbid with nervous system disorders (particularly sleep disorders), as well as cardiovascular, respiratory, musculoskeletal, and metabolic diseases. However, in the subsequent analyses you only focused on psychiatric–cardiometabolic comorbidity. Could you clarify the rationale for restricting the analyses to cardiometabolic diseases, rather than including other comorbid disease systems (respiratory, musculoskeletal)?

This is an excellent point. As the reviewer points out, psychiatric disorders are comorbid with a wide range of physical conditions, including respiratory, musculoskeletal, and immune diseases, and large GWAS are now available for some of these systems (e.g., lung function, Shrine et al., 2023). In the current study, however, we deliberately restricted our analyses to cardiometabolic diseases, specifically CAD and T2D, for three reasons: (i) cardiometabolic comorbidity is among the most consistent and clinically consequential across psychiatric disorders, contributing substantially to excess morbidity and mortality; (ii) both vascular and metabolic dysfunction have well-documented links to altered brain structure, making CAD and T2D particularly relevant for investigating body–brain mechanisms; and (iii) CAD and T2D have exceptionally large, well-powered GWAS, ensuring robust application of MiXeR, MR, and GenomicSEM. Incorporating additional comorbid disease systems would broaden the scope beyond the central aims of the present study. However, we agree that extending such analyses to, for example, respiratory or

musculoskeletal traits represents an important future direction and we now highlight this in the Discussion.

Line 599:
We restricted the scope to cardiometabolic diseases, given their high prevalence, major contributions to morbidity and premature mortality, strong brain links, and well-powered GWAS resources. Extending the framework to other systems such as respiratory traits remains an important future direction.

References:
Shrine, N. et al. Multi-ancestry genome-wide association analyses improve resolution of genes and pathways influencing lung function and chronic obstructive pulmonary disease risk. Nat Genet 55, 410–422 (2023).

2. Regarding the choice of imaging phenotypes, only cortical thickness and surface area were included. Other important brain phenotypes, such as subcortical volumes, functional connectivity, and white matter connectivity, which are highly relevant to psychiatric disorders (especially schizophrenia), were not considered. Please justify this choice and consider providing additional analyses.

We thank the reviewer for highlighting this important point. In the present study and consistent with large-scale imaging genetics work (Panizzon et al., 2009; Grasby et al., 2020), we focused on cortical thickness and surface area as fundamental, genetically dissociable dimensions of cortical morphology, providing a coherent starting point for interrogating body–brain–psychiatric convergence. Cortical thickness and surface area are well established in psychiatric genetics, with large-scale ENIGMA studies showing widespread and reproducible alterations in schizophrenia (van Erp et al., 2018) and ADHD (Hoogman et al., 2019). Their clear biological interpretation, relating to laminar organization and areal expansion respectively, further facilitates mechanistic insights when linking brain structure with psychiatric and cardiometabolic phenotypes.

Large-scale GWAS are indeed available for other brain phenotypes such as subcortical volumes, functional connectivity, and white matter connectivity. However, incorporating these modalities would have substantially broadened the scope of the current work and diluted the central message, which is to establish a clear proof-of-concept framework for mapping shared genetic architectures across cortical structure, psychiatric disorders, and cardiometabolic disease. In addition, GWAS for functional and diffusion measures currently involve greater methodological heterogeneity in parcellations and metrics, which would complicate integration within our multivariate framework. We fully agree that extending this framework to additional brain modalities represents an important future direction, and we have now explicitly noted this in the Introduction and Discussion.

Line 103:
For this purpose, we investigated genome-wide data from the five most prevalent psychiatric disorders—ADHD, autism spectrum disorder (ASD), major depressive disorder (MDD), bipolar disorder (BIP), and SCZ—together with average CT and total SA ~~(following 40)~~, as well as coronary artery disease (CAD) and type 2 diabetes (T2D). We focused on average CT and total SA as representative cortical morphology traits due to their high heritability, genetic dissociability, and consistent associations with psychiatric disorders (Grasby et al., 2020; Panizzon et al., 2009). We focused on CAD and T2D as representative

cardiometabolic diseases due to their high prevalence, consistent links to adverse brain outcomes, and complementary coverage of vascular and metabolic dysfunction[44,45].

Line 602:
Likewise, we limited our analyses to global CT and SA as foundational measures of cortical morphology, and future work should incorporate regional, subcortical, functional, and white matter phenotypes.

References:
Grasby, K. L. et al. The genetic architecture of the human cerebral cortex. Science 367, eaay6690 (2020).
Panizzon, M. S. et al. Distinct genetic influences on cortical surface area and cortical thickness. Cereb Cortex 19, 2728–2735 (2009).
van Erp, T. G. M. et al. Cortical Brain Abnormalities in 4474 Individuals With Schizophrenia and 5098 Control Subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium. Biol Psychiatry 84, 644–654 (2018).
Hoogman, M. et al. Brain Imaging of the Cortex in ADHD: A Coordinated Analysis of Large-Scale Clinical and Population-Based Samples. Am J Psychiatry 176, 531–542 (2019).

3. When performing genetic correlation analyses between diseases, did you apply multiple testing correction? Please report the adjusted P values.

Yes, multiple testing correction was applied using the false discovery rate (FDR). We now clarify this explicitly in the Methods and in the corresponding figure caption. All correlation values are now accompanied by their respective FDR-corrected p-value in the Results.

Line 135:
Specifically, ADHD and SCZ displayed the lowest genetic correlation among the investigated psychiatric disorders (rG = 0.20, $p_{FDR} < 1 \times 10^{-16}$; Fig. 1A). Furthermore, we observed striking differences in the genetic correlation of major mental disorders with cardiometabolic diseases represented by CAD and T2D (Fig. 1B).

Line 138:
ADHD showed a robust positive correlation with both CAD ($r_G = 0.30$, $p_{FDR} < 1 \times 10^{-16}$) and T2D ($r_G = 0.29$, $p_{FDR} < 1 \times 10^{-16}$), whereas SCZ displayed correlations close to zero (CAD: $r_G = -0.03$, $p_{FDR} = 0.36$; T2D: $r_G = -0.06$, $p_{FDR} = 0.003$). For comparison, MDD also correlated positively with CAD ($r_G = 0.25$, $p_{FDR} < 1 \times 10^{-16}$), while ASD and BIP showed estimates near zero (Fig. 1B). In addition, SCZ and ADHD ~~psychiatric disorders~~ differed in their associations with cortical morphology represented by CT and SA. While all psychiatric disorders ~~of them~~ showed minimal genetic correlation with CT, ADHD and MDD exhibited negative correlations with SA (ADHD: $r_G = -0.19$, $p_{FDR} < 1 \times 10^{-16}$: MDD: $r_G = -0.10$, $p_{FDR} = 0.01$).

Line 673:
P-values were corrected for multiple testing using the Benjamini–Hochberg procedure for controlling the false discovery rate (Benjamini & Hochberg, 1995). Correction was applied separately within each analysis (psychiatric correlations; correlations with cardiometabolic and cortical traits).

Line 816:

Figure 1: The distinct and shared genetic architecture of ADHD and SCZ
A. ADHD and SCZ show differences in genetic architecture. We calculated genetic correlations using LDSC between all pairs of the five most common psychiatric disorders. All p-values were statistically significant after FDR correction. The resulting heatmap is then re-represented as a network diagram where each node is a psychiatric disorder and each edge corresponds to genetic correlation.

4. Please specify in the Methods section the exact multiple testing correction procedure you used.

As detailed in the previous point, we explicitly state in the Methods that multiple testing was corrected using the Benjamini–Hochberg false discovery rate procedure, applied separately within each analysis (psychiatric correlations; correlations with cardiometabolic and cortical traits).

Line 673:
P-values were corrected for multiple testing using the Benjamini–Hochberg procedure for controlling the false discovery rate (Benjamini & Hochberg, 1995). Correction was applied separately within each analysis (psychiatric correlations; correlations with cardiometabolic and cortical traits).

References:
Benjamini, Y. & Hochberg, Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society. Series B (Methodological) 57, 289–300 (1995).

5. For mediation analyses using GWAS summary data, you employed a genomic SEM (gSEM) approach rather than the more classical multivariable Mendelian randomization (MVMR) framework. Could you explain the rationale for this choice and discuss the robustness of the two methods?

The reviewer raises an important point. We agree that multivariable MR (MVMR) is the classical framework for mediation and pleiotropy analyses. We performed standard QC checks in a bivariate MR setting to evaluate instrument strength and validity for the traits included. Instrument strength was adequate (all conditional $F > 10$), but several MR-Egger intercepts and Cochran's Q statistics were significant, indicating residual pleiotropy and heterogeneity. While weak-instrument bias appears unlikely, these findings suggest that causal estimates from an MVMR framework would be vulnerable to violations of core assumptions (Sanderson et al., 2021), particularly given the high polygenicity and genetic correlations among SCZ, cortical morphology, and T2D.

In addition, there is some sample overlap across the GWAS used, primarily through shared UK Biobank participants. Although this overlap is modest, even small degrees of overlap can bias MVMR estimates toward observational associations for genetically correlated traits. Genomic SEM, by contrast, leverages genome-wide covariance and explicitly accounts for sample overlap, making it more robust for mediation analyses in this context (Grotzinger et al., 2019).

For these reasons, we considered gSEM the most appropriate primary framework. MVMR remains a valuable complementary approach, but applying it robustly here would require stronger, more independent instruments than are currently available for these traits.

Line 746:

To determine whether brain morphology mediates the relationship between psychiatric and cardiometabolic traits, we conducted mediation analysis using the GenomicSEM R package (v0.0.5). We specified trivariate models with the psychiatric trait as the exposure, the cardiometabolic disease as the outcome, and cortical morphology as the mediator. SNP effect estimates as well as ~~and~~ standard errors were extracted from GWAS summary statistics for each phenotype, and LD score regression was used to derive the genetic covariance matrices. We calculated direct, indirect, and total effects, and evaluated the significance of each path. GenomicSEM models genome-wide covariance structures across traits while accounting for sample overlap, providing a flexible framework to estimate direct, indirect (mediated), and total genetic effects. This approach is particularly suitable for highly polygenic and genetically correlated traits such as SCZ, cortical morphology, and T2D. In contrast, widely used approaches such as multivariable Mendelian randomization (MVMR) require strong and independent instruments for each exposure. For highly polygenic and genetically correlated traits, these requirements are rarely met, which increases susceptibility to weak instrument bias and unstable estimates (Sanderson et al., 2021).

Reference:

Sanderson, E. Multivariable Mendelian Randomization and Mediation. Cold Spring Harb Perspect Med 11, a038984 (2021).

Grotzinger, A. D. et al. Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits. Nat Hum Behav 3, 513–525 (2019).

6. Are the GWAS summary statistics used in this study derived from the largest available European ancestry samples to date? If so, please state this explicitly in the Methods.

Yes, all GWAS summary statistics included in our analyses were derived from large-scale studies based primarily on European ancestry samples, and we selected the most up-to-date and well-powered resources available at the time of analysis. We now explicitly state this in the Methods section.

Line 653:

All GWAS summary statistics are based on Human Genome Build 37 (GRCh37/hg19). For each trait, we selected the largest and most up-to-date GWAS based primarily on European ancestry samples available at the time of analysis.

Reviewer #3 (Remarks to the Author):

This study explored the shared genetic architecture across psychiatric disorders (ADHD, ASD, MDD, BIP, SCZ), cardiometabolic diseases (CAD, T2D), and brain morphology (cortical thickness [CT], cortical surface area [SA]) using complementary genetic approaches including LDSC, trivariate MiXeR, Mendelian Randomization (MR), mediation analysis, and pathway enrichment. This study demonstrated the genetic basis of the comorbidity between psychiatric and cardiometabolic disorders, as well

as the role of brain structure in these relationships. Nevertheless, there are several aspects of the study that, in my opinion, could be enhanced.

We thank the reviewer for the positive evaluation of our work.

1. It is important to evaluate the presence of sample overlap among the included phenotypes, as such overlap could bias the identification of pleiotropic loci and causal associations.

We fully share the reviewer's concern regarding the sample overlap. The CARDIoGRAMplusC4D and DIAGRAM consortia both include UK Biobank participants, which was also the primary source for the CT and SA GWAS. In contrast, the PGC datasets for SCZ and ADHD do not include UK Biobank. Consequently, in our conjFDR analyses, where we combined SCZ or ADHD GWAS with CT, SA, T2D, or CAD, there was **no sample overlap**. For the causal analyses, we acknowledge that partial sample overlap is possible, as both the SA and T2D GWAS include UK Biobank participants. In DIAGRAM and CARDIoGRAMplusC4D, UK Biobank represents roughly one quarter of the total sample, limiting the extent of overlap relative to the overall GWAS sizes. Such overlap could still in principle bias Mendelian randomization estimates toward observational associations. However, in line with prior work (Burgess et al., 2016), any bias from sample overlap in MR is expected to attenuate rather than inflate causal estimates when instruments are reasonably strong. We have noted it explicitly in the Limitations. For the mediation analyses, overlap does not bias estimates, as Genomic SEM explicitly accounts for sample overlap through the cross-trait LDSC intercept when estimating the genetic covariance matrix (Grotzinger et al., 2019).

Line 607:
Finally, partial sample overlap in the MR analyses due to UK Biobank contributions may bias IVW estimates toward observational associations, though any such bias is expected to be modest and attenuating. No sample overlap was present between the GWAS pairs used in the conjFDR analyses. For the mediation analyses, gSEM explicitly accounts for any overlap through the cross-trait LDSC intercept, ensuring unbiased genetic covariance estimates.

Reference:
Burgess, S., Davies, N. M. & Thompson, S. G. Bias due to participant overlap in two-sample Mendelian randomization. Genet Epidemiol 40, 597–608 (2016).

2. The authors should ascertain whether the identified pleiotropic loci are associated with trait specificity, rather than being influenced by confounding factors that could affect the observed pleiotropic associations.

We thank the reviewer for raising this important point. We note that our analyses were conducted using GWAS summary statistics that underwent stringent quality control, including adjustments for population stratification and relatedness within each contributing cohort. Furthermore, our conjFDR approach leverages cross-trait enrichment of SNP-level associations, which reduces the likelihood that findings are driven by generic confounding factors and instead prioritizes loci with specificity to the trait combination under investigation (Smeland et al., 2020). Nevertheless, we acknowledge that residual confounding cannot be

fully excluded, and we have added a note to the Limitations to clarify that some identified loci may reflect shared influences (e.g., lifestyle or environmental correlates) rather than strictly trait-specific genetic effects.

Line 605:
Although the conjFDR approach enriches for jointly associated loci, residual confounding cannot be entirely excluded and some associations may reflect broad pleiotropic influences.

3. The introduction briefly notes that brain structure mediates genetic effects on psychiatric disorders, but it lacks discussion on regional specificity in brain morphology–disorder associations. The authors should justify the choice of CT and SA as the primary phenotypes, rather than more detailed regional brain phenotypes.

We appreciate the reviewer's thoughtful comment. In this study, our primary objective was to map genetic convergence across brain structure, psychiatric disorders, and cardiometabolic disease. We focused on global cortical thickness and surface area, which capture complementary and genetically dissociable dimensions of cortical organization (Panizzon et al., 2009; Grasby et al., 2020). Global measures provide a parsimonious and statistically powerful starting point for cross-domain analyses, reducing multiple testing burden and allowing us to focus on overarching genetic patterns across modalities. This is particularly important in a multivariate framework that integrates brain, psychiatric, and cardiometabolic traits at the genome-wide level.

We fully agree that there is important regional specificity in brain morphology–disorder associations. For example, ADHD is characterized by regionally patterned reductions in cortical surface area, particularly in prefrontal and temporal regions (Hoogman et al., 2019). Our current approach does not aim to resolve these spatially specific patterns, but rather to provide a broad genetic map that can guide more fine-grained follow-up analyses. Incorporating regional measures would require substantially larger numbers of tests and more complex multiple comparison corrections, which would reduce statistical power and shift the focus of the study. We have clarified this rationale in the revised Introduction and Discussion, and we consider regional analyses a valuable direction for future work.

Line 103:
For this purpose, we investigated genome-wide data from the five most prevalent psychiatric disorders—ADHD, autism spectrum disorder (ASD), major depressive disorder (MDD), bipolar disorder (BIP), and SCZ—together with average CT and total SA ~~(following 40)~~, as well as coronary artery disease (CAD) and type 2 diabetes (T2D). We focused on average CT and total SA as representative cortical morphology traits due to their high heritability, genetic dissociability, and consistent associations with psychiatric disorders (Grasby et al., 2020). We focused on CAD and T2D as representative cardiometabolic diseases due to their high prevalence, consistent links to adverse brain outcomes, and complementary coverage of vascular and metabolic dysfunction[44,45].

Line 602:
Likewise, we limited our analyses to global CT and SA as foundational measures of cortical morphology, and future work should incorporate regional, subcortical, functional, and white matter phenotypes.

References:

Grasby, K. L. et al. The genetic architecture of the human cerebral cortex. Science 367, eaay6690 (2020).
Panizzon, M. S. et al. Distinct genetic influences on cortical surface area and cortical thickness. Cereb Cortex 19, 2728–2735 (2009).
van Erp, T. G. M. et al. Cortical Brain Abnormalities in 4474 Individuals With Schizophrenia and 5098 Control Subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium. Biol Psychiatry 84, 644–654 (2018).
Hoogman, M. et al. Brain Imaging of the Cortex in ADHD: A Coordinated Analysis of Large-Scale Clinical and Population-Based Samples. Am J Psychiatry 176, 531–542 (2019).

4. While the pathway enrichment analyses, such as TP53-related pathways in ADHD and neurodevelopmental/immune pathways in SCZ, effectively highlight biological mechanisms, incorporating "tissue-specific enrichment analyses" would further refine the functional context of the identified genes. For instance, verifying if genes shared between psychiatric disorders and brain morphology are highly expressed in neurodevelopmental brain regions could clarify the tissue-specific drivers of comorbidity.

The reviewer makes an excellent suggestion. Tissue-specific enrichment analyses would indeed provide an additional layer of insight into the functional context of shared genes, for example by clarifying whether they are preferentially expressed in neurodevelopmental brain regions. In line with the comment, we performed tissue-specific expression enrichment analyses using GTEx v8 data (via FUMA GENE2FUNC) on the four gene sets derived from our conjFDR results. This revealed distinct enrichment patterns: ADHD–SA genes were enriched in pancreas, ADHD–T2D genes showed combined enrichment in brain regions and metabolic tissues, SCZ–CT genes displayed more restricted enrichment in hippocampus and frontal cortex, and SCZ–T2D genes demonstrated broad multi-tissue enrichment across both neural and peripheral tissues. These findings provide complementary functional context for the identified loci, supporting the involvement of both brain- and body-specific pathways in psychiatric–cardiometabolic comorbidity. We have added the analyses to the Results, described them in the Methods, and expanded the Discussion accordingly.

Line 339:

Overlapping biological pathways of multimorbidity

In the next step, the four gene sets derived from the combination of conjFDR results and gene mapping were sequentially tested for tissue-specific expression enrichment using GTEx v8 reference data. These analyses revealed distinct patterns across the four gene sets (Fig. 5a). Genes shared between ADHD & SA were enriched in pancreas, whereas ADHD & T2D genes showed broader enrichment spanning both brain regions (amygdala, anterior cingulate, caudate, frontal cortex, hippocampus, hypothalamus, putamen, substantia nigra) and peripheral tissues including heart, kidney cortex, liver, pancreas, and whole blood. SCZ & CT loci exhibited more restricted enrichment, limited to hippocampus and frontal cortex. In contrast, SCZ & T2D genes demonstrated widespread enrichment across multiple brain regions and peripheral tissues, highlighting broad pleiotropic involvement in both neural and metabolic systems.

Furthermore, we also tested the gene sets for enrichment of biological pathways from the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Reactome using DAVID (Database for Annotation, Visualization, and Integrated Discovery).

Line 570:

These results point to systemic metabolic processes as a shared mechanism, which aligns with prior evidence linking ADHD to insulin resistance, oxidative stress, and energy metabolism abnormalities[71,72]. Consistently, tissue-specific enrichment highlighted pancreatic signals alongside brain regions, suggesting that metabolic tissues may contribute to the ADHD–cardiometabolic genetic overlap. Overall, the enrichment profile suggests that metabolic vulnerability may represent key biological links between ADHD and T2D. In contrast, the SCZ & T2D overlap was enriched for pathways involved in protein homeostasis, chromatin organization, and immune regulation.

Line 554:

Moreover, genes jointly associated with SCZ and T2D have been found to show high expression in brain tissue and immune cells, and are enriched for pathways related to neurodevelopment, synaptic signaling, immune function, intracellular transport, and metabolic regulation[29,70]. Our tissue-specific enrichment analyses further supported this pattern, revealing broad enrichment of SCZ & T2D loci across brain regions as well as metabolic and immune-related tissues. These findings suggest that the SCZ & T2D genetic overlap involves interconnected neurodevelopmental and systemic biological pathways. ~~This brain- and immune-enriched functional profile aligns with our findings, suggesting that the SCZ & T2D genetic overlap may involve shared neurodevelopmental and systemic biological pathways.~~

Line 785:

Tissue-specific expression enrichment

Genes mapped to shared loci were tested for tissue-specific expression using the GENE2FUNC module of FUMA with GTEx v8 reference data (54 tissues) (Watanabe et al., 2017). Analyses were performed separately for upregulated, downregulated, and bidirectionally expressed gene sets, with all GTEx genes used as the background (Sup. Fig. 6). Enrichment p-values were corrected for multiple testing across tissues within each panel using the FDR procedure.

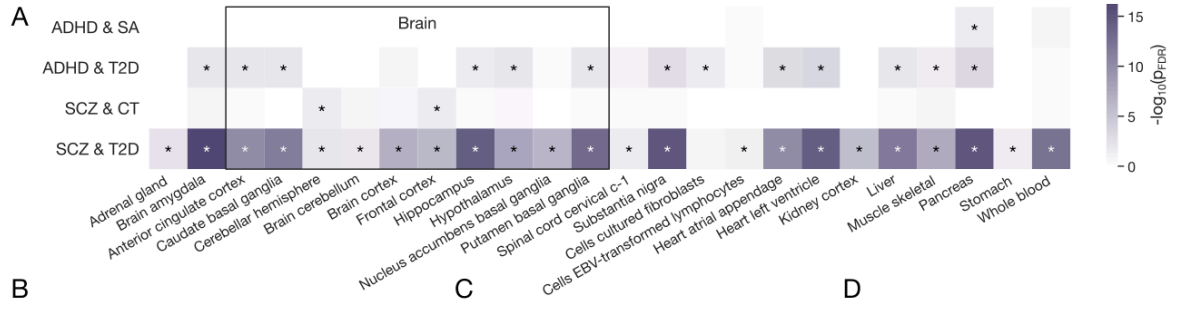
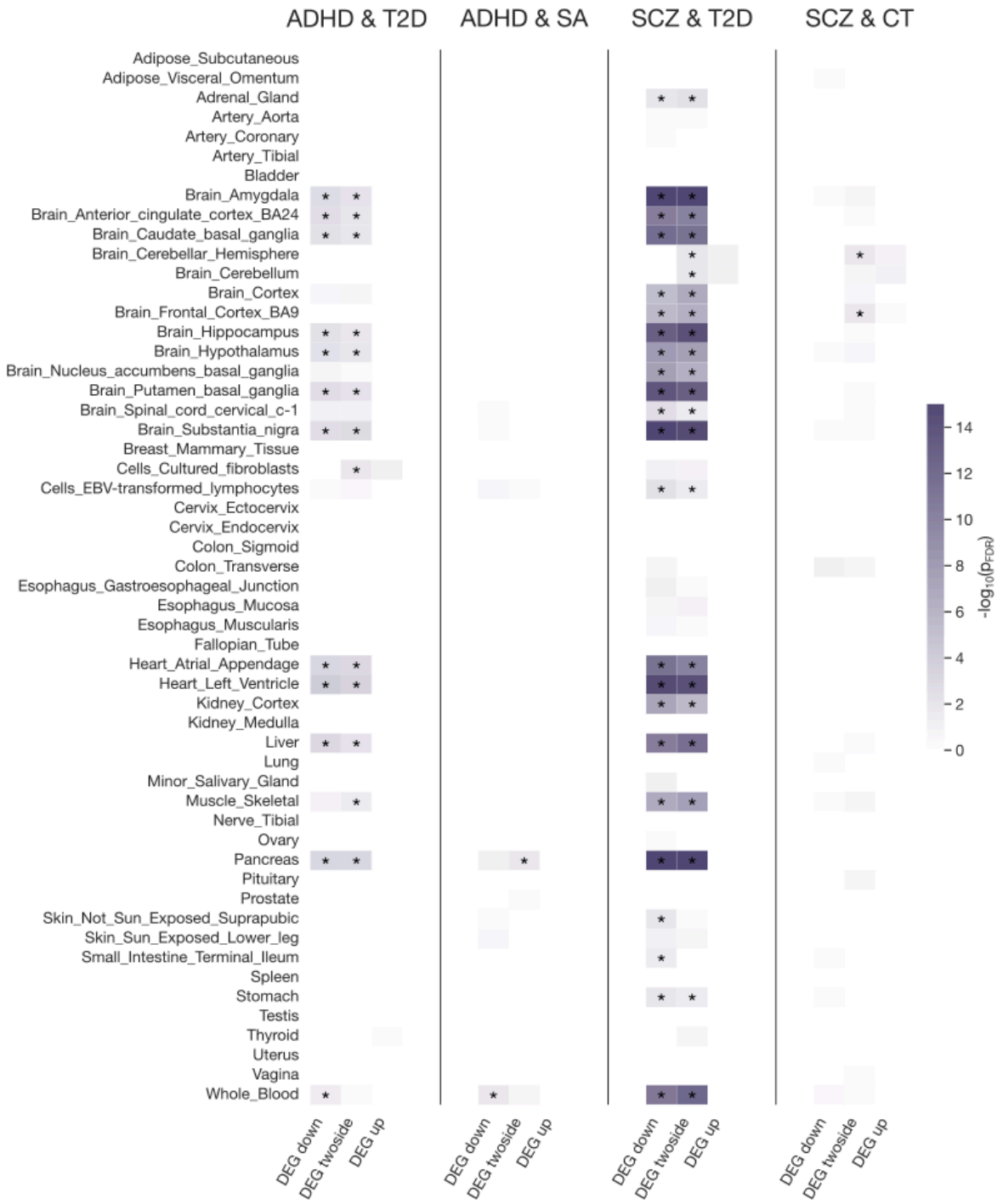


Figure 5: Biological pathways underlying multimorbidity

A. Tissue-specific expression enrichment of genes mapped using FUMA from the four conjFDR analyses. Heatmap shows significance from GTEx v8 differential expression analyses of genes mapped to loci shared between psychiatric, cardiometabolic, and cortical

traits. Asterisks mark significant enrichments ($p_{FDR} < 0.05$). Only tissues with at least one significant enrichment are displayed. Brain tissues are outlined in black. **B., C., D.** Mapped genes ~~mapped using FUMA from the four conjFDR analyses~~ were assessed for pathway enrichment using the DAVID tool, focusing on KEGG and Reactome databases.



Supplementary Figure 6. Tissue-specific expression enrichment of mapped genes across all tested tissues.

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 FDR < 0.05.

References:

Watanabe, K., Taskesen, E., van Bochoven, A. & Posthuma, D. Functional mapping and annotation of genetic associations with FUMA. Nat Commun 8, 1826 (2017).

5. While the trivariate MiXeR analysis effectively quantifies genetic overlap across three traits, the manuscript lacks a clear explanation of why trivariate results differ from bivariate analyses.

The reviewer raises an important point. Trivariate MiXeR does not simply combine results from a series of bivariate analyses. Instead, it estimates polygenicity and discoverability for all three traits simultaneously, partitioning the total genetic overlap into components that are unique to each pair of traits and components that are shared across all three. This joint modeling ensures that the trivariate solution is statistically coherent across all three traits, whereas bivariate analyses provide only marginal overlaps that do not account for the influence of the third trait. As shown in Shadrin et al. (2024), trivariate modeling can reveal genetic overlap structures that differ substantially from naïve expectations based on bivariate results. In their study of type 2 diabetes, estimated glomerular filtration rate, and high-density lipoprotein, the trivariate MiXeR solution uncovered a specific three-way shared component that could not be inferred from the three pairwise overlaps alone. This example illustrates that trivariate MiXeR provides a more accurate and informative characterization of shared genetic architecture than separate bivariate analyses. We have clarified this distinction in the Methods to emphasize why trivariate MiXeR provides information beyond what can be obtained from multiple bivariate analyses.

Line 113:

Notably, the novel trivariate MiXeR tool allowed us to deconstruct the patterns of polygenic overlap among three complex phenotypes that could not be deduced from bivariate methods (cf. Methods)[46].

Line 686:

The trivariate MiXeR extends the widely used univariate MiXeR[82] that calculates the number of genetic variants influencing a phenotype (i.e., polygenicity) and the bivariate MiXeR model[83] that quantifies the overlapping polygenic components between two phenotypes regardless of the effect directions. In our study, we also used univariate MiXeR to estimate the polygenicity of each phenotype individually prior to trivariate modeling. Despite the important insights that studying pairwise genetic overlaps has brought[12,14], genetic correlation and bivariate MiXeR cannot ~~directly estimate genetic overlap across three phenotypes.~~ reconstruct the full overlap among three traits. Apart from trivial cases of no overlap or complete overlap, inferring trivariate overlap from three bivariate estimates leads to indeterminate or biased results (Shadrin et al., 2024). The trivariate MiXeR overcomes this by modeling all three traits simultaneously, decomposing genetic effects into phenotype-specific, pairwise-shared, and triple-shared components in a coherent likelihood framework. By iteratively optimizing these parameters, the model identifies the overlap

configuration that best explains the observed GWAS summary statistics. In this way, trivariate MiXeR can disentangle complex patterns of shared genetic architecture among three phenotypes and uncover overlap structures that are distinct from naïve expectations based on bivariate MiXeR (Shadrin et al., 2024).~~Similarly to previous MiXeR implementations, the trivariate MiXeR decomposes the observed genetic effects into shared causal variants affecting multiple traits and unique causal variants affecting only one trait. By iteratively adjusting the model parameters, this tool identifies the configuration (number and size of shared/unique effects) that best fits the observed data, maximizing the likelihood of the summary statistics under the model.~~ Therefore, we used this tool to estimate the total number of shared and unique trait-influencing variants among psychiatric disorders, cardiometabolic disease, and cortical morphology. Results presented in the main body of the article represent optimal estimates across 100 independent optimization runs, while results for each of the 100 runs are available in Sup. Fig. 5.

Reference:

Shadrin, A. A. et al. Dissecting the genetic overlap between three complex phenotypes with trivariate MiXeR. medRxiv 2024.02.23.24303236 (2024) doi:10.1101/2024.02.23.24303236. In press.

6. Although the mediation analysis identifies SA as a partial mediator of the ADHD-T2D genetic link, the manuscript does not adequately discuss the clinical relevance of this modest mediation effect. The authors should explicitly acknowledge this limitation. Additionally, the need for longitudinal clinical studies to validate whether targeting SA-related pathways could meaningfully reduce T2D risk in ADHD patients should also be emphasized.

We thank the reviewer for this constructive comment. We agree that the mediation effect of SA on the ADHD–T2D relationship, while statistically robust, is modest and should be interpreted with caution. We now explicitly acknowledge this in the Discussion, noting that the clinical relevance remains uncertain. In particular, we highlight that longitudinal studies are needed to clarify whether interventions targeting SA-related pathways or their developmental correlates could meaningfully influence cardiometabolic risk in individuals with ADHD. This point has been added both as a limitation and as a direction for future research.

Line 464:

Conversely, ADHD showed a significant genetic correlation with SA[40]. This link is further supported by our MR results, which revealed a directional effect of SA on ADHD as well as a significant mediation pathway linking ADHD to T2D through SA. The mediation effect was modest, suggesting that SA contributes only partially to the ADHD–T2D genetic association. Its clinical significance therefore remains uncertain, and longitudinal studies will be needed to determine whether targeting SA-related pathways can meaningfully reduce T2D risk in individuals with ADHD. By contrast, our MR analyses did not detect evidence for an effect of SCZ on global CT, although previous studies have reported such associations when focusing on regional CT[54]. ~~Although our MR analysis did not identify a significant effect of SCZ on global CT, previous studies have reported such associations when focusing on regional CT[54].~~

Reviewer #4 (Remarks to the Author):

Kopal et al. investigated the genetic factors underlying psychiatric disorders, cardiometabolic diseases, and brain morphology using complementary genetic approaches, including LDSC, MR, trivariate MiXeR, conjFDR, and pathway enrichment analysis. They found that SCZ was genetically distinct from ADHD. Specifically, SCZ showed substantial polygenic overlap with CT and T2D, whereas ADHD was more genetically correlated with CAD and T2D but exhibited limited overlap with CT. MR results further revealed that T2D has a positive causal effect on ADHD, and SA has a negative causal effect on ADHD, while no causal effects were observed between T2D, CT, and SCZ. Overall, the study is well-designed and executed. Nevertheless, I have several minor suggestions that could further improve the clarity and impact of this work:

We thank the reviewer for their positive evaluation of our study.

1. Figure 1C – Is this intended to be a Manhattan plot for GWAS of SCZ and ADHD? The figure legend might be incorrect. Based on the P values, it appears that the inner ring displays the -log10(p-values) for SCZ. Please clarify.

Apologies, we have corrected the typo in the figure description and added the phenotype names directly to the figure for clarity.

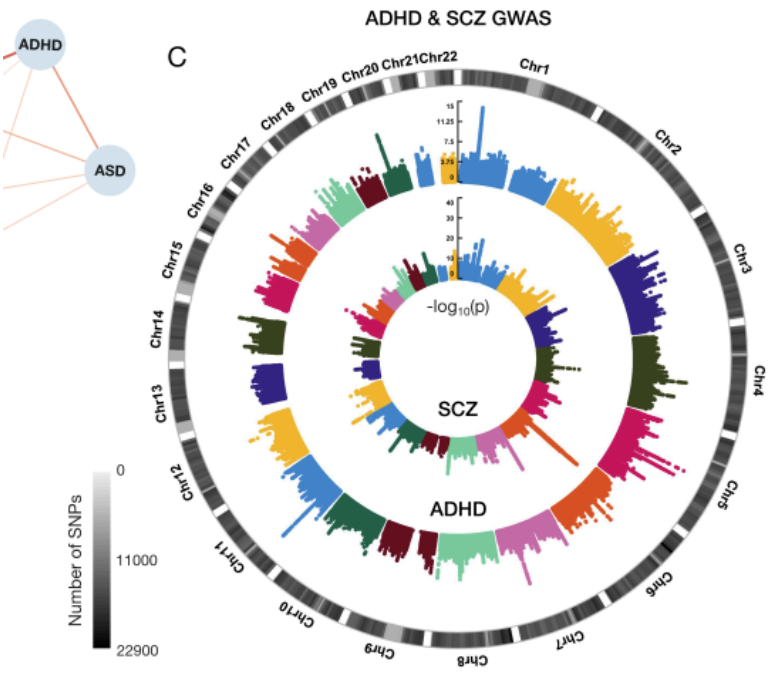


Figure 1: The distinct and shared genetic architecture of ADHD and SCZ
C. Genetic architecture of ADHD and SCZ. The outer ring shows the -$\log_{10}$(p-values) of SNP associations with ADHD, while the inner ring displays the -$\log_{10}$(p-values) for ~~ADHD~~SCZ. The color gradient on the left represents SNP density across the genome.

2. Figure 2 – It is recommended to retain the "percent of genetic overlap" values to one decimal place and to label all numerical values directly within the Venn diagrams for easier interpretation.

We retained the "percent of genetic overlap" values to one decimal place and labeled all numerical values directly within the Venn diagrams as suggested.

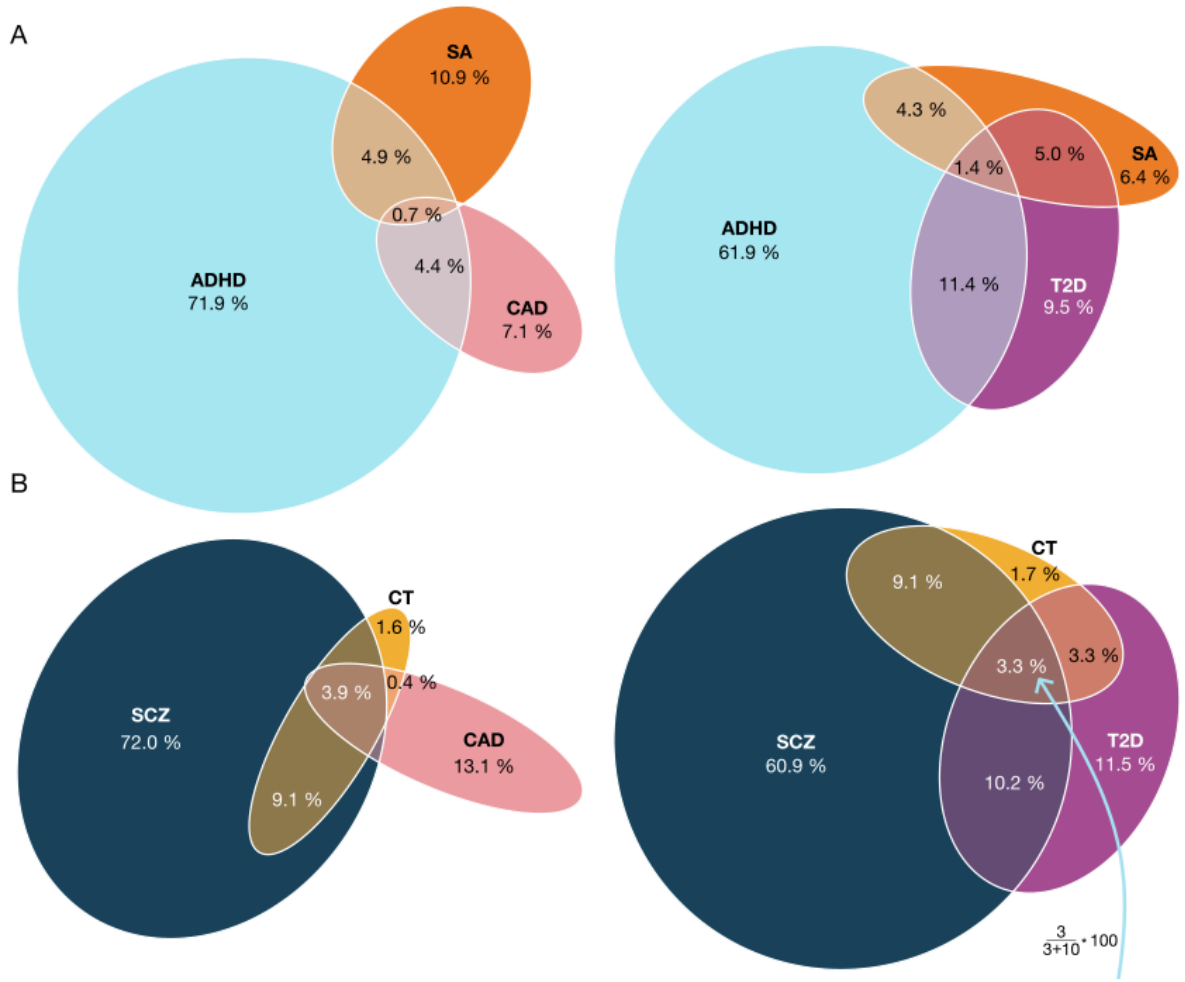


Figure 2: Trivariate overlap between psychiatric disorders, cardiometabolic disease and cortical morphology

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

3. Figure 2A and 2B – The authors presented MiXeR results for ADHD and SA (Figure 2A) and for SCZ and CT (Figure 2B), while the remaining results were shown in Figure S1. This split presentation is not very intuitive. It would be clearer to integrate all trivariate MiXeR results into the main Figure 2.

We appreciate this thoughtful suggestion. After careful consideration, we decide that integrating all trivariate MiXeR results into a single figure would make the figure overly large and difficult to interpret in the main text. To balance clarity and completeness, we revised the figure order so that Figure 2c now comes first, providing a complete overview of all trivariate overlaps. We then highlight the key comparisons using Venn diagrams in Figure 2A and 2B, while the full set of Venn diagrams is available in Supplementary Figure S1. We also reference Figure 2c more explicitly in the main text to guide readers to the complete results.

Line 157:
We leveraged trivariate MiXeR to directly estimate the genetic overlap between psychiatric disorders, cardiometabolic diseases and cortical morphology (Fig 2a).

Line 162:
Given that ADHD exhibited stronger genetic overlap and genetic correlation with SA, we focused on presenting the overlaps between ADHD, SA, and cardiometabolic diseases (Fig. 2B~~A~~). Results for CT are provided in Sup. Fig. 1.

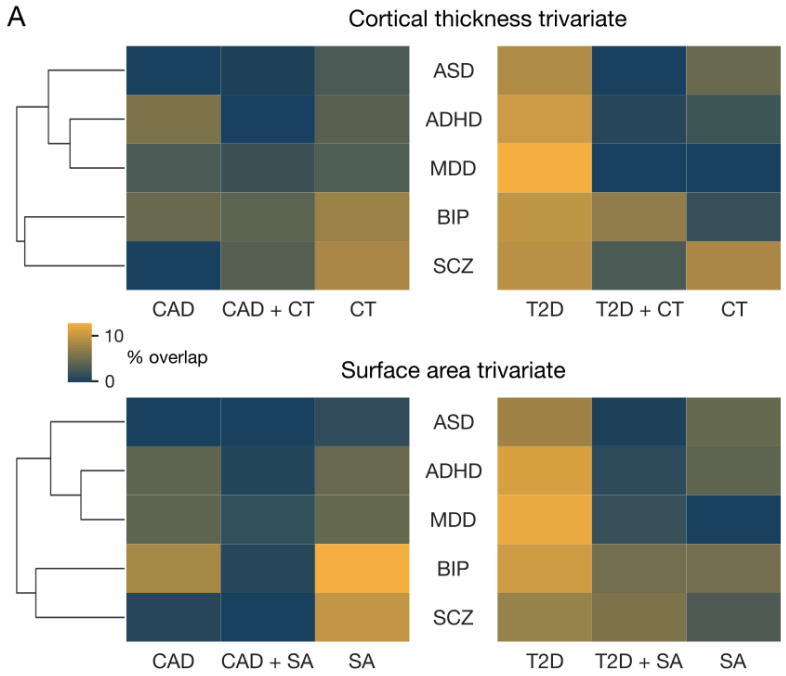


Figure 2: Trivariate overlap between psychiatric disorders, cardiometabolic disease and cortical morphology

A. Trivariate analyses for all five psychiatric disorders. The first three columns display overlaps between psychiatric disorders, cortical morphology, and CAD, while the second three columns display overlaps between psychiatric disorders, cortical morphology, and T2D. Results are first presented for CT followed by SA. Hierarchical clustering of disorders highlight their similarities in terms of morphology and cardiometabolic overlaps, shown separately for CT and SA. **B~~A~~.** Genetic overlap between ADHD, SA, and cardiometabolic disease. Based on trivariate MiXeR analyses, the Venn diagrams detail ~~illustrate~~ the extent of genetic overlap between cortical morphology (i.e., SA), ADHD, and cardiometabolic traits (CAD and T2D). ~~Only genetic overlaps exceeding 1% are annotated.~~ The complete set of overlaps and standard errors are provided in Sup. Fig. 4. **C~~B~~.** Genetic overlap between SCZ, CT, and cardiometabolic disease. Genetic overlaps between CT, SCZ, and the cardiometabolic traits CAD and T2D are presented using Venn diagrams. ~~**C.** Trivariate analyses for all five psychiatric disorders. The first three columns display overlaps between psychiatric disorders, cortical morphology, and CAD, while the second three columns display overlaps between psychiatric disorders, cortical morphology, and T2D. Results are first presented for CT followed by SA. Hierarchical clustering of disorders highlight their~~

~~similarities in terms of morphology and cardiometabolic overlaps, shown separately for CT and SA.~~

4. Figure 2B – From the left panel, SCZ and CT appear to share 4% + 9% = 13% of variants, but from the right panel, they share 9% + 3% = 12%. How should this discrepancy be interpreted?

The reviewer correctly notes this apparent discrepancy. This small discrepancy arises because each trivariate MiXeR analysis is run on the intersection of SNPs available across the three GWASs being modeled. Replacing one phenotype (e.g., CAD vs. T2D) changes the underlying set of SNPs included in the analysis, leading to minor differences in the estimated proportions. Additional variation comes from the stochastic variability across optimization runs. We have clarified this in the Results.

Line 203:
Notably, we did not observe trait-influencing variants uniquely shared between SCZ and CAD independent of CT. SCZ shared 9% of trait-influencing variants with CT, along with an additional 4% shared jointly among SCZ, CT, and CAD. Minor numerical differences in overlap proportions across analyses (e.g., SCZ–CT shared variants) arise because each trivariate analysis is based on the intersection of SNPs available across the three GWASs, which differs slightly depending on the third phenotype included (CAD vs. T2D). The genetic overlap between SCZ and T2D (10%) was comparable to that between SCZ and CT (9%), with an additional 3% of trait-influencing variants shared among SCZ, T2D, and CT. In summary, our trivariate analyses revealed substantial genetic overlap among SCZ, CT, and cardiometabolic diseases, suggesting a shared genetic basis among neurodevelopmental and metabolic phenotypes.

5. Line 166 – The conclusion that "ADHD exhibits a distinct genetic architecture characterized by smaller trivariate overlaps" seems difficult to support based solely on Figures 2A and 2B. Given that the GWAS of SCZ identified many more significant loci than ADHD, it is expected that ADHD would share fewer variants with traits such as SA or CT. This should be discussed more cautiously.

The reviewer rightly points out that this conclusion requires a more cautious interpretation. Differences in trivariate overlap estimates are partly influenced by the relative polygenicity and statistical power of the underlying GWAS, which is higher for SCZ compared to ADHD. We have therefore revised the text to note that ADHD shows comparatively smaller overlaps with CT and SA, while acknowledging that these differences may reflect both true differences in genetic architecture and disparities in GWAS power.

Line 211:
In summary, our trivariate analyses revealed substantial genetic overlap among SCZ, CT, and cardiometabolic diseases, suggesting a shared genetic basis among neurodevelopmental and metabolic phenotypes. By comparison, ADHD showed smaller trivariate overlaps with CT and SA than SCZ, although this pattern may in part reflect differences in GWAS power as well as underlying genetic architecture. ~~ADHD exhibited a distinct genetic architecture characterized by smaller trivariate overlaps.~~

Line 548:

In comparison to CAD, which showed overlap with only a subset of psychiatric disorders, T2D displayed polygenic overlap with all disorders examined in the trivariate MiXeR analyses. ~~In comparison to CAD, all studied psychiatric disorders displayed substantial overlap with T2D based on trivariate MiXeR analyses.~~ This aligns with prior evidence showing high comorbidity between psychiatric disorders and T2D, with suggestions of shared genetic underpinnings32,69.

Line 614:

In conclusion, we demonstrated how studying trivariate genetic overlaps can provide novel and more refined insights into the genetic etiology of multimorbidity. In doing so, we uncovered patterns of genetic overlap among psychiatric, cardiometabolic, and brain structural traits that are not detectable using traditional bivariate methods. Our results show that SCZ, T2D, and CT share extensive polygenic architecture, while ADHD shows relatively stronger overlap with T2D and SA. Pathway and tissue-specific enrichment analyses further indicate that these overlaps reflect distinct biological routes: SCZ overlaps involve brain and immune-related processes, whereas ADHD overlaps highlight metabolic stress pathways and pancreatic signals. Together, these findings illustrate that psychiatric–cardiometabolic comorbidity arises from both shared and disorder-specific mechanisms and emphasize the value of integrative approaches for disentangling complex multimorbidity. ~~Our findings highlight a substantial polygenic overlap between SCZ, T2D, and CT, suggesting that systemic processes such as neuroimmune signaling and cellular maintenance may contribute to their shared liability. In contrast, ADHD showed stronger genetic ties to SA and T2D, with enrichment in metabolic stress and autophagy-related pathways, pointing to a more direct, metabolically driven route to comorbidity. These disorder-specific signatures emphasize the importance of integrative, biologically informed approaches to understanding psychiatric–cardiometabolic comorbidity and may ultimately inform more targeted strategies for prevention and treatment.~~

6. Line 191 – Similarly, it is not straightforward to deduce "potential cardiometabolic contributions to brain-related genetic risk for psychiatric disorders" from the trivariate MiXeR results alone. This conclusion seems better supported by the MR findings and could be reframed accordingly.

We agree with the reviewer that a more cautious interpretation is warranted. Differences in overlap between ADHD and SCZ are influenced not only by genetic architecture but also by differences in GWAS power, which can affect MiXeR estimates. We have therefore revised the text to avoid over-interpreting trivariate MiXeR results.

Line 236:

Finally, we quantified the overall genetic overlap between cortical morphology and cardiometabolic disease by averaging trivariate MiXeR results across all psychiatric disorders. We observed a stronger average genetic overlap between T2D and both CT and SA compared to CAD (Fig. 2E). This pattern is partly expected, as T2D is more polygenic than CAD. Notably, the overlap between CAD and SA was smaller than that between CAD and TH, even though TH is less polygenic than SA. Together, these findings indicate that the extent of observed overlap reflects both trait polygenicity and the specificity of brain–cardiometabolic relationships. ~~We observed a stronger average genetic overlap~~

~~between T2D and both CT and SA compared to CAD (Fig. 2E). The overlap between CAD and SA was notably smaller, supporting a more prominent link between T2D and cortical morphology. Collectively, our results highlight potential cardiometabolic contributions to brain-related genetic risk for psychiatric disorders.~~

Line 427:
In contrast, ADHD displayed a more distinct genetic profile, with relatively greater polygenic overlap with cardiometabolic traits than with cortical morphology ~~with less polygenic overlap with cortical morphology but stronger connections to cardiometabolic traits.~~

7. Is it possible to identify the percentage of shared variants between ADHD & CT and SCZ & CT, ADHD & CAD and SCZ & CAD, …

We appreciate the reviewer's question. This information can indeed be obtained using bivariate MiXeR, and such analyses have already been performed in prior studies (Baranova et al., 2023; Cheng et al., 2021; Rødevand et al., 2023). To avoid redundancy, we focused here on extending the framework to trivariate MiXeR, which allows partitioning of shared variants across three traits simultaneously and provides additional resolution beyond pairwise overlaps. We have now referenced the relevant bivariate studies more explicitly in the Discussion to highlight how our results build on and extend previous findings.

Line 553:
Notably, despite a near-zero genetic correlation, SCZ and T2D have been shown to share substantial polygenic overlap (Rødevand et al., 2023).

Line 460:
Consistent with our findings, previous studies have identified greater genetic overlap (Cheng et al., 2021) and a higher number of jointly associated SNPs for SCZ and CT compared to ADHD and CT[52]. ~~In line with our results, greater genetic overlap and a significantly higher number of SNPs have been previously identified as jointly associated with SCZ and CT compared to ADHD and CT52.~~

Line 554:
Moreover, genes jointly associated with SCZ and T2D have been found to show high expression in brain tissue and immune cells, and are enriched for pathways related to neurodevelopment, synaptic signaling, immune function, intracellular transport, and metabolic regulation (Rødevand et al., 2023).

Line 543:
However, although genetic associations between ADHD and cardiometabolic disorders have been observed (Baranova et al., 2023), large-scale evidence indicates that their comorbidity is mainly explained by environmental factors[32]. ~~However, ADHD comorbidity with cardiometabolic disorders was proposed to be mainly driven by environmental factors rather than genetics[32], despite their genetic association.~~

References:
Baranova, A., Chandhoke, V., Cao, H. & Zhang, F. Shared genetics and bidirectional causal relationships between type 2 diabetes and attention-deficit/hyperactivity disorder. Gen Psychiatr 36, e100996 (2023).

Cheng, W. et al. Genetic Association Between Schizophrenia and Cortical Brain Surface Area and Thickness. JAMA Psychiatry 78, 1020–1030 (2021).
Rødevand, L. et al. Characterizing the Shared Genetic Underpinnings of Schizophrenia and Cardiovascular Disease Risk Factors. American Journal of Psychiatry (2023) doi:10.1176/appi.ajp.20220660.

8. Lines 200–201 – Odds ratios (ORs) might be more interpretable than β coefficients here.

We thank the reviewer for this helpful suggestion. We now report odds ratios (ORs) alongside β estimates wherever the outcome phenotype is binary, while retaining β values for continuous outcomes where ORs are less interpretable.

Line 263:

IVW MR did not provide evidence for a causal effect of ADHD on SA or T2D. Similarly, we found no significant evidence for a causal effect of SCZ on T2D or CT. In contrast, in the reverse direction, higher genetic liability for T2D was associated with increased susceptibility to ADHD ~~found evidence that genetic liability for T2D has a causal effect on ADHD risk, with higher T2D liability associated with increased genetic susceptibility to ADHD~~ (OR = 1.14, β = 0.13, FDR-correct p_{FDR} = 9.5×10^{-11}). ~~In addition, lower SA was associated with increased genetic risk for ADHD~~ We also found that lower SA exerted a causal effect on increased genetic risk for ADHD (OR = 0.77, β = –0.26, p_{FDR} = 0.0003). ~~In contrast to the findings for ADHD, IVW MR did not reveal any significant causal effect of SCZ on CT or T2D~~.

9. Lines 204–205 – The sentence "In contrast to the findings for ADHD, IVW MR did not reveal any significant causal effect of SCZ on CT or T2D" could be better contextualized by also reporting the causal effects of T2D and SA on SCZ. More broadly, the MR results might be presented in a more coherent structure: first forward MR (ADHD or SCZ → T2D and SA), followed by reverse MR (T2D or SA → ADHD or SCZ). This would also highlight that ADHD has a positive causal effect on T2D.

The reviewer makes an excellent point regarding the presentation of MR results. We have restructured the Results section and the figure to first present forward MR (ADHD/SCZ → T2D/SA), followed by reverse MR (T2D/SA → ADHD/SCZ), thereby also highlighting the positive causal effect of ADHD on T2D.

Line 260:

Focusing on the trait combinations with the highest genetic overlap, we further investigated the bidirectional causal relationships between ADHD, T2D, and SA, as well as SCZ, T2D, and CT, using inverse-variance weighted (IVW) Mendelian randomization (MR) (Fig. 3A, Sup. Tab. 2). IVW MR did not provide evidence for a causal effect of ADHD on SA or T2D. Similarly, we found no significant evidence for a causal effect of SCZ on T2D or CT. In contrast, in the reverse direction, higher genetic liability for T2D was associated with increased susceptibility to ADHD ~~found evidence that genetic liability for T2D has a causal effect on ADHD risk, with higher T2D liability associated with increased genetic susceptibility to ADHD~~ (OR = 1.14, β = 0.13, FDR-correct p_{FDR} = 9.5×10^{-11}). ~~In addition, lower SA was associated with increased genetic risk for ADHD~~ Notably, the MR-Egger intercept was significant for this analysis, indicating potential directional pleiotropy; however, the effect

remained robust across sensitivity analyses. It remained significant after MR-PRESSO outlier correction and showed consistent direction across MR-Egger, weighted median, and simple mode estimators, with the weighted median also reaching statistical significance. We also found that lower SA exerted a causal effect on increased genetic risk for ADHD (OR = 0.77, β = –0.26, p_{FDR} = 0.0003). ~~In contrast to the findings for ADHD, IVW MR did not reveal any significant causal effect of SCZ on CT or T2D.~~ Finally, we identified a significant negative effect of T2D on CT (β = –0.03, p_{FDR} = 0.03), suggesting that increased genetic liability for T2D may contribute to cortical thinning. ~~These findings suggest that ADHD is embedded in a bidirectional causal network involving SA and T2D risk, whereas SCZ may be indirectly shaped by T2D liability through its effects on CT.~~ In these significant analyses, MR-Egger intercepts were not significant. Overall, the results suggest that ADHD is influenced by both cortical surface area and T2D liability, In contrast, SCZ may be indirectly shaped by T2D liability through its effects on cortical thickness.

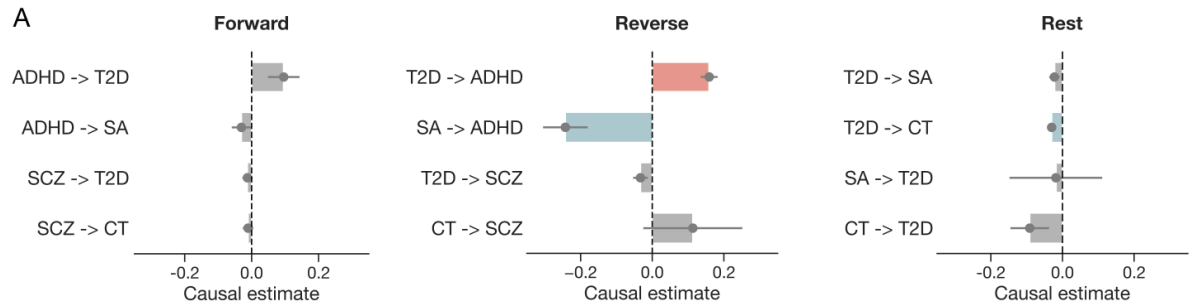


Figure 3: Causal and mediated genetic pathways from psychiatric traits to cardiometabolic risk
A. Bivariate causal effect mapping.

10. Line 238 – According to Figure 4B, this should refer to ADHD and SA.

Apologies, we have corrected the typo.

Line 325:
The first conjFDR analysis, conducted at a threshold of conjFDR < 0.05, revealed 93 lead SNPs jointly associated with ADHD and T2D (Fig. 4A). Applying the same threshold of conjFDR < 0.05, we identified 17 lead SNPs jointly associated with ADHD and SA~~T2D~~ (Fig. 4B).

11. Regarding conjFDR analyses: for ADHD, the authors conducted conjFDR with T2D and SA, while for SCZ they conducted conjFDR with T2D and CT. Why were the same sets of traits not analyzed across both disorders? This discrepancy should be justified.

The reviewer raises a valid point regarding the choice of trait combinations. These were guided by the preceding genome-wide overlap results: ADHD showed stronger genetic correlation and polygenic overlap with T2D and SA, whereas SCZ displayed stronger overlap with T2D and CT. To maximize the likelihood of identifying jointly associated loci, we therefore prioritized the trait pairs with the strongest evidence of shared genetic architecture. This choice directly follows the trivariate MiXeR results presented in Figure 2, and we

applied the same trait combinations in our MR analyses shown in Figure 4. We have strengthened this rationale in the Results.

Line 318:
To gain deeper biological insights into the mechanisms underlying multimorbidity, we aimed to identify shared biological pathways between ~~linking~~ mental health, ~~with~~ cardiometabolic disease, and cortical morphology. To do so, we began with a conjunctional FDR analysis (conjFDR) that identified genetic variants jointly associated with ~~that are shared between~~ ADHD and T2D, ADHD and SA, SCZ and T2D, as well as SCZ and CT. Identical to the previous MR analysis, these trait pairs were selected based on the strongest trivariate overlaps, in order to maximize the likelihood of identifying jointly associated loci.

Revision COMMSMED-25-1715A

Reviewer #2 (Remarks to the Author):

Thank you for your response. While I appreciate your rationale for initially focusing on cortical thickness (CT) and surface area (SA), I find the current justification insufficient to fully address my original concern. Cortical morphology is undoubtedly fundamental, but psychiatric disorders—particularly schizophrenia—are characterized by widespread alterations not only in cortical structure but also in subcortical volumes, functional connectivity, and white matter integrity. These modalities have substantial genetic underpinnings and are directly relevant to the disease mechanisms you aim to interrogate. Your response largely emphasizes the conceptual clarity of starting with CT and SA, as well as the methodological heterogeneity of other modalities. However, this reasoning does not preclude at least sensitivity or complementary analyses to demonstrate whether the genetic convergence you report is specific to cortical morphology or generalizable to other major brain phenotypes. I strongly encourage you to consider adding at least exploratory analyses using publicly available GWAS summary statistics for subcortical volumes or white matter connectivity, which are well-characterized (e.g., ENIGMA, UK Biobank).

We thank the reviewer for this suggestion. We agree that schizophrenia and related psychiatric disorders show alterations across several neural systems beyond cortical morphology, including subcortical structures and white-matter pathways. To address the reviewer's point and assess whether the observed genetic convergence is specific to cortical morphology or generalizable to other brain phenotypes, we conducted a new set of exploratory analyses using ENIGMA's latest GWAS of subcortical volumes (García-Marín et al., 2024). We focused on subcortical volumes rather than white-matter pathways because our study specifically examines structural morphology and its genetic convergence with psychiatric and cardiometabolic disease, whereas white-matter measures reflect connectivity and microstructure, which fall outside the structural framework of our primary research question.

We first estimated genetic correlations between the ten subcortical volumes and five psychiatric disorders (ADHD, ASD, BIP, MDD, SCZ) using LDSC (Sup. Fig. 3A). Overall, genetic correlations were modest in magnitude and highly structure-specific. ADHD showed several negative correlations, most prominently with the brainstem, intracranial volume (ICV), and ventral diencephalon (ventralDC), with the ADHD–ICV correlation exhibiting the largest absolute effect. SCZ showed small, consistently negative but non-significant correlations across all subcortical structures. MDD displayed a significant negative correlation with ICV and ventralDC, alongside significant positive correlations with the putamen and caudate. In contrast, ASD and BIP did not show any significant genetic correlations with the subcortical volumes examined.

We next quantified three-way polygenic overlap between each subcortical volume, a psychiatric disorder (ADHD or SCZ), and a cardiometabolic disease (CAD or T2D) using trivariate MiXeR (Sup. Fig. 3). For ADHD, we observed polygenic overlap with several subcortical structures, most notably the putamen and ICV. Overlap with CAD was minimal across all structures. In contrast, T2D showed modest shared components with selected nuclei. Importantly, trivariate overlap (ADHD + T2D + subcortical measure) was detectable for several regions, but no subcortical structure showed meaningful trivariate overlap with ADHD and CAD, reflecting the absence of shared polygenic signal between CAD and subcortical morphology. For SCZ, we observed consistently large bivariate overlaps with multiple subcortical structures, again paired with negligible overlap with CAD. Similarly, T2D showed

notable shared components with several subcortical volumes, and in most cases these overlaps were also shared with SCZ, resulting in substantial trivariate overlap across regions. This indicates that when subcortical–T2D overlap exists, it is largely driven by variants jointly shared with SCZ rather than by subcortical–T2D overlap independent of psychiatric liability.

These results are now included as a new Supplementary Figure and briefly described in the Results and Discussion sections.

Line 144:
Finally, GWAS of CT were based on the UK Biobank (UKB) sample. We accessed UKB data under accession number 27412. The design, participant composition, and data collection protocols of the UKB have been described in detail elsewhere80. We selected 39,098 unrelated individuals (KING cutoff = 0.0884)[81] with T1 MRI data. Supplementary analyses of subcortical volumes utilized ENIGMA GWAS summary statistics comprising 74,898 participants.

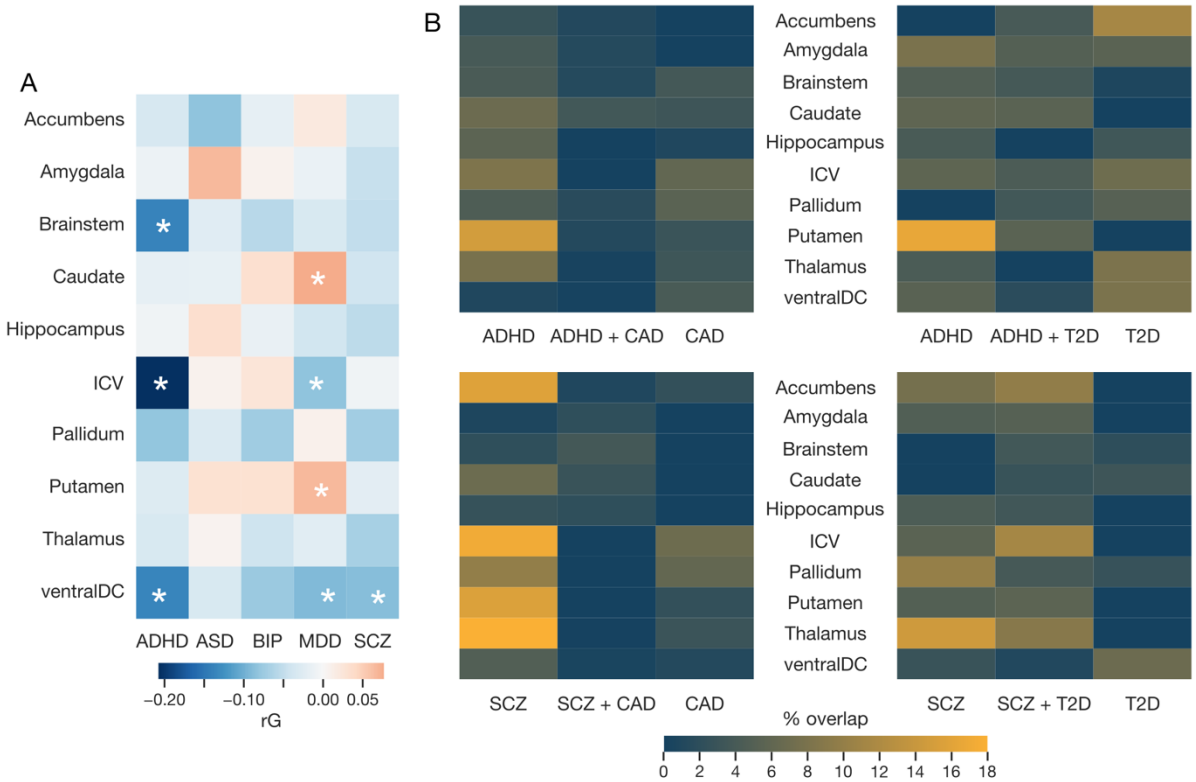
Line 305:
While all psychiatric disorders showed minimal genetic correlation with CT, ADHD and MDD exhibited negative correlations with SA (ADHD: rG = -0.19, pFDR < 1×10^{-16}, MDD: rG = -0.10, pFDR = 0.01). In addition, ADHD and MDD also showed the strongest genetic correlations across measures of subcortical volumes (Sup. Fig. 3).

Line 327:
We found a similar degree of genetic overlap between ADHD and CAD (4%) and between ADHD and SA (4%), while fewer than 1% of trait-influencing variants were shared across all three traits. In contrast, the overlap between ADHD and T2D was higher (11%), compared to SA (4%), with an additional 1% of trait-influencing variants shared jointly among ADHD, SA, and T2D. Supplementary analyses of subcortical volumes revealed substantial overlap with putamen and intracranial volume, but minimal convergence with CAD and only modest trivariate overlap with T2D (Sup. Fig. 3).

Line 347:
The genetic overlap between SCZ and T2D (10%) was comparable to that between SCZ and CT (9%), with an additional 3% of trait-influencing variants shared among SCZ, T2D, and CT. Supplementary analyses further demonstrate robust overlap between SCZ and subcortical volumes, including a large trivariate component with T2D (Sup. Fig. 3).

Line 566:
At least partially, these differences can be explained by the differences in genetic architecture. Here, we observed that SCZ aligned more closely with cortical and, to a lesser degree, subcortical morphology compared to ADHD.

Line 681:
~~Likewise, we limited our analyses to global CT and SA as foundational measures of cortical morphology, and future work should incorporate regional, subcortical, functional, and white matter phenotypes.~~ Likewise, we focused our primary analyses on global CT and SA as foundational measures of cortical morphology, complemented by exploratory subcortical analyses, and future work should further extend these findings to regional cortical, functional, and white-matter phenotypes.



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

A. Genetic correlation analyses. Genetic correlations (r_g) 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.