A Multivariate Analysis Observing the Shared Genetic Etiology of Cardiovascular and Psychological Illnesses

Connor Tallis

Department of Psychology and Neuroscience, University of Colorado Boulder

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Honors Thesis Advisor: Dr. Andrew Grotzinger

Defense Committee:

Dr. Andrew Grotzinger, Department of Psychology and Neuroscience, Thesis Advisor

Dr. Erik Knight, Department of Psychology and Neuroscience, Honors Council Representative

Dr. Luke Evans, Department of Ecology and Evolutionary Biology, Outside Reader

Abstract

At the forefront of current psychological research is the idea that the presence of a psychiatric disorder creates a high likelihood of being diagnosed with other psychiatric disorders, especially if the disorders are within an established domain (i.e., internalizing, substance use, etc.). This research will seek to build upon previous research on comorbidities within the psychiatric space by investigating whether psychiatric disorders also exhibit shared common genetic variant liability with non-psychiatric medical conditions. Although comorbidity between psychiatric and non-psychiatric medical conditions has been observed, the lack of proper genetic technological methods and large sample sizes result in ambiguous interpretations of risk pathways within said research. This study will aim to use cutting-edge multivariate genomic methods as well as large sample sizes from multiple large cohorts to limit the ambiguous interpretation and methodological barriers seen in previous research. A multivariable version of Linkage Disequilibrium Score Regression (LDSC) within GenomicSEM will be applied to all summary statistics in this study, which provides two significant sources of output: a genetic covariance matrix (i.e., the extent to which disorders covary at the level of common SNPs), and a sampling covariance matrix (i.e., the extent to which sample overlap exists among different summary statistics) across the included traits. This multivariate analysis uniquely permits the possibility of discovering both common and independent pathways among both psychiatric and non-psychiatric medical conditions included in this study. By discovering these pathways this study has the potential to develop a more reliable understanding of comorbidity between debilitating psychiatric and non-psychiatric medical conditions.

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Comorbid psychiatric diagnoses are so commonplace, that they're beginning to be considered the norm rather than the exception (Caspi & Moffitt, 2018). This is especially prevalent within certain domains of psychiatric disorders, such as internalizing and externalizing psychopathology (Brown, et al., 2001; Friborg et al., 2014). Large-scale epidemiological research has suggested a high likelihood of comorbidity between psychiatric and non-psychiatric diseases (Momen et al., 2020). In addition, the extant literature suggests that a psychiatric diagnosis can increase the likelihood of developing a plethora of medical illnesses, including cardiovascular disease. For example, neuroticism, measured with The Big Five Personality Inventory, has been previously associated with coronary artery disease (Zhang, Cao, & Baranova 2021). Meta-analytic literature has also indicated that those diagnosed with severe mental illness have an approximate 75% higher likelihood of developing a comorbid cardiovascular disease than control populations (Correll et al. 2017). Although comorbidities have been observed between psychiatric and non-psychiatric illnesses, it is difficult to determine the specificity of the previously observed risk pathways. If it's possible that a high rate of comorbidity exists between psychological and cardiovascular illness, it's crucial that future research investigate this relationship, as targeted intervention efforts may create opportunities to improve life satisfaction among afflicted populations. According to the CDC, nearly 700,000 people died of heart disease in 2021, making it the leading cause of death in the United States, accounting for 20% of all deaths. Our research aims to contribute to the knowledge of shared liability between risk for psychiatric and cardiovascular diseases. We hope that a greater understanding of the genetic basis between the factors included in this study will lead to better intervention efforts.

Despite the observations of comorbidities between psychiatric and medical diseases, we have yet to properly understand the intricate genetic relationships underlying these systems of relationships. This is at least partly due to practical challenges, which include a widespread difficulty in obtaining large samples that include a broad variety of medical and psychiatric disorders. Subsequently, these challenges give rise to a fragmented approach to investigating these comorbidities, which has led to an unclear and potentially inaccurate overview of risk pathways between psychiatric and medical disorders. For example, literature examining comorbidity with cases of major depressive disorder has found an increased risk for coronary artery disease associated with MDD (Rudisch & Nemeroff 2003), and prior analysis using genome-wide methods supports this outcome (Chen et al. 2023). However, it is unclear if the shared liability with coronary artery disease is unique to MDD or shared across other internalizing disorders that have been shown to overlap at phenotypic (Kessler et al. 2005) and genetic (Grotzinger et al. 2022) levels of analysis. Genetic analysis can be useful for answering questions about shared risk factors given the well-established finding that all human complex traits are heritable (Polderman et al. 2015). Also, this method allows us to include large sample sizes which empowers us to analyze both small and large genetic effects.

In the pursuit of adding clarity to current research regarding the genetic liability of psychological and medical comorbidities, we utilized the Genomic Structural Equation Modeling (Genomic SEM) package within R to synthesize and analyze Genome-wide association study (GWAS) summary statistics from large biobanks and meta-analyses. Genomic SEM's modeling capabilities provide a framework for multivariate genomic analysis, allowing us to identify genetic correlations between clusters of psychiatric and non-psychiatric medical illnesses.

Genome-wide studies have found a wide range of correlations between CVD and psychiatric disorders, including low correlations (r_g = 0.1 – 0.29), moderate correlations (r_g = .3 - .49) and high correlations (r_g = .5 - .7) (Chen et al. 2023). In addition, Genomic SEM's multivariate extension of Linkage disequilibrium score regression (LDSC) provides two significant sources of output: a genetic covariance matrix (i.e., the extent to which disorders covary at the level of common Single Nucleotide Polymorphisms (SNPs), and a sampling covariance matrix (i.e., the extent to which sample overlap exists among different summary statistics) across the included traits. This study intends to utilize cutting-edge multivariate genomic methods to circumvent methodological barriers and interpretive limitations seen in previous research to examine the shared and unique risk pathways between psychiatric disorders and cardiovascular diseases at the level of common (>1% allele frequency) single nucleotide polymorphisms (SNPs). By way of this multivariate research, we hypothesize that we'll discover a statistically significant genetic overlap between these two illness categories.

Methods

Cardiovascular and Psychiatric Trait Selection

Cardiovascular diagnostic categories featured in the UK Biobank (UKB) were used to devise a list of cardiac diseases, each including over 2,000 cases to ensure sufficient power. Psychiatric disorder categories and individual traits included in our analyses were garnered from Grotzinger et al. (2023), and their sample sizes were similarly > 2,000 cases to ensure adequate power. The list of cardiac diseases included the broadest category for each disorder. With Genomic SEM's ability to collect traits from multiple samples, this list of traits was updated with the most recent GWAS in the *GWAS catalog* (reference here, a comprehensive database of

genomic studies) for either *(a)* the broad disorder category obtained in the UKB or *(b)* the sub-disorder housed within the broader diagnostic category. The decision to include the broader or specific categories was determined by which has more cases, and the disorder with fewer cases was omitted from subsequent modeling. The use of cases as a selection criterion, rather than total sample size, is due to certain samples where the number of controls is largely disproportionate to the number of cases. Prioritizing high case sizes for modeling has the potential to increase the likelihood of identifying traits with significant SNP-based heritability. After each trait was input into Genomic SEM's multivariate extension of *ldsc*, the accompanying SNP-based heritability (h^2_{SNP}) *Z*-statistics was used to further filter out traits with an h^2_{SNP} *Z*-statistic < 4. This decision criterion is based on the guidelines outlined in Bulik-Sullivan et al. (2015) for interpretable genetic covariance estimates. Case numbers and sample characteristics for all traits among both psychiatric and cardiovascular illnesses are further described in Table 1.

Genomic Structure Equation Modeling (Genomic SEM)

To identify shared signal between cardiovascular illnesses and psychological diagnoses, our research team used the GenomicSEM package available in R (Grotzinger et al., 2019). Utilizing GenomicSEM, our team first munged all raw summary statistics of our cardiac traits to correctly format them for linkage disequilibrium score regression (LDSC), which transforms GWAS results to a Z-statistic metric and aligns the direction of effect to the same reference allele. The *munge* function within GenomicSEM requires SNP, allele, regression, and *p*-value information to create a file that can be analyzed using LDSC. These *munged* summary statistics were computed using the raw summary statistics from our cardiovascular illness and UKB traits with 6 arguments: 1) providing the name of the summary statistics file, 2) including the HapMap3 European reference file used to align the SNPs , 3) naming the given trait, 4)

providing the sample size, 5) including imputation quality cutoffs at a cut-off > 0.9, and 6) minor allele frequency (MAF) filters to exclude variants with an allele frequency < 1%.

LDSC

Following the *munging* of all raw summary statistics, the genetic covariance and sampling covariance matrices of our cardiac traits were computed using the *ldsc* function within the GenomicSEM package coupled with the LD scores computed from the European 1000 Genomes Phase 3 genotypes for HapMap3 SNPs. The *ldsc* function requires five arguments: 1) including a vector of the munged summary statistics, 2) including a vector of population prevalence for each trait, 3) the file path to the reference file containing LD scores and 4) weights, and finally 5) naming the traits. The resulting genetic covariance matrix features SNP-based heritability on the diagonal and genetic co-heritability (covariances) on the off-diagonal. The sampling covariance matrix contains the sampling variances on the diagonal (i.e., squared standard errors) and sampling covariances on the off-diagonal, which arise when there is sample overlap across included traits.

Exploratory Factor Analysis

Following LDSC, the genetic covariance and sample covariance matrices were used as input for explanatory and confirmatory multi-factor modeling of our cardiac traits. Results from the acceleration factor, optimal coordinates, and Kaiser rule suggested that a four-factor solution would provide sufficient fit. Thus, a four-factor genomic exploratory structural equation model was created using a weighted least squares regression (WLS) estimator to weight each loading by the standard error which allows for greater weight given to more precisely measured traits. A standardized loading cutoff of 0.4 (minimum variance accounted for by the factor: 16%) was

used to determine which traits were carried forward into confirmatory factor analysis (CFA), while those with standardized loadings < 0.4 were omitted.

Confirmatory Factor Analysis

The results of the CFA indicated that a four-factor solution fit the observed covariance amongst cardiac traits moderately well, *CFI =0.896, SRMR = .086*. Factor 1 contained six indicators: atrial fibrillation (AF), ischemic stroke (ISCH), abnormal heart sounds (AHS), cardiac conduction disorders (CCDS), and other aneurysms (OA). Factor 2 contained myocardial infarction (MI), nonspecific chest pain (NCS), and peripheral vascular disease (PVD). Factor 3 contained only two indicators: hemorrhoidal disease (HD) and NCS, so loading constraints were applied to each. Factor 4 contained other disorders of the circulatory system (ODCS), PVD, phlebitis and thrombophlebitis (PT), and varicose veins (VV).

The four-factor cardiac model was then modeled alongside five psychiatric factors described by Grotzinger et al. 2023. These five factors include 1) compulsive disorders (Comp) defined by Anorexia Nervosa (AN), Obsessive Compulsive Disorder (OCD), and Tourette Syndrome (TS); 2) thought disorders (Pysch) defined by Bipolar Disorder (BD) and Schizophrenia (SCZ); 3) neurodevelopmental disorders (Neuro) defined by Post-Traumatic Stress Disorder (PTSD), Attention-Deficit Hyperactivity Disorder (ADHD), Major Depressive Disorder (MDD), Autism Spectrum Disorder (ASD), and TS; 4) internalizing disorders (Int) defined by Anxiety (ANX), PTSD, and MDD; and 5) substance use disorders (SUD) defined by Alcohol Use Disorder (AUD), Opioid Use Disorder (OUD), and Cannabis Use Disorder (CUD). This allows for the estimation of inter-factor correlations between psychiatric and cardiac factors, which index the extent to which signal shared within each domain of illness is shared across domains. The inter-factor correlations between cardiac and medical factors are plotted in

Figure 4, with each cardiovascular factor granted its own panel to allow for a clear representation of the individual inter-factor genetic correlations between psychiatric and cardiovascular illness clusters. Within this figure, psychiatric factors were placed on the vertical axis ordered by their p-value, with the lowest value at the top of the axis.

A second representation of the inter-factor and factor-trait correlations is supplied in Figures 1, 2, and 3. These diagrams differ from the first model by way of 1) including the genetic correlations between factors as well as 2) the correlations between our factors and their individual traits or illnesses. Correlations between latent variables is shown with double-headed curved arrows while regression paths between latent variables and indicators are shown with single-headed straight arrows. However, this team's primary interest is the correlations between latent psychiatric and cardiac factors featured in Figures 3 and 4. The regression paths are described further in Figures 1 and 2.

Results

The genomic confirmatory factor analysis with cardiac and psychiatric traits in this study was computed utilizing the GenomicSEM package within R, and the analyses' objective was to determine the existence of genetic overlap between cardiovascular illnesses and psychiatric diagnoses. Genetic correlations among psychiatric and cardiovascular illness factors were shown to have a wide range of relationships with standardized coefficients of ranging from ~ -.2 to ~ .65. However, there are a select few inter-factor correlations that garnered significant interest. First, and most significant is a noticeably strong genetic linkage between our third cardiovascular factor (Nonspecific chest pain (NCP) and Hemorrhoidal disease (HD) and internalizing psychiatric disorders (r_g = 0.65, *SE =0 .07, p =0 .001)*, suggesting a high level of shared genetic liability. Further, our first, second, and fourth factors within our larger model containing

psychiatric traits displayed a practically null relationship with co-occurring thought disorders (F1: r_g = 0.053, *SE = 0.029, p = .06*; F2: r_g = -0.009; *SE = .03, p = .9,* F4: r_g = 0.1, *SE = .042, p = 0.01.* while our third-factor shows to have a minimal linkage with thought disorders (r_g = 0.298, *SE = 0.051, p = 9.2e^{-9}*). Lastly, our model shows a slightly protective trend among our first, second, and fourth factors with compulsive psychiatric disorders (F1: r_g = -0.100, *SE = 0.055, p = 0.06;* F2 r_g = -0.212, *SE = .053, p = 8.09e^{-5}*; F4: r_g = -0.05, *SE = 0.063, p = 0.422*) however this protective benefit is minimal. Our third cardiovascular factor showed moderate genetic liability with compulsive disorders (r_g = 0.334, *SE = 0.079, p = 3.89e^{-5})*. These outcomes are displayed visually in Figures 3 and 4.

Discussion

Utilizing genome-wide methods with data from large-scale GWAS meta-analyses and open-source biobanks, our research identified a generally low to moderate genetic risk liability between cardiovascular illnesses and psychiatric diagnoses of substance use, compulsive, and internalizing disorders. Notably, our third factor of cardiovascular illnesses was shown to have a strong genetic liability with internalizing disorders. Regarding thought disorders, our analysis indicates a moderate shared liability with only our third cardiovascular factor, while the three other cardiovascular factors were shown to have surprisingly null genetic effects, suggesting a general lack of shared genotypic liability, which does not reflect the genome-wide research we found in our initial literature review (Chen et al. 2023). A minimal genetically protective trend was observed with compulsive disorders amongst cardiovascular illnesses in our first, second, and third cardiac factors, as well as a moderate coefficient of shared risk with our third factor. Between our four cardiovascular factors, hemorrhoidal disorders and nonspecific chest pain

(Factor 3) uniquely showed a shared liability risk with all five psychiatric factors, with a much higher liability risk with internalizing disorders.

The high genetic overlap between indicators of our cardiac factor 3 (hemorrhoidal disease, nonspecific chest pain) and internalizing disorders is an observation of significant interest. Among our analyses between cardiovascular and psychiatric factors, this observed coefficient is a substantial outlier. This result suggests that over 60% of common variant genetic liability is shared between cardiac factor 3 and the internalizing factor, which is a surprising outcome. Further, there is a consistent trend that seems to suggest a common genetic overlap among all psychiatric illnesses with our third factor. A post-analysis literature review exhibited a lack of published genetic research between these factors, so subsequent replication using genome-wide methods is required to support or refute our findings. Admittedly, because we lack medical expertise regarding hemorrhoids and nonspecific chest pain, providing accurate implications concerning our cardiac factor 3 is difficult. Nonspecific chest pain is also a relatively ambiguous trait, so subsequent genomic research that includes specific forms of chest pain may be necessary to properly assess these outcomes.

However, outside of the genetic research space, Dang et al. (2023) found a correlation between a higher severity of reported low-risk chest pain within their sample of patients with symptoms of anxiety and depression. This unexpected outcome provides an incentive for further fine-grained analysis of the genetic risk sharing between our cardiac factor three and psychiatric disorders. It ought to be noted that among our cardiac traits, nonspecific chest pain within cardiac factor 3 contained one of the highest case sample sizes, which may have influenced its much higher correlation compared to our other factors.

Our results reflect a unique investigation into shared common variant genetic liability between cardiovascular illnesses and psychiatric diagnoses. Our method of analysis provides a novel and more fine-grained representation of how genetic risk sharing may influence comorbid psychiatric and cardiac phenotypic outcomes. Our confirmatory factor analysis with psychiatric traits indicates that certain SNP's may have the potential to increase the liability for developing co-occurring medical and psychiatric disorders. Although, besides the observed high coefficient of shared liability between our third cardiovascular factor and internalizing disorders, our analysis indicates only a minimal to moderate genetic effect toward our selected phenotypes, which suggests that a predisposed liability for developing comorbid psychiatric and cardiovascular illness isn't entirely explained by SNP-heritability, which aligns with much of the extant GWAS literature. However, subsequent replication of this form of analysis is necessary.

Future large-scale research is required to replicate our findings. Certain traits included in our analysis, although sufficiently powered, were included with relatively small sample sizes for genomic analysis. Future research that intends to study a similar genetic relationship ought to include larger case sizes, which may rely on an expansion of large-scale genomic databases. In addition, it's necessary to include the limitation of the lack of ethnic diversity in our analyses. Until large-scale genomic databases of non-European ancestries are further developed, GWAS results cannot reliably represent non-European populations, which limits the external validity of our research. We suggest that future GWAS utilize larger sample sizes and specifically direct attention to hemorrhoidal disorders and nonspecific chest pain that define cardiac factor 3, and investigate their relationship with internalizing disorders. If possible, we also suggest samples that they include non-European samples.

Despite these limitations, our genome-wide analyses offer important insight into the shared genetic etiology of psychiatric and medical illnesses. Our analyses additionally imply a necessity for novel intervention and treatment programs that take this high degree of common variant overlap between cardiac and psychiatric illness into account. Overall, our mixed findings have most importantly provided indication that shared risk pathways exist across specific subclusters of psychiatric and cardiovascular conditions.

References

Brown, T. A., Campbell, L. A., Lehman, C. L., Grisham, J. R., & Mancill, R. B. (2001). Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. *Journal of abnormal psychology*, *110*(4), 585–599. https://doi.org/10.1037//0021-843x.110.4.585

Bulik-Sullivan, B. K., Loh, P.-R., Finucane, H. K., Ripke, S., Yang, J., Patterson, N., Daly, M. J., Price, A. L., & Neale, B. M. (2015, February 2). *LD score regression distinguishes confounding from polygenicity in genome-wide association studies*. Nature Genetics. Retrieved March 3, 2023, from https://www.nature.com/articles/ng.3211

Correll, C. U., Solmi, M., Veronese, N., Bortolato, B., Rosson, S., Santonastaso, P., Thapa-Chhetri, N., Fornaro, M., Gallicchio, D., Collantoni, E., Pigato, G., Favaro, A., Monaco, F., Kohler, C., Vancampfort, D., Ward, P. B., Gaughran, F., Carvalho, A. F., & Stubbs, B. (2017). Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World psychiatry : official journal of the World Psychiatric Association (WPA)*, *16*(2), 163–180. https://doi.org/10.1002/wps.20420

Chen, C. J., Liao, W. Y., Chattopadhyay, A., & Lu, T. P. (2023). Exploring the genetic correlation of cardiovascular diseases and mood disorders in the UK Biobank. *Epidemiology and psychiatric sciences*, *32*, e31. https://doi.org/10.1017/S2045796023000252

Friborg, O., Martinsen, E. W., Martinussen, M., Kaiser, S., Overgård, K. T., & Rosenvinge, J. H. (2014). Comorbidity of personality disorders in mood disorders: a meta-analytic review of 122 studies from 1988 to 2010. *Journal of affective disorders*, *152-154*, 1–11. https://doi.org/10.1016/j.jad.2013.08.023

Grotzinger, A. D., Mallard, T. T., Akingbuwa, W. A., Ip, H. F., Adams, M. J., Lewis, C. M., McIntosh, A. M., Grove, J., Dalsgaard, S., Lesch, K. P., Strom, N., Meier, S. M., Mattheisen, M., Børglum, A. D., Mors, O., Breen, G., iPSYCH, Tourette Syndrome and Obsessive Compulsive Disorder Working Group of the Psychiatric Genetics Consortium, Bipolar Disorder Working Group of the Psychiatric Genetics Consortium, Major Depressive Disorder Working Group of the Psychiatric Genetics Consortium, … Nivard, M. G. (2022). Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic and molecular genetic levels of analysis. *Nature genetics*, *54*(5), 548–559. https://doi.org/10.1038/s41588-022-01057-4

Grotzinger, A. D., Rhemtulla, M., de Vlaming, R., Ritchie, S. J., Mallard, T. T., Hill, W. D., Ip, H. F., Marioni, R. E., McIntosh, A. M., Deary, I. J., Koellinger, P. D., Harden, K. P., Nivard, M. G., & Tucker-Drob, E. M. (2019). Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits. *Nature human behaviour*, *3*(5), 513–525. https://doi.org/10.1038/s41562-019-0566-x

Grotzinger, A. D., Singh, K., Miller-Fleming, T. W., Lam, M., Mallard, T. T., Chen, Y., Liu, Z., Ge, T., & Smoller, J. W. (2023). Transcriptome-Wide Structural Equation Modeling of

13 Major Psychiatric Disorders for Cross-Disorder Risk and Drug Repurposing. *JAMA psychiatry*, *80*(8), 811–821. https://doi.org/10.1001/jamapsychiatry.2023.1808

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry*, *62*(6), 593–602. https://doi.org/10.1001/archpsyc.62.6.593

Lawrence, J. M., Breunig, S., Foote, I. F., Tallis, C. B., & Grotzinger, A. D. (2024). Genomic SEM applied to explore etiological divergences in bipolar subtypes. *Psychological Medicine*, *54*(6), 1152–1159. doi:10.1017/S0033291723002957

Momen, N. C., Plana-Ripoll, O., Agerbo, E., Benros, M. E., Børglum, A. D., Christensen, M. K., Dalsgaard, S., Degenhardt, L., de Jonge, P., Debost, J. P. G., Fenger-Grøn, M., Gunn, J. M., Iburg, K. M., Kessing, L. V., Kessler, R. C., Laursen, T. M., Lim, C. C. W., Mors, O., Mortensen, P. B., Musliner, K. L., … McGrath, J. J. (2020). Association between Mental Disorders and Subsequent Medical Conditions. *The New England journal of medicine*, *382*(18), 1721–1731. https://doi.org/10.1056/NEJMoa1915784

Polderman, T. J., Benyamin, B., de Leeuw, C. A., Sullivan, P. F., van Bochoven, A., Visscher, P. M., & Posthuma, D. (2015). Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nature genetics*, *47*(7), 702–709. https://doi.org/10.1038/ng.3285

Rudisch, B., & Nemeroff, C. B. (2003). Epidemiology of comorbid coronary artery disease and depression. *Biological psychiatry*, *54*(3), 227–240. https://doi.org/10.1016/s0006-3223(03)00587-0

Zhang, F., Cao, H., & Baranova, A. (2021). Shared Genetic Liability and Causal Associations Between Major Depressive Disorder and Cardiovascular Diseases. *Frontiers in cardiovascular medicine*, *8*, 735136. https://doi.org/10.3389/fcvm.2021.735136

Figures

Table 1. Psychiatric and Cardiac Trait Sample Sizes

Case and control sample sizes for all cardiac and psychiatric outcomes included in this study. All case samples are > 2000 to ensure power. Cohorts were garnered from publicly available large-scale GWAS.

Trait	Case sample size	Control sample size	Source
Psychiatric Traits			
Alcohol Use Disorder (AUD)	8,485	20,272	Walters et al. 2018
Anorexia Nervosa (AN)	16,992	55,525	Watson et al. 2019
Anxiety Disorders (ANX)	31,977	82,114	Purves et al. 2020
Attention-Deficit Hyperactivity Disorder (ADHD)	38,691	186,843	Demontis et al. 2019
Autism Spectrum Disorder (ASD)	18,381	27,969	Richard et al. 2017
Bipolar Disorder (BD)	41,917	371,549	Mullins et al. 2021
Cannabis Use Disorder (CUD)	14,808	343,726	Johnson et al. 2020
Major Depressive Disorder (MDD)	170,756	329,443	Howard et al. 2019
Obsessive Compulsive Disorder (OCD)	2,688	7,037	Arnold et al. 2018
Opioid Use Disorder (OUD)	3,211	11,589	Polimanti et al. 2020
Post-Traumatic Stress Disorder (PTSD)	2,424	7,113	Duncan et al. 2018
Schizophrenia (SCZ)	53,286	77,258	Trubetskoy et al. 2020
Tourette Syndrome (TS)	4,819	9,488	Yu et al. 2019
Cardiac Traits			
Abnormal heart sounds (AHS)	12,183	400,902	Momen et al. 2020
Cardiac conduction disorders (CCD)	9,624	384,657	Momen et al. 2020
Nonspecific chest pain (NCS)	33,293	384,496	Momen et al. 2020
Other aneurysm (OA)	2,586	408,565	Momen et al. 2020
Other disorders of circulatory system (ODCS)	21,420	392,807	Momen et al. 2020
Peripheral vascular disease (PVD)	5,040	408,565	Momen et al. 2020
Phlebitis and thrombophlebitis (PT)	4,797	376,206	Momen et al. 2020
Varicose veins (VV)	13,440	376,206	Momen et al. 2020
Hypertension (HT)	129909	354689	Dönertaş et al. 2021

Myocardial infarction (MI)	17505	454212	Hartiala et al. 2021
Atrial fibrillation and flutter (AF)	60620	970216	Nielsen et al. 2018
Heart failure NOS (HF)	47309	930014	Shah et al. 2020
Cerebral ischemia (Ischemic Stroke) (ISCH)	62100	1234808	Mishra et al. 2022
Hemorrhoidal disease (HD)	218920	725213	Zheng et al. 2021

Figure 1. Psychiatric Path Diagram

The five latent psychiatric genomic factors are shown as green circles. The traits that define each factor are shown as clear ovals, and included under these are the residuals for each trait. Correlations (r_g) between latent variables is shown with double-headed curved arrows while regression paths between latent variables and indicators are shown with single-headed straight arrows.

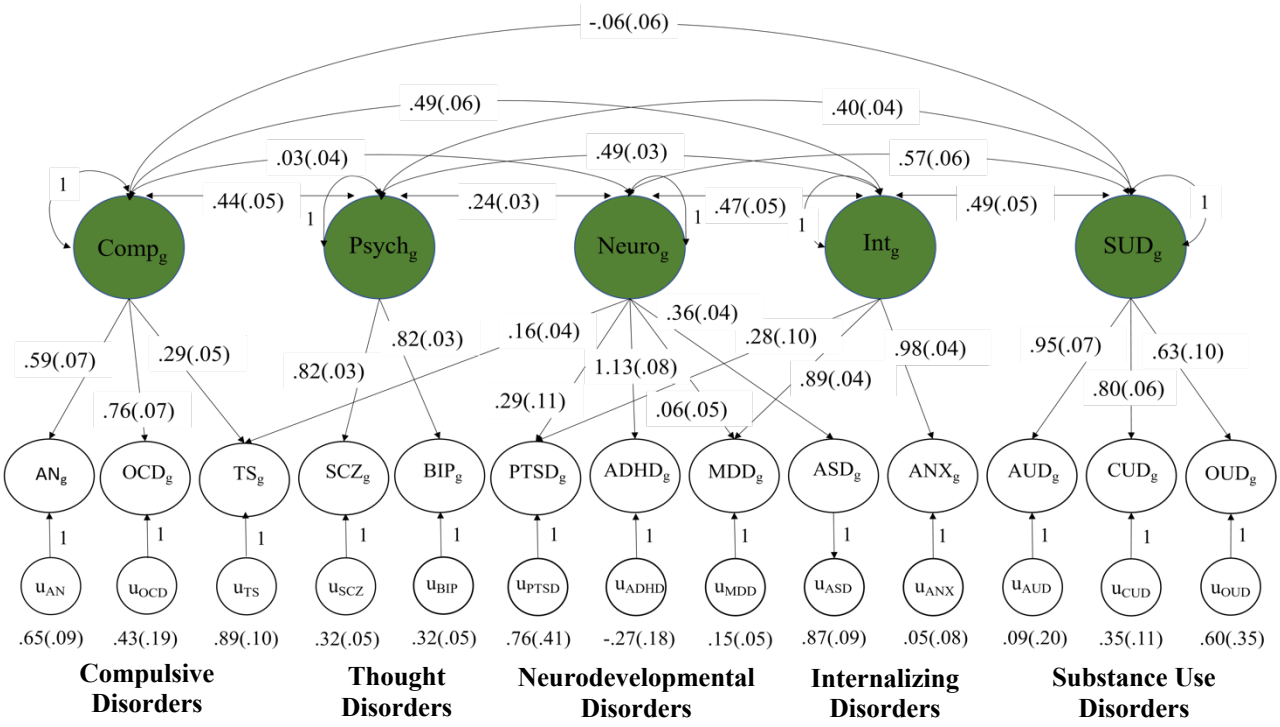

Figure 2. Cardiovascular Path Diagram

Cardiac factors are shown as blue circles. The traits that define each factor are shown as clear ovals, and included under these are the residuals for each trait. Correlations (r_g) between latent variables are shown with double-headed curved arrows while regression paths between latent variables and indicators are shown with single-headed straight arrows.

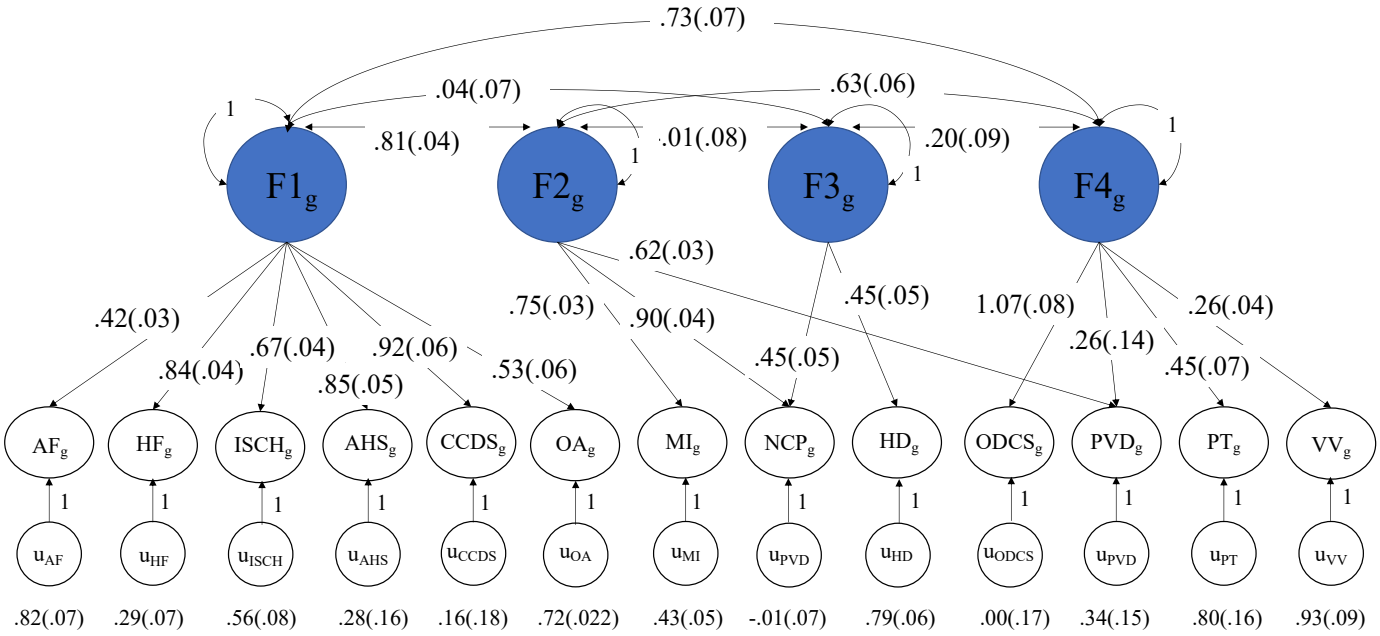

Figure3. Inter-factor Path Diagram

The four latent cardiac genomic factors are shown as blue circles. The five latent psychiatric genomic factors are shown as green circles. Because all factors included in the diagram are latent, all correlations (r_g) are shown with double headed arrows. Correlations that pass p-value significance are shown with solid arrows, while those that don't are shown with dashed arrows.

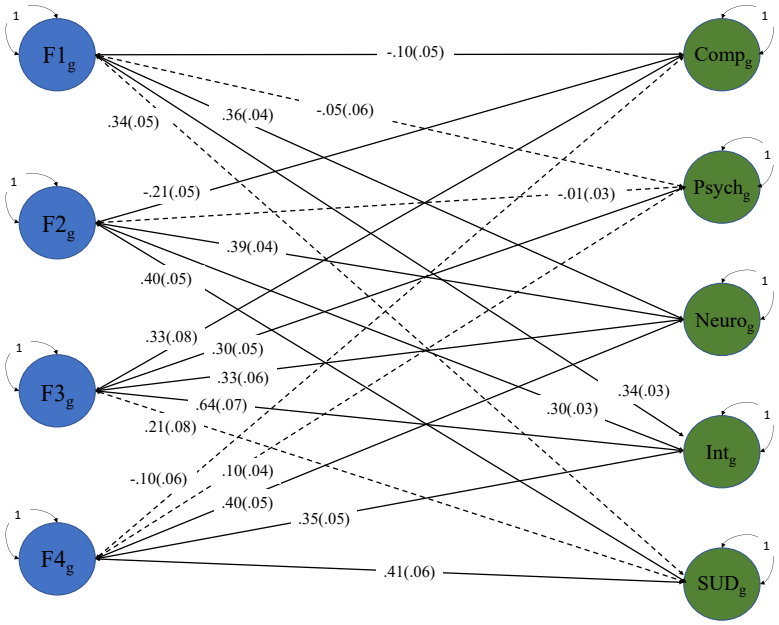

Figure 4. Inter-factor Correlation Model

Inter-factor genetic correlations are shown separately for each of our four cardiovascular illness factors. Each factor features a representation of the genetic overlap between each psychiatric factor. Error bars depict 95% confidence intervals garnered directly from the *GenomicSEM* software package within R. Correlations that pass p-value significance are shown with solid lines for error bars, while those that don't are shown with dotted lines. *CFI =0.896, SRMR = .086*