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Impact of polygenic risk for coronary artery disease and cardiovascular medication burden on cognitive impairment in psychotic disorders

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ETHICAL STATEMENT

The authors have read and have abided by the statement of ethical standards for manuscripts submitted to the Progress in Neuro-Psychopharmacology & Biological Psychiatry. All authors made a substantial contribution to the research and have approved the manuscript.

DECLARATION OF COMPETING INTERESTS

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Abstract

Background: Cognitive impairment is a core deficit across psychotic disorders, the causes and therapeutics of which remain unclear. Epidemiological observations have suggested associations between cognitive dysfunction in psychotic disorders and cardiovascular risk factors, but an underlying etiology has not been established.

Methods: Neuropsychological performance using the Brief Assessment of Cognition in Schizophrenia (BACS) was assessed in 616 individuals of European ancestry (403 psychosis, 213 controls). Polygenic risk scores for coronary artery disease (PRS_{CAD}) were quantified for each participant across 13 p-value thresholds (P_T 0.5-5e^{-8}). Cardiovascular and psychotropic medications were categorized for association analyses. Each PRS_{CAD} was examined in relation to the BACS and the optimized P_T was confirmed with five-fold cross-validation and independent validation. Functional enrichment analyses were used to identify biological mechanisms linked to PRS_{CAD}-cognition associations. Multiple regression analyses examined PRS_{CAD} under the optimal P_T and medication burden in relation to the BACS composite and subtest scores.

Results: Higher PRS_{CAD} was associated with lower BACS composite scores (p=0.001) in the psychosis group, primarily driven by the Verbal Memory subtest (p<0.001). Genes linked to multiple nervous system related processes and pathways were significantly enriched in PRS_{CAD}. After controlling for PRS_{CAD}, a greater number of cardiovascular medications was also correlated with worse BACS performance in patients with psychotic disorders (p=0.029).

Conclusions: Higher PRS_{CAD} and taking more cardiovascular medications were both significantly associated with cognitive impairment in psychosis. These findings indicate that cardiovascular factors may increase the risk for cognitive dysfunction and related functional outcomes among individuals with psychotic disorders.

Keywords

Coronary artery disease; polygenic risk score; cardiovascular medication; cognition; psychosis

1. INTRODUCTION

Individuals with psychotic disorders typically perform 1-2 standard deviations (SDs) lower than healthy controls on neuropsychological tests, representing a common and significant cause of functional disability.[1] The causes of this cognitive impairment are likely multifactorial but remain poorly understood and no therapeutics for these deficits have been established. Cardiovascular diseases (CVD) and risk factors along with their treatments are very common in patients with psychotic disorders,[2,3] and represent potential contributing causes to cognitive impairments with therapeutic implications.[4]

Comorbid cardiovascular risk factors have been associated with lower cognitive performance among individuals with psychotic disorders.[5,6] Poor cognitive performance is also a common complication of coronary artery disease (CAD) in the general population.[7] Individuals with CAD who are 45 years of age and older have an estimated 45% increased risk of cognitive impairment or dementia compared to controls without CAD.[8] The link between cardiovascular conditions and cognitive impairment, although relatively well known, involves complex relationships and mechanistic implications. Among patients with CAD, vascular insufficiencies may lead to cerebrovascular abnormalities, and subsequently contribute to brain hypoperfusion and white matter lesions, which are associated with cognitive decline and the risk of vascular dementia.[9] Despite phenotypical associations of CAD and reduced cognitive functioning, the exact biological mechanisms by which CAD is related to risk for cognitive impairment are largely unknown.

In addition to influences of risk and presence of CAD on cognition, one environmental factor that may influence cognition is medication exposure. Impacts of psychotropic medications[10-13] on cognition in patients with psychotic disorders are well established in clinical and preclinical models. However, the cognitive effects of commonly used cardiovascular medications in psychosis have not been extensively examined. In studies of non-psychiatric patients, findings regarding the impact of cardiovascular medications on cognition have been mixed.[14,15] Beta-blockers are widely used to treat cardiovascular conditions and, separately, to treat some antipsychotic side effects. Multiple studies have detected moderately impaired cognitive performance in non-psychiatric populations treated with beta blockers, particularly notable in some[15,16] but not all[17,18] studies of propranolol which has high CNS penetration. Some types of medications used for cardiovascular conditions, such as statins, may have a mixture of adverse and beneficial cognitive effects through different mechanisms.[19]

The extent to which CAD genetic predisposition and treatments for cardiovascular illness influence cognitive performance in individuals with psychotic disorders have not been clarified, but associations have been identified between these factors and dementia or cognitive ability in older adults.[20-22] No similar studies have been conducted in younger adults (age<65) and/or in individuals with psychotic disorders. Recent evidence

suggests genetic overlap between psychiatric illnesses and cardiovascular diseases and risk factors,[23,24] but whether the genetic link between diseases could impact cognitive and functional outcomes remains unclear.

Polygenic risk scores (PRS) quantify an individual's genetic risk for a given disease by aggregating the contribution of the germline genome.[25] While not currently used clinically, a growing number of studies have suggested the potential utility of PRS for CAD (PRS_{CAD}) for disease risk stratification and guidance for early intervention.[25,26] We have conducted, to our knowledge, the first study investigating the impact of polygenic risk for CAD along with concomitant cardiovascular medication use on cognitive performance in young to mid-life adults with psychotic disorders. The aims were: 1) to examine relationship of polygenic risk for CAD and cognitive performance in individuals with psychotic disorders and healthy control subjects; and 2) to investigate how concomitant cardiovascular medication exposure may be associated with cognitive function and interact with polygenic risk for CAD in relation to cognitive performance.

2. METHODS AND MATERIALS

2.1. Study participants

The study sample included 616 participants with self-reported European ancestry (n=403 with psychotic disorders, n=213 healthy controls) enrolled through the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) consortium.[27] All participants provided written informed consent (see Supplemental Methods for details on inclusion criteria). Individuals with psychotic disorders met diagnostic criteria for schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features. Psychiatric diagnoses were established through consensus meetings reviewing findings from the Structured Clinical Interview for DSM-IV.[28] Symptom severity was assessed with the Positive and Negative Syndrome Scale (PANSS).[29] All participants completed the Brief Assessment of Cognition in Schizophrenia (BACS).[30] The BACS assesses verbal declarative memory, working memory, motor speed, verbal fluency, information processing speed, and executive function, and uses tests of these dimensions to generate a composite total score of global cognitive performance. BACS results were corrected for age and sex and normalized to z-scores based on the cognition-intact reference cohort with winsorization to a range of ±4.0 as described previously.[1,30]

2.2. Medication assessments

Medication history for prescription and non-prescription medications was collected for each participant through a structured medication history interview on the day when BACS was administered, supplemented with medical record review where available. All cardiovascular medications, defined as agents with at least one indication to treat CVDs, were examined. Regardless of indication (e.g. whether a beta-blocker was used for a cardiovascular condition or antipsychotic-associated akathisia), cardiovascular medications were examined in relation to BACS due to prior studies indicating potential cognitive impact.[15] Cardiovascular medication categorization and descriptions of the rationale for including some medications which may have a dual or uncertain purpose are included in the Supplemental Methods.

The total number of cardiovascular agents was examined for relationships with cognitive performance. Psychiatric medications and anticholinergic drug burden scores (ADS scores) were also collected and characterized for analyses as published previously.[13,27]

2.3. Statistical analysis

Group comparisons between individuals with psychotic disorders (Psych) and healthy controls (HC) for demographic and clinical characteristics were performed using two-sample t-test for continuous variables, Chi-square or Fisher's Exact test for categorical variables, and the Mann-Whitney U test for ordinal variables. Considering previously described differences of BACS scores across psychotic diagnoses,[1] analysis of variance (AVOVA) was used to compare PRS_{CAD} across three diagnoses and the experimental neurophysiology-determined biotypes developed by the B-SNIP consortium.[31] A two-sample t-test was used to compare PRS_{CAD} between those with and without CVD (e.g. CAD, hypertension, hyperlipidemia, etc.). All statistical analyses were performed using R Statistical Software (version 4.0.2).

2.4. Genotyping and imputation

Genotyping was performed on blood-based DNA using the Illumina Infinium PsychChip array followed by quality control (QC) using PLINK 1.9[32] (see detailed QC procedures in Supplemental Methods). Imputation was performed using SNPs passing QC procedures using HAPI-UR for pre-phasing[33] and IMPUTE2 for imputation[34] with the 1000 Genome phase 1 multiethnic reference panel.[35] Post-imputation QC was performed to remove poorly imputed SNPs (information score<0.5) and SNPs with excessive missingness (>0.1), and MAF<5%, resulting in 4,322,238 common high-quality SNPs.

To account for genetically driven population substructure within subjects who self-identified as European descent, a multidimensional scaling (MDS) analysis was performed relative to the 1000 genome populations[36]. The first five MDS principal components (PCs) were used 1) as genomic ancestry covariates for association analyses, which captured the majority of ethnic-related variance (Supplemental Figures S1 and S2A); and 2) to determine genetically driven European ancestry for sensitivity analyses (see Supplement Methods).

2.5. Genetic risk scoring

The PRS model was defined as the sum of the effect allele dosage across a set of selected SNPs weighted by the effect size measure. CAD GWAS summary statistics from the Coronary Artery Disease Genome-Wide Replication and Meta-analysis plus the Coronary Artery Disease Genetics Consortium (CARDIoGRAMplusC4D)[37] (http://www.cardiogramplusc4d.org/data-downloads/) were used to compute PRS_{CAD}. The clumping and thresholding (pT-clump) procedure was performed using PRSice-2 software.[38] Clumping was conducted to select independent SNPs with the most significant statistical evidence in each LD block ($r^2 \geq 0.1$) within a 500kb window.[38] PRS_{CAD} was calculated under 13 p-value significance thresholds (P_T): $5e^{-8}$, $1e^{-7}$, $1e^{-6}$, $1e^{-5}$, $1e^{-4}$, $1e^{-3}$, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, and 0.5 as the best-fit P_T was no known *a priori*. For comparison, PRS_{CAD} was also calculated with PRScs, a Bayesian polygenic prediction method that applies a shrinkage

parameter to infer posterior SNP effect sizes[39,40] (see Supplemental Methods and Results for details on PRScs algorithm and results which were similar to pT-clump).

2.6. Cross-validation and independent validation of regression analysis of PRS_{CAD} and BACS

Cross-validation was carried out using the 'caret' R package with the same random seeds setting. The total study sample (N=616) was randomly split such that 80% of the participants were used as the cross-validation set and the remaining 20% as an independent validation set Linear regression models were fitted to test associations between the primary outcome variable (age- and sex-normed BACS composite z-scores) and PRS_{CAD} at each of 13 P_T values in the cross-validation set The top five ancestry PCs were included as covariates. Five-fold cross-validation was performed to test the performance of the regression model of BACS and PRS_{CAD} at the P_T optimizing the association signal indicated by the coefficient of determination (R^2). Independent validation for the PRS_{CAD} at the optimized P_T was performed in the independent set. The root mean square error (RMSE) was calculated as the primary parameter to assess the model fit. Small and similar RMSE values among all-sample regression, cross-validation, and independent validation indicated good model performance and prediction accuracy. Post-hoc analyses examined the linear regression of PRS_{CAD} and BACS at other P_T values in the independent test set and the whole cohort (the cross-validation set and independent test set combined) for comparison. To further account for potential overfitting and multiple testing for the analyses in the whole cohort, 10,000 random permutations were performed to compute empirical p-values (EMP) corresponding to each PRS (including the optimized P_T) and across all 13 PRS associations of the BACS (see Supplemental Methods for permutation procedures).

2.7. Association analyses of PRS_{CAD}, cardiovascular medication use, and cognition among individuals with psychotic disorders and healthy controls

Using the selected PRS_{CAD} of the optimized P_T value to further explore the impact of CAD polygenic load on cognitive function, BACS scores were compared across PRS_{CAD} quintiles. Secondary association analyses were performed with BACS subtests and stratified by Psych and HC groups. Discriminant analyses were conducted to contrast higher (≥2 medications) and lower (<2 medications) cardiovascular medication burden groups for association studies with the BACS (see Supplemental Methods for ascertaining threshold of cardiovascular medication burden on cognition).

The primary multiple regression analyses were performed to examine PRS_{CAD} and cardiovascular medication groups in relation to cognitive performance with the top five ancestry PCs as covariates within the total cohort and by group (Psych vs HC). Medication-gene interactions and CVD diagnosis interactions were explored but multicollinearity was found between the medication-gene interaction and the medication variables based on variance inflation factor (VIF) >151 (VIFs >10 indicate serious multicollinearity). To assess the potential effects of age, sex, and reported duration of illness for schizophrenia-spectrum or bipolar disorders on the associations of PRS_{CAD} and cardiovascular medications and BACS, sensitivity analyses further examined relationships within age strata (median split and tertile strata), males versus females, and longer vs shorter illness duration. The effects

of cardiovascular and psychotic disorder diagnoses, symptom severity of psychosis (PANSS total scores), polygenic risk scores for schizophrenia (PRS_{SCZ}) or bipolar disorder (PRS_{BD}), socioeconomic status (Hollingshead socioeconomic score), psychiatric medications, and ADS scores on the relationship of PRS_{CAD} and BACS were also investigated (see Supplement Methods).

2.8. Exploratory enrichment analysis

To explore biological processes and pathways of the genes included in PRS_{CAD}, pathway enrichment analysis was conducted using the R package gProfileR.[41] SNPs included in PRS_{CAD} were mapped to genes based on the Ensembl database. Enrichment analysis was performed with an unranked gene list using the hypergeometric test followed by Bonferroni correction to determine the over-representation of Gene Ontology Biological Processes, KEGG and Reactome pathways. Additionally, a gene set analysis of PRS_{CAD} genes accounting for the CAD disease risk p-value and LD from the training set GWAS was performed with MAGMA (v1.09b).[42]

2.9. Genetic correlation analysis

Linkage disequilibrium (LD) score regression was applied to calculate genetic correlations among large-scale GWAS summary statistics for CAD[37], schizophrenia[43], bipolar disorder[44], and general cognitive function[45] with the Python package LDSC v1.0.1. The GWAS summary statistics were downloaded from the consortium data repositories (see Supplement I for details). LD score regression quantifies shared genetic etiology between two traits, the pipeline of which was previously published by Bulik-Sullivan et al.[46] (available at https://github.com/bulik/ldsc).

3. RESULTS

3.1. Participant characteristics

Demographic and clinical characteristics are summarized by group in Table 1. On average, individuals with psychotic disorders were younger than the healthy control subjects ($p=0.001$). The median number of concomitant medications was higher in the Psych group, largely driven by psychotropic medication use. In the Psych group, 85% of participants were treated with at least one antipsychotic medication (see Supplemental Table S1 for the summary of major psychotropic categories). The proportion of participants who reported taking at least one cardiovascular medication was similar between Psych and HC groups across different medication classes, except the use of antiplatelets (Table 2). Among cardiovascular medication users, the median number of blood pressure lowering agents was significantly higher in Psych than HC, primarily driven by propranolol use in the Psych group. There were no significant differences in PRS_{CAD} across healthy control and psychosis diagnoses (e.g. schizophrenia vs schizoaffective disorder vs psychotic bipolar disorder) or neurophysiology-determined biotypes[31] (Supplemental Table S2). Only six participants reporting CAD diagnosis limited the statistical power to examine genetic relationships; while there was a trend of higher PRS_{CAD} among individuals who reported hypertension diagnosis than those without ($t=-1.846$, $p=0.068$), consistent with previous evidence of shared genes between CAD and other cardiovascular risk factors.[47]

3.2. PRS_{CAD} associations with the performance on the BACS composite and subtests

Figure 1 presents the model fit of PRSs at 13 prespecified P_T values in association with BACS composite z-scores in the whole cohort (Psych+HC N=616) and model performance comparison with cross-validation and independent validation under the optimized P_T. Higher PRS_{CAD} was significantly associated with lower BACS scores (worse cognitive performance) at P_T of 0.05-0.5. From the lowest to the highest P_T values, the variance explained by PRS_{CAD} (R^2) reached the plateau at P_T of 0.2, which indicated a maximization of model fit at $P_T \geq 0.2$, ranging from 1.593% to 1.729%. The model performance at P_T of 0.2 was highly consistent across cross-validation, independent validation and the full-cohort regression based on similar Root Mean Square Error (RMSE) (see Supplemental Table S3-4 for the summary of all PRS models). The PRS_{CAD} at P_T of 0.2 comprised of 35,462 SNPs (see Supplement II for gene annotations of the top 100 variants) was therefore used for subsequent analyses. The empirical p-values from permutation tests were 0.002 at P_T of 0.2 and 0.007 while adjusting for all 13 P_T values for multiple testing correction (Supplemental Table S4).

Among all 616 participants, higher PRS_{CAD} (at P_T of 0.2) was associated with lower BACS composite scores (R^2=1.593%, p=0.002) (Figure 2). Follow-up exploratory tests revealed associations with three subtests: Verbal Memory (R^2=2.162%, p<0.001), Symbol Coding (R^2=0.876%, p=0.021), and Tower of London (R^2=1.029%, p=0.012) (Table 3). In subgroup analyses stratified by Psych and HC, PRS_{CAD} was significantly associated with performance on the BACS composite (R^2=2.618%, p=0.001) (Figure 2), Verbal Memory (R^2=3.097%, p<0.001), Token Motor (R^2=1.051%, p=0.041), and Tower of London (R^2=1.842%, p=0.007) among 403 individuals with psychotic disorders, whereas no statistically significant associations between PRS_{CAD} and BACS were identified among 213 controls (Table 3).

In post-hoc exploratory analyses, associations of PRS_{CAD} at other P_T values and BACS composite z-scores were examined with the same regression model stratified by Psych and HC groups (Supplemental Table S5). Similar to P_T of 0.2, at other P_T values ranging from 0.05 to 0.5, the PRS-cognition association was significant in the Psych but not the HC group. Furthermore, cardiovascular and psychotic diagnoses, PANSS total scores, PRS_{SCZ}, PRS_{BD}, socioeconomic status, psychiatric medications, and ADS scores did not confound the inverse correlation of PRS_{CAD} and cognitive performance in the Psych group (see Supplemental Table S6 for details on examining PRS_{SCZ} and PRS_{BD}). Within the Psych group, PRS_{CAD} associations with BACS were more pronounced in younger males and those with shorter duration of illness (see Supplemental Results for detailed statistics). PRS_{CAD} associations with BACS were retained regardless of approaches used to define and adjust for genomic ancestry (Supplemental Table S7).

To further quantify and illustrate the clinical impact of CAD polygenic risk relationships with cognitive impairment within the Psych group, participants were divided into PRS_{CAD} quintiles using P_T of 0.2 and mean BACS composite z-scores were compared across PRS_{CAD} quintiles. As shown in Figure 3, cognitive impairment was more prominent in the fourth and fifth PRS quintiles, on average, 1.3 and 1.7 standard deviations (SDs) lower BACS scores than the cognition-intact healthy individuals (the reference cohort for BACS),

whereas individuals with psychotic disorders within the first three PRS quintiles have ~1 SD lower performance on BACS.

3.3. Enrichment and pathway analyses of PRS_{CAD}

Of 35,462 SNPs included in PRS_{CAD} at P_T of 0.2, 10,355 gene IDs representing 7,993 proteincoding genes were mapped based on Ensembl and included in the enrichment analysis. A total of 250 biological processes or pathways were significantly enriched with PRS_{CAD} genes at P_T of 0.2 (194 gene ontology (GO) biological processes (BP), 28 KEGG pathways, 28 Reactome pathways, using a Bonferroni-adjusted p-value < 0.05). A large proportion of BP and pathways identified are involved in neuronal development and functions. Eight out of the top 20 enriched GO BP terms ($p_{adj}<3.010e^{-21}$) were specific to nervous system development (Figure 4). The cognition BP (GO:0050890) was found to be significantly enriched with PRS_{CAD} genes at P_T of 0.2 ($p_{adj}=0.019$). The overrepresentation of multiple nervous system related processes or pathways enriched in gene lists under PRS_{CAD} P_T of 0.2 was also found among the gene lists for smaller P_T values ($1e^{-3}$, 0.01, 0.05, 0.1). There was a trend of more CNS related pathways being overrepresented as P_T value increases along with cardiovascular related pathways (see Supplement III for full results). The MAGMA gene set analysis among PRS_{CAD} genes represented by SNPs at P_T of 0.2 also identified pathways/processes related to neurodevelopment, amyloid-beta homeostasis, and neurotransmitter clearance (see Supplement IV for full results).

3.4. PRS_{CAD} and cardiovascular medication associations with BACS among individuals with psychotic disorders

The results of multiple regression of cognitive performance in relation to PRS_{CAD} and cardiovascular medication use among individuals with psychotic disorders are summarized in Table 4. After accounting for cardiovascular medication use, associations of higher PRS_{CAD} with lower BACS composite z-scores remained significant (p<0.001), which appeared to be mostly driven by Verbal Memory subtest performance (p<0.001). Independent of CAD genetic predisposition, cardiovascular medication burden ($N_{cv\text{-}meds}\geq2$) was also inversely correlated with BACS performance (p=0.029). PRS_{CAD} and cardiovascular medication burden together explained 4.357% variance of the BACS composite z-scores in the Psych group. Cardiovascular and psychotic diagnoses, medication exposure and other clinical variables did not alter the association of either PRS_{CAD} or cardiovascular medication burden with BACS (see Supplemental Results).

3.5. Genetic correlation of general cognitive function with diseases of interest

Figure 5 presents the results of LD score regression-based genetic correlations (rg) among general cognitive function, CAD, schizophrenia, and bipolar disorder. The p-values for the corresponding rg values are detailed in Supplement I. Significant negative correlations were observed between general cognitive function and all three diseases (CAD: p-value=$2.177e^{-9}$; schizophrenia: p-value=$3.159e^{-36}$; bipolar disorder: p-value=$1.785e^{-7}$). Consistent with previous findings,[46] no significant genetic correlation was observed between CAD and either schizophrenia (p-value=0.989) or bipolar disorder (p-value=0.640).

4. DISCUSSION

To our knowledge, this is the first investigation to examine relationships between genetic risk for CAD and cardiovascular medication use with cognition in a study sample of individuals with psychotic disorders and healthy controls. Higher PRS_{CAD} was associated with lower cognitive performance, driven by associations among individuals with psychotic disorders. This association was not influenced by cardiovascular or psychiatric diagnoses, psychiatric medications, or other clinical factors. Independent to PRS_{CAD}, CVD diagnoses reflecting cardiac disease burden and other established covariates, high cardiovascular medication burden was also associated with lower cognitive performance. Results also suggest a stronger relationship between cardiovascular genetics and cognition in younger males with psychotic disorders. These findings present opportunities to further clarify treatment versus disease relationships and the biological mechanisms by which genetic predisposition for CAD impacts cognitive function.

Previous studies investigating the impact of cardiovascular disease risk factors, including genetics and medication exposure, on cognitive function and dementia risk have been primarily assessed in older patient populations. In these prior studies, most participants did not have predisposing cognitive vulnerability due to neuropsychiatric illness.[7,14,16-18,21] Individuals younger than 65 tend to be underrepresented in these studies despite prevalence estimates of cognitive impairment ranging 4-8% among young adults.[48] The present study is unique in that we examined relatively young healthy adults and individuals with psychotic disorders. Our findings demonstrated that 4.4% of variance in cognitive function can be attributed to cardiovascular genetics and medication risk factors in individuals with psychotic disorders. We did not find significant associations between cardiovascular genetics and cognitive performance in analyses limited to healthy controls although Mendelian Randomization studies have previously identified evidence for causal relationships in large repository studies of the general population.[49,50] The range of cognitive performance was much more restricted in HC than Psych, and the sample of HC was smaller, which may have resulted in lower statistical power to detect significant gene-cognition associations in the HC group (Figure 2B). However, the relative difference in effect sizes may also indicate that cardiovascular illness and treatments could have greater adverse effects on cognition in individuals with pre-existing cognitive impairment related to their psychiatric illness.

In the present study, symptom severity, polygenic risk for schizophrenia or bipolar disorder, socioeconomic status, age, psychiatric medications, and anticholinergic drug burden did not moderate the inverse correlation of PRS_{CAD} and cognitive performance in individuals with psychotic disorders. Thus, cardiovascular health and CVD prevention may represent important considerations in the clinical care and treatment strategies for patients with psychotic disorders, especially for those with cognitive impairment. To date, PRS association studies of cognitive phenotypes have largely focused on risk for assorted mental health disorders.[51-53] Investigating PRS_{CAD} associations in the context of psychosis is novel in its conceptual approach and has important clinical and mechanistic implications for patients with serious mental illnesses.

There has been evidence suggesting a shared genetic etiology between cognitive function and cardiovascular conditions and risk factors.[20,46,54] Our genetic correlation findings suggest that CAD may have shared genetic etiology with cognitive function separate from psychiatric illnesses. The present findings add to the literature supporting significant association between PRS_{CAD} and cognition and extend those observations to patients with psychotic disorders. Across BACS domains, the association was most pronounced in verbal declarative memory, with less pronounced, albeit significant, associations with executive function and information processing speed. Alterations in these cognitive domains have been frequently reported among individuals with chronic coronary heart diseases and/or after a major cardiovascular event with pathophysiological implications such as vascular damage and cerebral perfusion.[55-57] Multiple brain areas/systems involved in those cognitive domains (such as prefrontal cortex and hippocampus) are also known to be influenced by cardiovascular risk factors.[58,59]

Emerging studies have explored the correlation of cardiovascular risk and neural connectivity from the level of molecular and biological pathways, such as regulation of neurogenesis, dendrite development, and synaptic connection, in relation to cognition and brain structure integrity.[60,61] A recent study found genetic variants contributing to structural cardiac development were significantly associated with human brain connectome measures.[62] Our preliminary pathway analyses identified multiple biological processes and pathways related to nervous system development that were enriched in genes involved in PRS_{CAD}. These findings provide mechanistic insights linking the cardiovascular polygenic architecture to brain development and cognitive function. High genetic predisposition for CVDs may affect both synaptic transmission and the early stage of neuronal development Future studies are warranted to further elucidate the underlying biology and etiology of cerebrovascular risk factors in relation to cognition and brain structure integrity, particularly in the context of psychotic disorders.

Among individuals with psychotic disorders, 2.62% of BACS variance was explained by CAD polygenic risk. The resulting relatively small variance explained by PRS is similar or greater than previous studies using disease traits PRSs to predict cognitive function (e.g. 0.49% and <0.7% variation in cognition measures explained by PRS for all ischemic stroke[63] and schizophrenia[64] respectively). Nevertheless, while mechanistically informative, clinical utility of PRS_{CAD} at this effect size is likely limited and highlights the multifactorial nature of cognitive function deficits in psychosis. Several other limitations in our study are also important to consider. The cross-sectional design and the age range of participants preclude an investigation of the longitudinal impact of CVD risk, illness and treatment on cognition. Second, medication treatment duration, dosing over time, adherence and longitudinal disease severity, and the longitudinal quality of health care were not reliably quantified by the cross-sectional design and the use of patient self-reports. Third, an important caveat when interpreting associations between medication exposure and cognitive outcomes is the challenge in distinguishing whether the significant relationship was due to medication or the disease. In this regard, etiological and clinical heterogeneity of CVDs may complicate the causal interpretability of the observed findings. Future Mendelian Randomization studies may be useful to explore causality. Fourth, the small sample size of the healthy control group limits our statistical power to detect smaller effect size associations

of PRS_{CAD} with cognition. Finally, we only included B-SNIP participants self-identified as European descent because the CAD GWAS for PRS calculation was performed and established in a predominantly white study sample. This limits the generalizability of our findings to other populations where CVDs are known to be common and important health factors. Thus, replication in an independent sample remains important.

5. CONCLUSION

In summary, our findings suggest CAD polygenic risk and medications for CVD are significantly associated with cognitive impairment among individuals with psychotic disorders. These findings highlight a significant contribution of cardiovascular factors to cognitive deficits that are an important source of functional disability in these patients. This underscores the importance of CAD factors in treatment planning for patients with severe mental illness. Preemptive strategies including lifestyle modifications, pharmacological interventions, or tailored medication selection and dosing approaches, could be explored to minimize illness-associated cognitive impairments and the large contribution to adverse functional outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES:

1. Hill SK, Reilly JL, Keefe RSE, et al. Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. Am J Psychiatry. 2013;170(11):1275–1284. doi:10.1176/appi.ajp.2013.12101298 [PubMed: 23771174]
2. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. Am Heart J. 2005;150(6):1115–1121. doi:10.1016/j.ahj.2005.02.007 [PubMed: 16338246]

3. De Hert M, Detraux J, Vancampfort D. The intriguing relationship between coronary heart disease and mental disorders. Dialogues Clin Neurosci. 2018;20(1):31–40. [PubMed: 29946209]
4. Emul M, Kalelioglu T. Etiology of cardiovascular disease in patients with schizophrenia: current perspectives. Neuropsychiatr Dis Treat. 2015;11:2493–2503. doi:10.2147/NDT.S50006 [PubMed: 26491327]
5. Friedman JI, Wallenstein S, Moshier E, et al. The effects of hypertension and body mass index on cognition in schizophrenia. Am J Psychiatry. 2010;167(10):1232–1239. doi:10.1176/appi.ajp.2010.09091328 [PubMed: 20634363]
6. Foguet-Boreu Q, Guàrdia Sancho A, Santos Lopez JM, et al. Association between cognitive impairment and cardiovascular burden in patients with severe mental disorder. Cogn Neuropsychiatry. 2020;25(1):1–13. doi:10.1080/13546805.2019.1676709 [PubMed: 31599190]
7. Burkauskas J, Lang P, Bunevičius A, Neverauskas J, Bučiūtė-Jankauskienė M, Mickuvienė N. Cognitive function in patients with coronary artery disease: A literature review. J Int Med Res. 2018;46(10):4019–4031. doi:10.1177/0300060517751452 [PubMed: 30157691]
8. Deckers K, Schievink SHJ, Rodriquez MMF, et al. Coronary heart disease and risk for cognitive impairment or dementia: Systematic review and meta-analysis. PLOS ONE. 2017;12(9):e0184244. doi:10.1371/journal.pone.0184244 [PubMed: 28886155]
9. de la Torre JC. Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. Cardiovasc Psychiatry Neurol. 2012;2012:367516. doi:10.1155/2012/367516 [PubMed: 23243502]
10. Sweeney JA, Keilp JG, Haas GL, Hill J, Weiden PJ. Relationships between medication treatments and neuropsychological test performance in schizophrenia. Psychiatry Research. 1991;37(3):297–308. doi: 10.1016/0165-1781(91)90065-W [PubMed: 1679950]
11. Reilly JL, Lencer R, Bishop JR, Keedy S, Sweeney JA. Pharmacological treatment effects on eye movement control. Brain and Cognition. 2008;68(3):415–435. doi: 10.1016/j.bandc.2008.08.026 [PubMed: 19028266]
12. Hill SK, Bishop JR, Palumbo D, Sweeney JA. Effect of second-generation antipsychotics on cognition: current issues and future challenges. Expert Review of Neurotherapeutics. 2010;10(1):43–57. doi:10.1586/ern.09.143 [PubMed: 20021320]
13. Eum S, Hill SK, Rubin LH, et al. Cognitive burden of anticholinergic medications in psychotic disorders. Schizophrenia Research. 2017;190:129–135. doi:10.1016/j.schres.2017.03.034 [PubMed: 28390849]
14. Rohde D, Hickey A, Williams D, Bennett K. Cognitive impairment and cardiovascular medication use: Results from wave 1 of The Irish Longitudinal Study on Ageing. Cardiovasc Ther. 2017;35(6). doi: 10.1111/1755-5922.12300
15. Marvanova M. Drug-induced cognitive impairment: Effect of cardiovascular agents. Ment Health Clin. 2016;6(4):201–206. doi: 10.9740/mhc.2016.07.201 [PubMed: 29955471]
16. Burkauskas J, Noreikaite A, Bunevicius A, et al. Beta-1-Selective Beta-Blockers and Cognitive Functions in Patients With Coronary Artery Disease: A Cross-Sectional Study. J Neuropsychiatry Clin Neurosci. 2016;28(2):143–146. doi: 10.1176/appi.neuropsych.15040088 [PubMed: 26715033]
17. Safarudin F, Iloabuchi CO, Ladani A, Sambamoorthi U. The Association of Beta-Blocker Use to Cognitive Impairment among Adults with Hypertension or Cardiovascular Diseases in the United States. Chronic Pain Manag. 2020;4. doi: 10.29011/2576-957x.100025
18. Gelber RP, Ross GW, Petrovitch H, Masaki KH, Launer LJ, White LR. Antihypertensive medication use and risk of cognitive impairment: the Honolulu-Asia Aging Study. Neurology. 2013;81(10):888–895. doi:10.1212/WNL.0b013e3182a351d4 [PubMed: 23911753]
19. Schultz BG, Patten DK, Berlau DJ. The role of statins in both cognitive impairment and protection against dementia: a tale of two mechanisms. Transl Neurodegener. 2018;7:5. doi: 10.1186/s40035-018-0110-3 [PubMed: 29507718]
20. Hagenaars SP, Harris SE, Clarke T-K, et al. Polygenic risk for coronary artery disease is associated with cognitive ability in older adults. Int J Epidemiol. 2016;45(2):433–440. doi: 10.1093/ije/dyv354 [PubMed: 26822939]

21. Karlsson IK, Ploner A, Song C, Gatz M, Pedersen NL, Hägg S. Genetic susceptibility to cardiovascular disease and risk of dementia. Transl Psychiatry. 2017;7(5):e1142. doi: 10.1038/tp.2017.110 [PubMed: 28556832]
22. Elman JA, Panizzon MS, Logue MW, et al. Genetic risk for coronary heart disease alters the influence of Alzheimer's genetic risk on mild cognitive impairment. Neurobiol Aging. 2019;84:237.e5–237.e12. doi:10.1016/j.neurobiolaging.2019.06.001
23. Strawbridge RJ, Johnston KJA, Bailey MES, et al. The overlap of genetic susceptibility to schizophrenia and cardiometabolic disease can be used to identify metabolically different groups of individuals. Sci Rep. 2021;11(1):632. doi:10.1038/s41598-020-79964-x [PubMed: 33436761]
24. Bahrami S, Steen NE, Shadrin A, et al. Shared Genetic Loci Between Body Mass Index and Major Psychiatric Disorders: A Genome-wide Association Study. JAMA Psychiatry. 2020;77(5):503–512. doi: 10.1001/jamapsychiatry.2019.4188 [PubMed: 31913414]
25. Lambert SA, Abraham G, Inouye M. Towards clinical utility of polygenic risk scores. Hum Mol Genet. 2019;28(R2):R133–R142. doi:10.1093/hmg/ddz187 [PubMed: 31363735]
26. Levin MG, Rader DJ. Polygenic Risk Scores and Coronary Artery Disease. Circulation. 2020;141(8):637–640. doi: 10.1161/CIRCULATIONAHA.119.044770 [PubMed: 32091922]
27. Tamminga CA, Ivleva EI, Keshavan MS, et al. Clinical phenotypes of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). Am J Psychiatry. 2013;170(11):1263–1274. doi:10.1176/appi.ajp.2013.12101339 [PubMed: 23846857]
28. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P). New York: New York State Psychiatric Institute; 1995.
29. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261–276. doi:10.1093/schbul/13.2.261 [PubMed: 3616518]
30. Keefe RSE, Harvey PD, Goldberg TE, et al. Norms and standardization of the Brief Assessment of Cognition in Schizophrenia (BACS). Schizophr Res. 2008;102(1-3):108–115. doi:10.1016/j.schres.2008.03.024 [PubMed: 18495435]
31. Clementz BA, Sweeney JA, Hamm JP, et al. Identification of Distinct Psychosis Biotypes Using Brain-Based Biomarkers. AJP. 2015;173(4):373–384. doi: 10.1176/appi.ajp.2015.14091200
32. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007;81(3):559–575. doi: 10.1086/519795 [PubMed: 17701901]
33. Williams AL, Patterson N, Glessner J, Hakonarson H, Reich D. Phasing of many thousands of genotyped samples. Am J Hum Genet. 2012;91(2):238–251. doi:10.1016/j.ajhg.2012.06.013 [PubMed: 22883141]
34. Howie B, Fuchsberger C, Stephens M, Marchini J, Abecasis GR. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. Nat Genet. 2012;44(8):955–959. doi: 10.1038/ng.2354 [PubMed: 22820512]
35. 1000 Genomes Project Consortium, Auton A, Brooks LD, et al. A global reference for human genetic variation. Nature. 2015;526(7571):68–74. doi:10.1038/nature15393 [PubMed: 26432245]
36. Clarke L, Fairley S, Zheng-Bradley X, et al. The international Genome sample resource (IGSR): A worldwide collection of genome variation incorporating the 1000 Genomes Project data. Nucleic Acids Res. 2017;45(D1):D854–D859. doi:10.1093/nar/gkw829 [PubMed: 27638885]
37. Nikpay M, Goel A, Won H-H, et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. Nat Genet. 2015;47(10):1121–1130. doi:10.1038/ng.3396 [PubMed: 26343387]
38. Choi SW, Mak TS-H, O'Reilly PF. Tutorial: a guide to performing polygenic risk score analyses. Nat Protoc. 2020;15(9):2759–2772. doi:10.1038/s41596-020-0353-1 [PubMed: 32709988]
39. Ge T, Chen C-Y, Ni Y, Feng Y-CA, Smoller JW. Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat Commun. 2019;10(1):1776. doi: 10.1038/s41467-019-09718-5 [PubMed: 30992449]
40. Pain O, Glanville KP, Hagenaars SP, et al. Evaluation of polygenic prediction methodology within a reference-standardized framework. PLoS Genet. 2021;17(5):e1009021. doi: 10.1371/journal.pgen.1009021 [PubMed: 33945532]

41. Raudvere U, Kolberg L, Kuzmin I, et al. g:Profiler: a web server for functional enrichment analysis and conversions of gene lists (2019 update). Nucleic Acids Res. 2019;47(W1):W191–W198. doi:10.1093/nar/gkz369 [PubMed: 31066453]
42. de Leeuw CA, Mooij JM, Heskes T, Posthuma D. MAGMA: generalized gene-set analysis of GWAS data. PLoS Comput Biol. 2015;11(4):e1004219. doi: 10.1371/journal.pcbi.1004219 [PubMed: 25885710]
43. Ripke S, Walters JT, O'Donovan MC. Mapping genomic loci prioritises genes and implicates synaptic biology in schizophrenia. medRxiv. January 2020:2020.09.12.20192922. doi:10.1101/2020.09.12.20192922
44. Mullins N, Forstner AJ, O'Connell KS, et al. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. Nat Genet. 2021;53(6):817–829. doi: 10.1038/s41588-021-00857-4 [PubMed: 34002096]
45. Davies G, Lam M, Harris SE, et al. Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function. Nat Commun. 2018;9(1):2098. doi: 10.1038/s41467-018-04362-x [PubMed: 29844566]
46. Bulik-Sullivan BK, Loh P-R, Finucane HK, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet. 2015;47(3):291–295. doi: 10.1038/ng.3211 [PubMed: 25642630]
47. LeBlanc M, Zuber V, Andreassen BK, et al. Identifying Novel Gene Variants in Coronary Artery Disease and Shared Genes With Several Cardiovascular Risk Factors. Circ Res. 2016;118(1):83–94. doi: 10.1161/CIRCRESAHA.115.306629 [PubMed: 26487741]
48. CDC. Cognitive Impairment: A Call for Action, Now! https://www.cdc.gov/aging/pdf/cognitive_impairment/cogimp_poilicy_final.pdf. Published 2011.
49. Sun L, Dimitromanolakis A. PREST-plus identifies pedigree errors and cryptic relatedness in the GAW18 sample using genome-wide SNP data. BMC Proc. 2014;8(Suppl 1 Genetic Analysis Workshop 18Vanessa Olmo):S23. doi:10.1186/1753-6561-8-S1-S23 [PubMed: 25519375]
50. Hagenaars SP, Gale CR, Deary IJ, Harris SE. Cognitive ability and physical health: a Mendelian randomization study. Sci Rep. 2017;7(1):2651. doi:10.1038/s41598-017-02837-3 [PubMed: 28572633]
51. Chaudhury S, Brookes KJ, Patel T, et al. Alzheimer's disease polygenic risk score as a predictor of conversion from mild-cognitive impairment. Translational Psychiatry. 2019;9(1):1–7. doi: 10.1038/s41398-019-0485-7 [PubMed: 30664621]
52. Mallet J, Le Strat Y, Dubertret C, Gorwood P. Polygenic Risk Scores Shed Light on the Relationship between Schizophrenia and Cognitive Functioning: Review and Meta-Analysis. Journal of Clinical Medicine. 2020;9(2):341. doi:10.3390/jcm9020341
53. Richards AL, Pardiñas AF, Frizzati A, et al. The Relationship Between Polygenic Risk Scores and Cognition in Schizophrenia. Schizophr Bull. 2020;46(2):336–344. doi: 10.1093/schbul/sbz061 [PubMed: 31206164]
54. Luciano M, Batty GD, McGilchrist M, et al. Shared genetic aetiology between cognitive ability and cardiovascular disease risk factors: Generation Scotland's Scottish family health study. Intelligence. 2010;38(3):304–313. doi:10.1016/j.intell.2010.03.002
55. Gayda M, Gremeaux V, Bherer L, et al. Cognitive function in patients with stable coronary heart disease: Related cerebrovascular and cardiovascular responses. PLoS One. 2017;12(9):e0183791. doi:10.1371/journal.pone.0183791 [PubMed: 28937981]
56. Schievink SHJ, van Boxtel MPJ, Deckers K, van Oostenbrugge RJ, Verhey FRJ, Köhler S. Cognitive changes in prevalent and incident cardiovascular disease: a 12-year follow-up in the Maastricht Aging Study (MAAS). Ear Heart J. July 2017. doi: 10.1093/eurheartj/ehx365
57. Sachdev PS, Brodaty H, Valenzuela MJ, et al. The neuropsychological profile of vascular cognitive impairment in stroke and TIA patients. Neurology. 2004;62(6):912–919. doi:10.1212/01.wnl.0000115108.65264.4b [PubMed: 15037692]
58. Hedden T, Schultz AP, Rieckmann A, et al. Multiple Brain Markers are Linked to Age-Related Variation in Cognition. Cereb Cortex. 2016;26(4): 1388–1400. doi: 10.1093/cercor/bhu238 [PubMed: 25316342]

59. Song R, Xu H, Dintica CS, et al. Associations Between Cardiovascular Risk, Structural Brain Changes, and Cognitive Decline. Journal of the American College of Cardiology. 2020;75(20):2525–2534. doi:10.1016/j.jacc.2020.03.053 [PubMed: 32439001]

60. Boots EA, Zhan L, Dion C, et al. Cardiovascular disease risk factors, tract-based structural connectomics, and cognition in older adults. NeuroImage. 2019;196:152–160. doi: 10.1016/j.neuroimage.2019.04.024 [PubMed: 30980900]

61. Marebwa Barbara K, Adams Robert J, Magwood Gayenell S, et al. Cardiovascular Risk Factors and Brain Health: Impact on Long-Range Cortical Connections and Cognitive Performance. Journal of the American Heart Association. 2018;7(23):e010054. doi: 10.1161/JAHA.118.010054 [PubMed: 30520672]

62. Ji W, Ferdman D, Copel J, et al. De novo damaging variants associated with congenital heart diseases contribute to the connectome. Scientific Reports. 2020;10(1):7046. doi: 10.1038/s41598-020-63928-2 [PubMed: 32341405]

63. Harris SE, Malik R, Marioni R, et al. Polygenic risk of ischemic stroke is associated with cognitive ability. Neurology. 2016;86(7):611–618. doi:10.1212/WNL.0000000000002306 [PubMed: 26695942]

64. Mistry S, Harrison JR, Smith DJ, Escott-Price V, Zammit S. The use of polygenic risk scores to identify phenotypes associated with genetic risk of schizophrenia: Systematic review. Schizophr Res. 2018;197:2–8. doi:10.1016/j.schres.2017.10.037 [PubMed: 29129507]

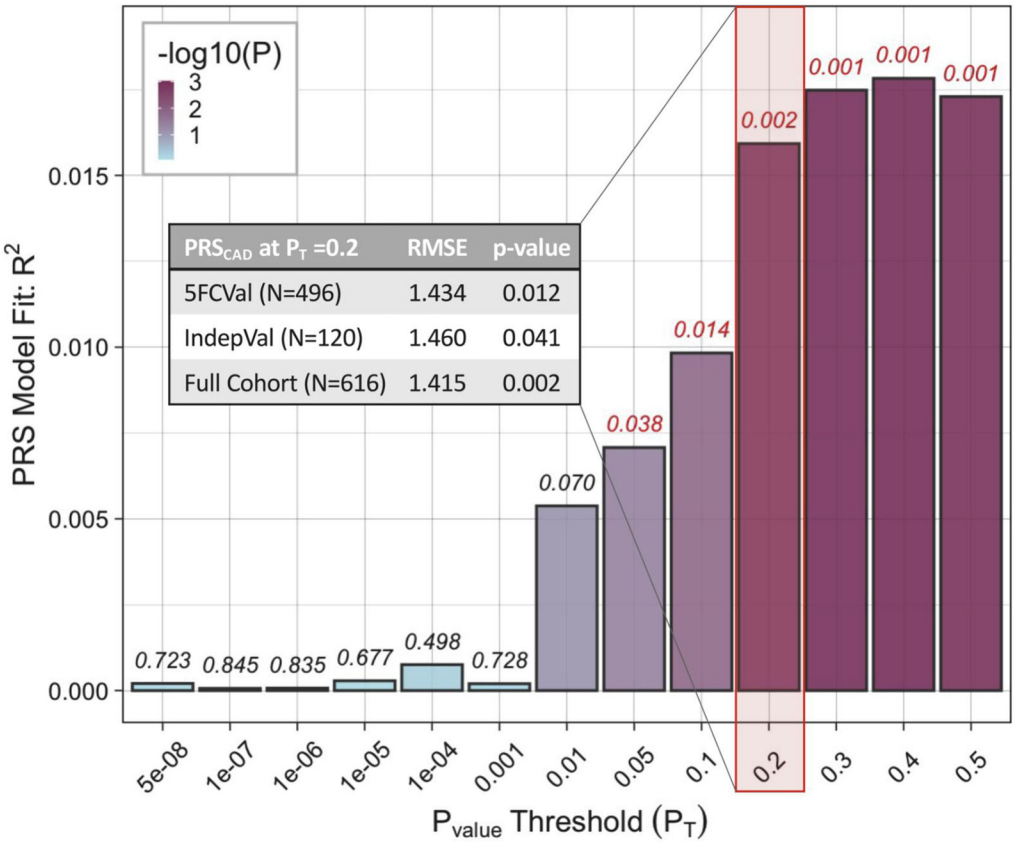

Figure 1. Polygenic Risk Scores for Coronary Artery Disease (PRS$_{CAD}$) Explained Variance in the BACS Composite Z-Scores (R^2) in the Full Cohort (Psych+HC N= 616).

Linear regression of the BACS composite scores on PRS$_{CAD}$ at 13 p-value thresholds (P_T) from $5e^{-8}$ to 0.5 among 616 B-SNIP participants (cross-validation set and independent validation set combined) after adjusting for the genomic population substructure (first five MDS components). Five-fold cross-validation (5FCVal) of the regression was performed among 80% of the full cohort and independent validation (IndepVal) with 20% of the full cohort. The model fit comparison under the optimal P_T of 0.2 is summarized in the embedded table (See Supplemental Table S2 for full results of regression across 13 P_T). The root mean square error (RMSE) indicates model fit. PRS$_{CAD}$ at P_T from 0.05 to 0.5 had statistically significant impact on BACS (highlight in red). HC: healthy controls; Psych: individuals with psychotic disorders.

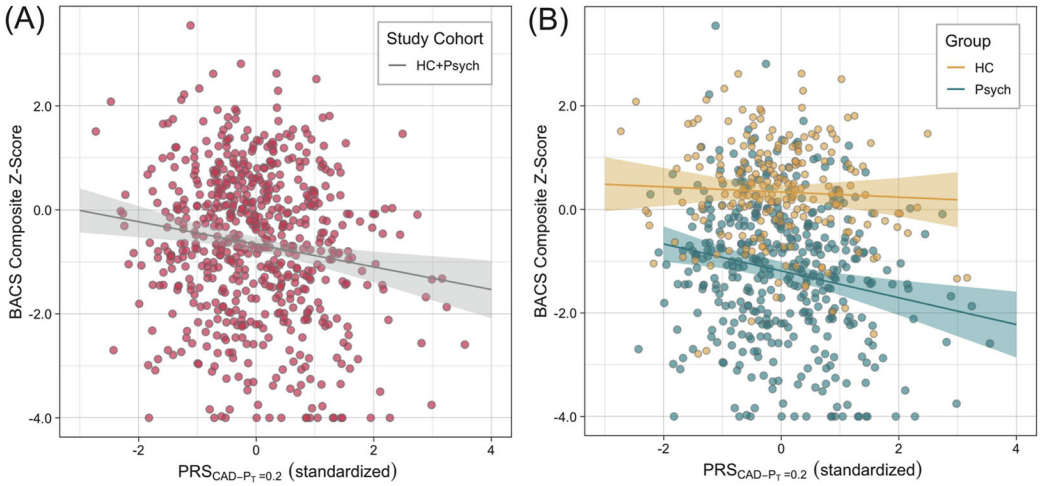

Figure 2. Scatter Plots with Linear Regression Lines of Polygenic Risk Scores for Coronary Artery Disease (PRS$_{CAD}$) and BACS Composite Z-Scores in All 616 Participants (Panel A) and Stratified by 403 Individuals with Psychotic Disorders vs 213 Healthy Controls (Panel B).

The effect size of the negative relationship between PRS$_{CAD}$ and cognitive performance is more prominent in the psychosis group (Beta: −0.069; p-value: 0.001) than the control group (Beta: −0.013; p-value:0.565). The x-axis shows the standardized PRScad and the y-axis shows the BACS composite z-scores as the global cognitive performance measure. The confidence band around the regressions line represents 95% the confidence interval.

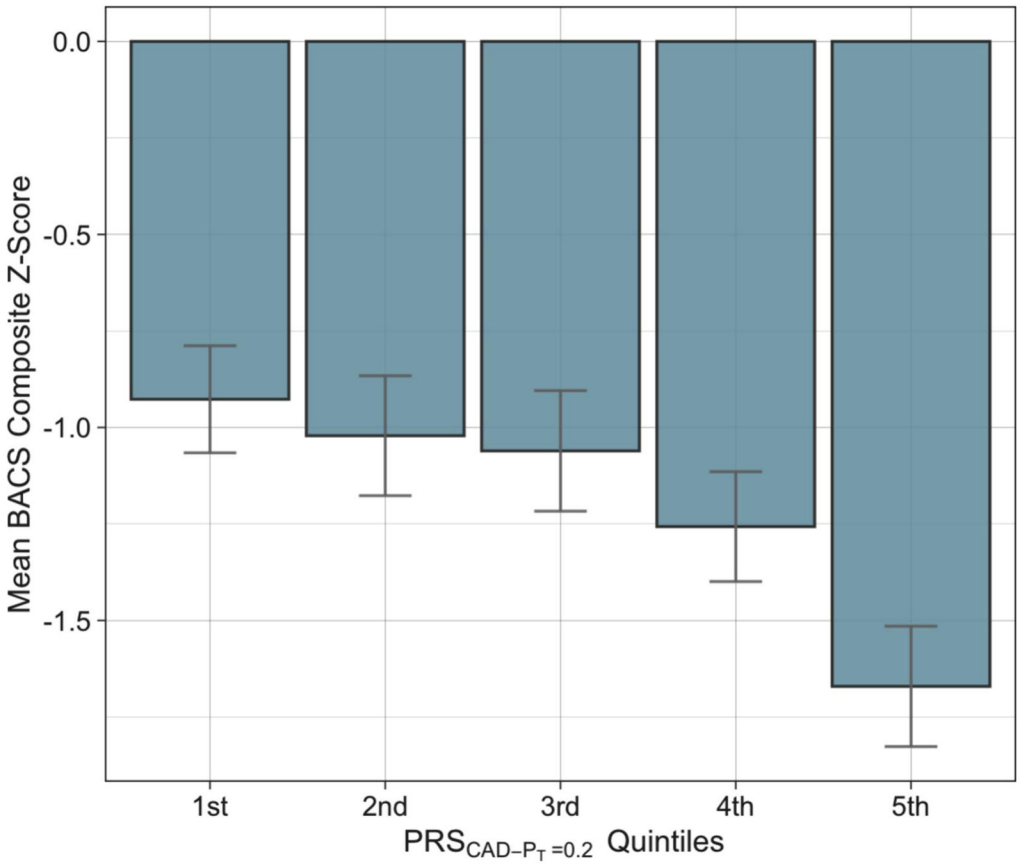

Figure 3. Cognitive Impairment Across Quintiles of Polygenic Risk Scores for Coronary Artery Diseases (PRS_{CAD}) Among 403 Individuals with Psychotic Disorders.

The mean BACS composite z-scores across five PRScad quintiles at p-value threshold (P_T) of 0.2. The vertical grey lines show the standard errors of the mean (SEM).

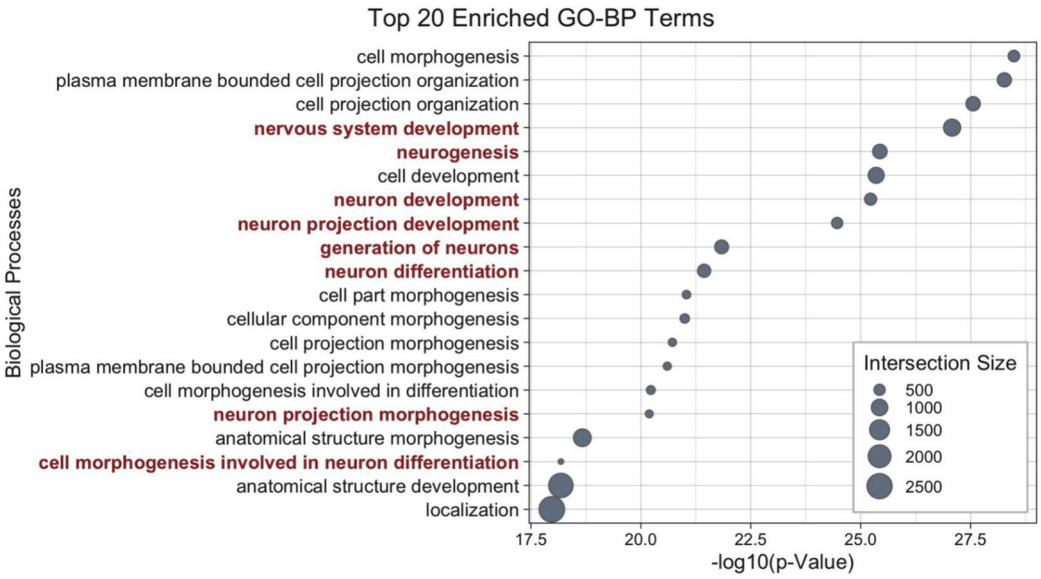

Figure 4. Gene Ontology (GO) Biological Process (BP) Enrichment Analysis of Genes Involved in Polygenic Risk Score for Coronary Artery Diseases (PRS_{CAD}) at P-value Threshold (P_T) of 0.2.

Among the top 20 GO BP terms overrepresented within PRScad genes, eight biological processes were relevant to neuronal development and functions. The intersection size denotes the number of input genes annotated to each GO BP term.

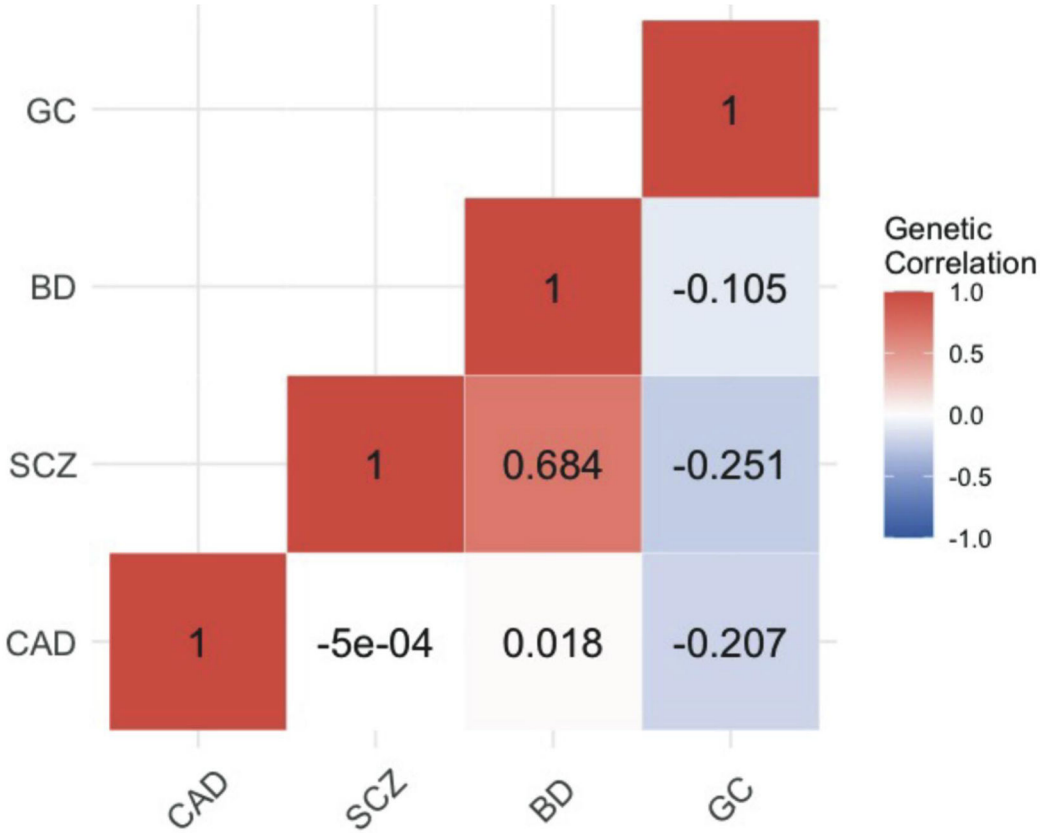

Figure 5. Genetic Correlations of Coronary Artery Disease, Schizophrenia, Bipolar Disorder, and General Cognitive Function Using LD Score Regression.

The color scale indicates the direction of correlation (red for positive and blue for negative genetic correlation r_g ranging from −1.0 to 1.0).

BD: bipolar disorder; CAD: coronary artery disease; GC: general cognitive function; LD: linkage disequilibrium; SCZ: schizophrenia.

Table 1.

Demographic and Clinical Characteristics for Individuals with Psychotic Disorders and Healthy Controls (Total N=616)[a].

Variable[b]	Individuals with Psychotic Disorders (N=403)	Healthy Controls (N=213)	Group Comparisons[c]
	Mean (S.D) or N (%)	Mean (S.D) or N (%)	p-value[d]
Female	184 (45.7%)	111 (52.1%)	0.149
Psychotic Disorder Diagnoses			
Schizophrenia	133 (33.0%)		
Schizoaffective Disorder	95 (23.6%)		
Bipolar Disorder with Psychosis	175 (43.4%)		
Cardiovascular Diagnoses[e]			
Hypertension (HTN)	59 (14.9%)	12 (5.7%)	< **0.001**
Coronary Artery Disease (CAD)	4 (1.0%)	2 (0.9%)	1.000
Hyperlipidemia	89 (22.5%)	23 (11.0%)	< **0.001**
Unspecified	21 (6.8%)	5 (3.0%)	0.093
Age	34.77 (12.70)	38.33 (13.02)	**0.001**
Education (Years)	13.80 (2.33)	15.15 (2.54)	< **0.001**
WRAT-IV Reading	101.98 (13.71)	107.20 (12.86)	< **0.001**
Duration of Illness (Years)[f]	15.01 (11.95)		
PANSS Total Score	59.97 (17.57)		
BACS Composite	−1.19 (1.36)	0.34 (1.00)	< **0.001**
BACS Subtests			
Verbal Memory	−0.67 (1.39)	0.14 (1.07)	< **0.001**
Digit Sequencing	−0.79 (1.17)	0.15 (1.01)	< **0.001**
Token Motor	−1.10 (1.19)	0.15 (0.94)	< **0.001**
Verbal Fluency	−0.43 (1.23)	0.36 (1.01)	< **0.001**
Symbol Coding	−1.14 (1.16)	0.24 (0.95)	< **0.001**
Tower of London	−0.37 (1.29)	0.19 (1.02)	< **0.001**
	Individuals with Psychotic Disorders (N=386)	**Healthy Controls (N=109)**	**Group Comparisons**
	N (%) or Median (IQR)	**N (%) or Median (IQR)**	**p-value**
Medications			
Total Number of AllMedications	4 (3 - 6)	1 (1 - 2)	< **0.001**
Total Number ofPsychotropic Medications	3 (2 - 4)	0 (0 - 0)	< **0.001**
Total ADS Score	2 (0 - 4)	0 (0 - 0)	< **0.001**
Having Cardiovascular Medications	95 (24.6%)	35 (32.1%)	0.139

[a.] Among the total N=616 participants involved in the primary analysis of polygenic risk score for coronary artery disease (PRS_{CAD}) in relation to BACS, total N=495 individuals had detailed medication information available for analyses.

[b] WRAT-IV Reading: Wide-Range Achievement Test 4th Edition, reading subtest; PANSS: Positive and Negative Syndrome Scale; BACS: Brief Assessment of Cognition in Schizophrenia; ADS: Anticholinergic Drug Scale.

[c] Two-tailed p-value under 0.05 significant level for group comparisons performed with Fisher's Exact test for categorical variables, independent samples t-tests for continuous variables, and the Mann-Whitney U test for ordinal variables.

[d] **Bold:** statistically significant under 0.05 significance level (two-tailed).

[e] Cardiovascular diagnoses were collected from participants whose information was ascertained: N=607 for coronary artery disease, N=605 for hypertension, N=605 for hyperlipidemia, and N=478 for other cardiovascular diagnoses.

[f] Duration of illness for schizophrenia-spectrum or bipolar disorders.

IQR: interquartile range.

Table 2.

Cardiovascular Medication Use Among Individuals with Psychotic Disorders (N=386) and Healthy Controls (N=109).

Cardiovascular medication variable	Individuals with Psychotic Disorders (N=386)	Healthy Controls (N=109)	Fisher's Exact Test Statistics[a]
	N (%)	N (%)	p-value[b]
Any cardiovascular Agents	95 (24.6%)	35 (32.1%)	0.139
Any BP-Lowering Agents	70 (18.1%)	18 (16.5%)	0.777
Beta Blockers	39 (10.1%)	5 (4.6%)	0.086
Calcium Channel Blockers	7 (1.8%)	0 (0.0%)	0.356
RAAS Blockers	26 (6.7%)	11 (10.1%)	0.301
Diuretics	12 (3.1%)	5 (4.6%)	0.550
Any Lipid-Lowering Agents	50 (13.0%)	17 (15.6%)	0.526
Statins	38 (9.8%)	14 (12.8%)	0.378
Other Lipid-Lowering Agents	18 (4.7%)	3 (2.8%)	0.590
Any Antiplatelets	18 (4.7%)	14 (12.8%)	**0.007**
Any Alpha Blockers	4 (1.0%)	0 (0.0%)	0.581
Any Other Cardiovascular Agents	1 (0.3 %)	0 (0.0%)	1.000
	Individuals with Psychotic Disorders Having CV agents (N=95)	**Healthy Controls Having CV agents (N=34)**	**Mann-Whitney U Test Statistics[a]**
	Median (IQR)	**Median (IQR)**	**p-value**
Total Number of BP-Lowering Agents	1 (0 - 1)	1 (0 - 1)	**0.009**
Total Number of Lipid-LoweringAgents	1 (0 - 1)	0 (0 - 1)	0.550
Total Number of Cardiovascular Agents	1 (1 - 2)	1 (1 - 2)	0.251

a. Two-tailed p-value under 0.05 significant level for group controls performed with Fisher's Exact Test for categorical variables and the Mann-Whitney U test for ordinal variables.

b. **Bold:** statistically significant under 0.05 significance level (two-tailed).

BP: blood pressure; IQR: interquartile range; RAAS: the renin-angiotensin-aldosterone system.

Table 3.

Correlation of Polygenic Risk Score for Coronary Artery Disease at P-value Threshold (P_T) at 0.2 and Performance on BACS Composite and Subtests Among Individuals with Psychotic Disorders and Healthy Controls (Total N=616)[a].

Cognitive Outcomes	Independent variable: $PRS_{CAD, 0.2}$;covariates:first five PCs					
	Psych+HC (N=616)		Psych (N=403)		HC (N=213)	
	R^2 (%)[b,c]	p-value[c]	R^2 (%)	p-value	R^2 (%)	p-value
BACS Composite	**1.593**	**0.002**	**2.618**	**0.001**	0.161	0.565
BACS Subtests						
Verbal Memory	**2.162**	**< 0.001**	**3.097**	**< 0.001**	0.562	0.282
Digit Sequencing	0.094	0.448	0.062	0.619	0.060	0.725
Token Motor	0.527	0.073	**1.051**	**0.041**	0.146	0.584
Verbal Fluency	0.454	0.096	0.548	0.140	0.020	0.839
Symbol Coding	**0.876**	**0.021**	1.022	0.044	0.474	0.323
Tower of London	**1.029**	**0.012**	**1.842**	**0.007**	0.012	0.875

[a] The analyses controlled for genomic ancestry (first five PCs).

[b] R^2 indicates the (percent) variance explained by PRS_{CAD}.

[c] **Bold:** statistically significant under 0.05 significance level (two-tailed).

BACS: Brief Assessment of Cognition in Schizophrenia; PCs: principal components; Psych: individuals with psychotic disorders only; HC: healthy control participants only.

Table 4.

Unstandardized Coefficients (Beta) of Polygenic Risk Score for Coronary Artery Diseases at P-value Threshold of 0.2 ($PRS_{CAD,0.2}$) and Cardiovascular Medication Burden ($N_{CV\text{-}meds}\geq 2$) from Linear Regression of Cognitive Performance in Individuals with Psychotic disorders (N=386)[a].

Cognitive Outcomes	$PRS_{CAD,\ 0.2}$		$N_{CV\text{-}meds} \geq 2$		Model Fit
	Beta[b]	p-value[b]	Beta	p-value	R^2 (%)[c]
BACS Composite	**−0.072**	**< 0.001**	**−0.473**	**0.029**	4.357
BACS subtests					
Verbal Memoiy	**−0.081**	**< 0.001**	**−0.495**	**0.021**	5.451
Digit Sequencing	−0.014	0.472	**−0.430**	**0.023**	2.015
Token Motor	−0.034	0.076	−0.066	0.731	0.873
Verbal Fluency	−0.034	0.089	−0.222	0.264	1.174
Symbol Coding	**−0.040**	**0.033**	−0.319	0.087	2.232
Tower of London	**−0.054**	**0.010**	−0.208	0.322	1.974

[a] The analyses controlled for genomic ancestry (first five PCs).

[b] **Bold:** statistically significant under 0.05 significance level (two-tailed).

BACS: Brief Assessment of Cognition in Schizophrenia; PCs: principal components.