7-2022

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Brain, Behavior, & Immunity - Health 22 (2022) 100459

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Inflammation subtypes in psychosis and their relationships with genetic risk for psychiatric and cardiometabolic disorders

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ARTICLE INFO

Keywords:
Cardiometabolic syndrome
Genetic risk score
Peripheral inflammation
Psychotic disorders

ABSTRACT

Cardiometabolic disorders have known inflammatory implications, and peripheral measures of inflammation and cardiometabolic disorders are common in persons with psychotic disorders. Inflammatory signatures are also related to neurobiological and behavioral changes in psychosis. Relationships between systemic inflammation and cardiometabolic genetic risk in persons with psychosis have not been examined. Thirteen peripheral inflammatory markers and genome-wide genotyping were assessed in 122 participants (n = 86 psychosis, n = 36 healthy controls) of European ancestry. Cluster analyses of inflammatory markers classified higher and lower inflammation subgroups. Single-trait genetic risk scores (GRS) were constructed for each participant using previously reported GWAS summary statistics for the following traits: schizophrenia, bipolar disorder, major depressive disorder, coronary artery disease, type-2 diabetes, low-density lipoprotein, high-density lipoprotein, triglycerides, and waist-to-hip ratio. Genetic correlations across traits were quantified. Principal component (PC) analysis of the cardiometabolic GRSs generated six PC loadings used in regression models to examine associations with inflammation markers. Functional module discovery explored biological mechanisms of the inflammation association of cardiometabolic GRS genes. A subgroup of 38% persons with psychotic disorders was characterized with higher inflammation status. These higher inflammation individuals had lower BACS scores ($p = 0.038$) compared to those with lower inflammation. The first PC of the cardiometabolic GRS matrix was related to higher inflammation status in persons with psychotic disorders (OR = 2.037, $p = 0.001$). Two of eight modules within the functional interaction network of cardiometabolic GRS genes were enriched for immune processes. Cardiometabolic genetic risk may predispose some individuals with psychosis to elevated inflammation which adversely impacts cognition associated with illness.

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https://doi.org/10.1016/j.bbih.2022.100459
Received 26 March 2022; Accepted 31 March 2022
Available online 8 April 2022

1. Introduction

Psychotic disorders represent a spectrum of severe mental illnesses with clinical and etiologic heterogeneity (Garver, 1997). Immune and inflammatory dysregulation has been implicated in patients with psychotic disorders (Pathmanandavel et al., 2013) and linked to symptoms, brain structural alternations, and cognitive impairment (Bishop et al., 2022). Alterations of CRP, multiple proinflammatory cytokines, and vascular markers (e.g., IL1, IL1RA, IL2R, IL4, IL6, IL8, IL10, IL12, TNFα, TGFβ, IFNγ, and VEGFA) have all been identified in case-control studies (Goldsmith et al., 2016; Lizano et al., 2016, 2021; Miller et al., 2011). Some (e.g., IL1RA, sIL2R, IL6, VEGF, and CRP) also appear to decrease after antipsychotic treatment (Bishop et al., 2022). Emerging studies have explored inflammation subgrouping approaches based on the aggregation of multiple peripheral markers and multivariate patterns of inflammation dysregulation (Fillman et al., 2016; Hoang et al., 2022; Lizano et al., 2021).

Genetic studies represent a promising approach for enhancing our mechanistic understanding of the potential etiologies of these immune and inflammatory alterations in individuals with psychosis (McGrath et al., 2013; Bishop et al., 2022). Large-scale genome-wide association studies (GWAS) of disease risk have revealed an enrichment for immune system genes amongst loci associated with schizophrenia (SCZ) risk (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Subsequent studies have advanced our understanding of the immunogenetic architectures of SCZ (Lin et al., 2016) and the possible shared genetic etiology with autoimmune diseases (Pouget et al., 2019). Multiple gene candidates within and outside the major histocompatibility complex (MHC) regions have significant associations with both genetic liability to psychosis and immune and inflammatory processes (Pouget et al., 2016; Sekar et al., 2016). These findings have collectively led to a hypothesis that genetic liability for psychotic disorders is related to immune dysregulation. However, the links between genetic risk for psychosis and other psychiatric conditions with measures of peripheral inflammation have not been extensively explored. Only two prior studies examined correlations between genetic risk scores (GRSs) of mental illnesses and peripheral inflammatory markers (Maj et al., 2020; Morgan et al., 2017). These findings provided some biological insights into the relationships of genetic liability to SCZ, bipolar disorder (BD), and Alzheimer's disease with peripheral alterations of individual inflammatory markers, including as CRP, clusterin, C1 inhibitor, and ghrelin.

Cardiometabolic diseases, including coronary heart disease, obesity, diabetes, and dyslipidemia, are highly prevalent in persons with psychotic disorders and have been associated with poor cognitive and functional outcomes and reduced life expectancy in this population (DE HERT et al., 2009; Saha et al., 2007; Perry et al., 2019; Hagi et al., 2021). Excess cardiometabolic risks are commonly attributed to side effects from antipsychotic drugs used to treat these illnesses, unhealthy lifestyle, poor access or engagement with healthcare, or other socioeconomic factors (Correll et al., 2014; Smith et al., 2020). However, these risks have also been reported in antipsychotic-naïve patients with first-episode psychosis (Correll et al., 2014; Perry et al., 2016; Garcia-Rizo et al., 2017) and their first-degree relatives (Fernandez-Egea et al., 2008), suggesting a genetic etiology independent of treatment effects. Extensive evidence has established a role of immune and inflammation alterations in the pathogenesis of cardiometabolic diseases, involving abnormal lipid and glucose metabolism and increased adiposity (DeMarco et al., 2010; Donath et al., 2019). GWASs of risk for cardiovascular and metabolic conditions have revealed multiple disease risk loci linked to inflammatory processes (Kraja et al., 2014; Mauersberger et al., 2021).

Recent studies leveraging large-scale genetic findings have explored the shared genetic etiology and pleiotropy between SCZ and cardiometabolic conditions. Liu et al. (2020) identified 21 pleiotropic genes shared between SCZ and cardiometabolic diseases. So et al. (2019) investigated the genetic associations of SCZ and BD with 28 cardiometabolic traits and reported relationships between elevated triglycerides (TG) and SCZ risk. Polygenic associations with SCZ also indicated abnormal adipokine profile and glucose metabolism, visceral adiposity, and increased waist-to-hip ratio. Among numerous genetic variants and biological pathways found to be shared between SCZ and cardiometabolic traits, some were related to immune function and inflammation.

Overall, prior studies collectively suggest that genetic risk factors for psychiatric illnesses and cardiometabolic disorders may be related to elevated inflammation in psychotic disorders. Genetic studies, to date, however, have not directly tested this hypothesis, nor have they examined the relationship between genetic risk for psychiatric or cardiometabolic diseases and inflammatory dysregulation. Furthermore, it remains to be determined whether this is a general association amongst all patients or limited to a subgroup. Thus, we performed, to our knowledge, the first study exploring multivariate signatures of peripheral inflammation in persons with psychotic illnesses (Psychosis) and healthy controls (HC) and their relation to summarizing genetic risk for cardiometabolic and psychiatric illness. We hypothesized that elevated inflammation would be associated with higher psychiatric and cardiometabolic GRSs, worse psychosis symptoms and lower cognitive performance.

2. Methods and materials

2.1. Study participants

This study included 122 participants (n = 86 Psychosis, n = 36 HC) enrolled through the Chicago site of the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B–SNIP) consortium (Tamminga et al., 2013). These participants were a subgroup of self-identified white/-European ancestry from the multiracial cohort previously characterized for peripheral inflammation measures and their relationships to neurobiological phenotypes and clinical and medication variables (Lizano et al., 2021). The rationale for examining persons of white/European ancestry is to ensure the appropriateness of genetic risk scoring, which was based on the results of large-scale GWAS primarily conducted in European subjects, not representative of other ancestry groups (Lewis and Vassos, 2020). All participants provided written informed consent and blood samples (see Supplemental Methods for inclusion criteria). Persons with psychotic disorders had consensus diagnoses of SCZ, schizoaffective disorder (SAD), or BD with psychotic features based on the Structured Clinical Interview for DSM-IV. Further details on inclusion/exclusion criteria and participant assessments are available at Tamminga et al. (2013). Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale (YMRS), and Montgomery Åsberg Depression Rating Scale (MADRS) were administered to assess symptom severity. Cognitive performance was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004). Details on medication history collection are available in Supplemental Methods.

2.2. Inflammation subtyping based on peripheral inflammatory markers

Serum inflammatory markers assays and analyses were performed as previously reported (Lizano et al., 2021) (see Supplemental Methods and Table S1 for details). Briefly, serum concentrations of 13 inflammatory and microvascular markers (selected based on meta-analyses of implications in psychosis) were measured by using the customized V-Plex sandwich immunoassays and the Sector 6000 Microplate ELISA System from Meso Scale Diagnostics (MSD, Rockville, MD) [CRP, Flt1, IFNγ, IL1β, IL6, IL8, IL10, IL12/IL23p40, TNFα, TNFβ, VEGF, VEGFD] and solid-phase sandwich ELISA (Beckton, Dickinson and Company BD Biosciences, San Jose, CA) [C4a] and passed quality control.

An unsupervised exploratory factor analysis was performed using the inflammatory markers to uncover the underlying factor structure of the markers and to provide factor loadings for each participant. Specifically, a multivariate linear regression of the markers was firstly fitted on

covariates (hemolysis score, storage days, sample set, sex, age, and ancestry) to adjust for these potential confounders, then principal component analysis (PCA) was performed for the residual from the regression model. This resulted in a five-factor model representing ~70% cumulative variance of inflammatory markers. Hierarchical clustering was performed using these inflammation factors and identified an optimal clustering solution with the first inflammation factor, representing seven elevated markers (CRP, IFNγ, IL1β, IL8, IL10, TNFα, and VEGF). The clustering solution revealed higher and lower inflammation subtypes based on Silhouette coefficients of 0.59, maximized gap statistic, and minimized connectivity index (see Lizano et al. (2021) for details). The stability and consistency of additional clustering performance metrics was confirmed, which were nearly identical in this subsample of the previously reported group (e.g., confirmed two-cluster solution, Silhouette values of 0.58 versus 0.59, maximized gap statistic values of 0.32 versus 0.34). The dichotomous higher and lower inflammation status and continuous inflammation loading score were defined as the primary and secondary inflammatory outcomes for subsequent association analyses described herein.

2.3. Genotyping, single-trait genetic risk scoring, and genetic correlation analysis

Genotyping was performed with the Illumina Infinium PsychChip array (Illumina Inc., San Diego, CA, USA) on blood-based DNA followed by quality control (QC) with PLINK 1.9 (Purcell et al., 2007). Details on QC and imputation procedures are summarized in Supplemental Methods. Post-imputation QC removed poorly imputed SNPs (information score <0.5), missingness >0.1, and MAF <0.05, resulting in 4,322, 238 high-quality common SNPs. A multidimensional scaling (MDS) analysis was performed among a list of relatively independent SNPs after clumping based on the 1000 Genomes population data (Clarke et al., 2017). The first five MDS principal components (PCs) were applied as population substructure covariates for subsequent analyses.

Three psychiatric traits, including SCZ (n = 306,011) (Ripke et al., 2020), BD (n = 413,466) (Mullins et al., 2021), and major depressive disorder (MDD, n = 807,553) (Howard et al., 2019), and six cardiometabolic traits, including coronary artery disease (CAD, n = 184, 305) (Nikpay et al., 2015), type-2 diabetes (T2D, n = 898,130) (Mahajan et al., 2018), low-density lipoprotein (LDL, n = 196,475), high-density lipoprotein (HDL, n = 196,475), TG (n = 196,475) (Willer et al., 2013), and waist-to-hip ratio adjusted for BMI (WHR, n = 142,762) (Shungin et al., 2015) were selected for genetic risk scoring. The corresponding GWAS summary statistics files were downloaded from the consortium data repositories as training sets (see Supplemental Table S2 for study information). The genetic risk score (GRS) of each trait for each participant was defined as the sum of the effect allele dosage across independent GWAS significant SNPs ($p < 5e^{-8}$) weighted by the effect size as a quantification of the genetic risk conferred for cardiometabolic or psychiatric illnesses. Each GRS was constructed across independent GWAS significant SNPs. The most significant association in each linkage disequilibrium (LD) block ($r^2 \geq 0.1$) within a 500 kb window was obtained from the clumping procedure by using PRSice-2 software (Choi et al., 2020). Exploratory post-hoc analyses examined GRSs calculated under other p-value thresholds (i.e., $P_T = 1e^{-7}$to $P_T = 0.5$). Genetic correlations among GWAS summary statistics for cardiometabolic and psychiatric traits were performed with linkage disequilibrium score regression (LDSC) (Bulik-Sullivan et al., 2015) (see Supplemental Methods).

2.4. Statistical analyses

Demographic and clinical characteristics of participant groups were compared using Fisher's exact test for categorical variables and two-sample *t*-test for continuous variables. To examine the association between higher/lower inflammation level (dependent variable) and single-trait GRS among all participants, a total of nine logistic regression models were fitted with each GRS as an independent variable while accounting for population substructure and psychosis vs control status. Multiple testing correction was performed with the false discovery rate (FDR) approach by calculating q-values. Analyses were performed using R Statistical Software v4.0.2.

2.5. Multivariate cardiometabolic polygenic scoring and inflammation associations

Based on inflammation associations with single-trait GRS and significant genetic correlations across traits identified with LDSC, PCA was performed on the matrix of GRS values for six cardiometabolic traits (standardized z-score) combined. This resulted in six PC loadings. The first PC was defined as cardiometabolic GRS and was examined for associations with inflammation outcomes. This was achieved by fitting logistic regression models for the dichotomous inflammation level (primary outcome), and linear regression models for continuous inflammation factor 1 (secondary outcome) while accounting for psychosis vs control status and population substructure. Empirical *p* values were calculated with 10,000-time permutation procedures for primary inflammation outcome to account for overfitting. Sensitivity analyses were performed to determine the influence of DSM diagnoses (SCZ vs SAD vs BD), cardiometabolic diagnoses and medication status as dichotomous covariates (Yes/No) on the associations of inflammation with cardiometabolic GRS. Exploratory post-hoc analyses examined inflammation relationships with the other five PCs identified from the cardiometabolic GRS matrix. Separate linear regression models of cardiometabolic GRS in relation to the seven inflammatory markers that significantly loaded on inflammation factor 1 (CRP, IFNγ, IL1β, IL8, IL10, TNFα, and VEGF) were fitted to investigate the impact of each inflammatory marker on the association of cardiometabolic genetics and inflammation phenotypes. To ascertain the clinical implications of cardiometabolic genetics and peripheral inflammation, the associations with diagnoses, psychosis symptoms (PANSS total score), cognitive performance (BACS score), depression symptoms (MADRS), and mania symptoms (YMRS) were examined with regression analyses.

2.6. Exploratory functional module detection

Functional enrichment analysis and module discovery were performed among cardiometabolic GRS genes (six traits combined) by using the online HumanBase toolkit (https://hb.flatironinstitute.org/) to explore the biological implications of the cardiometabolic genetic risk and inflammation relationship identified in primary analyses (see Supplemental Methods).

3. Results

3.1. Participant characteristics

Clinical and demographic characteristics are presented in Table 1. Age and sex had similar distributions between Psychosis and HC groups. Persons with psychotic disorders were more likely to report a hypertension diagnosis ($p = 0.010$) and more concurrent cardiovascular medications ($p = 0.021$). There was a trend of more cardiometabolic conditions and medications reported by the Psychosis group than the HC group. There was a trend for a greater proportion of participants categorized as having higher inflammation levels in the Psychosis (n = 33, 38%) as compared to the HC group (n = 8, 22.2%) ($p = 0.097$). Similarly, the inflammation factor 1 scores trended higher in the Psychosis than the HC group (p = 0.098).

Table 1
Demographic and clinical characteristics for participants.

Variable	Psychosis (N = 86)	HC (N = 36)
	Mean (S.D.) or n (%)	Mean (S.D.) or n (%)
Age	33.3 (13.2)	37.5 (13.5)
Female	52 (60.5%)	20 (55.6%)
Psychotic Diagnoses		
Schizophrenia	20 (23.3%)	
Schizoaffective Disorder	17 (19.8%)	
Bipolar Disorder with Psychotic Features	49 (57.0%)	
PANSS Total Score	66.0 (17.8)	
MADRS Total Score	11.7 (9.7)	
YMRS Total Score	6.9 (6.8)	
Having Antipsychotic Medications		
First Generation Antipsychotic	8 (9.3%)	
Second Generation Antipsychotic	60 (69.8%)	
Cardiometabolic Diagnoses		
Coronary Artery Disease	1 (1.2%)	0 (0.0%)
Hypertension[a]	13 (15.1%)	0 (0.0%)
Hyperlipidemia	12 (14.0%)	2 (5.6%)
Type 2 Diabetes	6 (7.0%)	0 (0.0%)
Having Cardiovascular Medications	20 (23.3%)	2 (5.6%)
Having Diabetic Medications[a]	7 (8.1%)	0 (0.0%)
Higher Inflammation Level	33 (38.4%)	8 (22.2%)
Inflammation Factor 1 Loading Score	0.342 (1.68)	−0.214 (1.66)

HC: healthy controls; MADRS: Montgomery–Åsberg Depression Rating Scale; PANSS: Positive and Negative Syndrome Scale; Psychosis: persons with psychotic disorders; S.D.: standard deviation; YMRS: Young Mania Rating Scale.

[a] Psychosis group vs HC group comparisons, two-tailed p value < 0.05 (Fisher's exact test for categorical variables, t-test for continuous variables).

3.2. Genetic correlations between psychiatric and cardiometabolic traits and single-trait GRS associations with inflammation

Significant genetic correlations were identified across six cardiometabolic traits. CAD, T2D, LDL, TG, and WHR had positive correlations with each other while HDL was negatively correlated with the other five traits (Fig. 1A; Supplemental Table S3). No significant genetic correlations were identified between SCZ and any cardiometabolic trait. In contrast, MDD was positively correlated with CAD, T2D, LDL, TG, WHR and negatively correlated with HDL. A significant positive correlation was observed between BD and WHR.

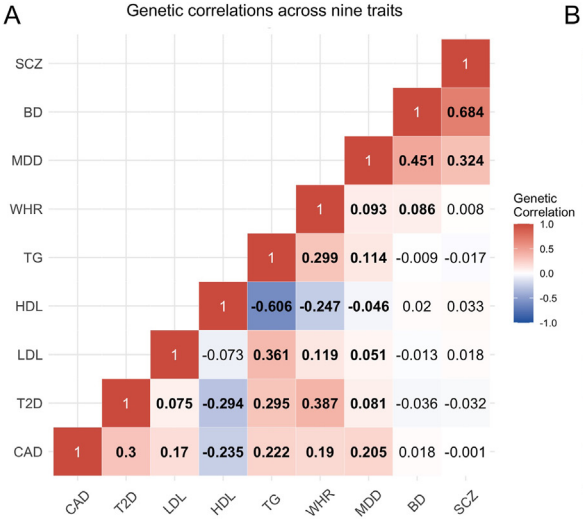
Fig. 1B presents the logistic regression results of higher inflammation level and single-trait GRS comprised of GWAS-significant SNPs among all participants. Across cardiometabolic traits, high inflammation level was associated with CAD ($R^2 = 0.110$, $p = 0.002$), T2D ($R^2 = 0.058$, $p = 0.025$), and TG ($R^2 = 0.081$, $p = 0.032$). After adjustments for multiple testing, the inflammation associations remained significant with CAD ($q = 0.016$) and TG ($q = 0.032$). No significant associations were identified between higher inflammation level and GRSs for any of the psychiatric illnesses examined herein (see Supplemental Table S4 for results among all participants and stratified by Psychosis and HC groups).

3.3. Multivariate cardiometabolic GRS and inflammation relationships

Principal component analysis using GRSs for CAD, T2D, LDL, TG, HDL, and WHR resulted in six PCs (see Supplemental Tables S5 and S6 for eigenvalues and eigenvectors). The scree plot (Fig. 2A) shows the percentage of variance explained by each PC. The PC1 accounted for 28.4% of the variance in the six-trait cardiometabolic GRS matrix. The heatmap (Fig. 2B) depicts the contribution of each cardiometabolic trait to a given GRS PC. PC1 had significant contribution of GRSs for CAD, LDL, TC and HDL (PCA loading>0.5 for each GRS) and lesser contributions of T2D and WHR (PCA loading <0.25). Fig. 2C summarizes the logistic regression results of higher and lower inflammation status predicted by each GRS PC.

Higher inflammation level was significantly associated with PC1 GRS (OR = 1.760, $p = 0.001$). *Post-hoc* analyses examining the other five GRS PCs did not reveal significant associations with inflammation (Fig. 2C) or result in better model performance when compared to the model including PC1 (see Supplemental Table S7). Thus, PC1 was defined as multivariate cardiometabolic GRS for subsequent association analyses with inflammation.

Fig. 3 illustrates the results of regression analyses of cardiometabolic GRS and inflammation outcomes among all participants and further stratified by Psychosis and HC groups. The significant association of higher inflammation level and high cardiometabolic GRS was driven primarily by the Psychosis group (OR = 2.037, 95% CI [1.295, 3.206], empirical $p = 0.001$). No significant associations between inflammation status and cardiometabolic GRS were identified in HCs (OR = 0.875, 95% CI [0.335, 2.287], empirical $p = 0.802$) (Fig. 3A & C). A significant positive association between inflammation factor 1 and cardiometabolic GRS was also observed in the Psychosis group but not in the HC group or among all participants (Fig. 3B & C). Examining the influence of DSM diagnoses as well as cardiometabolic diagnoses and medication use did not alter or confound the inflammation associations with



B Single-trait genetic associations with higher inflammation level

GRS Trait	R^2	p value	q value
CAD	0.110	0.002	0.016
T2D	0.058	0.025	0.068
LDL	0.020	0.196	0.313
TG	0.081	0.008	0.032
HDL	0.026	0.137	0.275
WHR	0.013	0.302	0.345
MDD	1.74×10^{-3}	0.702	0.790
BD	0.015	0.266	0.345
SCZ	1.55×10^{-4}	0.909	0.909

Fig. 1. Genetic correlations across six cardiometabolic and three psychiatric traits and genetic risk associations with inflammation subtypes. Panel **A**: LD Score Regression revealing genetic correlations across eight cardiometabolic and psychiatric traits (see Supplemental Table S3 for details). 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. Bold font indicates statistical significance (p value < 0.05). Panel **B**: Logistic regression of higher and lower inflammation status and GRS for each trait after adjusting for psychosis vs control status and population substructure (first five MDS PCs). Multiple testing correction was performed with the False Discovery Rate. Both unadjusted p values and the adjusted p values (q values) are reported (significance level of 0.05). Red indicates statistical significance. BD: bipolar disorder; CAD: coronary artery disease; GRS: genetic risk score; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MDD: major depressive disorder; TG: triglyceride; T2D: type-2 diabetes; WHR: waist-to-hip ratio; SCZ: schizophrenia. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

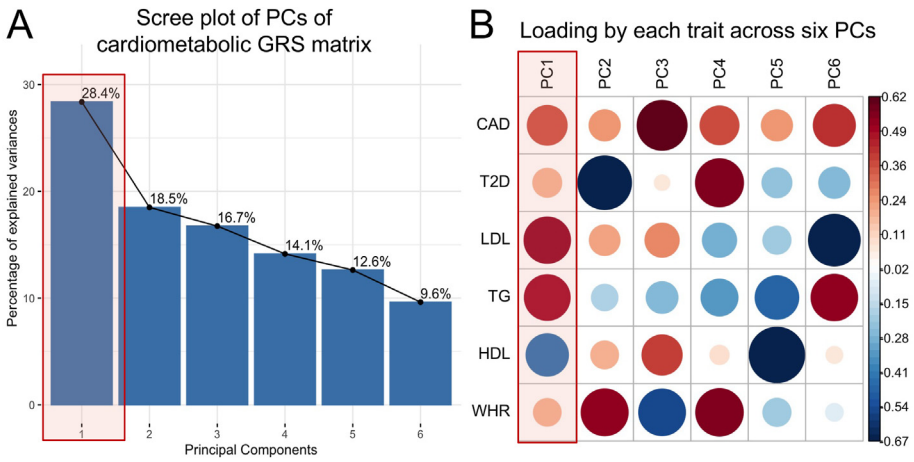


Fig. 2. Principal component analysis of genetic risk scores (GRS) for cardiometabolic traits and inflammation relationships. Scree plot (panel **A**) showing the percentage of variance explained by each principal component (PC) of the matrix composed of GRSs for six cardiometabolic traits. Heat map (panel **B**) illustrating loading by each trait across six PCs. PC1 explained 28.4% variance of the six-trait cardiometabolic GRS matrix (panel **A**) with significant contribution of CAD, LDL, TG and HDL (loading >50%) and T2D and WHR to a lesser extend (loading ~25%) (panel **B**). PC1 was defined as the multivariate cardiometabolic GRS and significantly associated with higher inflammation level (panel **C**). CAD: coronary artery disease; GRS: genetic risk score; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride; T2D: type-2 diabetes; WHR: waist-to-hip ratio.

C

Associations of each cardiometabolic GRS PC and inflammation level

	PC1	PC2	PC3	PC4	PC5	PC6
R^2	0.121	0.038	0.036	0.004	0.000	0.030
OR	1.760	0.688	1.466	1.147	1.030	1.557
p value	0.001	0.070	0.082	0.564	0.904	0.111

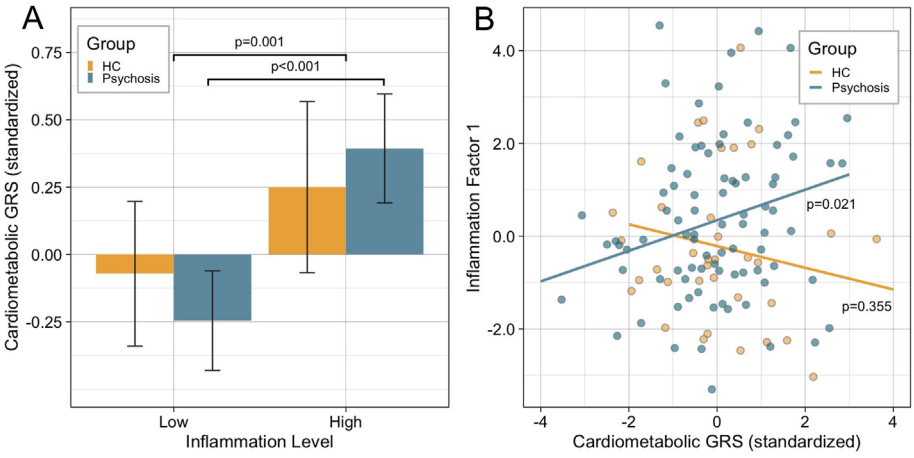


Fig. 3. Inflammation relationships with multivariate cardiometabolic genetic risk score (GRS) stratified by persons with psychotic disorders vs healthy controls. Associations of cardiometabolic GRS (the first PC of six-trait GRS matrix) with higher/lower inflammation status (panel A and C) and inflammation factor 1 (panel B & C) stratified by persons with psychotic disorders vs healthy controls. Red (in panel C) indicates statistical significance at 0.05 significance level. GRS: genetic risk score; OR: odds ratio. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

C

	Inflammation Level (High/Low)				Inflammation Factor 1		
	R^2	OR	*p* value	Empirical *p* value	R^2	Beta	*p* value
Psychosis + HC	0.121	1.760	0.001	0.002	0.023	0.205	0.105
Psychosis Only	0.181	2.037	6.1×10^{-4}	0.001	0.065	0.329	0.021
HC Only	0.004	0.875	0.785	0.802	0.030	-0.234	0.355

cardiometabolic GRS (see Supplemental Results). See Supplemental Results and Table S9 for individual markers and cardiometabolic GRS at other P_T values.

3.4. *Functional module discovery of cardiometabolic GRS genes with immune-inflammatory implications*

Of 683 SNPs included in cardiometabolic GRS, 396 gene IDs were mapped using the Ensembl database. These were included in functional module discovery analyses. A total of 250 genes were assigned to one of eight cohesive functional modules based upon a comembership score ≥0.9. The top three gene ontology (GO) pathways enriched within the gene list of cardiometabolic GRS are listed corresponding to the module assignment in Fig. 4 (see Supplement I for the mapped gene list and full results of functional enrichment). Two out of eight functional modules (M5, M8) containing 40 and 14 genes with 66 and three overrepresented GO terms, respectively, were comprised of immune or inflammation associated processes and pathways.

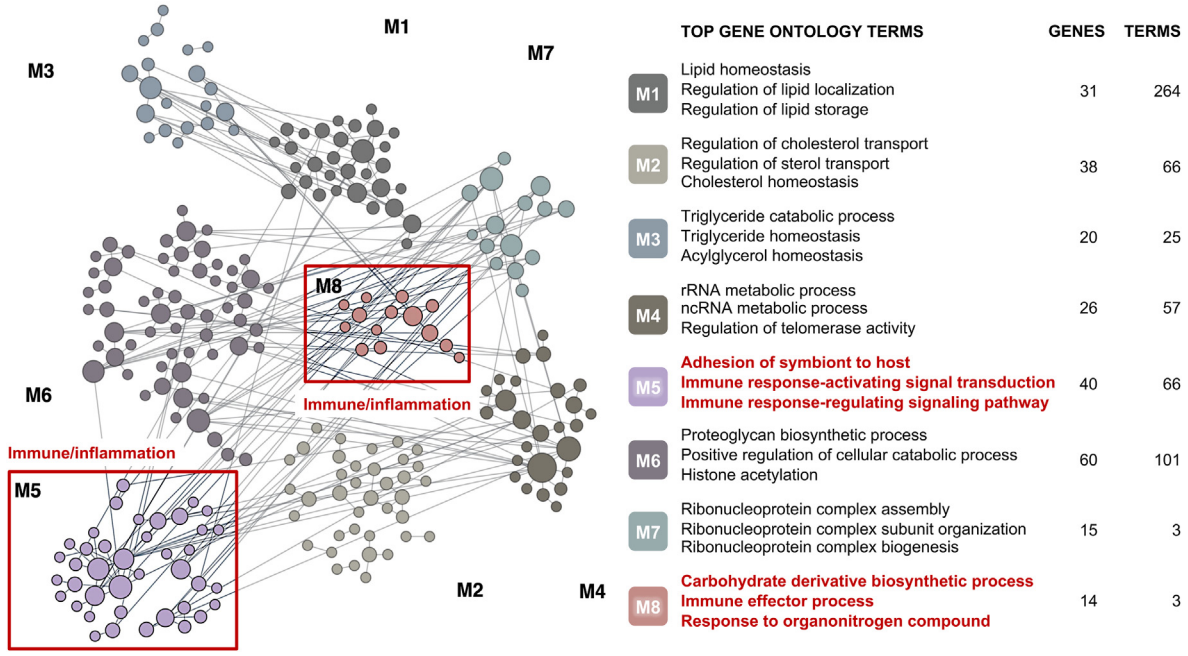


Fig. 4. Functional modules and enrichment of cardiometabolic risk genes. A total of 250 genes were assigned to one of eight modules based on enrichment significance. The top enriched Gene Ontology (GO) terms with each module were listed on the right (see Supplement I for the mapped gene list and full results of functional enrichment). M5 and M8 containing a total of 40 and 14 genes, with 66 and 3 enriched GO terms, respectively, had significant immune and inflammation implications.

3.5. Cardiometabolic genetic risk and inflammation associations with clinical outcomes

Across diagnostic groups (SCZ, SAD, BD, and HC), there were no differences in enrichment for higher inflammation level ($p = 0.277$) or cardiometabolic GRS ($p = 0.942$). Among persons with psychotic disorders, higher inflammation status was associated with lower BACS scores (beta = −0.586, $p = 0.038$) with a trend toward higher PANSS total scores (beta = 7.315, $p = 0.076$). Higher inflammation factor 1 was also associated with lower BACS scores (beta = −0.174, p = 0.033) but not with PANSS total scores (beta = 0.770, $p = 0.527$). Neither MADRS nor YMRS were associated with inflammation measures. There were no significant associations of cardiometabolic GRS with BACS or PANSS total scores (see Supplemental Table S10 for detailed results).

4. Discussion

To our knowledge, this is the first study examining relationships between genetic risk scores for psychiatric and cardiometabolic conditions and peripheral inflammation in persons with psychotic disorders. The findings, considered preliminary given the sample size, suggest that elevated peripheral inflammation was associated with higher cardiometabolic GRS in participants of European descent with psychotic disorders, but not with SCZ, BD or MDD GRSs. In the psychosis group, high inflammation status was identified in 38% of participants and was also significantly associated with worse cognitive performance. These findings represent an important advancement in our understanding of possible genetic etiologies for elevated inflammation in psychosis and their relationships to elevated cardiovascular risk in this population.

To date, there have not been comprehensive investigations characterizing the univariate and multivariate patterns of elevated genetic risk for multiple cardiometabolic disorders in persons with psychotic disorders. Only a few studies have examined the clustering pattern of established cardiometabolic risk factors (e.g., lipid, adiposity, blood pressure, sedentary lifestyle, etc.) and the joint influence of unfavorable cardiometabolic profile in non-psychiatric populations (Stoner et al., 2017; Tsai et al., 2020; Klisic et al., 2021). No previous work has examined the aggregation of genetic risks for multiple cardiometabolic traits in psychiatric populations. Our multivariate examination and characterization of cardiometabolic GRSs represent a novel advancement by characterizing the pattern of genetic liability of six cardiometabolic traits that have significant genetic correlations and pathophysiological convergence.

The present findings suggest that accumulating genetic risk for cardiometabolic diseases may play a predisposing role for elevated inflammation in patients with psychotic disorders. Our findings demonstrate that a one standard deviation increase in cardiometabolic GRS among persons with psychotic disorders was associated with a two-fold increase in the odds of being in the higher inflammation subtype. Relationships with elevated inflammation status suggest that the higher cardiometabolic genetic risk may play an intrinsic role in immune and inflammatory overactivation in some patients with psychotic disorders. One interesting finding in the *post hoc* analyses of individual inflammatory markers is that there was no robust correlation between cardiometabolic PRS and any single inflammatory marker, except for IL8 ($R^2 = 0.059$; $p = 0.029$), although there were trend level findings for CRP, IFNγ, TNFα, and VEGF in the psychosis group. The inflammation subtype resulting from multivariate analyses across intercorrelated inflammatory markers may therefore quantify a pattern of overactivation due to the dysregulation of immune/inflammation processes.

In exploratory analyses, the network of functional interactions among cardiovascular risk genes included in the GRS calculation clustered into eight functional modules comprising of a total of 585 GO terms. Most of them represented biological pathways of metabolism and trafficking of lipids, carbohydrates, and proteins related to cardiometabolic function with two modules also enriched with genes related to immune/inflammatory processes. The biological processes for module-M5 and module-M8 were highly related to lipid and carbohydrate homeostasis and activation of the immune response. These findings are consistent with previous reports supporting the involvement of lipids and carbohydrates in the immune system and the complex interplay with pathogenesis of cardiometabolic risks (Cobb and Kasper, 2005; Bernardi et al., 2018). In addition, 31 out of 54 genes in two immune modules were determined to have “druggable”

potential based on the Drug Gene Interaction Database (Freshour et al., 2021). Nine genes therein (*DNMT3A, EHMT2, GALNT2, PLTP, SCARB1, ARID1A, FTO, RAF1, and SIK3*) were determined to have direct interactions with FDA-approved drugs (See Supplement II for the list of druggable genes and interacting drugs.). These drugs include some cardiometabolic agents (e.g. statins, beta-blockers, etc.) and immune modulating biologics (e.g. trastuzumab, etc.) that have replicated findings of efficacy in psychoses and other psychiatric illnesses. These preliminary explorations of immune pathways and interacting with pharmacological agents inform hypothesis generation for further exploration.

Consistent with our previous findings from the larger multiracial cohort (Lizano et al., 2021) and other studies (Ribeiro-Santos et al., 2014; Fillman et al., 2016), the present findings demonstrate that higher inflammation status was associated with lower cognitive performance in European ancestry participants with psychotic disorders. There have been clinical trials examining the adjunctive anti-inflammatory medications on in psychosis symptoms, but treatment efficacy has been mixed (Bishop et al., 2022). This might be due to the choice of anti-inflammatory drug or the fact that only a subgroup of psychotic disorder patients with elevated inflammation might respond to the treatments. Findings linking inflammation and cognition suggest that cognition may be a target to examine in future trials of anti-inflammatory treatments of patients with inflammatory overactivation. We did not observe a significant association between cardiometabolic GRS and cognition despite the association with inflammation. This may be due to our limited sample size, or because additional factors beyond genetic features contribute to peripheral inflammation which is the endpoint directly related to adverse cognitive performance. We did not identify associations of higher inflammation status with severity of psychotic, depressive, or manic symptoms, nor cardiometabolic GRS. This is in contrast with previous findings linking inflammation with symptoms of psychiatric illnesses (Miller, 2020). One possible explanation is that our participants were all clinically stable, albeit with mild-moderate symptoms of psychosis, depression, or mania. The restricted range of symptoms in this investigation along with the smaller sample size may have limited the ability to ascertain these relationships.

Contrary to our hypotheses, we did not observe relationships between genetic risk for SCZ, BD, or MDD with peripheral inflammation measures. This also may be related to our observation that inflammation features were altered only in a subset of affected individuals, which would limit power to detect such effects when examined at the level of the full sample. Previous evidence suggests a shared genetic etiology between some autoimmune conditions and psychiatric illnesses based on genome-wide estimates of genetic correlations (Pouget et al., 2019; Tylee et al., 2018). Future studies in larger sample sizes should examine GRS at larger P_T values, or calculated with other algorithms (Pain et al., 2021), to further explore the polygenic architecture of psychosis and other mental illnesses and the immune/inflammatory implications.

Limitations are important to consider when interpreting these findings. First, due to the relatively small sample size of HCs, we were underpowered to detect associations with clinical phenotypes in that group (see Supplemental Methods for power analysis and Supplemental Discussion for elaboration). This attenuated the power to detect statistical significance for relationships with smaller effect sizes. Second, while we adjusted for multiple comparisons and potential overfitting, we acknowledge the need for confirmation of these findings in a larger study sample. Third, we only conducted analyses in persons of white/European ancestry to ensure appropriate use of GRS calculations. This, however, limits the generalizability of our findings to other populations. Further study of these relationships in other populations remains important. Fourth, the cross-sectional study design precludes longitudinal investigations of the change of systemic inflammation and the impact of other confounders, including disease progression, treatment duration, medication exposure over time, adherence, and quality of medical care. Fifth, gene expression of inflammation markers was not measured and controlled for, which will be valuable to investigate in future studies. Lastly, lifestyle and environmental factors, such as body mass index, smoking status, physical activities, dietary habits, and maternal or early-life infectious exposure, were not measured in this study. These factors may impact both inflammation and mental health (Kolb and Mandrup-Poulsen, 2010; Johannsen et al., 2014; Aas et al., 2017).

5. Conclusion

In summary, in persons with psychotic disorders, elevated inflammation was associated with lower cognitive performance and trend towards more psychotic symptoms. Elevated inflammation was associated with greater combined genetic risk for cardiometabolic diseases, but not genetic risk for SCZ, BD or MDD in persons with SCZ spectrum or psychotic BD. These findings suggest that cardiometabolic genetic factors may contribute to the inflammation overactivation in some individuals with psychosis that may then adversely impact brain anatomy and function, symptom severity and cognition.

Declaration of competing interest

CAT declares an *ad hoc* consulting relationship with Sunovion, Astellas and Merck and membership on a Merck DSMB; CAT is on the Clinical Advisory Board at Kynexis and Karuna Therapeutics and holds stock in Karuna. MSK has received support from Sunovion and GlaxoSmithKline; MSK is a consultant to Forum Pharmaceuticals. JAS has received support from VeraSci. JRB has served as a consultant to OptumRx. The other authors report no related disclosures.

Acknowledgements

We are thankful for the patients and their families who participated in this study, and Gunvant K. Thaker, MD, for his scientific contributions to the B–SNIP consortium. We thank the GWA meta-analysis data on coronary artery disease available through the CARDIoGRAMplusC4D and UK Biobank CardioMetabolic Consortium CHD working group who used the UK Biobank Resource (application number 9922) (Data were downloaded from www.CARDIOGRAMPLUSC4D.org). We thank the Psychiatric Genomics Consortium Schizophrenia and Bipolar Disorder working groups for the availability of GWA meta-analysis on schizophrenia, major depressive disorder, and bipolar disorder (Data were downloaded from https://www.med.unc.edu/pgc/download-rfesults/). We thank the DIAGRAM, GIANT, and Global Lipids Genetics consortiums for the availability of GWA meta-analysis on type-2 diabetes (https://diagram-consortium.org/downloads.html), waist-to-hip ratio (http://portals.broadinstitute.org/collaboration/giant/images/e/eb/GIANT_2015_WHRadjBMI_COMBINED_EUR.txt.gz), and lipids (http://csg.sph.umich.edu/willer/public/lipids2013/).

This work was supported in part by the National Institute of Mental Health (NIMH) grants MH-077851 (to CAT), MH-077945 (to GDP), MH-078113 (to MSK), MH-077862 (to JAS), MH-103366 (to BAC), MH-103368 (to ESG and SKK), MH-083888 (to JRB), MH-077852 (to GKT); Dupont Warren and Livingston Award from Harvard Medical School (to PL); Commonwealth Research Center (grant SCDMH82101008006 to MSK); the NIH's National Center for Advancing Translational Sciences (pilot grant (UL1TR000114) to JRB). Portions of this work were presented at the 2021 Society of Biological Psychiatry (SOBP) Virtual Annual Meeting and as a part of symposium at the 2021 American College of Neuropsychopharmacology (ACNP) annual meeting. The funding agencies had no role in the design and conduct of the study collection, management, analysis, and interpretation of the data, and preparation, review, or approval of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2022.100459.

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