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Genetic predisposition to schizophrenia and circulating proteins in 44,661 UK Biobank participants

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Abstract

Schizophrenia (SCZ) is a highly polygenic disorder and is associated with several comorbidities, including depression, cardiovascular disease, and diabetes; yet the biological pathways underlying this clustering remain poorly understood. This study examined associations between a polygenic risk score for SCZ (PRS-SCZ) and circulating protein levels in 44,661 participants of the UK Biobank. We assessed 1,459 proteins (with ≤ 10% missingness) spanning neurological, inflammatory, cardiometabolic, and oncology panels. After adjustment for technical (population structure, genotyping chip), individual (age, sex, lifestyle), and clinical (comorbidities and medication) variables and multiple testing correction, the standardised PRS-SCZ was significantly negatively associated with C2, RNASET2, BTN2A1, CDSN, HLAE, LTA, MICA-MICB, CNTN3, FCER2, INHBC and CPVL concentrations, and positively with ICAM3, BTN3A2, IL5RA, SLAM7 concentrations. These protein biomarkers may provide insights into the biological pathways underlying schizophrenia and/or its comorbidities.

Introduction

Schizophrenia is a complex and chronic mental health disorder that disrupts thought processes, perception, emotional regulation, and social functioning [1]. Schizophrenia symptoms are typically classified as positive, which includes hallucinations, delusions, and disorganised thinking, and negative, which involve diminished emotional expression, lack of motivation (avolition), reduced ability to experience pleasure (anhedonia) and cognitive defects. The severity of schizophrenia varies between individuals, but the disorder generally imposes a significant and lifelong burden [1].

People with schizophrenia have a significantly reduced life expectancy, typically by 12–15 years, compared with the general population [2]. A meta-analysis indicated that individuals with schizophrenia have a 2.5 times higher risk of all-cause mortality, nearly 10 times higher risk of suicide, and up to 7 times higher risk for premature mortality compared to the general population [2]. Much of the premature mortality is due to cardiometabolic diseases [3]. Despite decades of research, the biological mechanisms underlying schizophrenia and its association with other comorbidities remain poorly understood, complicating diagnosis, treatment and prevention of physical comorbidities. Identification of molecular pathways of schizophrenia pathophysiology would be an important step towards improved treatment of schizophrenia and ultimately improving quality of life. A substantial body of evidence suggests that schizophrenia has a strong genetic basis, with heritability estimates ranging from 60% to 80% [4]. The disorder is influenced by multiple genetic variations, including rare genetic variants with large effects and common single nucleotide polymorphisms (SNPs) each of which contribute a small effects [4]. A landmark genome-wide association study (GWAS) identified 108 genetic signals associated with schizophrenia, which explained about 7% of schizophrenia risk [4]. As with most complex diseases, most genetic variants associated with schizophrenia risk are outside of protein coding regions, therefore how the genetic variants influence molecular pathways leading to schizophrenia is unclear. However, these findings have facilitated the development of polygenic risk scores for schizophrenia (PRS-SCZ), which aggregate the contributions of multiple SNPs into a single metric, weighted by the SNP's effect size estimating an individual's overall genetic predisposition to schizophrenia [5]. Importantly, as genetic variation is set at conception, polygenic risk scores are not influenced by disease processes.

A diagnosis of schizophrenia relies on subjective symptom descriptions. Precision psychiatry aims to identify objective measures to improve risk stratification and diagnosis, with such measures potentially including circulating biomarkers [6]. Here both PRS [7, 8] and biomarker research can contribute. Identifying reliable biomarkers for schizophrenia risk could facilitate risk stratification and personalised treatment strategies, ultimately improving patient outcomes [6]. For example, genetic studies are increasingly contributing towards drug target identification and/or prioritisation [9]. Current research into schizophrenia biomarkers is limited, with uncertainty around their role in neural dysfunction and clinical application [6]. Previous research has identified growth factors (BDNF [10], transforming growth factor beta (TGFß) [11]), inflammatory mediators (C-Reactive Protein (CRP), complement component 4 (C4) [10] interleukin 1 (IL-6), tumour necrosis factor alpha (TNF-α) [10–12], interleukin 1 beta (IL1ß), interleukin 12 (IL12) soluble interleukin 12 receptor (sIL12R), interferon gamma (IFNy) [11]) and lipid metabolism components (apolipoproteins [10]) and chaperone proteins (transthyretin (TTR) [13] and Selenium Binding Protein 1 (SELENBP1) [14]) as potential biomarkers for schizophrenia. However, these findings are limited by small sample sizes, inconsistent results, and clinical cohorts with varied use of anti-psychotic medication, and these biomarkers do not appear to be specific to schizophrenia [10]. Combining polygenic risk scores for a disease and proteomics can help systematically assess biomarkers that might contribute to the pathology of that disease.

The UK Biobank study (UKB) [15–17] has extensive phenotypic and genetic data and has recently employed proteomics to analyse ~ 3000 circulating protein concentrations in ~ 50,000 individuals [18], making it one of the largest biomarker studies (of any phenotype or general population) available.

This study set out to explore associations between PRS-SCZ and circulating biomarkers in UKB.

Materials and Methods

Study population

The UKB is a large-scale, prospective cohort study comprising over 500,000 participants aged 40–69 years, recruited from the general population between 2006 and 2010 via 22 assessment centres across the United Kingdom [16, 17]. The initial recruitment visit included questionnaires on lifestyle, health, demographics as well as physical and functional assessments, and the collection of biological samples including blood, urine and saliva [16, 17]. The blood samples enabled DNA extraction, genome-wide genotyping, and biochemical analyses [15, 16].

Ethical Approval

All UKB participants gave informed written consent, and ethical approval was granted by the North-West Multicentre Research Ethics Committee on the 29th of June 2021 (Ref 21/NW/0157). This study was conducted under application #71392 (PI. RJS).

Genetic data

The central UKB team performed DNA extraction from stored blood samples, followed by genotyping (using either Affymetrix UK BiLEVE Axiom or UKB Axiom), imputation to the Haplotype Reference Consortium and 1000Genomes, and standard quality control (pre and post imputation) [15]. Additionally, the UKB team computed principal genetic components (PGCs) that can be used to control for population stratification [15]. To ensure data integrity, participants were excluded if they exhibited more than 10% missing genetic data, had sex chromosome aneuploidy, were identified as heterozygosity outliers, or if their self-reported sex did not align with their genetically determined sex [15]. From each pair of related individuals, one was kept at random, leaving only unrelated (not closer than second cousins) individuals (N=44,661).

Polygenic risk score for schizophrenia (PRS-SCZ)

The PRS for schizophrenia (PRS-SCZ) was derived from the Psychiatric Genetics Consortium GWAS meta-analyses of schizophrenia [4] which included 36,989 individuals with schizophrenia and 113,075 control participants. PRS-SCZ was calculated using LDpred [19], which sums the risk alleles, weighted according to their effect sizes, incorporates all genetic variants across the genome (including the MHC region). This method accounts for linkage disequilibrium (LD) patterns using a reference panel [19], which here was 1,000 self-reported white British UKB participants who were not included in the main analyses but met the required genetic quality control standards. The use of all variants in an LD-informed manner, rather than selecting a p value threshold, means that LDPred is considered a more accurate estimate of genetic predisposition [19]. Because PRS are only reliable in the same ancestry group as the underlying GWAS [20], only unrelated individuals of self-reported white British or white European ancestry were included. The PRS-SCZ was standardised (PRS-SCZ-std), ensuring a mean of 0 and a standard deviation of 1 where higher scores reflect greater predisposition to schizophrenia.

OLINK proteomic outcome data

The UKB Pharma Proteomics Project examined plasma proteomic profiles from 54,219 participants within the UKB cohort using blood samples collected at baseline [18]. Individuals included were a) randomly selected (N=46,595), b) selected by the UKB-PPP consortium members (N=6,376) or c) participants in the COVID-19 repeat-imaging study (N=1,268).

Plasma samples were analysed using the Olink Explore 3072 platform [18], providing measurements of 2,923 proteins (Table S1). These proteins were chosen based on their associations (established or putative) with cardiometabolic, inflammatory or neurological diseases or oncology [18].

Proteins with ≥10% missingness were considered potentially low quality and excluded from further analyses (N=1,459, Table S1).

Covariates

At baseline, participants provided information on age, sex, smoking status (#20116, coded as current vs never or former) and alcohol consumption (#20117, coded as current vs never or former), self-reported physician-diagnosed health conditions (#20002, "have you ever been diagnosed with…") including ischaemic heart disease (IHD, specifically angina and myocardial infarction), stroke (any form), depression (including post-natal depression), bipolar disorder (including mania and manic depression) and schizophrenia. A composite variable, any self-reported mental illness, was constructed including depression, bipolar disorder and schizophrenia. Current medication use was also reported (#20003), including anti-hypertensive and lipid-lowering medication, lithium/mood-stabilisers, anti-depressant and anti-psychotic medication. The central UKB team calculated BMI from height and weight measurements recorded at baseline (kg/m^2, #21001). Similarly, the UKB central team derived Townsend deprivation index from postcode of residence at baseline (#22189). Type 2 diabetes was defined as per Eastwood et al (from self-report and medication data) [21]. Responses of don't know or prefer not to answer were set to missing (Table 1).

Statistical methods

Descriptive statistics, overall and by sex, were derived for the cohort characteristics and protein concentrations, with mean and standard deviation for continuous variables and N and % for binary variables.

Spearman Rank correlations were computed between PRS-SCZ and protein concentrations. Bonferroni correction for 1459 proteins would be 5.43×10^{-5}, but we approximated this using a threshold of $p<0.0001$.

Where protein concentrations demonstrated significant correlations with PRS-SCZ, these were further explored in linear regression analyses (using PRS-SCZ-std) adjusting for relevant covariates in three models. The large number of proteins available prompted the stepwise approach. Model 1 assessed genetic associations between the PRS-SCZ-std and protein concentrations, adjusting for age, sex and standard genetic covariates (PGC1-8 and genotyping chip), Model 2 assessed the associations when also considering (in addition to Model1) impact of socioeconomic status (Townsend deprivation index), lifestyle factors (current smoking and alcohol consumption) and comorbid conditions (BMI, IHD, stroke, T2D). Model 3 further adjusted for medication use (anti-hypertensive, lipid lowering, anti-depressant and anti-psychotic medication and lithium/mood-stabilisers). For proteins that showed significant associations in Model 3, sensitivity analysis was conducted by excluding individuals with self-reported depression, bipolar disorder or schizophrenia to assess the robustness of these findings. Sex-stratified regression analyses were conducted as per the models and sensitivity analysis described above, and sex-interactions tested. For each Model, multiple testing correction was applied based on the number of proteins analysed. Only individuals with complete data for each model were included in analyses. All statistical analyses were conducted in STATA 18.0 (STATAcorp).

Results

In total, of 44,661 UKB participants were included (mean age 57.2 years; 46.2% men) The characteristics of the cohort are provided in Table 1. Supplemental Table 1 describes the distributions and missingness of the proteins measured, Supplemental Figure 1 provides an overview of the analyses and Figure 1 provides an overview of the results.

Correlation Analyses

Of the 2,923 measured proteins, 1,459 had ≤10% missing values and were analysed for Spearman's rank correlations with PRS-SCZ. Of these, 47 (13 cardiometabolic, 16 inflammatory, 11 neurological and 7 oncological) proteins demonstrated significant correlations with PRS-SCZ at p ≤0.0.0001 (Table 2 and Supplementary Table 2). BTN3A2 showed the strongest positive correlation (ρ = 0.060 p ≤0.0001), and MICB_MICA showed the strongest negative correlation (ρ = -0.052, p ≤ 0.0001).

Primary Linear Regression Analyses

Of the 47 proteins with significant Spearman's rank correlations, 33 were significantly associated (p<0.0011, Bonferroni correction for 47 proteins) with PRS-SCZ-std in Model 1, and 16 were still significantly associated with PRS-SCZ-std in Model 2 (p<0.0015, Bonferroni correction for 33 proteins) (Table 3). These 16 proteins were still significantly associated with PRS-SCZ-std in model 3, but only 15 remained significant after sensitivity analyses where individuals with severe mental illness were excluded (Table 3 and Supplementary Table 3). Higher PRS-SCZ-std was associated with lower C2, RNASET2 (cardiometabolic), BTN2A1, CDSN, HLAE, LTA, MICA-MICB (inflammatory), CNTN3, FCER2, INHBC (neurology) and CPVL (oncology) concentrations, but with higher ICAM3 (cardiometabolic), BTN3A2, IL5RA, SLAM7 (inflammatory) concentrations.

Sex-stratified Linear Regression Analyses

Of the 47 proteins significant in the correlation analyses, 13 were significantly associated with PRS-STCZ-std in Model 1 in males, and 10 remained significantly associated with PRS-SCZ-std in males in Models 2 and 3 (Supplementary Table 4). All 10 proteins remained significant in the sensitivity analysis excluding individuals with self-reported mental illness. Higher PRS-SCZ-std was associated with reduced concentrations of BTN2A1, CDSN, LTA, MICB_MICA and FCER2, but increased concentrations of ICAM3, BTN3A2, IL5RA, SLAMF7.

Of the 47 proteins significant in the correlation analyses, 14 proteins were significant in Model 1 in females (Supplementary Table 5). Of these, seven proteins remained significant in Models 2 and 3, and these seven remained significant in the sensitivity analysis excluding individuals with self-reported mental illness (Supplemental Table 5). Higher PRS-SCZ-std was associated with reduced concentrations of BTN2A1, HLAE, MICB_MICA, C2, CNTN3 and CPVL but increased concentrations of BTN3A2.

Table 4 and Figure 1 provide a comparison of proteins that were associated with PRS-SCZ-std in sex-combined and sex-specific analyses. Sex-interaction analyses demonstrated no significant differences between associations in males and females (significance at p<0.0028, Bonferroni corrected for 18 proteins, Table 4).

Discussion

This study assessed the relationship between genetic predisposition to schizophrenia (estimated with a polygenic risk score) and proteins implicated in neurological, inflammatory, cardiometabolic or oncology pathways. Of 1459 proteins (with <10% missingness), 47 were significantly correlated with PRS-SCZ, and 15 were significantly and robustly associated with PRS-SCZ-std (after extended adjustments and exclusion of individuals with self-reported mental illness).

Of the 15 proteins significantly associated with PRS-SCZ-std in sex-combined analyses, four were neurological (CD74, CNTN3, INHBC, FCER2), eight inflammatory (BTN3A, SLAMF7, IL5RA, HLA-E, BTN2A1, CDSN, MICB_MICA, LTA AND SCGB1A1), three cardiometabolic (ICAM3, C2, RNASET2) and one oncology (CPVL). It is worth noting that the panel to which a protein was assigned reflects current knowledge of its implications in neurological, inflammatory, oncological and cardiometabolic diseases. However, many of the proteins included here have diverse functions and contribute to more than one of these conditions. Current knowledge of these proteins functions and relevance to mental illness generally and schizophrenia in particular are summarised in Table 5. Supplemental Table 6 provides a summary of expression patterns of the 16 proteins.

Robust, significant associations were identified for 10 proteins in male-only analyses and seven in females-only analyses, however formal testing of a sex-interaction identified no significant interactions between PRS-SCZ and sex. Differences in the findings between sexes may reflect genuine biological variation, such as sex-related differences in immune regulation or hormonal influences on protein expression but could also arise from sampling variability.

Another recent study [22] examined associations between PRS-SCZ and OLINK biomarkers in the UK Biobank, excluding individuals with psychosis. A look-up of the 16 proteins associated with PRS-SCZ-std in our model 3 in the Kendall et al [22] results demonstrated nominally significant ($p<0.05$) associations with BTN3A2, SLAMF7, CNTN3, INHBC and KLK1, but only the association with KLK1 survived FDR correction of p values. ICAM5 (significantly associated with PRS-SCZ-std in model 1 but not model 2) and ENAH (correlated with PRS-SCZ but not associated with PRS-SCZ-std in model 1) were also nominally significant in the Kendal et al analyses [22], but theses associations did not survive multiple testing correction.

Of the four proteins (TMPRSS15, ADGRB3, CEACAM21, and KLK1) associated with PRS-SCZ in the study by Kendall et a [22], subsequent case–control analyses showed that only TMPRSS15 (higher in psychosis) and KLK1 (lower in psychosis) differed between cases and controls. In our analyses, TMPRSS15 and ADGRB3 were not significantly correlated with PRS-SCZ. CEACAM21 showed an initial association in Model 1, which did not persist after further adjustment. KLK1 was positively associated with PRS-SCZ across all models, but this association was attenuated when individuals with severe mental illness were excluded. We interpret these findings as consistent with Kendall et al. [22], in that the PRS-SCZ–KLK1 association was evident in participants without psychosis, whereas our broader exclusion of psychiatric diagnoses likely removed this signal.

Dysregulated neurodevelopment [23] and neuroinflammation [24, 25] have been proposed as mechanisms leading to schizophrenia There is a wealth of clinical and experimental evidence supporting both hypotheses. The findings from this study also provide support for both hypotheses, with proteins involved in inflammatory processes and brain development being robustly associated with PRS-SCZ (Table 5 and Supplemental Table 6).

Strengths and limitations

This study is one of the largest biomarker cohorts to date, with 2093 proteins measured on ~ 50,000 participants. A wealth of demographic, lifestyle, clinical and medication variables enabled adjustment for a wide range of potential confounders.

There are also some limitations. Of biomarkers previously associated with schizophrenia, some were measured but excluded for having missingness >10%: BDNF (15.8%), APOA1, APOA4 and APOE (all 15.6%), APOA2, APOB, APOF, APOL1 (all 15.7%), APOC1 (15.8%), APOBR (18%) and APOD (19.4%) (Supplemental Table 1). Other, APOH, APOM, TNF-α, IL6 and IL6R alpha and beta subunits, were included in the correlation analyses but were not significantly correlated with PRS-SCZ, so were not further investigated. Other biomarkers were not measured (complement 4 (C4) [10], transthyretin (TTHY) [13] and Methanethiol oxidase (SELENBP1) [14]) or have been measured but not using this technology (C-reactive protein (CRP)) [10].

Despite careful statistical adjustments, residual confounding cannot be excluded in observational studies. The UKB study population is not representative of the UK general population. [26, 27] but effect estimates should nonetheless be generalisable [28]. Reliance on self-reported covariates, such as lifestyle, may introduce inaccuracies. Protein concentrations were measured peripherally, which may not accurately reflect central nervous system concentrations or activity. As interpreting serum concentrations is often challenging; it can be difficult to determine whether increases in proteins arise from brain-derived leakage or peripheral sources, and the extent to which circulating proteins cross the blood brain barrier and impact brain function varies considerably [29]. Many proteins had high levels of missing data - possibly due to low abundance. By excluding proteins with >10% missing data, we might have missed meaningful associations. For sex-specific analyses, we would ideally calculate the PRS based on sex-specific GWAS of Schizophrenia, however that is not yet possible.

The inclusion of only self-reported white British and European individuals is a pragmatic, but not ideal, use of the data [30]. This choice was also driven by the need to ancestry match the data to the underlying GWAS [4], which again limits the generalisability to only European ancestry individuals. More broadly, advancing genetic studies in non-European ancestry individuals is required [30].

Future Directions

These findings should be further explored using longitudinal studies, studies in different populations and studies in different age groups as well as causal analytical methods to better understand their roles in relation to schizophrenia risk. Finally, the analysis would benefit from the inclusion of additional covariates that were not available in this dataset, such as confirmed schizophrenia diagnoses and substance misuse history. A necessary step towards clinical application of these proteins as biomarkers would be comparing protein levels in individuals with and without schizophrenia — and with or without treatment — which provide important insights into whether these markers reflect disease state, treatment effects, or underlying genetic vulnerability. Although the associations observed were very small, they may reflect subtle biological differences linked to genetic liability, underscoring the potential of large-scale proteomics to inform biomarker discovery in psychiatric disorders.

Given the cross-sectional design and potential for residual confounding, extension of this study in independent and diverse cohorts will be essential to determine the relevance of these proteins as biomarkers or contributors to disease mechanisms.

In conclusion, this study identified 16 proteins robustly associated with genetic risk for schizophrenia, including cardiometabolic (C2, ICAM3, RNASET2), inflammatory (BTN2A1, BTN3A2, CDSN, HLAE, IL5RA, LTA, MICA-MICB, SLAM7), neurological (CNTN3, FCER2) and oncology (CPVL) proteins. No sex-interactions were identified. These proteins have potential as biomarkers and should be further investigated in the context of schizophrenia.

Declarations

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The funders played no role in the study design, analyses or interpretation.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Tables

Table 1

Descriptive statistics of the study population. Data is provided as N (%) for categorical variables or mean (standard deviation) for continuous variables.

N (% men)	All	Men	Females
	44661 (46.2)	**20622 (100)**	**24039 (0)**
Age	57.2 (8.1)	57.5 (8.2)	57.0 (8.0)
deprivation	-1.48 (3.00)	-1.44 (3.06)	-1.50 (2.94)
BMI	27.5 (4.8)	27.9 (4.2)	27.1 (5.2)
WHR	0.87 (0.09)	0.94 (0.07)	0.81 (0.07)
SBP	138 (19)	141 (17)	136 (19)
DBP	82 (10)	84 (10)	81 (10)
SBP*	142 (21)	145 (19)	138 (21)
DBP*	84 (11)	87 (11)	82 (11)
t2d	2064 (4.6)	1354 (6.6)	710 (3.0)
stroke	798 (2.5)	478 (4.0)	320 (1.8)
ish	2366 (7.2)	1671 (11.4)	695 (3.8)
lipid-lowering	8453 (19.1)	5231 (25.6)	3222 (13.5)
htnmed	9994 (22.5)	5546 (27.1)	4448 (18.6)
any anti-dep	3489 (8.1)	1140 (5.7)	2349 (10.2)
any anti-psych	214 (0.5)	121 (0.6)	93 (0.4)
any mood stabiliser	45 (1.1)	231 (1.2)	222 1.0)
Current alcohol	41599 (93.2)	19536 (94.8)	22063 (91.9)
current smoking	4523 (10.2)	2444 (11.9)	2079 (8.7)
self reported dep, bd, scz	2784 (6.2)	1013 (4.9)	1771 (7.4)
PRS-SCZ	-0.96 (0.26)	-0.96 (0.26)	-0.96 (0.26)

Table 2
Proteins significantly correlated with PRS-SCZ.

panel	protein	N	rho	p
CM	CTSZ	43,493	-0.027	< 0.0001
CM	CCL15	43,974	-0.024	< 0.0001
CM	C2	43,559	-0.024	< 0.0001
CM	PTPRF	43,974	-0.023	< 0.0001
CM	IGFBP6	43,271	-0.023	< 0.0001
CM	CD59	41,902	-0.021	< 0.0001
CM	SSC4D	43,392	-0.020	< 0.0001
CM	FAS	43,835	-0.020	< 0.0001
CM	RNASET2	43,771	-0.020	< 0.0001
CM	FCGR3B	43,500	0.021	< 0.0001
CM	ICAM3	43,974	0.024	< 0.0001
CM	ICAM5	43,461	0.029	< 0.0001
CM	BPIFB1	43,354	0.031	< 0.0001
Inflam	MICB_MICA	43,354	-0.052	< 0.0001
Inflam	BTN2A1	43,637	-0.048	< 0.0001
Inflam	HLAE	43,354	-0.034	< 0.0001
Inflam	SCGB1A1	43,489	-0.025	< 0.0001
Inflam	CDSN	43,775	-0.024	< 0.0001
Inflam	LTA	43,354	-0.022	< 0.0001
Inflam	IL18R1	43,906	-0.021	< 0.0001
Inflam	ENAH	42,626	-0.020	< 0.0001
Inflam	CSF1	43,637	-0.020	< 0.0001
Inflam	IFNGR1	43,637	-0.020	< 0.0001
Inflam	CD40	43,428	-0.020	< 0.0001
Inflam	CCL20	43,906	0.020	< 0.0001
Inflam	IL5RA	43,354	0.022	< 0.0001
Inflam	CXCL17	43,906	0.024	< 0.0001
Inflam	SLAMF7	43,354	0.029	< 0.0001
Inflam	BTN3A2	43,354	0.060	< 0.0001
Neuro	CNTN3	43,443	-0.035	< 0.0001
Neuro	INHBC	43,443	-0.024	< 0.0001
Neuro	FCER2	43,443	-0.023	< 0.0001
Neuro	ADAM22	43,103	-0.021	< 0.0001
Neuro	CD74	43,816	-0.021	< 0.0001
Neuro	SCARA5	43,816	-0.021	< 0.0001
Neuro	PIGR	42,878	0.021	< 0.0001
Neuro	SUSD2	43,443	0.021	< 0.0001
Neuro	SPINT1	43,294	0.022	< 0.0001
Neuro	TFF1	43,241	0.023	< 0.0001
Neuro	ISLR2	41,793	0.026	< 0.0001
Onc	CPVL	43,727	-0.039	< 0.0001

panel	protein	N	rho	p
Onc	RTN4R	43,797	-0.024	< 0.0001
Onc	KLK14	43,797	0.022	< 0.0001
Onc	CEACAM5	41,859	0.023	< 0.0001
Onc	ALPP	43,227	0.025	< 0.0001
Onc	KLK13	42,476	0.025	< 0.0001
Onc	KLK1	43,015	0.028	< 0.0001

Table 3

Proteins significantly associated with PRS-SCZ-std.

panel		Model 1			Model 2			Model 3		
	protein	adjr2	beta (se)	P	adjr2	beta (se)	P	adjr2	beta (se)	P
CM	C2	0.02	-0.008 (0.001)	1.10E-09	0.06	-0.008 (0.002)	1.60E-06	0.06	-0.008 (0.002)	9.30E-07
CM	ICAM3	0.01	0.007 (0.001)	1.30E-06	0.02	0.010 (0.002)	5.30E-09	0.02	0.009 (0.002)	1.40E-07
CM	RNASET2	0.04	-0.007 (0.002)	2.00E-05	0.07	-0.006 (0.002)	0.0010	0.07	-0.007 (0.002)	0.0001
Inflam	BTN2A1	0.05	-0.014 (0.002)	6.90E-20	0.08	-0.012 (0.002)	2.40E-13	0.08	-0.014 (0.002)	5.30E-16
Inflam	BTN3A2	0.03	0.034 (0.002)	2.00E-52	0.04	0.034 (0.003)	5.30E-39	0.04	0.033 (0.003)	4.60E-37
Inflam	CDSN	0.02	-0.013 (0.002)	1.30E-07	0.02	-0.015 (0.003)	3.10E-07	0.02	-0.015 (0.003)	1.40E-07
Inflam	HLAE	0.06	-0.011 (0.002)	4.10E-11	0.06	-0.010 (0.002)	1.50E-07	0.06	-0.011 (0.002)	2.80E-08
Inflam	IL5RA	0.02	0.018 (0.003)	3.40E-08	0.02	0.018 (0.004)	1.20E-06	0.02	0.018 (0.004)	2.00E-06
Inflam	LTA	0.04	-0.013 (0.002)	3.70E-08	0.05	-0.009 (0.003)	0.0014	0.05	-0.010 (0.003)	0.0002
Inflam	MICB_MICA	0.01	-0.093 (0.008)	2.10E-28	0.01	-0.086 (0.010)	1.70E-17	0.01	-0.087 (0.10)	4.70E-17
Inflam	SLAMF7	0.01	0.016 (0.003)	3.90E-06	0.01	0.021 (0.004)	1.80E-07	0.01	0.021 (0.004)	2.90E-07
Neuro	CNTN3	0.12	-0.013 (0.002)	5.10E-12	0.21	-0.010 (0.002)	1.10E-05	0.21	-0.010 (0.002)	8.70E-06
Neuro	FCER2	0.02	-0.016 (0.003)	1.00E-07	0.06	-0.014 (0.003)	3.90E-05	0.06	-0.015 (0.003)	1.00E-05
Neuro	INHBC	0.03	-0.016 (0.003)	1.40E-09	0.18	-0.011 (0.003)	0.0001	0.18	-0.012 (0.003)	5.90E-05
Onc	CPVL	0.01	-0.021 (0.002)	3.60E-18	0.01	-0.022 (0.003)	3.80E-14	0.01	-0.023 (0.003)	6.10E-15
Onc	KLK1	0.01	0.027 (0.007)	0.0003	0.01	0.029 (0.009)	0.0008	0.01	0.028 (0.009)	0.0014
CM	BPIFB1	0.06	0.020 (0.004)	2.20E-07	0.14	0.010 (0.004)	0.0269			
CM	CCL15	0.04	-0.009 (0.002)	0.0004	0.05	-0.008 (0.003)	0.0051			
CM	CTSZ	0.05	-0.008 (0.002)	1.20E-05	0.11	-0.006 (0.002)	0.0069			
CM	ICAM5	0.01	0.012 (0.003)	5.10E-06	0.07	0.006 (0.003)	0.0679			
CM	PTPRF	0.06	-0.007 (0.002)	2.70E-05	0.09	-0.005 (0.002)	0.0079			
CM	SSC4D	0.11	-0.032 (0.007)	7.80E-06	0.30	-0.005 (0.008)	0.4667			
Inflam	CXCL17	0.19	0.016 (0.003)	1.40E-08	0.42	0.007 (0.003)	0.0097			
Inflam	IL18R1	0.02	-0.008 (0.002)	0.0001	0.13	-0.004 (0.002)	0.1068			
Inflam	SCGB1A1	0.06	-0.013 (0.003)	3.10E-05	0.10	-0.012 (0.004)	0.0016			

Where: Model 1 adjusted for age, sex, PGC1-8 and genotyping chip, and $p < 0.0011$ (Bonferroni correction for 47 proteins) was considered significant. Model 2 adjusted for Model1, Townsend deprivation index, current smoking, alcohol consumption, BMI, IHD, stroke, T2D and $p < 0.0015$ (Bonferroni correction for 33 proteins) was considered significant. Model 3 adjusted for Model 2 and anti-hypertensive, lipid lowering, anti-depressant and anti-psychotic medication and lithium/mood-stabilisers use, and $p < 0.0031$ (Bonferroni correction for 16 proteins) was considered significant.

panel		Model 1			Model 2			Model 3		
	protein	adjr2	beta (se)	P	adjr2	beta (se)	P	adjr2	beta (se)	P
Neuro	ADAM22	0.02	-0.007 (0.002)	0.0009	0.03	-0.004 (0.002)	0.0553			
Neuro	CD74	0.09	-0.010 (0.002)	3.50E-07	0.14	-0.007 (0.002)	0.0016			
Neuro	SUSD2	0.05	0.007 (0.002)	1.70E-05	0.13	0.005 (0.002)	0.0185			
Onc	ALPP	0.03	0.029 (0.007)	4.00E-05	0.32	0.013 (0.007)	0.0742			
Onc	CEACAM5	0.03	0.017 (0.004)	1.50E-05	0.12	0.012 (0.004)	0.0081			
Onc	KLK13	0.04	0.011 (0.003)	3.00E-05	0.09	0.007 (0.003)	0.0140			
Onc	KLK14	0.04	0.011 (0.003)	7.80E-05	0.07	0.004 (0.003)	0.1982			
Onc	RTN4R	0.05	-0.009 (0.002)	3.20E-05	0.17	-0.002 (0.002)	0.3297			
CM	CD59	0.14	-0.003 (0.001)	0.0116						
CM	FAS	0.10	-0.005 (0.002)	0.0157						
CM	FCGR3B	0.02	0.009 (0.003)	0.0021						
CM	IGFBP6	0.24	-0.006 (0.002)	0.0012						
Inflam	CCL20	0.02	0.014 (0.005)	0.0075						
Inflam	CD40	0.01	-0.009 (0.003)	0.0024						
Inflam	CSF1	0.03	-0.005 (0.002)	0.0031						
Inflam	ENAH	0.02	-0.009 (0.003)	0.0018						
Inflam	IFNGR1	0.03	-0.003 (0.001)	0.0212						
Neuro	ISLR2	0.10	0.006 (0.002)	0.0050						
Neuro	PIGR	0.02	0.006 (0.002)	0.0040						
Neuro	SCARA5	0.12	-0.005 (0.002)	0.0026						
Neuro	SPINT1	0.01	0.004 (0.001)	0.0062						
Neuro	TFF1	0.09	0.014 (0.004)	0.0017						

Where: Model 1 adjusted for age, sex, PGC1-8 and genotyping chip, and $p < 0.0011$ (Bonferroni correction for 47 proteins) was considered significant. Model 2 adjusted for Model1, Townsend deprivation index, current smoking, alcohol consumption, BMI, IHD, stroke, T2D and $p < 0.0015$ (Bonferroni correction for 33 proteins) was considered significant. Model 3 adjusted for Model 2 and anti-hypertensive, lipid lowering, anti-depressant and anti-psychotic medication and lithium/mood-stabilisers use, and $p < 0.0031$ (Bonferroni correction for 16 proteins) was considered significant.

Table 4

Comparison of significant associations in sex-combined and sex-specific analyses.

panel		sex-combined				Men				Females			
	protein	beta (se)	p_model1	beta (se)	p_Model3 sens	beta (se)	p_model1	beta (se)	p_Model3 sens	beta (se)	p_model1	beta (se)	p_Mo sens
CM	BPIFB1	0.020	2.20E-07			0.016	0.0056			0.023	5.90E-06		
CM	C2	-0.008	1.10E-09	-0.008	2.50E-06	-0.005	0.0065			-0.011	1.70E-08	-0.008	0.000
CM	CCL15	-0.009	0.0004			-0.006	0.0766			-0.011	0.0015		
CM	CTSZ	-0.008	1.20E-05			-0.007	0.0178			-0.009	0.0002		
CM	ICAM3	0.007	1.30E-06	0.010	2.30E-07	0.009	5.40E-05	0.011	0.0002	0.006	0.0042		
CM	ICAM5	0.012	5.10E-06			0.013	0.0016			0.012	0.0007		
CM	PTPRF	-0.007	2.70E-05			-0.004	0.1274			-0.009	3.80E-05		
CM	RNASET2	-0.007	2.00E-05	-0.006	0.0005	-0.005	0.0459			-0.008	0.0001		
CM	SSC4D	-0.032	7.80E-06			-0.046	4.40E-05			-0.018	0.0434		
Inflam	BTN2A1	-0.014	6.90E-20	-0.013	5.30E-15	-0.014	7.50E-10	-0.014	3.60E-07	-0.013	2.60E-11	-0.013	1.90E
Inflam	BTN3A2	0.034	2.00E-52	0.033	1.40E-34	0.033	4.70E-25	0.029	1.10E-11	0.034	2.50E-29	0.038	2.50E
Inflam	CDSN	-0.013	1.30E-07	-0.015	4.20E-07	-0.016	1.40E-05	-0.019	8.30E-05	-0.011	0.0016		
Inflam	CXCL17	0.016	1.40E-08			0.016	0.0001			0.016	1.80E-05		
Inflam	HLAE	-0.011	4.10E-11	-0.011	3.60E-08	-0.008	0.0021			-0.014	9.90E-10	-0.015	1.00E
Inflam	IL18R1	-0.008	0.0001			-0.003	0.2792			-0.011	3.10E-05		
Inflam	IL5RA	0.018	3.40E-08	0.019	3.30E-06	0.022	2.20E-06	0.022	0.0006	0.013	0.0025		
Inflam	LTA	-0.013	3.70E-08	-0.010	0.0003	-0.017	3.60E-07	-0.021	2.20E-06	-0.009	0.0053		
Inflam	MICB_MICA	-0.093	2.10E-28	-0.080	4.70E-14	-0.111	3.40E-19	-0.104	7.70E-10	-0.078	1.20E-11	-0.064	1.60E
Inflam	SCGB1A1	-0.013	3.10E-05			-0.011	0.0137			-0.015	0.0007		
Inflam	SLAMF7	0.016	3.90E-06	0.020	1.50E-06	0.021	5.30E-05	0.026	0.0001	0.011	0.0134		
Neuro	ADAM22	-0.007	0.0009			-0.008	0.0070			-0.006	0.0390		
Neuro	CD74	-0.010	3.50E-07			-0.007	0.0117			-0.013	5.40E-06		
Neuro	CNTN3	-0.013	5.10E-12	-0.010	1.00E-05	-0.011	1.20E-05			-0.015	1.20E-07	-0.013	0.000
Neuro	FCER2	-0.016	1.00E-07	-0.015	3.60E-05	-0.019	1.90E-05	-0.024	1.60E-05	-0.013	0.0012		
Neuro	INHBC	-0.016	1.40E-09	-0.011	0.0004	-0.013	0.0002			-0.018	2.10E-06		
Neuro	SUSD2	0.007	1.70E-05			0.009	0.0003			0.006	0.0069		
Onc	ALPP	0.029	4.00E-05			0.037	0.0004			0.022	0.0205		
Onc	CEACAM5	0.017	1.50E-05			0.017	0.0028			0.017	0.0012		
Onc	CPVL	-0.021	3.60E-18	-0.022	1.10E-13	-0.022	1.30E-10	-0.025	6.90E-08	-0.019	5.20E-09	-0.021	2.80E
Onc	KLK1	0.027	0.0003			0.028	0.0082			0.025	0.0126		
Onc	KLK13	0.011	3.00E-05			0.012	0.0023			0.010	0.0028		
Onc	KLK14	0.011	7.80E-05			0.014	0.0004			0.008	0.0354		
Onc	RTN4R	-0.009	3.20E-05			-0.011	0.0003			-0.007	0.0173		

Where: Model 1 adjusted for age, sex, PGC1-8 and genotyping chip, and p < 0.0011 (Bonferroni correction for 47 proteins) was considered significant. Model Model1, Townsend deprivation index, current smoking, alcohol consumption, BMI, IHD, stroke, T2D and p < 0.0015 (Bonferroni correction for 33 proteins) wa significant. Model 3 adjusted for Model 2 and anti-hypertensive, lipid lowering, anti-depressant and anti-psychotic medication and lithium/mood-stabilisers u 0.0031 (Bonferroni correction for 16 proteins) was considered significant.

Table 5

summary of protein functions and relevance for schizophrenia

Protein	Biology	Relevance to schizophrenia or other mental illnesses	Our findings
BTN 2A1	Butyrophilin subfamily 2 member A1, an immunoglobulin superfamily receptor protein. Increased BTN2A1 gene expression has been reported in response to a mediterranean diet in primates, in a manner that suggests a protective effect against neuroinflammation [31].	Implicated in shared pathology of major depressive disorder, bipolar disorder and Schizophrenia [32] and positively associated with chronic pain [33]. Implicated as a causal factor in anxiety (with unclear direction) [34].	Increased PRS-SCZ, decreased BTN2A1.
BTN3A2	Butyrophilin subfamily 3 member A2 is a primate-specific immunoglobulin superfamily receptor with immunomodulatory roles including inhibiting the release of IFN-γ [35]. In experimental animals, overexpression of BTN3A2 has been shown to suppress excitatory synaptic activity on specific neurons [35].	Proposed as a circulating biomarker for cross-psychiatric disorder risk (specifically major depressive disorder, schizophrenia, and bipolar disorder) [32].	Higher PRS-SCZ, increased BTN3A2.
C2	Complement 2 is part of the complement cascade immune response.	High serum levels of C2 proposed as a biomarker for diagnosis of first episode Schizophrenia [36] and change in C2 levels might reflect treatment response in first episode Schizophrenia [37].	Increased PRS-SCZ, decreased C2.
CDSN	Corneodesmosin is a component of desmosomes, which are important cell-cell connections essential for the integrity of skin and mucosal membranes [38]. CDSN loss of function variants contribute to skin and mucosal membrane disorders [39].	CDSN loss of function variants might impact the intestinal barrier deregulation observed in Schizophrenia [38].	Increased PRS-SCZ, decreased CDSN.
CNTN3	Contactin-3 has a primary role in the development and organisation of the nervous system.	Deletions of the CNTN3 gene have been implicated in autism spectrum disorder [40] .	Increased PRS-SCZ, decreased CNTN3.
CPVL	Carboxypeptidase, vitellogenic-like has mainly been studied in cancer, with both tumour promoting [41–43] and tumour suppressor roles reported [44], which may reflect tissue specificity. Lack of CPVL was shown to promote glioma cell death [41].	The CPVL locus has also been implicated in stimulant dependence [45], which frequently occurs alongside mental illnesses including Schizophrenia.	Increased PRS-SCZ, decreased CPVL levels.
FCER2	Low affinity immunoglobulin epsilon (IgE) Fc receptor is Immunoglobulin E receptor critical for B-cell differentiation and antigen presentation to T cells [46]. Expression of FCER2 on B cells has been reported as part of IgE response, with high FCER2 levels on B cells being observed in atopic disorders (excessive responses to normally harmless environmental stimuli) [47].		Increased PRS-SCZ, decreased FCER2.
HLA-E	HLA class I histocompatibility antigen, alpha chain E is a non-classical MHC class I protein involved in immune regulation by interacting with and regulating natural killer (NK) cell responses, to prevent inappropriate activation against self [48]. Soluble HLA-E is released in response to inflammation or infection stress [48].	HLA-E levels have been shown to be elevated in Schizophrenia and bipolar disorder than healthy controls [48], but higher soluble HLA-E in acute vs stable mood disorder was inconsistent between Schizophrenia and bipolar disorder controls [48].	Increased PRS-SCZ, decreased HLA-E.
ICAM3	Intercellular adhesion molecule 3 is expressed on resting leukocytes and involved in the recruitment of leukocytes to sites of injury [49]. ICAM3 is also involved in phagocytosis of neutrophils [50].	Dysregulated phagocytosis has been implicated in excessive microglial pruning of synapses in Schizophrenia [51].	Increased PRS-SCZ, increased ICAM3 levels
IL5RA	Interleukin-5 receptor subunit alpha. ell surface receptor that plays an important role in the survival, differentiation, and chemotaxis of eosinophils [52]	A locus containing IL5RA has been implicated in mental retardation [53] and IL5RA has been implicated in anti-depressant response [54].	Increased PRS-SCZ, increased IL5RA.
INHBC	Inhibin beta C chain. Inhibins oppose the functions of activins, which have a wide range of roles in hormone regulation and cellular development and survival. Increased levels of INHBC have been associated with increased risk of sepsis (an inappropriate inflammatory response) [55]. T		Increased PRS-SCZ, decreased INHBC.
LTA	Lymphotoxin-alpha or TNFB is an inflammatory cytokine, which contribute to development of neurones and synapses [25].	A causal negative effect of circulating LTA on Schizophrenia has been reported [25], however increased LTA protein levels in post-mortem brain samples were increased in Schizophrenia compared to controls [56].	Increased PRS-SCZ, decreased LTA.
MICA-MICB	MHC class I polypeptide-related sequence A and B, respectively, are non-classical HLA class I proteins which bind and activate NK cells and some T cell subsets [57], thus have a clear role in immune and inflammatory responses. MICA/MICB are normally expressed at low levels, but are upregulated in response to cellular stress [58].	Genetic variants in MICA have been associated with Schizophrenia, in a population-specific manner [57]. Genetic analyses suggests that increased MICB levels in cerebrospinal fluid (but not the blood) have a causal role in increasing SCZ risk {Gu, 2022 #1543.	Increased PRS-SCZ, decreased MICA/MICB.
RNASET	Ribonuclease T2 has pro- and anti- inflammatory effects. Proinflammatory effect occur via degradation of microbial RNA to		Increased PRS-SCZ, decreased

Protein	Biology	Relevance to schizophrenia or other mental illnesses	Our findings
	generate ligands that activate TLR8 [59].However, lack of RNASET2 (in mice and humans) presents a neuroinflammatory phenotype [60].		RNASET2.
SLAM7	Signaling lymphocytic activation molecule family member 7 connects the innate and adaptive immune responses. SLAMF7 has both pro- and anti-inflammatory effects on a variety of immune cell types [61], depending upon the cofactors or ligands present.	Dysregulated peripheral inflammation might contribute to neuroinflammation [24]. Increased Schizophrenia risk ia associated with autoimmune diseases, especially those with brain-reactive autoantibodies capable of disrupting the blood–brain barrier [62].	Increased PRS-SCZ, increased SLAM7.

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Figures

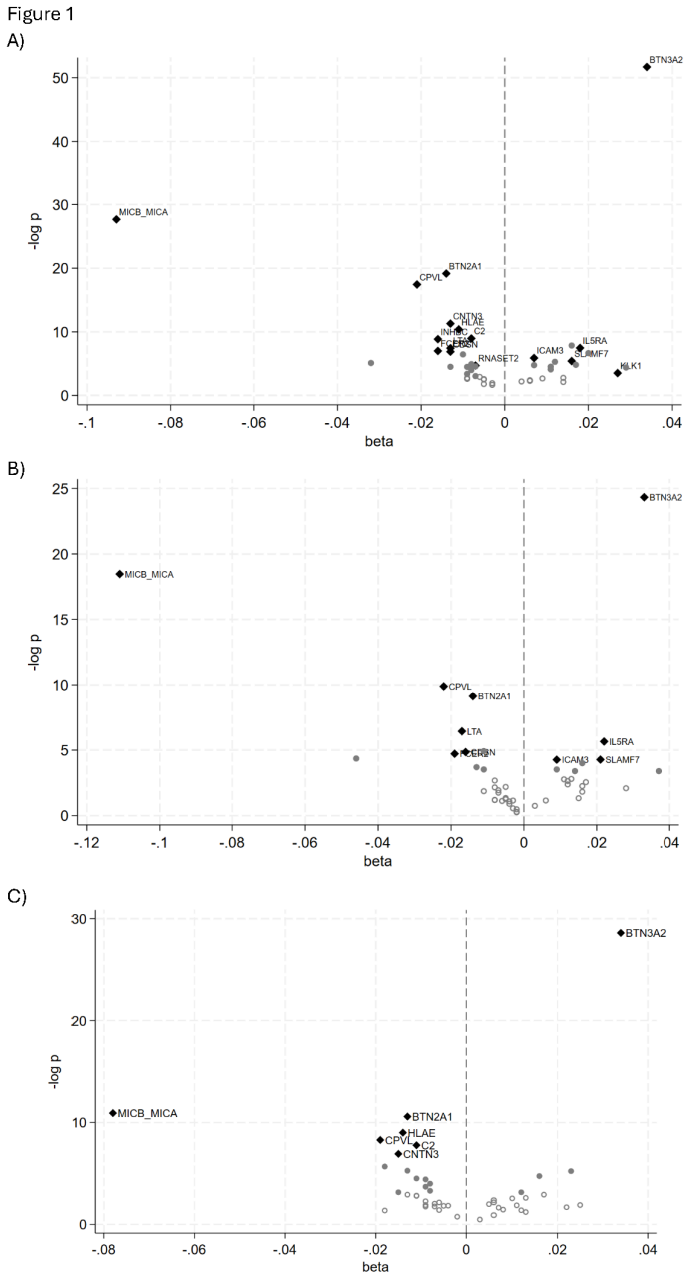


Figure 1

Volcano plots of significant associations with PRS-SCZ-std in a) sex-combined analyses, b) men-only analyses and c) females only-analyses. Where green indicates non-significant and red indicates significantly associated proteins in basic analyses (adjusted for age, sex, population structure and genotyping chip) whilst blue indicates significantly associated proteins in sensitivity testing (without self-reported mental illness and the extended model 2 (adjusted for age, sex, PGCs1-8 and genotyping chip, Townsend deprivation index, body mass index (BMI), ischaemic heart disease (ISH), Stroke, type 2 diabetes (T2D), current smoking and current alcohol consumption, alanine aminotransferase levels, gamma-glutamyl transferase levels, aspartate aminotransferase, alkaline phosphatase (reflecting liver function), lymphocyte count, neutrophil count (reflection immune function) and whether the participant was on anti-hypertensives, lipid lowering medication, lithium/mood-stabilisers, antidepressants and anti-psychotics).

Supplementary Files

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