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Shared Genetic Loci Between Schizophrenia and White Blood Cell Counts Suggest Genetically Determined Systemic Immune Abnormalities

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***Background*: Immune mechanisms are indicated in schizophrenia (SCZ). Recent genome-wide association studies (GWAS) have identified genetic variants associated with SCZ and immune-related phenotypes. Here, we use cutting edge statistical tools to identify shared genetic variants between SCZ and white blood cell (WBC) counts and further understand the role of the immune system in SCZ. *Study Design*: GWAS results from SCZ (patients, n = 53 386; controls, n = 77 258) and WBC counts (n = 56 3085) were analyzed. We applied linkage disequilibrium score regression, the conditional false discovery rate method and the bivariate causal mixture model for analyses of genetic associations and overlap, and 2 sample Mendelian randomization to estimate causal effects. *Study Results*: The polygenicity for SCZ was 7.5 times higher than for WBC count and constituted 32%–59% of WBC count genetic loci. While there was a significant but weak positive genetic correlation between SCZ and lymphocytes (r_g = 0.05), the conditional false discovery rate method identified 383 shared genetic loci (53% concordant effect directions), with shared variants encompassing all investigated WBC subtypes: lymphocytes, n = 215 (56% concordant); neutrophils, n = 158 (49% concordant); monocytes, n = 146 (47% concordant); eosinophils, n = 135 (56% concordant); and basophils, n = 64 (53% concordant). A few causal effects were suggested, but consensus was lacking across different Mendelian randomization methods. Functional analyses indicated cellular functioning and regulation of translation as overlapping mechanisms. *Conclusions*: Our results suggest that genetic factors involved in WBC counts are associated with the risk of SCZ, indicating a role of immune mechanisms in subgroups of SCZ with potential for stratification of patients for immune targeted treatment.**

Key words: psychosis/severe mental disorder/pleiotropy/polygenicity/inflammation/leucocyte

Introduction

Schizophrenia (SCZ) is a leading global health challenge. The majority of patients suffer most of their lives and some are in need of long hospital stays.[1] These characteristics have major consequences in key areas of life, including education, work, and social networks.[2,3] However, despite high heritability, we still lack a detailed understanding of the genetic causes, interplay with environmental factors, and the underlying disease mechanisms.

Involvement of the immune system is one of the leading pathophysiological hypotheses in SCZ.[4] Studies of maternal gestational infections have identified a range of pathogens associated with SCZ,[5] suggesting neurodevelopmental effects of microbe triggered immune

activation[6,7] involving sustained changes of microglia.[8] Recent health register studies have similarly identified associations between SCZ and hospital-treated infections as well as autoimmune diagnoses,[9,10] linking immune responses to illness development. These findings are supported by direct biological assessments in patients[11] with findings suggestive of neuroinflammation[12–14] and abundant studies of inflammatory markers in the peripheral circulation showing low-grade inflammation in SCZ, typically evidenced by elevated levels of upstream cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor.[15] A recent meta-analysis of SCZ spectrum disorders indicated increased total white blood cell (WBC) counts including increases across WBC subtypes.[16] Furthermore, leukocyte counts are linked to clinical symptomatology and brain tissue loss[17] and there is evidence of leukocyte infiltration in the brain in SCZ.[18–20] However, the causal relationship between sterile and nonsterile (infection triggered) inflammation or immune activation and illness development is yet to be elucidated. There is evidence of more frequent infections in relatives of patients, and individuals with SCZ continue to have more infections after diagnosis, suggesting shared genetic susceptibility.[21] Notably, a genetic correlation and association with polygenic risk of infection was recently indicated for SCZ, with only a small proportion mediated by infection diagnoses.[22] Moreover, studies of central and peripheral immune markers in SCZ are prone to bias from a range of factors including smoking, body-mass index, symptoms,[23] stress,[24] and diet.[14] Also, corresponding to the increased risk associated with postgestational infections, SCZ seems to be associated with infections throughout pregnancy, not merely in specific neurodevelopmental windows.[25]

Further, a range of genetic associations shed light on the immune link in SCZ. In addition to associations with the major histocompatibility complex (MHC),[26,27] SCZ correlates outside the MHC with several immune disorders including inflammatory bowel diseases, psoriasis[28] and rheumatoid arthritis,[29] suggesting complex immune mechanisms including both nonsterile and sterile inflammation. However, translating immune-related genetic correlations and variants into specific mechanisms is challenging. The function of the immune system goes beyond protection against microbes and nonself antigens, and also involves brain development, function, and plasticity.[30–33] Whereas a balanced immune response is thought to be protective, an imbalanced immune response may harm rather than protect the body including the brain. It is difficult to experimentally study immune mechanisms related to neuronal development and function in human brain disorders. An alternative approach is to investigate the overlapping genetic architecture between known immune-related phenotypes and SCZ, to dissect the molecular mechanisms involved.[27,29,34] Recently, new statistical approaches have been developed to characterize the genetic overlap between complex phenotypes not captured by standard genetic correlation methods,[34] suggesting genetic overlap by a mixture of concordant and discordant allelic effect directions.[35,36] Further, a new GWAS of peripheral WBC counts implicated a series of genetic determinants of the number of WBCs independent of infections, providing a novel opportunity to investigate if core immune mechanisms overlap with SCZ-related cellular and molecular factors.[37]

Given the challenge of translating immune findings of standard SCZ genome-wide association studies (GWASs) to biological pathways and the significant issue with bias in studies of immune markers, we aimed to disentangle immune mechanisms in SCZ by combining GWAS of SCZ with those of WBCs, investigating genetic overlap by applying statistical tools that are able to identify a mixture of effect directions.[38] In line with the established genetic immune link and associations with low-grade inflammation and WBCs, we hypothesized genetic overlap with a preponderance of concordant effect directions in SCZ and total WBC count including counts of WBC subtypes.

Methods

Samples

We used GWAS summary statistics of SCZ (schizophrenia and schizoaffective disorder; N_{case} = 53 386 and $N_{control}$ = 77 258 of European ancestry) from the Psychiatric Genomic Consortium (PGC).[26] GWAS summary statistics of total WBC, basophil, eosinophil, lymphocyte, monocyte, and neutrophil counts were used of N = 40 8112 participants from the UK Biobank and an additional N = 15 4973 participants from Blood Cell Consortium Phase 2 (BCX2),[37] all with European ancestry.

GWASs investigated were approved by local ethics committees. The Regional Committee for Medical Research Ethics—South East Norway evaluated the current protocol and found that no additional institutional review board approval was necessary as no individual data were used.

Data Analysis

The bivariate causal mixture model (MiXeR) (v1.3)[38] was applied to SCZ and each of total WBC, basophil, eosinophil, lymphocyte, monocyte and neutrophil counts to quantify the polygenicity of individual phenotypes and polygenic overlap between SCZ and WBC and WBC subtypes. MiXeR estimates the numbers of shared and unique trait-influencing variants irrespective of genetic correlation between 2 traits, using GWAS summary statistics. We report the numbers of causal variants as 31.9% of their total estimate, which jointly accounts for 90% of SNP heritability in each phenotype, to avoid extrapolating model parameters into the area

of infinitesimally small effects. The model fit was evaluated based on modeled vs actual conditional Q–Q plots, negative log-likelihood plots and Akaike information criterion. Genetic correlations between SCZ and WBC and WBC subtype counts were estimated using LDSC (LD Score) (v1.0.1) from respective GWAS summary stats.[39] The MHC region was excluded to avoid potential bias due to intricate LD patterns. Furthermore, we supplemented LDSC with analysis of local genetic correlations using LAVA,[40] to aid interpretation of genetic correlations versus overlap. To estimate the causal effects between WBC (and subtypes) and SCZ we performed bidirectional Mendelian randomization analyses using the "TwoSampleMR" package implemented in R.[41] For the purpose of sensitivity analysis, 4 different Mendelian randomization methods were performed: inverse variance weighted (IVW), weighted median (WM), weighted mode, and MR-Egger (bootstrap).

Conditional/conjunctional false discovery rate (condFDR and conjFDR, respectively) methods[42] were used to identify specific genetic loci associated with SCZ and WBC and WBC subtype phenotypes. The condFDR approach was used to identify the strength of the genetic association between SCZ and cell phenotypes. CondFDR builds on Bayesian statistics and re-ranks test-statistics. After performing condFDR analysis for both traits, shared genetic loci were identified using conjFDR.[43] Thus, conjFDR identifies loci associated with both traits jointly (ie, both SCZ and cell count), and is defined as the maximum of both condFDR values, providing a conservative estimate of FDR for a single nucleotide polymorphism (SNP) association with both phenotypes. The thresholds used were condFDR < 0.01 and conjFDR < 0.05. The MHC and 8p23.1 regions were excluded from model fit due to complex LD structures. All *P*-values were corrected for inflation using a genomic inflation control procedure.[42]

We used conditional quantile–quantile (Q–Q) plots to show cross-trait enrichments.[44] The conditional Q–Q plots explore the association with 1 trait within SNPs strata determined by the strength of association with a secondary trait. The enrichment is identified visually, with more leftward deflection from the null diagonal line indicating more enrichment.[42,45,46] The effect direction of the shared lead SNPs between SCZ and cell phenotypes were calculated by comparing the Z-scores of the original GWAS summary stats.

We used FUMA[47] to identify the independent genomic loci. In the first step of the procedure to identify genomic loci, $r^2 = 0.6$ was used as threshold to define independent significant SNPs among SNPs with condFDR < 0.01 or conjFDR < 0.05. In the second step, $r^2 = 0.1$ was used to define lead SNPs, corresponding to independent loci.[47] SNPs were implicated with genes using FUMA. FUMA genes were used for enrichment tests and functional annotations using pathfinder.[48]

Table 1. Polygenicity Per Trait Estimated by MiXeR Univariate Model

Traits	*N* (mean)	SE
SCZ	9648	255.80
Basophil count	839	30.79
Eosinophil count	1228	87.78
Lymphocyte count	1624	160.87
Monocyte count	1118	143.25
Neutrophil count	1619	138.30
WBC count	1800	230.35

Note: WBC, white blood cell; *N*, estimated number of genetic variants of the respective trait; SE, standard error.

Results

Polygenicity

The Univariate MiXeR model estimated SCZ to be highly polygenic with $N = 9600$ (SE = 300) variants estimated to be associated with SCZ. This is consistent with previous findings regarding the polygenicity of SCZ.[34] Of WBC subtypes, basophil count was suggested to be the least polygenic ($N = 800$, SE = 30) and lymphocyte and neutrophil counts to be the most polygenic ($N = 1600$, SE = 200; and $N = 1600$, SE = 100, respectively). SCZ was on average 7.5 times (min 5, max 11) more polygenic than WBC or any of the WBC subtype counts (table 1).

Polygenic Overlap

The bivariate MiXeR model estimates overlap between 2 traits and number of unique variants influencing each trait (figure 1). Lymphocyte count was suggested to have the largest number of overlapping SNPs with SCZ compared to any other cell phenotypes ($N = 1000$, SE = 110). Estimates should be considered in the context of their uncertainty as fewer overlapping variants were indicated between total WBC count and SCZ ($N = 800$, SE = 130). However, the standard error of genetic overlap estimation between SCZ and lymphocytes was smaller than the standard error of overlap estimations between SCZ and any other cell phenotype (table 2).

Genetic Correlations

LDSC analysis showed that the genetic correlations between SCZ and WBC and WBC subtype counts were nonsignificant, except for lymphocyte counts that was weakly correlated with SCZ ($r_g = 0.0535$, $P = .0016$) (table 3). Basophils reached nominal level correlation with SCZ ($r_g = 0.0493$, $P = .0417$). The results of local genetic correlation analyses (LAVA) among SCZ and WBC counts, supporting shared genetics with mixed effect directions, are given in supplementary figure S1. Results of LDSC analyses among WBC counts are given in supplementary table S1.

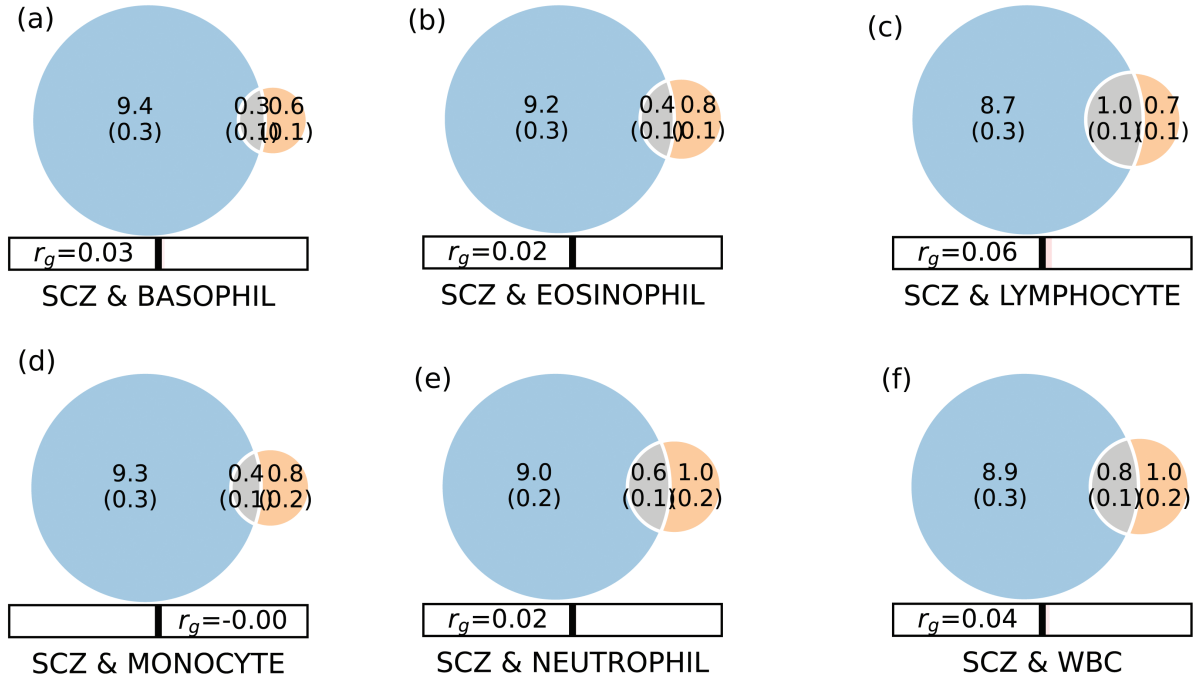

Fig. 1. Venn diagrams of shared variants between traits and unique variants per trait. rg: genetic correlation estimated by MiXeR (v1.3). The traits are SCZ and (a) basophil, (b) eosinophil, (c) lymphocyte, (d) monocyte, (e) neutrophil and (f) WBC counts. Numbers of variants shown in thousands with standard error in parenthesis.

Table 2. Polygenic Overlap Estimated by Bivariate MiXeR Model

Trait_1	Trait_2	*N*_1 (mean)	SE_1	$N\_2_{overlap-}$ (mean)	$SE\_2_{overlap-}$	$N\_2_{overlap+}$ (mean)	$SE\_2_{overlap+}$
SCZ	Basophil count	9368.77	297.93	560.33	134.10	279.30	133.58
SCZ	Eosinophil count	9209.16	280.17	789.28	148.57	438.91	127.53
SCZ	Lymphocyte count	8695.55	305.86	672.38	143.53	952.52	111.54
SCZ	Monocyte count	9288.47	260.43	759.36	165.58	359.60	121.55
SCZ	Neutrophil count	9001.42	234.16	972.81	165.39	646.65	130.89
SCZ	WBC count	8859.36	280.73	1011.5	202.64	788.71	128.50

Note: *N*_1 is estimated number of genetic variants of trait_1, and $N\_2_{overlap-}$ and $N\_2_{overlap+}$ are the estimated number of variants of trait_2 not overlapping and overlapping, respectively, with trait_1. SE, standard error; WBC, white blood cell.

Causal Effects

Mendelian randomization analysis suggested 3 unidirectional causal effects at nominal level, but consensus was lacking across the different methods (IVW, WM, weighted mode, and MR-Egger [bootstrap]): (1) eosinophil count (exposure variable) showed a nominal positive effect on SCZ (outcome variable) (b = 0.085, *P* = .022) with the MR-Egger (bootstrap) method (IVW: b = 0.022, *P* = .53; WM: b = 0.021, *P* = .59; weighted mode: b = 0.112, *P* = .13); (2) SCZ (exposure variable) showed a nominal positive effect on the lymphocyte count (outcome variable) (b = 0.019, *P* = .023) with the IVW method (WM: b = 0.007, *P* = .20; weighted mode: b = −0.015, *P* = .37; MR-Egger [bootstrap]: b = 0.027, *P* = .09); and (3) SCZ (exposure variable) showed a nominal positive effect on total WBC count (outcome variable) (b = 0.019, *P* = .033) with the IVW method (WM: b = 0.008, *P* = .14; weighted mode: b = 0.004, *P* = .80; MR-Egger [bootstrap]: b = 0, *P* = .48) (supplementary table S2).

Shared Genomic Loci Between SCZ and WBC Counts

At condFDR < 0.01, we identified 252, 291, 297, 285, 282, and 307 loci associated with SCZ conditionally on basophil, eosinophil, lymphocyte, monocyte, neutrophil, and total WBC counts, respectively, giving a total of 370 independent SCZ loci (overlapping distance is 250K BP) (table 4). The reversed condFDR analysis showed 360, 795, 969, 897, 820, and 955 loci associated with basophil, eosinophil, lymphocyte, monocyte, neutrophil, and total WBC counts, respectively, conditionally on SCZ.

Table 3. Genetic Correlation and Number of Shared SNPs With Effect Directions, Between SCZ and WBC and WBC Subtype Counts

Trait	r_g	SE	*P* Value	LEAD SNP (*N*)	Concord Effect (%)	h2	SE (h2)
Basophil count	0.0493	0.0242	.0417	64	53.13	0.0738	0.0094
Eosinophil count	0.0269	0.0177	.1289	135	56.30	0.1844	0.0227
Lymphocyte count	0.0535	0.0169	.0016*	215	55.81	0.1875	0.0153
Monocyte count	−0.0072	0.0183	.6956	146	46.58	0.1836	0.0206
Neutrophil count	0.0039	0.0189	.8365	158	49.37	0.1575	0.0198
WBC count	0.0267	0.0189	.1566	185	54.89	0.1772	0.0181

Note: Here, WBC = white blood cell, r_g = genetic correlation estimated by linkage disequilibrium score regression, SE = standard error, LEAD SNP = SNP with the lowest FDR value in a loci (conjFDR < 0.05) among all SNPs in a loci that are significantly jointly associated with both traits, Concord effect = Z-score for both traits has the same sign (+/−), h2 = heritability (estimated by univariate MiXeR), SE(h2) = standard error for h2.
*Significant at $P < .008$ (0.05/6).

This gave a total of 1633 independent SNPs associated with WBC and WBC subtypes (overlapping distance is 250K BP) (table 4, supplementary tables S9–S20, S34, and S35).

In a Bayesian statistical framework conjFDR identified SNPs that are jointly associated with both traits leveraging cross-trait enrichments. At conjFDR < 0.05, SCZ shared most loci with lymphocyte count (n = 215), followed by WBC (n = 185), neutrophil (n = 158), monocyte (n = 146), eosinophil (n = 135) and basophil (n = 64) counts (supplementary figure S2). This gave a total of 383 independent loci associated with both SCZ and WBC and WBC subtypes (overlapping distance is 250K BP). This observation supports the MiXeR finding of the highest genetic overlap between SCZ and lymphocytes compared to other cell phenotypes. There were mixed effect directions with a small majority of concordant directions between SCZ and WBC, lymphocyte, eosinophil, and basophil counts (53.1%–56.3%), respectively, and a small majority of discordant directions between SCZ and monocyte count (46.6% concordance) (table 3, supplementary tables S3–S8 and S33, associated candidate SNPs are in supplementary tables S21–S26). To assess the potential impact of smoking on the genetic overlap, we performed additional analyses adjusting for smoking in the SCZ GWAS with mtCOJO[49] before conjFDR analyses. These adjustments resulted in more shared loci in most cases, and loci identified in smoking-adjusted conjFDR analyses typically overlapped with >80% of loci identified in the original conjFDR analyses (supplementary tables S36–S47).

Functional Annotation of Loci Shared Between SCZ and WBC Counts

The functional annotations of SNPs at conjFDR less than 0.05 for SCZ vs basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC counts are shown in supplementary tables S48–S53 (related genes are in supplementary tables S27–S32). The shared loci were associated with pathways such as cell-cell adhesion, intracellular transport, vesicular transport, spliceosome, proteasome, ribosome, and NF-KappaB binding, shown by pathfindR enrichment analysis. Moreover, FUMA analysis identified enriched pathways of 22q11.2 deletion syndrome (eosinophils) and mRNA processing (eosinophils and monocytes).

Table 4. Number of SNPs Associated With Each Trait in CondFDR Analysis (FDR < 0.01)

Trait_1	Trait_2	LEAD SNP (*N*)
Basophil count	SCZ	360
Eosinophil count	SCZ	795
Lymphocyte count	SCZ	969
Monocyte count	SCZ	897
Neutrophil count	SCZ	820
WBC count	SCZ	955
SCZ	Basophil count	252
SCZ	Eosinophil count	291
SCZ	Lymphocyte count	297
SCZ	Monocyte count	285
SCZ	Neutrophil count	282
SCZ	WBC count	307

Note: WBC, white blood cell.

The most enriched KEGG pathways of only similar effect directions were oxidative phosphorylation, diabetic cardiomyopathy, focal adhesion, bladder cancer, long-term potentiation, GnRH signaling pathway, etc. The most enriched pathways found only in opposite effect directions were leukocyte transendothelial migration, nonhomologous end-joining, biosynthesis of unsaturated fatty acids, mismatch repair, arrhythmogenic right ventricular cardiomyopathy, and collecting duct acid secretion. Pathways in common between same and opposite direction categories include such as adherens junction, ErbB signaling pathway, hepatitis B, viral carcinogenesis, nonalcoholic fatty liver disease, human T-cell leukemia virus 1 infection, chemical carcinogenesis—reactive oxygen species, nucleocytoplasmic transport, etc (supplementary tables S54–S70).

Discussion

The main finding is a significant genetic overlap between SCZ and various WBC counts with a mixture of effect directions. We identified a total of 383 independent genetic loci shared between SCZ and WBCs, with 53% in the same direction, but with varying degree of concordance across WBC subtypes, suggesting slightly different genetic relationships. Lymphocytes were suggested to have the largest overlap and a small positive correlation with SCZ, and were together with total WBC and eosinophils, weakly linked to SCZ in Mendelian randomization analyses. SCZ was estimated to be on average 7.5 times more polygenic than the WBC counts. The functional analyses implicated cellular functioning and translation regulatory processes among the putative shared molecular mechanisms. These findings suggest genetically determined peripheral immune factors associated with SCZ linking systemic immune regulation with pathophysiological mechanisms.

MiXeR analysis showed that significant parts of the WBC count genetic architecture overlap with that of SCZ; however, with SCZ being several times more polygenic. While the current estimation of about 1.8K WBC count variants is novel, our group has demonstrated the extensive polygenic nature of SCZ,[38] as well as substantial genetic overlap with a range of other mental and somatic phenotypes such as bipolar disorder,[38,50] personality traits,[50,51] variation in brain structure,[33,52] and cardiovascular risk factors,[53,54] including shared genetic loci. The level of overlap and concordance rate were higher between SCZ and mental disorders[50] than what we observed with WBC counts in the present study. Notably, a link between SZC and the immune system is well-established including associations with immune loci[26,55] and genetic overlap with immune mediated diseases[27,28]; however, the exact immune mechanisms are unclear. Despite the robust evidence for the complement cascade,[56] functional implications of immune loci in SCZ pathophysiology are undetermined, and there are conflicting results of immune pathway enrichment analyses.[55] However, MiXeR enables estimates of overlap of genetic architecture between the phenotypes,[38] and our findings suggest an easily interpretable association between SCZ genetics and the immune system; that a small part of the SCZ genetic architecture is associated with regulation of systemic WBC counts. A substantial part of WBC and WBC subtype count genetics were associated with SCZ, ranging from 32% to 59%, with possibly the largest overlap for lymphocytes. The conversely small amount of the overall SCZ genetic makeup related to WBC count corresponds to the difference in polygenicity; nevertheless, it may suggest a propensity for WBC based immune abnormalities in a subset of patients with SCZ. The findings are in line with the LAVA results which indicated local genetic correlations and a mixture of effect directions (supplementary figure S1).

The conjFDR analysis identified between 64 and 215 specific loci shared between SCZ and each of the WBC and WBC subtype counts. These associations demonstrate a mixture of effect directions and a majority of net concordant effects. The concordant effects might partly explain the overall increased WBC count in SCZ, as shown by a recent meta-analysis.[16] Interestingly, a recent article demonstrated a positive association between depression polygenic scores and WBC count.[57] While low-grade inflammation is well-established in SCZ, the tissues and mechanisms involved in the inflammatory activity remain undetermined. Potential tissues include WBCs, adipose tissue, the gut, the vascular endothelium, lymphoid tissue, and glial cells of the brain.[58] Regulatory dynamics of WBCs and cytokines and the fact that the immune activation and inflammation could be primarily restricted to the tissue and microenvironment further complicates interpretation of peripheral measurements. Notably, systemic immunity influences the brain, and it might be involved in SCZ pathophysiology[59,60] by increasing blood-brain barrier (BBB) permeability.[61] There is evidence of infiltration of immune cells in the brain.[18–20] While the large difference in polygenicity and the small fraction of SCZ variants coding for WBC counts do not make the findings suitable for general clinical prediction, they hold promise for identifying subgroups with inherent immune abnormalities through future assessment of peripheral WBCs and other immune markers together with immune genetic scores. As antipsychotic agents show immune effects,[15] and there are ongoing trials with immune modifying agents in SCZ,[62] the current findings might be relevant in identifying individuals who will clearly benefit from immune targeted treatment.

The genetic overlap with all WBC subtypes suggests regulatory mechanisms across both the innate and the adaptive immune system in SCZ subgroups. There was a pattern of concordant associations across WBC and WBC subtypes; however, shared loci between SCZ and monocytes being a major part of the innate immune system, stood out with a majority of discordant effects. This contrasts findings of increased monocyte counts in SCZ[16,63] and might suggest a particular abnormality of the innate monocyte-macrophage cell lineage in a subset of patients, potentially with concurrent microglial dysregulation, the macrophage-like cell in the central nervous system. Thus, in addition to the model of an underlying monocyte and microglia activation in SCZ,[64] we hypothesize a subgroup of patients with an underlying downregulation of monocyte/microglia activity. Moreover, an adaptive component with lymphocytes was identified by a significant small positive genetic correlation, largest genetic overlap and most detected specific shared loci, and by a suggested positive effect of SCZ (exposure variable) in Mendelian randomization. The

model of macrophage activation also involves activated T-lymphocytes with cytokine abnormalities[65] causing dysregulation of neurotransmitters including dopamine and glutamate.[60,66,67] Several studies have found lower T-lymphocyte and increased B-lymphocyte levels in acute illness with normalization during treatment.[68,69] An imbalance in helper T-cells type 1 (Th1) and type 2 (Th2) immunity is also suggested.[70] Furthermore, decreased expression of the regulatory T cell (Treg) specific marker *FOXP3* was found in the blood of patients with SCZ relative to healthy individuals.[71] Other lymphocyte related mechanisms might involve infections and in particular viral infection and autoantibodies.[72–74] Interestingly, postmortem studies have shown increased brain infiltration of effector T and B lymphocytes in SCZ,[75] in line with BBB impairment and lymphocyte mediated activation of microglia.[73] This mechanism, in combination with decreased numbers and/or limited ingress of anti-inflammatory Treg cells into the brain parenchyma, may contribute to the maintenance of inflammatory environment in the CNS.[71] Lastly, a potential SCZ mechanism includes neurodevelopmental effects by immune activation during gestation or early life, involving immune components crucial in brain development.[76–78] While microglia is the main innate immune cell in the brain with established neurodevelopmental and homeostatic functions, lymphocytes are also demonstrated in the developing brain at least partly involving their bidirectional interaction with microglia cells.[77] Based on the current findings, it is tempting to speculate on genetically determined lymphocyte as well as monocyte abnormalities involved in SCZ subgroups both by early neurodevelopmental processes and by cell and cytokine-mediated mechanisms in the adult brain. Moreover, a recent article demonstrated a negative genetic correlation between cortical surface area and WBC counts.[79]

Functional annotation and enrichment analyzes of shared loci broadly indicated cellular biology including translation regulatory processes. Cell-cell adhesion and 22q11.2 deletion syndrome were amongst the most enriched loci and pathways. The cell junction component is relevant to BBB permeability abnormalities in SCZ.[61] Notably, adherens junction was enriched in the concordance specific analysis. Similarly, our group recently indicated cell adhesion molecule involvement in SCZ both at systemic and cerebral level.[80] The association of 22q11.2 deletion syndrome with psychosis is well-known, with immune aberrations being part of the syndrome phenotype and possibly related to development of psychosis.[81–83] Interestingly, immune aberrations involve decreased T-cell counts following thymic hypoplasia, B-cell dysfunction due to T cell abnormalities and skewing towards Th2 immunity.[84] The extent of immune abnormalities are associated with the size of the deletion.[85] The syndrome is also associated with autoimmune diseases.[84] Although we here indicate genetically increased lymphocytes in SCZ, the detected enrichment of 22q11.2 deletion syndrome further support an adaptive immunity component in SCZ pathophysiology.

As GWAS summary statistics data of SCZ and WBC counts are based on multiple cohorts from international collaborations, including population-based data, patients may have been included in both SCZ and WBC GWASs. However, based on the low prevalence of SCZ, and patients having reduced likelihood of consenting to study participation related to the quality and level of mental symptoms,[86] a major issue of sample overlap seems less likely. However, sampling bias in the GWASs and overlap is possible, and inflation of the shared genetic statistics cannot be fully ruled out. Further, we cannot rule out that there are unknown factors biasing the current summary statistics analyses, but this is highly unlikely. Further, the underlying assumption of MiXeR of even distribution of associated variants across the genome increases the uncertainty of findings of the less polygenic WBCs. Together with suggested small and no genetic correlations and the possibility that overlapping genetic variants might affect separate biological processes in the 2 phenotypes, inferences of underlying mechanisms in common should be drawn with caution. Moreover, the distinct causal variants driving the estimated overlap remains to be clarified, which could include shared as well as separate variants. While WBCs genetic data pertain to cell counts, they are uninformative of cell activation associated with cytokine release and level of inflammatory activity. Moreover, we were not able to analyze WBC count genetics with actual WBC count in patients. Lastly, the immune system in the brain remains to be fully elucidated, and it is difficult to make assumptions regarding the interplay of the systemic and the brain immune system. Nevertheless, the current findings suggest links between SCZ and peripheral immune regulatory aspects, and the large GWAS data limit the impact of major confounders regularly associated with peripheral measurement of unstable inflammatory markers, such as smoking and intercurrent infections.

In the current study we estimate that 32%–59% of the WBC count and WBC subtype counts genetic makeups are shared with SCZ and identify 383 specific shared genetic loci with a pattern of concordant effects. Both systemic innate and adaptive immune mechanisms are indicated, with lymphocytes showing the largest overlap and a genetic correlation, particularly suggesting an inherent systemic adaptive immune component in SCZ. These findings might be relevant for identifying patients with increased susceptibility of systemic immune abnormalities, potentially by a risk score, and together with peripheral immune marker assessments identify subgroups that may benefit from specific immune targeted treatment.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

Code Availability

Codes used to complete the analyses are available here:
https://github.com/precimed/pleiofdr
https://github.com/precimed/mixer
https://github.com/bulik/ldsc.

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Conflict of Interest

OAA is a consultant to Cortechs.ai, and has received speaker's honorarium from Lundbeck, Sunovion, and Janssen. AMD is a founder and owner of Cortechs.ai. The other authors report no conflict of interest.

Data Availability

SCZ sumstats: https://www.med.unc.edu/pgc/download-results/
White blood cells sumstats: http://www.mhi-humangenetics.org/en/resources/.

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