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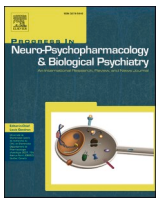

Limited association between infections, autoimmune disease and genetic risk and immune activation in severe mental disorders

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ABSTRACT

Background: Low-grade inflammation may be part of the underlying mechanism of schizophrenia and bipolar disorder. We investigated if genetic susceptibility, infections or autoimmunity could explain the immune activation.

Methods: Seven immune markers were selected based on indicated associations to severe mental disorders (IL-1Ra, sIL-2R, IL-18, sgp130, sTNFR-1, APRIL, ICAM-1) and measured in plasma of patients with schizophrenia (SCZ, $N = 732$) and bipolar spectrum disorders (BD, $N = 460$) and healthy controls (HC, $N = 938$). Information on rate of infections and autoimmune diseases were obtained from Norwegian national health registries for a twelve-year period. Polygenic risk scores (PRS) of SCZ and BD were calculated from genome-wide association studies. Analysis of covariance were used to test effects of infection rate, autoimmune disease and PRS on differences in immune markers between patients and HC.

Results: Infection rate differed between all groups (BD > HC > SCZ, all $p < 0.001$) whereas autoimmune disease was more frequent in BD compared to SCZ ($p = 0.004$) and HC ($p = 0.003$). sIL-2R was positively associated with autoimmune disease ($p = 0.001$) and negatively associated with PRS of SCZ ($p = 0.006$) across SCZ and HC; however, associations represented only small changes in the difference of sIL-2R levels between SCZ and HC.

Conclusion: There were few significant associations between rate of infections, autoimmune disease or PRS and altered immune markers in SCZ and BD, and the detected associations represented only small changes in the immune aberrations. The findings suggest that most of the low-grade inflammation in SCZ and BD is explained by other factors than the underlying PRS, autoimmunity and infection rates.

1. Introduction

Schizophrenia and bipolar disorder are severe mental disorders with shared genetic risk factors and clinical characteristics (Owen et al., 2016; Vieta et al., 2018). Parts of the genetic structure of these disorders was recently determined by large international genetic consortia (Mullins et al., 2021; The Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2020), enabling studies beyond effects of

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single genetic variants. Moreover, environmental factors appear to impact risk throughout the entire early lifespan potentially involving epigenetic modifications (Aldinger and Schulze, 2017; McDonald and Murray, 2000), with large effects on disease occurrence (Marangoni et al., 2016; Stilo and Murray, 2019; van Os et al., 2010; van Os et al., 2005). However, despite recent scientific progress, the mechanisms at the interface of risk factors and pathophysiology are generally unknown, impeding progress in prevention and treatment.

The immune system has emerged as a pathophysiological candidate of severe mental disorders, however, with more heterogeneous findings in bipolar disorder than schizophrenia. Associations between psychosis and infectious disorders have long been suspected (Kępińska et al., 2020; Noll, 2007), including infections with toxoplasma gondii, influenza virus, herpes simplex virus type 2, cytomegalovirus and Borna disease virus (Arias et al., 2012; Benros and Mortensen, 2020; Brown and Derkits, 2010; de Barros et al., 2017). The increased risk of schizophrenia and bipolar disorder has been associated with infections both during (Barichello et al., 2016; Khandaker et al., 2013; Parboosing et al., 2013) and after (Benros et al., 2011; Benros et al., 2013; Hickie et al., 2009; Oliveira et al., 2017) pregnancy as well as with paternal infections (Nielsen et al., 2013). A suggested mechanism in schizophrenia involves triggering of various cellular pathways within the central nervous system (CNS) secondary to activation of microglia by systemic inflammatory mediators (Monji et al., 2009; Smith, 1992). This "inflammatory hypothesis" is supported by evidence of low-grade systemic inflammation in both schizophrenia and bipolar disorder by findings of abnormal levels of several peripheral immune activation markers (Kroken et al., 2018; Rosenblat and McIntyre, 2017). Immune aberrations that have been repeatedly associated with these disorders include increased soluble interleukin 2 receptor (sIL-2R) levels, reflecting T cell activation, and activation of the proinflammatory interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF) signalling pathways as reflected by secreted levels of IL-1-receptor antagonist (IL-1Ra), IL-18, IL-6 and soluble TNF receptor 1 (sTNFR-1) (Hope et al., 2009; Hope et al., 2013; Kroken et al., 2018; Luo et al., 2019; Luo et al., 2016; Mørch et al., 2016; Rosenblat and McIntyre, 2017; Wedervang-Resell et al., 2020a, 2020b). A meta-analysis indicated similar cytokine patterns in schizophrenia and bipolar disorder in both acute and chronic phases showing elevated sIL-2R, IL-1Ra, TNF-α and IL-6 in acutely ill patients and sIL-2R, IL-1β and IL-6 in chronic patients (Goldsmith et al., 2016; Kroken et al., 2018). Moreover, a proliferating inducing ligand (APRIL), a cytokine belonging to the TNF-family, was recently found reduced in both schizophrenia and bipolar spectrum disorder compared with healthy controls (Engh et al., 2022). Alterations in cell adhesion molecules (CAMs) include elevated levels of the intercellular cell adhesion molecule 1 (ICAM-1) (Müller, 2019; Wedervang-Resell et al., 2020a, 2020b), which is expressed in microglial cells and astrocytes as well as on circulating lymphocyte subsets.

A range of autoimmune conditions are associated with schizophrenia and bipolar disorder (Chen et al., 2021; Eaton et al., 2006; Rosenblat and McIntyre, 2017) and seem to exert a small, but synergetic effect with hospital-treated infections on disease risk (Benros et al., 2011; Benros et al., 2013). Increased autoantibodies against neuronal cells (Ezeoke et al., 2013) and a genetic relationship between severe mental disorders and autoimmune diseases (Andreassen et al., 2015; Stringer et al., 2014; Wang et al., 2015) further support the immune system as a pathophysiological candidate.

Schizophrenia and bipolar disorder are highly heritable disorders (Smeland et al., 2020; Stahl et al., 2019) with immune candidate genes identified in genome-wide-association studies both within the Major Histocompatibility Complex (MHC) and outside MHC (Pouget, 2018). Of note, the MHC region which encodes a range of proteins critical for immune defence is the strongest signal in schizophrenia GWAS' (The Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2020). In particular there is a strong association with complement component 4 genes (Sekar et al., 2016). The MHC region was recently also linked with bipolar disorder (Mullins et al., 2021). Infection (Klebanov, 2018) and autoimmune (Hu and Daly, 2012; Skov et al., 2020) susceptibility similarly have strong genetic components; however, studies investigating the relationship between genetic risk of severe mental disorders and immune activation are few and inconclusive. One small report indicated associations between PRS of schizophrenia and bipolar disorder and increased C—C Motif Chemokine Ligand 4 (CCL4) in first-episode psychosis patients (Maj et al., 2019). Benros et al. (2016) found no effect of PRS of schizophrenia on the association between infections and the risk of schizophrenia.

Thus, we still not know whether the low-grade inflammation of schizophrenia and bipolar disorder originate from associated infections, autoimmunity or overlapping genetic risk factors. The aim of the current study is to investigate the relationship between altered immune markers and the rate of infections, autoimmune disease and PRS. Immune markers were chosen based on robust links with schizophrenia or bipolar disorder. The study sample includes patients with schizophrenia and bipolar spectrum disorders and healthy controls, and national registry data are applied to obtain a comprehensive estimate of differences in occurrence of infections and autoimmune diseases.

2. Methods

2.1. Study setting

The study is a part of the Thematically Organized Psychosis study (TOP) at the Norwegian Centre for Mental Disorders Research (NORMENT). Patients between the ages of 18–65, recruited from the major hospitals in the Oslo region, with a diagnosis of schizophrenia spectrum disorders ('SCZ': schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder and psychosis not otherwise specified (NOS)) or bipolar spectrum disorders ('BD': bipolar 1 disorder, bipolar 2 disorder, bipolar disorder NOS and major depressive disorder with psychosis) were included. All participants must understand verbal and written information to the study and make a written informed consent. Patients were excluded if they had a history of severe somatic disease interfering with brain functioning including neurological disease, history of moderate or severe head trauma, or an IQ below 70. Healthy controls ('HC') in the same age span as the patients were randomly selected from statistical records from the same catchment areas and invited to participate. HC inclusion was also based on lack of history of severe mental illness, neurological disorder, severe brain trauma, illicit drug abuse or dependency, or somatic conditions that interfere with brain function or close relatives with severe mental illness. Participants with CRP level above 10 mg/L were excluded from the analyses to remove a potential effect of acute infection on the immune markers. In the current study we included patients ($N = 1484$) and HCs ($N = 1041$) with registry data (Table 1) of which immune marker assessments during 2002–2018 and PRS data were available in 732 and 740 patients with SCZ, 460 and 475 patients with BD, and 938 and 915 HCs, respectively.

2.2. Clinical assessment

The Structured Clinical Interview (SCID-1) (First et al., 1995) for the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV (American Psychiatric Association, 2000) was used for diagnostic assessment. Diagnostic interviews were performed by clinical psychologists and physicians supervised by a senior professor of psychiatry. The research personnel were comprehensively trained for the interviews based on a UCLA training program (Ventura et al., 1998). The diagnostic inter-rater reliability of the TOP study has been found good with a diagnostic agreement of 82% and an overall kappa score of 0.77 (95% CI, 0.60–0.94) (Ringen et al., 2008).

Table 1
Demographic and clinical data.

	SCZ, *N* = 926	BD, *N* = 558	HC, N = 1041	p-value[h]	Group comparisons
Sex female, N (%)	369 (39.8)	325 (58.2)	482 (46.3)	<0.001	BD > HC > SCZ
Age[a], median (IQR)	28 (14)	31 (18)	33 (15)	<0.001	BD, HC > SCZ
Ethnicity European[b], N (%)	748 (80.8)	494 (88.5)	1017 (98.3)	<0.001	HC > BD > SCZ
Diagnosis, N (%)					
Schizophrenia	543 (58.6)				
Schizophreniform	51 (5.5)				
Schizoaffective	129 (13.9)				
Bipolar disorder 1		307 (55.0)			
Bipolar disorder 2		163 (29.2)			
Bipolar disorder NOS		29 (5.2)			
Major depressive disorder		59 (10.6)			
Psychosis NOS	130 (14.0)				
Brief psychotic disorder	20 (2.2)				
Delusional disorder	53 (5.7)				
Medication, N (%)					
Antipsychotics[c]	774 (83.7)	282 (50.7)		<0.001	SCZ > BD
Anticonvulsants	110 (11.9)	199 (35.7)		<0.001	BD > SCZ
Lithium	18 (1.9)	89 (15.9)		<0.001	BD > SCZ
Antidepressants	267 (28.8)	206 (36.9)		<0.001	BD > SCZ
CRP[d], median (IQR)	1.9 (3.4)	1.4 (3.0)	1.1 (2.1)	<0.001	SCZ > BD > HC
Total infections[e], median (min-max)	2 (0–35)	5 (0–42)	3 (0–35)	<0.001	BD > HC > SCZ
Infections, specialist health care, median (min-max)	0 (0–10)	0 (0–14)	0 (0–7)	<0.001	BD > SCZ > HC
Autoimmune disease, N (%)	92 (9.9)	83 (14.9)	101 (9.7)	0.003	BD > SCZ, HC
PRS-SCZ 0.05[f,g], median (IQR)	0.582 (1.4)	0.317 (1.2)	−0.223 (1.2)	<0.001	SCZ > BD > HC
PRS-BD 0.05[f,g], median (IQR)	0.283 (1.4)	0.368 (1.3)	−0.087 (1.4)	<0.001	SCZ, BD > HC

Missing data for [a]13, [b]6 and [c]1 participants. Data available for [d]2128 and [f]2133 participants. [e]Total infections between year 2006 and 2018 summarized from primary health care (2006–2018) and specialist health care (2008–2018) national registries. [g]Standardized values. [h]Kruskal-Wallis for continuous variables, chi quadrat test for categorical variables.
Abbreviations: BD = bipolar spectrum disorders, CRP = C-reactive protein, HC = healthy controls, IQR = interquartile range, NOS = not otherwise specified, N = number, PRS-BD = polygenic risk score of bipolar disorder, PRS-SCZ = polygenic risk score of schizophrenia, SCZ = schizophrenia spectrum disorders.

2.3. Registry data

Registry data of type and time of infections and autoimmune disease from 2006 to 2018 were available from the Norway Control and Payment of Health Reimbursement database (KUHR), including data from primary health care, and from 2008 to 2018 from the Norwegian Patient Registry (NPR), including data from the specialist health care. ICD-10 diagnostic codes (Quan et al., 2008) are used in NPR and ICPC-2 diagnostic codes (Hofmans-Okkes and Lamberts, 1996) in KUHR.

Number of infections for the twelve-year period 2006–2018 ('*rate of infections*') was retrieved from KUHR and NPR for all groups as an estimate of differences in rates prior to immune assessments; that is, number of infections was summed up for each participant and used as a continuous variable. Repeats of the same diagnosis of infection within and across NPR and KUHR in one person were individually evaluated as constituting the same or different illness episodes based on all available information including length of the interval between the diagnoses. If not possible to determine by the available information, diagnoses were assessed as unique episodes if consecutive equivalent diagnoses were registered more than one month a part; however, repeats of a diagnosis with similar time intervals were considered check-ups and constituting the same episode. All cases of doubt were determined by two physicians. Participants that were neither registered in NPR nor in KUHR were coded with no previously treated infection or autoimmune diseases (*N* = 78). Six participants were excluded from our analysis due to mismatching of IDs between the TOP sample and the registries.

Presence of autoimmune diseases was retrieved from KUHR and NPR for the 2006–2018 period for all groups as an estimate of differences prior to immune assessments; that is, autoimmune disease was coded as present or absent for each participant and used as a dichotomous variable. Details about infections and autoimmune diagnoses included are given in Supplementary Material.

2.4. Polygenic risk score (PRS)

DNA was extracted from blood and saliva samples collected at inclusion. Genotyping was performed on Human Omni Express-24 v.1.1 (Illumina Inc., San Diego, CA, USA) at deCODE Genetics (Reykjavik, Iceland). Pre-imputation quality control was performed using PLINK 1.9 (Chang et al., 2015). Briefly, variants were excluded if they had low genotyping rate (<95%), deviated from Hardy-Weinberg equilibrium ($p < 10^{-4}$), or occurred at significantly different frequencies in different genotyping batches (FDR < 0.5). Whole individual genotypes were excluded if they had low coverage (<80%) or high likelihood of contamination (heterozygosity above mean + 5 standard deviations). The quality-controlled genotypes were phased using Eagle (Loh et al., 2016), and missing variants were then imputed with MaCH (Das et al., 2016; Li et al., 2010) using haplotype reference consortium (HRC) trans-ethnic reference panel (version 1.1) (McCarthy et al., 2016). Following the quality control and imputation procedure, variants with information score < 0.8 or minor allele frequency < 1% were removed. Additionally, individual genotypes imputed with less than 75% confidence were set to missing, the remaining ones were converted to best guess hard allelic dosages. PRS' were computed following the method described by Purcell et al. (2009) using PRSice-2 (Choi and O'Reilly, 2019) with default clumping parameters (250 kb clumping window, 0.1 LD r2 threshold using target sample for LD estimation). The high linkage disequilibrium (LD)-regions MHC region (chr6:25119106–33,854,733) and 8p23.1 (chr8:7200000–12,500,000) were excluded in all analyses. The PRS of schizophrenia, 'PRS-SCZ', was based on the latest meta-analysis from the Psychiatric Genomics Consortium Schizophrenia Working Group and included participants with European ancestry with schizophrenia and schizoaffective disorder (The Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2020), after removing the TOP cohort. The PRS of bipolar disorder, 'PRS-BD', was based on a meta-analysis of 56 cohorts and included patients with European ancestry meeting international consensus criteria (DSM-IV, ICD-9, or ICD-10) for a lifetime diagnosis of bipolar disorder (Mullins et al., 2021), after

removing the TOP cohort. In accordance with previous literature (Wimberley et al., 2017; Wray et al., 2014), we used a *p*-value threshold of 0.05 for selection of single nucleotide polymorphisms (SNPs) in our PRS computation. The PRS-SCZ and PRS-BD were standardized before the analyses were performed.

2.5. Immune markers

Immune markers were selected based on previous evidence of associations to patient status, and constitute sIL-2R, a marker of T-cell activity, IL-1Ra, a marker of IL-1b activity, IL-18, a cytokine belonging to the IL-1 superfamily, soluble glycoprotein 130 (sgp130), a soluble form of the IL-6 co-receptor reflecting activity in the IL-6 system, sTNFR-1, one of the two main receptors of TNF-α reflecting TNF-activity, APRIL, a cytokine belonging to the TNF-family, and ICAM-1, a cell adhesion molecule (Askevold et al., 2014; Dinarello, 2018; Drexhage et al., 2010; George-Chandy et al., 2008; Girardin et al., 1992; Goldsmith et al., 2016; Kroken et al., 2018; Mørch et al., 2016; Mørch et al., 2019; Müller, 2019; Potvin et al., 2008). Following the same methods as described in Mørch et al. (2019) plasma levels of the immune markers were measured in duplicate by enzyme immunoassays (EIA) by using commercially available antibodies (R&D Systems, Minneapolis, MN, USA) in a 384 format using a combination of a SELMA (Jena, Germany) pipetting robot and a BioTek (Winooski, VT, USA) dispenser/washer. Absorption was read at 450 nm with wavelength correction set to 540 nm using an ELISA plate reader (Bio-Rad, Hercules, CA, USA). Intra- and inter-assay coefficients of variation were < 10% for all EIAs. For immunoassays, blood was sampled using EDTA vials and the plasma was isolated within the next working day and stored at −80 °C. Blood sampling was performed between 8:00 and 17:00.

2.6. Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago II, version 26). For demographic and clinical data, we used Kruskal-Wallis test for continuous variables and chi-square test for categorical variables. The main analyses were performed with analysis of covariance (ANCOVA). To comply with test assumptions, immune markers were logarithmically transformed with standardized removal of residuals more than 3 x interquartile range (IQR) or 1.5 x IQR below and above the first and third quartile, respectively, depending on the degree of deviation (3 IQR for sgp130, sTNFR-1, IL-18 and ICAM-1 and 1.5 IQR for IL-1Ra, sIL-2R and APRIL). Histograms, Q-Q-plots and Kolmogorov-Smirnov statistics were used to assess normal distribution. Potential issues with multicollinearity were ruled out. We first compared immune marker levels across groups (SCZ, BD, HC) using ANCOVA. We then ran bivariate correlations between rate of infections, presence of autoimmune disease and PRSs and immune markers in the patient groups, to select variables ($p \leq 0.1$) for fully adjusted ANCOVAs. Lastly, we compared patient groups to HC with and without adjustments for of infections (twelve-year), presence of autoimmune disease and PRS, respectively, to address the impact of these factors on the effect of patient group. These main ANCOVA analyses were adjusted for age, sex and freezer storage time (Enroth et al., 2016) and additionally for ethnicity (European, Asian, African and others), batch and the two first genetic principal components in the PRS analyses. PRS-SCZ and PRS-BD were tested in analyses of SCZ and BD, respectively. To exclude major confounding effects of body mass index (BMI), smoking status (smoking regularly, yes/no) and alcohol use (number of units of alcohol last two weeks) of which we had incomplete data (40–80%), separate bivariate correlations were performed with significant factors of the main ANCOVA analyses (autoimmune disease, PRS-SCZ); if significant, these variables were also tested in fully adjusted ANCOVAs. Moreover, the main ANCOVAs were redone without participants with MDD ($N = 59$) to exclude potential bias due to heterogeneity within the BD group. Due to the established association of the selected immune markers with affective and psychotic conditions, we applied a corrected significance level of $p = 0.025$ due to testing of non-genetic and genetic models (0.05/2).

3. Results

3.1. Demographic, clinical, genetic and immune data

Median age was significantly lower in SCZ compared to BD and HC (both $p < 0.001$). Frequency of European ethnicity differed between all groups (HC > BD > SCZ, all $p < 0.001$). Rate of infections differed significantly between groups (BD > HC > SCZ, all $p < 0.001$), as did rate of specialist health care treated infections (BD > SCZ, $p = 0.043$, SCZ > HC, $p < 0.001$ and BD > HC, $p < 0.001$). A diagnosis of one or more autoimmune diseases was significantly more frequent in BD than in SCZ and HC ($p = 0.004$ and $p = 0.003$, respectively). The PRS-SCZ differed significantly between all three groups (SCZ > BD > HC, all $p < 0.001$), and the PRS-BD was significantly higher in both patient groups compared to HCs (both $p < 0.001$). See Table 1 for details.

3.2. Associations of immune marker levels with diagnosis, rate of infections, autoimmune disease and PRS

Plasma levels of all immune markers differed significantly between patients and HC (Supplementary Table 1); however, case-control differences are more specifically reported in other papers from our group (Engh et al., 2022; Mørch et al., 2017; Mørch et al., 2019; Sheikh et al., 2021; Szabo et al., 2022). *Infection rate* correlated negatively with plasma levels of sgp130 (SCZ, $r_s = -0.09$, $p = 0.04$; BD, $r_s = -0.16$, $p = 0.01$) and IL-18 (BD, $r_s = -0.10$, $p = 0.05$). *Presence of autoimmune disease* correlated positively with IL-1Ra (SCZ, $r = 0.11$, $p = 0.01$), sIL-2R (SCZ, $r = 0.16$, $p < 0.001$), sgp130 (SCZ, $r = 0.13$, $p = 0.002$), sTNFR-1 (SCZ, $r = 0.08$, $p = 0.05$), ICAM-1 (SCZ, $r = 0.07$, $p = 0.10$) and negatively with APRIL (BD, $r = -0.10$, $p = 0.06$). *PRS-SCZ* correlated negatively with sIL-2R (SCZ, $r = -0.11$, $p = 0.02$). See Supplementary Table 2 for details of all correlation analyses.

3.3. Immune aberrations in patients explained by rate of infections, autoimmune disease and PRS

Comparisons of immune marker levels with and without adjustment of each of rate of infections, autoimmune disease and PRS of SCZ and BD versus HC were as follows:

Infection rate had no significant effect [$p = 0.97$ (sgp130, SCZ), $p = 0.66$ (sgp130, BD), $p = 0.30$ (IL-18, BD)] on the indicated immune markers in comparisons of patient groups with HC in fully adjusted models.

Presence of autoimmune disease was significantly positively associated with sIL-2R [$F(1,1021) = 10.305$, $p = 0.001$, partial eta squared = 0.010] in the adjusted model; the difference between SCZ and HC in plasma level of sIL-2R decreased from 11.2% to 10.7% when adding autoimmune disease to the model, reflecting a minor impact of presence of autoimmune disease on increased sIL-2R levels in SCZ. IL-1Ra, sgp130, sTNFR-1, APRIL and ICAM-1 were not significantly associated to autoimmune disease in the adjusted models ($p = 0.12$, $p = 0.09$, $p = 0.40$, $p = 0.60$ and $p = 0.07$, respectively).

PRS-SCZ was negatively associated with sIL-2R [$F(1, 922) = 7.107$, $p = 0.01$, partial eta squared = 0.008] in the adjusted model; the difference between SCZ and HC in sIL-2R level increased from 15.1% to 17.2% when adding PRS-SCZ, reflecting a minor negative impact of PRS-SCZ on sIL-2R levels in SCZ. See Table 2 for details of all ANCOVAs. In subsample analyses, BMI, but not smoking status or alcohol use, was significantly correlated with autoimmune disease and PRS-SCZ; however, no significant effect of BMI on sIL-2R levels were suggested in fully adjusted models ($p = 0.99$ and $p = 0.69$, respectively). Moreover, additional analyses of BD without participants with MDD did not change the main findings.

Table 2
Main effects of rate of infections, autoimmune disease and PRS on immune markers in ANCOVA analyses.[a]

Independent variable	Groups	Immune marker	df	F-ratio	p-value
Rate of infections	SCZ and HC	sgp130	11,091	0.001	0.97
Rate of infections	BD and HC	sgp130	1836	0.194	0.66
		IL-18	11,188	1.056	0.30
Autoimmune disease	SCZ and HC	IL-1Ra	11,067	2.435	0.12
		sIL-2R	11,021	10.305	0.001
		sgp130	11,091	2.858	0.09
		sTNFR-1	11,090	0.708	0.40
		ICAM-1	11,460	3.301	0.07
Autoimmune disease	BD and HC	APRIL	11,167	0.275	0.60
PRS-SCZ	SCZ and HC	sIL-2R	1922	7.107	0.01

Abbreviations: APRIL = a proliferation inducing ligand, BD = bipolar spectrum disorder, df = degrees freedom, ICAM-1 = Intercellular Adhesion Molecule 1, IL-18 = interleukin-18, IL-1Ra = interleukin-1 receptor antagonist, PRS = polygenic risk score, SCZ = schizophrenia spectrum disorder, sIL-2R = soluble interleukin-2 receptor, sgp130 = soluble glycoprotein 130.

[a] Adjusted for: age, sex, freezer storage time, group, and additionally ethnicity, genetic principal component 1 and 2 and genetic batch in PRS analyses, dependent variables: immune markers.

4. Discussion

While we found significant differences in rate of infections and autoimmune diseases in patients with SCZ and BD compared to HC, only minor associations with abnormal immune marker levels were indicated. The highest rate of total infections was found in BD and the lowest in SCZ, while presence of autoimmune disease was higher in BD than in SCZ and HC. While some correlations with immune markers were observed, only sIL-2R was significantly associated with autoimmune disease and PRS-SCZ in fully adjusted models across SCZ and HC; however, these associations represented only minor changes in immune marker differences between the groups. Thus, although we found increased frequency of infections and autoimmunity in BD, the present results did not provide strong evidence that infectious or autoimmune burden or genetic risk contributes to the systemic inflammation observed in SCZ and BD.

The immune hypothesis of severe mental disorders states that infections and autoimmune diseases may be involved in the development of the disorders through activation of inflammatory and immune-mediated processes (Benros and Mortensen, 2020; Köhler et al., 2017). Indeed, numerous studies support a role of inflammatory factors in SCZ and BD pathophysiology as reflected by dysregulated levels of systemic inflammatory markers. Although the current findings cannot disprove the hypothesis, they provide little support. Rather, a pattern of minor or non-detectable influences of infections and autoimmune diseases on the inflammatory state was suggested. This adds novel information to our understanding of the inflammatory processes of these disorders. Notwithstanding, inflammatory and immune mediated mechanisms do not "depend on" classical autoimmune and infectious disorders. Several factors such as altered gut microbiota, molecular mimicry, danger associated molecular patterns (DAMPs) and enhanced oxidative stress could elicit local and systemic inflammation in patients with SCZ and BD. Importantly, metabolic disturbances including dyslipidaemia and insulin resistance secondary to antipsychotic treatment and decreased physical activity are frequent in severe mental disorders and promote subclinical inflammation (Henderson et al., 2015).

While the investigated markers were chosen based on previous findings of differences between patients and controls (Kroken et al., 2018; Mørch et al., 2016), we cannot exclude that other markers of inflammation and immune activation than those selected in this study could be of importance in the pathogenesis of SCZ and BD and in addition related to infections, autoimmunity and PRS. However, current variation in the immune markers is in line with low-grade inflammation in SCZ and BD and supports their role in these disorders.

The current results provide some interesting insights into the role of specific immune marker levels and association with autoimmunity and PRS-SCZ. In analysis of SCZ and HC, associations to sIL-2R, a stable and reliable marker of T cell activation, survived adjustments for all confounders. The relationship between autoimmune disease and sIL-2R corresponds to previous studies indicating correlations of sIL-2R with disease activity in autoimmune diseases in the general population (Rubin and Nelson, 1990). sIL-2R might particularly be associated with immune diseases where enhanced T cell activation is thought to play an important pathogenic role (Adachi et al., 1990; Barak et al., 2009; Mavropoulou et al., 2020), some of which share genetic risk variants with SCZ (Pouget, 2018). IL-2R is implicated in the macrophage T-lymphocyte theory of SCZ, which involves failing of activated macrophages to properly control T-lymphocyte secretion of IL-2 and IL-2R (Smith, 1992). sIL-2R is also part of the compensatory immune-regulatory reflex system (CIRS) which has been implicated in the SCZ pathophysiology (Roomruangwong et al., 2020). While our findings indicate that sIL-2R is related to autoimmune disease as well as to PRS-SCZ, plasma level increases in SCZ is not explained by the associations. Still, a common genetic susceptibility for SCZ and immune system activity is suggested.

A unique feature of the current study is the access to diagnostic data from primary care physicians in addition to the specialist health care. When analyzing hospital data separately, we found increased rates of infections in both SCZ and BD compared with HC; this is in line with previous reports (Jeppesen and Benros, 2019) of large registry-based studies showing increased risk of both disorders with more hospital-treated infections (Benros et al., 2011; Benros et al., 2013; Köhler-Forsberg et al., 2019; Pankiewicz-Dulacz et al., 2018). By adding data from primary health care, we obtained a more comprehensive characterization of the infection rate, which interestingly indicated increased rates in BD, and not in SCZ. However, the finding need replication and should be interpreted with caution, as the sample size and assessed period is limited and confounds are likely. Differences in help-seeking behaviour (Oud and Meyboom-de Jong, 2009) is a potential explanation, as people with SCZ and BD might be less eager to seek help from primary care while at the same time more frequent users of emergency departments (Niedzwiecki et al., 2018). Also, presence of autoimmune disease was more prevalent in BD, but not in SCZ, compared with HC. This is in contrast with previous findings of increased prevalence of autoimmune disease in both groups (Chen et al., 2021; Eaton et al., 2006) and may partly explain the minor impact of the association between autoimmune disease and sIL-2R on sIL-2R aberrations in SCZ. (Benros et al., 2011).

Associations of immune genetic variants with SCZ and BD and genetic pleiotropy with immune related phenotypes (Andreassen et al., 2015; Tylee et al., 2018; Wang et al., 2015), suggest that the low-grade inflammation of these disorders involve a shared genetic liability (Ripke et al., 2014; Stefansson et al., 2009). The current results indicate that alterations in immune markers display only a minimal degree of association with disease genetics. We found a significant negative association between PRS-SCZ and one immune marker level (sIL-2R); however, the effect was small, and the direction did not explain the increased level in SCZ. The lack of other significant associations with PRS in our study complement previous findings of no significant interaction between PRS-SCZ and hospital-treated infections on risk of SCZ (Benros et al., 2016). The findings also fit with the results from a twin study showing that variations in the human immune system is largely driven by non-heritable influences (Brodin et al., 2015). Still, it is possible that the PRS does not capture the selected immune markers, although a smaller study indicated an effect on the CCL4 chemokine (Maj et al., 2019).

Moreover, as immune activation might vary with clinical characteristics, such as negative symptoms (Goldsmith et al., 2018) or acute relapse (Miller et al., 2011), one might hypothesize associations in clinical subgroups. It is also possible that current PRS are not adequately powered, as they only capture up to 7.7% of the variance in the phenotype (The Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2020), and that the standard removal of the high LD MHC region to avoid spurious findings, might have limited the ability to indicate true associations (Mangalam et al., 2013; Sekar et al., 2016).

Strengths of the current study includes detailed characterized data and a large sample size. To our knowledge this is the first study to investigate the associations between immune markers and PRS, infections and autoimmunity in SCZ and BD simultaneously. This combination enabled us to probe the current immune-etiopathogenic model linking immunogenic conditions with inflammation and severe mental disorders. Limitations include lack of registry data before 2006, thus we were unable to record the complete life-time number of infections and autoimmune diagnoses prior to immune assessments. However, available twelve-year complete registry data, also including diagnoses after immune assessments, allowed us to compare diagnosis rates between groups and assess the impact of this variation on immune marker alterations. In line with previous studies, we found higher rates of specialist health care treated infections in SCZ and BD compared to HC, indicating valid data. Still, lack of life-time data, including perinatal and early childhood infection rate (Barichello et al., 2016; Blomström et al., 2014), may be a reason for the negative findings, although supplementing the tests of twelve-year rate of infections with years at risk of infections prior to immune assessments (i.e. impact of age in adjusted models, data not shown), showed similar results. However, due to genetic components in susceptibility to infections (Chapman and Hill, 2012), one could speculate that current rates of infections retrieved from registries, might also be an indicator of early infection rates. Other limitations are the cross-sectional design with measurement at one time point as well as assessing a limited range of immune markers and pathways; however, the immune marker selection was based on robust associations previous findings. Also, several factors suggested to increase inflammation, such as social impairments, stress or trauma (Baumeister et al., 2016; Buske-Kirschbaum et al., 2007; Khandaker et al., 2017; Wieck et al., 2013) were not included. Due to the lack of consensus for choosing *p*-value threshold for PRS calculation, we cannot exclude the possibility of more appropriate thresholds than 0.05, with impact on the results. Lastly, the use of PRS' computed from GWAS of participants of European ancestry in a sample of admixed ancestries, could affect PRS performance (Duncan et al., 2019), however, the target sample for PRS is mostly (90%) of European ancestry and all main analyses of PRS were adjusted for ethnicity.

By investigating central immune activating conditions, genetics and inflammatory mediators in SCZ and BD concomitantly, we were able to test the immune etiopathogenic model of these severe mental disorders. Our findings of sparse association between markers of immune activation in SCZ and BD and rate of infections, autoimmune disease and genetic susceptibility suggest that the inflammatory abnormalities of these disorders are mainly driven by other factors. Larger studies with longitudinal data are needed to further clarify the mechanisms involved in inflammatory processes in SCZ and BD.

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Ethical statement

The TOP study has been approved by the Regional Ethics Committee and the Data Inspectorate. The Biobank is approved by the Norwegian Directorate of Health. Participation is based on a written, informed consent.

CRediT authorship contribution statement

Maren Caroline Frogner Werner: Conceptualization, Resources, Investigation, Methodology, Formal analysis, Writing – original draft. **Katrine Verena Wirgenes**: Conceptualization, Methodology, Supervision, Resources, Investigation, Writing – review & editing. **Alexey A. Shadrin**: Formal analysis, Writing – review & editing. **Synve Hoffart Lunding**: Resources, Investigation, Writing – review & editing. **Linn Rødevand**: Resources, Investigation, Writing – review & editing. **Gabriela Hjell**: Resources, Investigation, Writing – review & editing. **Monica Bettina Elkjaer Greenwood Ormerod**: Resources, Investigation, Writing – review & editing. **Marit Haram**: Resources, Investigation, Writing – review & editing. **Ingrid Agartz**: Resources, Investigation, Writing – review & editing. **Srdjan Djurovic**: Resources, Investigation, Writing – review & editing. **Ingrid Melle**: Resources, Investigation, Writing – review & editing. **Pål Aukrust**: Resources, Investigation, Writing – review & editing. **Thor Ueland**: Resources, Investigation, Writing – review & editing. **Ole Andreas Andreassen**: Conceptualization, Methodology, Supervision, Funding acquisition, Project administration, Resources, Writing – review & editing. **Nils Eiel Steen**: Conceptualization, Methodology, Supervision, Project administration, Investigation, Resources, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

Author OAA has received Speaker's honorarium from Lundbeck, Sunovion, and is a consultant to HealthLytix. All other authors declare that they have no conflicts of interest.

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References

Adachi, K., Kumamoto, T., Araki, S., 1990. Elevated soluble interleukin-2 receptor levels in patients with active multiple sclerosis. Ann. Neurol. 28 (5), 687–691. https://doi.org/10.1002/ana.410280514.

Aldinger, F., Schulze, T.G., 2017. Environmental factors, life events, and trauma in the course of bipolar disorder. Psychiatry Clin. Neurosci. 71 (1), 6–17. https://doi.org/10.1111/pcn.12433.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association, Washington, DC.

Andreassen, O.A., Harbo, H.F., Wang, Y., Thompson, W.K., Schork, A.J., Mattingsdal, M., et al., 2015. Genetic pleiotropy between multiple sclerosis and schizophrenia but not bipolar disorder: differential involvement of immune-related gene loci. Mol. Psychiatry 20 (2), 207–214. https://doi.org/10.1038/mp.2013.195.

Arias, I., Sorlozano, A., Villegas, E., de Dios Luna, J., McKenney, K., Cervilla, J., et al., 2012. Infectious agents associated with schizophrenia: a meta-analysis. Schizophr. Res. 136 (1–3), 128–136. https://doi.org/10.1016/j.schres.2011.10.026.

Askevold, E.T., Gullestad, L., Dahl, C.P., Yndestad, A., Ueland, T., Aukrust, P., 2014. Interleukin-6 signaling, soluble glycoprotein 130, and inflammation in heart failure. Curr Heart Fail Rep 11 (2), 146–155. https://doi.org/10.1007/s11897-014-0185-9.

Barak, V., Selmi, C., Schlesinger, M., Blank, M., Agmon-Levin, N., Kalickman, I., Shoenfeld, Y., et al., 2009. Serum inflammatory cytokines, complement components, and soluble interleukin 2 receptor in primary biliary cirrhosis. J. Autoimmun. 33 (3–4), 178–182. https://doi.org/10.1016/j.jaut.2009.09.010.

Barichello, T., Badawy, M., Pitcher, M.R., Saigal, P., Generoso, J.S., Goularte, J.A., Carvalho, A.F., et al., 2016. Exposure to perinatal infections and bipolar disorder: a systematic review. Curr. Mol. Med. 16 (2), 106–118. https://doi.org/10.2174/1566524016666160126143741.

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C.M., Mondelli, V., 2016. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive

protein, interleukin-6 and tumour necrosis factor-α. Mol. Psychiatry 21 (5), 642–649. https://doi.org/10.1038/mp.2015.67.
Benros, M.E., Mortensen, P.B., 2020. Role of infection, autoimmunity, atopic disorders, and the immune system in schizophrenia: evidence from epidemiological and genetic studies. Curr. Top. Behav. Neurosci. 44, 141–159. https://doi.org/10.1007/7854_2019_93.
Benros, M.E., Nielsen, P.R., Nordentoft, M., Eaton, W.W., Dalton, S.O., Mortensen, P.B., 2011. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. Am. J. Psychiatry 168 (12), 1303–1310. https://doi.org/10.1176/appi.ajp.2011.11030516.
Benros, M.E., Waltoft, B.L., Nordentoft, M., Ostergaard, S.D., Eaton, W.W., Krogh, J., Mortensen, P.B., 2013. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. JAMA Psychiatry 70 (8), 812–820. https://doi.org/10.1001/jamapsychiatry.2013.1111.
Benros, M.E., Trabjerg, B.B., Meier, S., Mattheisen, M., Mortensen, P.B., Mors, O., Agerbo, E., et al., 2016. Influence of polygenic risk scores on the association between infections and schizophrenia. Biol. Psychiatry 80 (8), 609–616. https://doi.org/10.1016/j.biopsych.2016.04.008.
Blomström, Å., Karlsson, H., Svensson, A., Frisell, T., Lee, B.K., Dal, H., Dalman, C., et al., 2014. Hospital admission with infection during childhood and risk for psychotic illness–a population-based cohort study. Schizophr. Bull. 40 (6), 1518–1525. https://doi.org/10.1093/schbul/sbt195.
Brodin, P., Jojic, V., Gao, T., Bhattacharya, S., Angel, C.J., Furman, D., Davis, M.M., et al., 2015. Variation in the human immune system is largely driven by non-heritable influences. Cell 160 (1–2), 37–47. https://doi.org/10.1016/j.cell.2014.12.020.
Brown, A.S., Derkits, E.J., 2010. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. Am. J. Psychiatry 167 (3), 261–280. https://doi.org/10.1176/appi.ajp.2009.09030361.
Buske-Kirschbaum, A., Kern, S., Ebrecht, M., Hellhammer, D.H., 2007. Altered distribution of leukocyte subsets and cytokine production in response to acute psychosocial stress in patients with psoriasis vulgaris. Brain Behav. Immun. 21 (1), 92–99. https://doi.org/10.1016/j.bbi.2006.03.006.
Chang, C.C., Chow, C.C., Tellier, L.C., Vattikuti, S., Purcell, S.M., Lee, J.J., 2015. Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience 4, 7. https://doi.org/10.1186/s13742-015-0047-8.
Chapman, S.J., Hill, A.V., 2012. Human genetic susceptibility to infectious disease. Nat Rev Genet 13 (3), 175–188. https://doi.org/10.1038/nrg3114.
Chen, M., Jiang, Q., Zhang, L., 2021. The prevalence of bipolar disorder in autoimmune disease: a systematic review and meta-analysis. Ann Palliat Med 10 (1), 350–361. https://doi.org/10.21037/apm-20-2293.
Choi, S.W., O'Reilly, P.F., 2019. PRSice-2: polygenic risk score software for biobank-scale data. Gigascience 8 (7). https://doi.org/10.1093/gigascience/giz082.
Das, S., Forer, L., Schonherr, S., Sidore, C., Locke, A.E., Kwong, A., Fuchsberger, C., et al., 2016. Next-generation genotype imputation service and methods. Nat. Genet. 48 (10), 1284–1287. https://doi.org/10.1038/ng.3656.
de Barros, J., Barbosa, I.G., Salem, H., Rocha, N.P., Kummer, A., Okusaga, O.O., Teixeira, A.L., et al., 2017. Is there any association between toxoplasma gondii infection and bipolar disorder? A systematic review and meta-analysis. J. Affect. Disord. 209, 59–65. https://doi.org/10.1016/j.jad.2016.11.016.
Dinarello, C.A., 2018. Overview of the IL-1 family in innate inflammation and acquired immunity. Immunol. Rev. 281 (1), 8–27. https://doi.org/10.1111/imr.12621.
Drexhage, R.C., Knijff, E.M., Padmos, R.C., Heul-Nieuwenhuijzen, L., Beumer, W., Versnel, M.A., Drexhage, H.A., 2010. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. Expert. Rev. Neurother. 10 (1), 59–76. https://doi.org/10.1586/ern.09.144.
Duncan, L., Shen, H., Gelaye, B., Meijsen, J., Ressler, K., Feldman, M., Domingue, B., et al., 2019. Analysis of polygenic risk score usage and performance in diverse human populations. Nat. Commun. 10 (1), 3328. https://doi.org/10.1038/s41467-019-11112-0.
Eaton, W.W., Byrne, M., Ewald, H., Mors, O., Chen, C.Y., Agerbo, E., Mortensen, P.B., 2006. Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. Am. J. Psychiatry 163 (3), 521–528. https://doi.org/10.1176/appi.ajp.163.3.521.
Engh, J.A., Ueland, T., Agartz, I., Andreou, D., Aukrust, P., Boye, B., Andreassen, O.A., et al., 2022. Plasma Levels of the Cytokines B Cell-Activating Factor (BAFF) and a Proliferation-Inducing Ligand (APRIL) in Schizophrenia, Bipolar, and Major Depressive Disorder: A Cross Sectional, Multisite Study. Schizophr Bull. 48 (1), 37–46. https://doi.org/10.1093/schbul/sbab106.
Enroth, S., Hallmans, G., Grankvist, K., Gyllensten, U., 2016. Effects of long-term storage time and original sampling month on biobank plasma protein concentrations. EBioMedicine 12, 309–314. https://doi.org/10.1016/j.ebiom.2016.08.038.
Ezeoke, A., Mellor, A., Buckley, P., Miller, B., 2013. A systematic, quantitative review of blood autoantibodies in schizophrenia. Schizophr. Res. 150 (1), 245–251. https://doi.org/10.1016/j.schres.2013.07.029.
First, M.B., Gibbon, M., Williams, J.B.W., 1995. Structured Clinical Interview for DSM-IV Axis I Disorders: Patient Edition (SCID-P), Version 2. Biometrics Research. New York State Psychiatric Institute, New York.
George-Chandy, A., Trysberg, E., Eriksson, K., 2008. Raised intrathecal levels of APRIL and BAFF in patients with systemic lupus erythematosus: relationship to neuropsychiatric symptoms. Arthritis Res Ther 10 (4), R97. https://doi.org/10.1186/ar2484.
Girardin, E., Roux-Lombard, P., Grau, G.E., Suter, P., Gallati, H., Dayer, J.M., 1992. Imbalance between tumour necrosis factor-alpha and soluble TNF receptor concentrations in severe meningococcaemia. The J5 Study Group. Immunology 76 (1), 20–23.
Goldsmith, D.R., Rapaport, M.H., Miller, B.J., 2016. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol. Psychiatry 21 (12), 1696–1709. https://doi.org/10.1038/mp.2016.3.
Goldsmith, D.R., Haroon, E., Miller, A.H., Strauss, G.P., Buckley, P.F., Miller, B.J., 2018. TNF-α and IL-6 are associated with the deficit syndrome and negative symptoms in patients with chronic schizophrenia. Schizophr. Res. 199, 281–284. https://doi.org/10.1016/j.schres.2018.02.048.
Henderson, D.C., Vincenzi, B., Andrea, N.V., Ulloa, M., Copeland, P.M., 2015. Pathophysiological mechanisms of increased cardiometabolic risk in people with schizophrenia and other severe mental illnesses. Lancet Psychiatry 2 (5), 452–464. https://doi.org/10.1016/s2215-0366(15)00115-7.
Hickie, I.B., Banati, R., Stewart, C.H., Lloyd, A.R., 2009. Are common childhood or adolescent infections risk factors for schizophrenia and other psychotic disorders? Med. J. Aust. 190 (S4), S17–S21.
Hofmans-Okkes, I.M., Lamberts, H., 1996. The international classification of primary care (ICPC): new applications in research and computer-based patient records in family practice. Fam. Pract. 13 (3), 294–302. https://doi.org/10.1093/fampra/13.3.294.
Hope, S., Melle, I., Aukrust, P., Steen, N.E., Birkenaes, A.B., Lorentzen, S., Andreassen, O.A., et al., 2009. Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor. Bipolar Disord. 11 (7), 726–734. https://doi.org/10.1111/j.1399-5618.2009.00757.x.
Hope, S., Ueland, T., Steen, N.E., Dieset, I., Lorentzen, S., Berg, A.O., Andreassen, O.A., et al., 2013. Interleukin 1 receptor antagonist and soluble tumor necrosis factor receptor 1 are associated with general severity and psychotic symptoms in schizophrenia and bipolar disorder. Schizophr. Res. 145 (1–3), 36–42. https://doi.org/10.1016/j.schres.2012.12.023.
Hu, X., Daly, M., 2012. What have we learned from six years of GWAS in autoimmune diseases, and what is next? Curr. Opin. Immunol. 24 (5), 571–575. https://doi.org/10.1016/j.coi.2012.09.001.
Jeppesen, R., Benros, M.E., 2019. Autoimmune diseases and psychotic disorders. Front Psychiatry 10, 131. https://doi.org/10.3389/fpsyt.2019.00131.
Kępińska, A.P., Iyegbe, C.O., Vernon, A.C., Yolken, R., Murray, R.M., Pollak, T.A., 2020. Schizophrenia and influenza at the centenary of the 1918-1919 Spanish influenza pandemic: mechanisms of psychosis risk. Front Psychiatry 11, 72. https://doi.org/10.3389/fpsyt.2020.00072.
Khandaker, G.M., Zimbron, J., Lewis, G., Jones, P.B., 2013. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. Psychol. Med. 43 (2), 239–257. https://doi.org/10.1017/s0033291712000736.
Khandaker, G.M., Dantzer, R., Jones, P.B., 2017. Immunopsychiatry: important facts. Psychol. Med. 47 (13), 2229–2237. https://doi.org/10.1017/s0033291717000745.
Klebanov, N., 2018. Genetic predisposition to infectious disease. Cureus 10 (8), e3210. https://doi.org/10.7759/cureus.3210.
Köhler, O., Petersen, L., Mors, O., Mortensen, P.B., Yolken, R.H., Gasse, C., Benros, M.E., 2017. Infections and exposure to anti-infective agents and the risk of severe mental disorders: a nationwide study. Acta Psychiatr. Scand. 135 (2), 97–105. https://doi.org/10.1111/acps.12671.
Köhler-Forsberg, O., Petersen, L., Gasse, C., Mortensen, P.B., Dalsgaard, S., Yolken, R.H., Benros, M.E., et al., 2019. A Nationwide study in Denmark of the association between treated infections and the subsequent risk of treated mental disorders in children and adolescents. JAMA Psychiatry 76 (3), 271–279. https://doi.org/10.1001/jamapsychiatry.2018.3428.
Kroken, R.A., Sommer, I.E., Steen, V.M., Dieset, I., Johnsen, E., 2018. Constructing the immune signature of schizophrenia for clinical use and research; an integrative review translating Descriptives into diagnostics. Front Psychiatry 9, 753. https://doi.org/10.3389/fpsyt.2018.00753.
Li, Y., Willer, C.J., Ding, J., Scheet, P., Abecasis, G.R., 2010. MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. Genet. Epidemiol. 34 (8), 816–834. https://doi.org/10.1002/gepi.20533.
Loh, P.R., Danecek, P., Palamara, P.F., Fuchsberger, C., Reshef, Yakir A., Finucane, Hilary K., et al., 2016. Reference-based phasing using the haplotype reference consortium panel. Nat. Genet. 48 (11), 1443–1448. https://doi.org/10.1038/ng.3679.
Luo, Y., He, H., Zhang, M., Huang, X., Fan, N., 2016. Altered serum levels of TNF-α, IL-6 and IL-18 in manic, depressive, mixed state of bipolar disorder patients. Psychiatry Res. 244, 19–23. https://doi.org/10.1016/j.psychres.2016.07.027.
Luo, Y., He, H., Zhang, J., Ou, Y., Fan, N., 2019. Changes in serum TNF-α, IL-18, and IL-6 concentrations in patients with chronic schizophrenia at admission and at discharge. Compr. Psychiatry 90, 82–87. https://doi.org/10.1016/j.comppsych.2019.01.003.
Maj, C., Tosato, S., Zanardini, R., Lasalvia, A., Favaro, A., Leuci, E., , et al.Bocchio-Chiavetto, L., 2019. Correlations between immune and metabolic serum markers and schizophrenia/bipolar disorder polygenic risk score in first-episode psychosis. Early Interv Psychiatry. https://doi.org/10.1111/eip.12906.
Mangalam, A.K., Taneja, V., David, C.S., 2013. HLA class II molecules influence susceptibility versus protection in inflammatory diseases by determining the cytokine profile. J. Immunol. 190 (2), 513–518. https://doi.org/10.4049/jimmunol.1201891.
Marangoni, C., Hernandez, M., Faedda, G.L., 2016. The role of environmental exposures as risk factors for bipolar disorder: a systematic review of longitudinal studies. J. Affect. Disord. 193, 165–174. https://doi.org/10.1016/j.jad.2015.12.055.
Mavropoulou, E., Mechie, N.C., Knoop, R., Petzold, G., Ellenrieder, V., Kunsch, S., Amanzada, A., et al., 2020. Association of serum interleukin-6 and soluble interleukin-2-receptor levels with disease activity status in patients with

inflammatory bowel disease: a prospective observational study. PLoS One 15 (5), e0233811. https://doi.org/10.1371/journal.pone.0233811.
McCarthy, S., Das, S., Kretzschmar, W., Delaneau, O., Wood, A.R., Teumer, A., Durbin, R., et al., 2016. A reference panel of 64,976 haplotypes for genotype imputation. Nat. Genet. 48 (10), 1279–1283. https://doi.org/10.1038/ng.3643.
McDonald, C., Murray, R.M., 2000. Early and late environmental risk factors for schizophrenia. Brain Res. Brain Res. Rev. 31 (2–3), 130–137. https://doi.org/10.1016/s0165-0173(99)00030-2.
Miller, B.J., Buckley, P., Seabolt, W., Mellor, A., Kirkpatrick, B., 2011. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol. Psychiatry 70 (7), 663–671. https://doi.org/10.1016/j.biopsych.2011.04.013.
Monji, A., Kato, T., Kanba, S., 2009. Cytokines and schizophrenia: microglia hypothesis of schizophrenia. Psychiatry Clin. Neurosci. 63 (3), 257–265. https://doi.org/10.1111/j.1440-1819.2009.01945.x.
Mørch, R.H., Dieset, I., Færden, A., Hope, S., Aas, M., Nerhus, M., Andreassen, O.A., et al., 2016. Inflammatory evidence for the psychosis continuum model. Psychoneuroendocrinology 67, 189–197. https://doi.org/10.1016/j.psyneuen.2016.02.011.
Mørch, R.H., Dieset, I., Faerden, A., Hope, S., Aas, M., Nerhus, M., Andreassen, O.A., et al., 2017. Persistent increase in TNF and IL-1 markers in severe mental disorders suggests trait-related inflammation: a one year follow-up study. Acta Psychiatr. Scand. 136 (4), 400–408. https://doi.org/10.1111/acps.12783.
Mørch, R.H., Dieset, I., Færden, A., Reponen, E.J., Hope, S., Hoseth, E.Z., Andreassen, O.A., et al., 2019. Inflammatory markers are altered in severe mental disorders independent of comorbid cardiometabolic disease risk factors. Psychol. Med. 49 (10), 1749–1757. https://doi.org/10.1017/s0033291718004142.
Müller, N., 2019. The role of intercellular adhesion Molecule-1 in the pathogenesis of psychiatric disorders. Front. Pharmacol. 10, 1251. https://doi.org/10.3389/fphar.2019.01251.
Mullins, N., Forstner, A.J., O'Connell, K.S., Coombes, B., Coleman, J.R.I., Qiao, Z., Andreassen, O.A., et al., 2021. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. Nat. Genet. https://doi.org/10.1038/s41588-021-00857-4.
Niedzwiecki, M.J., Sharma, P.J., Kanzaria, H.K., McConville, S., Hsia, R.Y., 2018. Factors associated with emergency department use by patients with and without mental health diagnoses. JAMA Netw. Open 1 (6), e183528. https://doi.org/10.1001/jamanetworkopen.2018.3528.
Nielsen, P.R., Laursen, T.M., Mortensen, P.B., 2013. Association between parental hospital-treated infection and the risk of schizophrenia in adolescence and early adulthood. Schizophr. Bull. 39 (1), 230–237. https://doi.org/10.1093/schbul/sbr149.
Noll, R., 2007. Kraepelin's 'lost biological psychiatry'? Autointoxication, organotherapy and surgery for dementia praecox. Hist Psychiatry 18 (71 Pt 3), 301–320. https://doi.org/10.1177/0957154x07078705.
Oliveira, J., Oliveira-Maia, A.J., Tamouza, R., Brown, A.S., Leboyer, M., 2017. Infectious and immunogenetic factors in bipolar disorder. Acta Psychiatr. Scand. 136 (4), 409–423. https://doi.org/10.1111/acps.12791.
Oud, M.J., Meyboom-de Jong, B., 2009. Somatic diseases in patients with schizophrenia in general practice: their prevalence and health care. BMC Fam. Pract. 10, 32. https://doi.org/10.1186/1471-2296-10-32.
Owen, M.J., Sawa, A., Mortensen, P.B., 2016. Schizophrenia. Lancet 388 (10039), 86–97. https://doi.org/10.1016/s0140-6736(15)01121-6.
Pankiewicz-Dulacz, M., Stenager, E., Chen, M., 2018. Incidence rates and risk of hospital registered infections among schizophrenia patients before and after onset of illness: a population-based Nationwide register study. J. Clin. Med. 7 (12) https://doi.org/10.3390/jcm7120485.
Parboosing, R., Bao, Y., Shen, L., Schaefer, C.A., Brown, A.S., 2013. Gestational influenza and bipolar disorder in adult offspring. JAMA Psychiatry 70 (7), 677–685. https://doi.org/10.1001/jamapsychiatry.2013.896.
Potvin, S., Stip, E., Sepehry, A.A., Gendron, A., Bah, R., Kouassi, E., 2008. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol. Psychiatry 63 (8), 801–808. https://doi.org/10.1016/j.biopsych.2007.09.024.
Pouget, J.G., 2018. The emerging Immunogenetic architecture of schizophrenia. Schizophr. Bull. 44 (5), 993–1004. https://doi.org/10.1093/schbul/sby038.
Purcell, S.M., Wray, N.R., Stone, J.L., Visscher, P.M., O'Donovan, M.C., Sullivan, P.F., Sklar, P., 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460 (7256), 748–752. https://doi.org/10.1038/nature08185.
Quan, H., Li, B., Saunders, L.D., Parsons, G.A., Nilsson, C.I., Alibhai, A., Ghali, W.A., 2008. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. Health Serv. Res. 43 (4), 1424–1441. https://doi.org/10.1111/j.1475-6773.2007.00822.x.
Ringen, P.A., Lagerberg, T.V., Birkenaes, A.B., Engn, J., Faerden, A., Jónsdottir, H., Andreassen, O.A., et al., 2008. Differences in prevalence and patterns of substance use in schizophrenia and bipolar disorder. Psychol. Med. 38 (9), 1241–1249. https://doi.org/10.1017/s003329170700236x.
Ripke, S., Neale, B.M., Corvin, A., Walters, J.T.R., Farh, K.-H., Holmans, P.A., et al., 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511 (7510), 421–427. https://doi.org/10.1038/nature13595.
Roomruangwong, C., Noto, C., Kanchanatawan, B., Anderson, G., Kubera, M., Carvalho, A.F., Maes, M., 2020. The role of aberrations in the immune-inflammatory response system (IRS) and the compensatory immune-regulatory reflex system (CIRS) in different phenotypes of schizophrenia: the IRS-CIRS theory of schizophrenia. Mol. Neurobiol. 57 (2), 778–797. https://doi.org/10.1007/s12035-019-01737-z.
Rosenblat, J.D., McIntyre, R.S., 2017. Bipolar disorder and immune dysfunction: epidemiological findings, proposed pathophysiology and clinical implications. Brain Sci. 7 (11) https://doi.org/10.3390/brainsci7110144.
Rubin, L.A., Nelson, D.L., 1990. The soluble interleukin-2 receptor: biology, function, and clinical application. Ann. Intern. Med. 113 (8), 619–627. https://doi.org/10.7326/0003-4819-113-8-619.
Sekar, A., Bialas, A.R., de Rivera, H., Davis, A., Hammond, T.R., Kamitaki, N., McCarroll, S.A., et al., 2016. Schizophrenia risk from complex variation of complement component 4. Nature 530 (7589), 177–183. https://doi.org/10.1038/nature16549.
Sheikh, M., Ueland, T., O'Connell, K.S., Agartz, I., Andreou, D., Aukrust, P., Andreassen, O., et al., 2021. Systemic cell-adhesion molecules (CAM) in severe mental illness-potential role of intracellular CAM-1 in linking peripheral and neuro-inflammation (submitted).
Skov, J., Eriksson, D., Kuja-Halkola, R., Höijer, J., Gudbjörnsdottir, S., Svensson, A.M., Bensing, S., et al., 2020. Co-aggregation and heritability of organ-specific autoimmunity: a population-based twin study. Eur. J. Endocrinol. 182 (5), 473–480. https://doi.org/10.1530/eje-20-0049.
Smeland, O.B., Frei, O., Dale, A.M., Andreassen, O.A., 2020. The polygenic architecture of schizophrenia - rethinking pathogenesis and nosology. Nat. Rev. Neurol. 16 (7), 366–379. https://doi.org/10.1038/s41582-020-0364-0.
Smith, R.S., 1992. A comprehensive macrophage-T-lymphocyte theory of schizophrenia. Med. Hypotheses 39 (3), 248–257. https://doi.org/10.1016/0306-9877(92)90117-u.
Stahl, E.A., Breen, G., Forstner, A.J., McQuillin, A., Ripke, S., Trubetskoy, V., Sklar, P., et al., 2019. Genome-wide association study identifies 30 loci associated with bipolar disorder. Nat. Genet. 51 (5), 793–803. https://doi.org/10.1038/s41588-019-0397-8.
Stefansson, H., Ophoff, R.A., Steinberg, S., Andreassen, O.A., Cichon, S., Rujescu, D., Collier, D.A., et al., 2009. Common variants conferring risk of schizophrenia. Nature 460 (7256), 744–747. https://doi.org/10.1038/nature08186.
Stilo, S.A., Murray, R.M., 2019. Non-genetic factors in schizophrenia. Curr Psychiatry Rep 21 (10), 100. https://doi.org/10.1007/s11920-019-1091-3.
Stringer, S., Kahn, R.S., de Witte, L.D., Ophoff, R.A., Derks, E.M., 2014. Genetic liability for schizophrenia predicts risk of immune disorders. Schizophr. Res. 159 (2–3), 347–352. https://doi.org/10.1016/j.schres.2014.09.004.
Szabo, A., O'Connell, K.S., Ueland, T., Sheikh, M.A., Agartz, I., Andreou, D., Djurovic, S., et al., 2022. Increased circulating IL-18 levels in severe mental disorders indicate systemic inflammasome activation. Brain Behav. Immun. 99, 299–306. https://doi.org/10.1016/j.bbi.2021.10.017.
The Schizophrenia Working Group of the Psychiatric Genomics Consortium, Ripke, S., Walters, J.T., O'Donovan, M.C., 2020. Mapping genomic loci prioritises genes and implicates synaptic biology in schizophrenia. medRxiv. https://doi.org/10.1101/2020.09.12.20192922, 2020.2009.2012.20192922.
Tylee, D.S., Sun, J., Hess, J.L., Tahir, M.A., Sharma, E., Malik, R., Glatt, S.J., et al., 2018. Genetic correlations among psychiatric and immune-related phenotypes based on genome-wide association data. Am. J. Med. Genet. B Neuropsychiatr. Genet. 177 (7), 641–657. https://doi.org/10.1002/ajmg.b.32652.
van Os, J., Krabbendam, L., Myin-Germeys, I., Delespaul, P., 2005. The schizophrenia envirome. Curr Opin Psychiatry 18 (2), 141–145. https://doi.org/10.1097/00001504-200503000-00006.
van Os, J., Kenis, G., Rutten, B.P., 2010. The environment and schizophrenia. Nature 468 (7321), 203–212. https://doi.org/10.1038/nature09563.
Ventura, J., Liberman, R.P., Green, M.F., Shaner, A., Mintz, J., 1998. Training and quality assurance with the structured clinical interview for DSM-IV (SCID-I/P). Psychiatry Res. 79 (2), 163–173. https://doi.org/10.1016/s0165-1781(98)00038-9.
Vieta, E., Berk, M., Schulze, T.G., Carvalho, A.F., Suppes, T., Calabrese, J.R., Grande, I., et al., 2018. Bipolar disorders. Nat Rev Dis Primers 4, 18008. https://doi.org/10.1038/nrdp.2018.8.
Wang, Q., Yang, C., Gelernter, J., Zhao, H., 2015. Pervasive pleiotropy between psychiatric disorders and immune disorders revealed by integrative analysis of multiple GWAS. Hum. Genet. 134 (11–12), 1195–1209. https://doi.org/10.1007/s00439-015-1596-8.
Wedervang-Resell, K., Friis, S., Lonning, V., Smelror, R.E., Johannessen, C., Reponen, E. J., Myhre, A.M., et al., 2020a. Increased interleukin 18 activity in adolescents with early-onset psychosis is associated with cortisol and depressive symptoms. Psychoneuroendocrinology 112, 104513. https://doi.org/10.1016/j.psyneuen.2019.104513.
Wedervang-Resell, K., Ueland, T., Aukrust, P., Friis, S., Holven, K.B., et al., 2020b. Reduced levels of circulating adhesion molecules in adolescents with early-onset psychosis. NPJ Schizophr. 6 (1), 20. https://doi.org/10.1038/s41537-020-00112-5.
Wieck, A., Grassi-Oliveira, R., do Prado, C.H., Rizzo, L.B., de Oliveira, A.S., Kommers-Molina, J., et al., 2013. Differential neuroendocrine and immune responses to acute psychosocial stress in women with type 1 bipolar disorder. Brain Behav. Immun. 34, 47–55. https://doi.org/10.1016/j.bbi.2013.07.005.
Wimberley, T., Gasse, C., Meier, S.M., Agerbo, E., MacCabe, J.H., Horsdal, H.T., 2017. Polygenic risk score for schizophrenia and treatment-resistant schizophrenia. Schizophr. Bull. 43 (5), 1064–1069. https://doi.org/10.1093/schbul/sbx007.
Wray, N.R., Lee, S.H., Mehta, D., Vinkhuyzen, A.A., Dudbridge, F., Middeldorp, C.M., 2014. Research review: polygenic methods and their application to psychiatric traits. J. Child Psychol. Psychiatry 55 (10), 1068–1087. https://doi.org/10.1111/jcpp.12295.