Psychological Medicine

cambridge.org/psm

Transdiagnostic dimensions of symptoms and experiences associated with immune proteins in the continuity of psychosis

Fabiana Corsi-Zuelli[1,2], Diego Quattrone[3], Taciana Cristina Carvalho Ragazzi[1], Camila Marcelino Loureiro[1], Rosana Shuhama[1], Paulo Rossi Menezes[4], Paulo Louzada-Junior[5,2] and Cristina Marta Del-Ben[1]

[1]Department of Neuroscience and Behaviour, University of São Paulo, Ribeirão Preto Medical School, São Paulo, Brazil; [2]Center for Research on Inflammatory Diseases – CRID, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil; [3]Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK; [4]Department of Preventive Medicine, University of São Paulo, Faculty of Medicine, São Paulo, Brazil and [5]Department of Internal Medicine, University of São Paulo, Ribeirão Preto Medical School, São Paulo, Brazil

Original Article

Cite this article: Corsi-Zuelli F, Quattrone D, Ragazzi TCC, Loureiro CM, Shuhama R, Menezes PR, Louzada-Junior P, Del-Ben CM (2024). Transdiagnostic dimensions of symptoms and experiences associated with immune proteins in the continuity of psychosis. *Psychological Medicine* **54**, 2099–2111. https://doi.org/10.1017/S0033291724000199

Received: 15 June 2023
Revised: 21 December 2023
Accepted: 22 January 2024
First published online: 28 February 2024

Keywords:
inflammation; psychosis continuum; psychotic experiences; schizophrenia; siblings

Corresponding author:
Fabiana Corsi-Zuelli;
Email: fabiana.zuelli@usp.br

Abstract

Background. There is limited evidence as to whether the immune protein profile is associated with a particular symptomatology pattern across the psychosis *continuum*.

Methods. We estimated two bifactor models of general and specific dimensions of psychotic experiences in unaffected siblings of patients ($n = 52$) and community controls ($n = 200$), and of psychotic symptoms in first-episode psychosis (FEP) patients ($n = 110$). We evaluated associations between these transdiagnostic dimensions and trait (TNF-α, IFN-γ), state (IL-6, IL-1β), and regulatory (TGF-β, IL-10, IL-4) cytokines. We explored whether schizophrenia genetic liability (schizophrenia polygenic risk score; SZ-PRS) modified the associations.

Results. High levels of trait marker IFN-γ were associated with the severity of general psychosis dimension in the unaffected siblings and community controls, expanding to the depressive dimension in siblings and to the manic dimension in FEP. High TNF-α levels were associated with more positive psychotic experiences in unaffected siblings and manic symptoms in FEP. Low levels of state markers IL-6 and IL-1β were observed in unaffected siblings presenting more depressive experiences. Still, high levels of IL-6 and IL-1β were associated with the severity of the depressive and negative symptom dimensions at FEP. The severity of transdiagnostic dimension scores across the three groups was associated with lower regulatory cytokines. Exploratory analysis suggested that a high SZ-PRS contributed mostly to associations with psychotic dimensions.

Conclusions. IFN-γ mapped onto the multidimensional expression of psychosis, reinforcing the trait concept. State markers IL-6 and IL-1β may fluctuate along the spectrum. Dysfunction in the regulatory arm may disinhibit the inflammatory system. Associations with psychotic dimensions may be more prone to SZ-PRS susceptibility.

Introduction

The current nosology classifies psychotic disorders in categories of non-affective (i.e. schizophrenia and schizoaffective disorder) and affective psychosis (i.e. bipolar and major depressive disorder with psychotic features) based on the type and course of symptomatology (American Psychiatric Association, 2013). However, the diagnosis of psychotic disorders at first is unstable longitudinally (Heslin et al., 2015), and there is significant comorbidity between non-affective psychotic disorders with either bipolar (BD) or major depressive disorders (MDD) (Laursen, Agerbo, & Pedersen, 2009; Upthegrove, Marwaha, & Birchwood, 2016). Genome-wide association studies (GWAS) have also revealed shared genetic risks among these disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). Recent evidence suggests that the existing categorical classification system may be too simplistic to unravel the complex heterogeneity of the psychotic phenomena. Instead, non-categorical and transdiagnostic dimensional approaches are recommended (Quattrone et al., 2019; Quattrone et al., 2021a, 2021b). Item response modeling and factor analysis have been utilized to explore these non-categorical approaches. Indeed, psychotic disorders can be statistically conceptualized using a bifactorial model, with one general factor reflecting the mood-psychosis spectrum and a set of specific factors representing dimensions that can encompass positive, negative, disorganization, manic and depressive symptoms (Quattrone et al., 2019; Quattrone et al., 2021a, 2021b).

The transdiagnostic multidimensional model of psychopathology can be integrated into the continuity conceptualization of psychosis (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). The psychosis *continuum* or extended psychosis phenotype model (Linscott & van Os, 2010; Linscott & van Os, 2013) postulates that all psychotic phenomena exist on a *continuum*. At one end are individuals with psychotic disorders who experience severe and frequent psychotic symptoms. The healthier end of this *continuum*, however, constitutes individuals of the general population who experience attenuated psychotic symptoms expressed in the form of psychotic experiences (PEs) that do not fulfill the diagnosis criteria (Ragazzi et al., 2020). PEs are usually transient, although the prevalence is much higher (~7%) than the clinical phenotype (~3%), and they can become persistent to pose longitudinal risks for the development of psychotic disorders and common mental disorders (van Os & Reininghaus, 2016).

Several lines of evidence suggest that immune dysfunction is implicated in the pathophysiology of psychotic disorders (Corsi-Zuelli & Deakin, 2021; Goldsmith, Rapaport, & Miller, 2016), MDD and BD (Çakici et al., 2020; Goldsmith et al., 2016). A low level of non-resolving inflammation is already present in first-episode patients, even before psychopharmacological treatment initiation (Çakici et al., 2020; Pillinger et al., 2019). In addition, schizophrenia GWAS show the strongest association with the major histocompatibility complex, which encodes proteins essential for the functioning of the immune system (Trubetskoy et al., 2022).

Only a few studies examined the contribution of blood immune proteins to clinical and subclinical symptom domains across the psychosis *continuum*, and most studies focused only on C-reactive protein (CRP) and interleukin (IL)-6, with mixed findings. For example, in early-stage psychosis, increased CRP levels were positively related to the severity of positive but not negative symptoms (Fernandes et al., 2016), and higher IL-6 levels were positively associated with negative but not positive symptoms (Stojanovic et al., 2014). However, these CRP and IL-6 findings were not replicated in a later study of early-stage schizophrenia (Krynicki et al., 2021). In addition, depressive symptoms were positively associated (Noto et al., 2015), weakly associated (Krynicki et al., 2021) or unrelated (Borovcanin et al., 2012; Noto et al., 2019) to increased IL-6 in recent-onset schizophrenia. The inconsistencies across studies could be related to differences in study design and methods, including assessment tools, sample sizes, age of assessment, and illness stage.

Given that PEs are common in the general population and share many etiological and pathophysiological backgrounds with psychotic disorders (Monshouwer et al., 2022; Staines et al., 2022), examining their biological correlates could aid in comprehending the pathophysiology of the psychotic phenomena. This exploration also offers the potential to identify promising targets for early intervention, with the added benefit of reducing the influence of confounding factors related to illness duration and prolonged exposure to antipsychotics. However, the investigation of immune proteins and dimensions of PEs in non-clinical samples is scarce. A population-based study of adolescents found that raised CRP levels measured at age 16 were longitudinally associated with both positive and negative subclinical psychotic symptoms at age 17 (Khandaker et al., 2021). Another study from the same cohort found that raised IL-6 but not CRP levels measured during childhood at age nine correlated with negative symptom dimension at age 24 (Perry, Zammit, Jones, & Khandaker, 2021). We are not aware of other studies.

We aimed to investigate how immune proteins map onto a transdiagnostic multidimensional framework across the psychosis *continuum* in first-episode psychosis patients (FEP), their unaffected siblings, and community controls. Previous studies primarily focused on total scores of positive and negative symptoms, often neglecting immune proteins other than CRP or IL-6. In our study, we employed item response modeling and factor analysis to robustly estimate the transdiagnostic expression of psychosis. We then examined associations between the estimated transdiagnostic dimensions with a range of immune proteins, including trait (tumor necrosis factor (TNF)-α, interferon(IFN)-γ), state (IL-6, IL-1β), and regulatory (transforming growth factor (TGF)-β, IL-10, IL-4) (Capuzzi, Bartoli, Crocamo, Clerici, & Carrà, 2017; Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011), along with high-sensitive (hs)-CRP. To evaluate the role of disease endophenotypes without the interference of illness confounding factors, we considered first-degree unaffected siblings, who have an elevated risk of developing the disorder (ten-fold to 10% increased morbidity risk) (Lichtenstein et al., 2009). Finally, given the high genetic liability to develop schizophrenia (~80%) (Sullivan, Kendler, & Neale, 2003), we explored if any significant associations would vary according to the degree of polygenic liability, as summarized into a schizophrenia polygenic risk score (SZ-PRS).

We predicted that higher levels of trait, state, and hs-CRP but lower regulatory markers would be associated with transdiagnostic dimensions along the psychosis *continuum*, with the unaffected siblings constituting an intermediate group between patients and controls. We also expected that significant associations would depend on a higher degree of SZ-PRS across the three groups.

Methods

We used data from the *Schizophrenia and Other Psychosis Translational Research: Environment and Molecular Biology* (STREAM) study, an incidence and case–sibling–control investigation conducted in the Ribeirão Preto catchment area (São Paulo, Brazil) (Del-Ben et al., 2019), which integrates the international multicenter consortium EU-GEI (Gayer-Anderson et al., 2020). The present study is cross-sectional, and we only included the Brazilian participants because blood cytokine measurement was a protocol specific from Brazil.

The study was approved by the local Research Ethics Committee (12606/2012), and written informed consent was obtained from all the participants. All data were collected by clinical psychologists and nurses with experience in mental health, with weekly supervision from senior psychiatrists.

Participants

All the STREAM participants were recruited from Ribeirão Preto city (São Paulo, Brazil) and the surrounding 25 municipalities during a three-year recruitment period (April 2012 until March 2015). The sample comprised FEP patients, their unaffected siblings, and community controls (Del-Ben et al., 2019).

As part of the incidence study, we screened all individuals referred to mental health services with a suspected FEP within the Ribeirão Preto catchment area during the study period. Inclusion criteria were the following: (a) aged between 16–64 years; (b) presentation with a clinical diagnosis of FEP (International Classification of Diseases (ICD)-10 diagnoses F20-33), even if longstanding; (c) residing within the Ribeirão

https://doi.org/10.1017/S0033291724000199 Published online by Cambridge University Press

Preto catchment area during the study period. Exclusion criteria were: (a) previous contact with psychiatric services for psychosis; (b) FEP related to other medical conditions (ICD-10: F09); (c) transient psychotic symptoms resulting from substance intoxication/withdrawal (ICD-10: F1X.5); (d) severe learning disabilities (intelligent quotient <50 or diagnosis of intellectual disability, ICD-10: F70-79).

First-degree biological siblings of patients aged 16–64 years and residing within the same catchment area of cases were invited to participate in the study following the patients' agreement. Community controls aged 16–64 years were recruited using a quota-sampling method according to the Brazilian Official Census Bureau 2010 (www.ibge.gov.br) with stratification by age and sex to ensure representativeness of the Ribeirão Preto catchment area's population at risk. Siblings of patients and community controls were only excluded if they had a lifetime history of psychosis or had ever been treated for psychosis. Per the EU-GEI protocol, those with a current or previous history of other mental disorders were not excluded to ensure the representativeness of the catchment area under study (Gayer-Anderson et al., 2020).

For the present investigation, we discussed with a rheumatologist to identify medical conditions that could potentially influence the biological variables of interest. Consequently, we excluded participants who, either at the time of blood collection or during the past month, were receiving treatment with anti-inflammatory or immunosuppressive medications, were pregnant or lactating, and had chronic or acute immunological or inflammatory medical conditions. These excluded conditions encompassed but were not limited to nephropathy, urinary tract infection, dengue fever, rheumatic fever, human immunodeficiency virus, syphilis, Crohn's disease, throat infection, multiple sclerosis, pneumonia, hidradenitis suppurative; for details see (Corsi-Zuelli et al., 2020; Corsi-Zuelli et al., 2022a, 2022b). To further minimize the effect of confounding by infection or chronic inflammatory illness, we excluded participants with hs-CRP levels >10 mg/L (FEP $n = 14$; unaffected sibling $n = 6$; community control $n = 21$), as suggested in the literature (Perry et al., 2021). A total of 134 FEP patients, 66 unaffected siblings, and 235 community controls had complete data on immune proteins and dimensions of psychopathology. However, genotype data were missing for 24 FEP patients, 14 unaffected siblings, and 35 community controls. These participants were excluded from the analyses investigating associations between symptom dimensions and immune proteins, leaving 362 participants.

Sociodemographic and clinical assessment

We used the Medical Research Council Sociodemographic Schedule (Mallet, 1997) for the acquisition of sociodemographic and clinical data, the Structured Clinical Interview for DSM-IV clinical version (Del-Ben et al., 2001; First, 1997) for diagnosis assessment, the Brief Psychiatry Rating Scale (BPRS) (Crippa, Sanches, Hallak, Loureiro, & Zuardi, 2001; Overall & Gorham, 1962) to measure illness severity, and the Nottingham Onset Schedule (Singh et al., 2005) for registration of psychosis onset date and pharmacological treatment starting date. Given the influence of smoking on inflammation (Yuan, Chen, Xia, Dai, & Liu, 2019), we used the Composite International Diagnostic Interview (Robins et al., 1988) to register the history of tobacco smoking during the last 12 months relative to the interview, and added this variable as a covariate in our analyses.

Subclinical and clinical dimensions of psychopathology

The Community Assessment of Psychic Experiences

For unaffected siblings of patients and community controls, three dimensions of PEs (positive, negative, and depressive) and a general dimension were evaluated using the Community Assessment of Psychic Experiences (CAPE) (Ragazzi et al., 2020; Stefanis et al., 2002). CAPE is a self-report instrument consisting of 42 items rated on a four-point Likert scale (1–4; never to nearly always) used to evaluate the frequency of psychotic experiences (PEs). Although it is a self-report instrument, the evaluation of PEs in our studied site occurred with the close supervision of a mental health specialist to ensure the quality of assessment.

The Operational Criteria System

For FEP patients, we used the Operational CRITeria (OPCRIT) system (McGuffin, Farmer, & Harvey, 1991) to assess psychopathology and generate symptom dimensions (general, delusion, hallucination, negative, disorganization, manic, depressive). The OPCRIT system consists of a checklist with 59 items related to examining the mental state that can be filled using different sources, including clinical interviews or case records, allowing the establishment of diagnoses based on algorithms.

Blood immune proteins

Cytokines and hs-CRP were measured in plasma. For cytokines, we used panels assessing the inflammatory (IL-1β, IL-6, TNF-α, IFN-γ) and compensatory systems (TGF-β, IL-10, and IL-4), quantified using the Milliplex MAP human cytokine/chemokine magnetic bead panels. For more information, see Supplementary Material and our previous publications (Corsi-Zuelli et al., 2020; Corsi-Zuelli et al., 2022a, 2022b). hs-CRP levels were measured using the latex immunoturbidimetric method according to the manufacturer's instructions with a detection limit of 0.1 mg/L (Wiener Laboratorios, Rosario, Argentina).

Schizophrenia Polygenic Risk Score

Genotyping of the present sample was carried out at the MRC Centre for Neuropsychiatric Genetics and Genomics in Cardiff (UK) using a custom Illumina HumanCoreExome-24 BeadChip array which included 570 038 genetic variants (Quattrone et al., 2021a, 2021b), and detailed in the Supplementary Material.

Statistical analyses

Demographic and clinical data

We used Pearson's Chi-square test to compare differences in categorical data (self-reported ethnicity, years of study, and tobacco smoking) across FEP patients, their unaffected siblings and community controls. For continuous data, quantile–quantile (Q-Q) plots and histograms were examined for inspection of the Gaussian Distribution. Parametric (CAPE) and non-parametric data (age, body mass index (BMI), and BPRS) were analyzed using a One-way Analysis of Variance or Kruskal–Wallis test, respectively, with Bonferroni post-hoc when appropriate.

Subclinical and clinical dimensions of psychopathology

The estimation of subclinical and clinical dimensions of psychopathology is fully described in previous publications of the

https://doi.org/10.1017/S0033291724000199 Published online by Cambridge University Press

EU-GEI consortium (Quattrone et al., 2019; Quattrone et al., 2021a, 2021b). Briefly, two bifactor models were estimated in Mplus, version 7.4 (Muthén & Muthén, 2012) based on the associations among self-ratings of psychotic experiences in non-clinical samples (CAPE data) and observer ratings of psychotic symptoms in patients (OPCRIT data). Model fit statistics Log-Likelihood (LL), Akaike information criterion (AIC), Bayesian information criterion (BIC), and Sample-size Adjusted BIC (SABIC) of the bifactor solutions were compared with other solutions (i.e. unidimensional, multidimensional and hierarchical models). Then, the reliability and strength indices of the bifactor models were estimated using McDonald's omega (ω) (Rodriguez, Reise, & Haviland, 2016), omega hierarchical (ω H)) (Rodriguez et al., 2016), and index H (Hancock & Mueller, 2001). Using the 'FSCORE' function in M*plus*, factor scores were computed for (1) one general psychotic experience dimension and three specific dimensions of positive, negative, and depressive psychotic experiences for non-clinical samples; and (2) one general psychotic symptom dimension and six specific dimensions of delusions, hallucinations, negative, disorganization, manic, and depressive symptoms for patients. Please refer to (Quattrone et al., 2019; Quattrone et al., 2021a, 2021b) for further details.

Subclinical and clinical dimensions of psychopathology and immune proteins

We evaluated associations between subclinical and clinical dimensions of psychopathology with immune proteins separately in FEP patients, unaffected siblings, and community controls. For that, we used generalized linear models with robust estimators. In the FEP group, outcome variables were one general and six specific dimensions of delusion, hallucination, negative, disorganization, manic, and depressive symptoms derived from the OPCRIT. For unaffected siblings and community controls, outcomes variables were one general and three specific dimensions of positive, negative, and depressive experiences derived from the CAPE. Independent variables included data on eight immune proteins, both inflammatory (IL-1β, IL-6, TNF-α, IFN-γ, hsCRP) and regulatory (TGF-β, IL-10, and IL-4). Immune protein data were natural log-transformed and z-scored. Thus, regression coefficients and 95% confidence intervals (95% CI) represent changes per standard deviation (S.D.) of the exposure. All analyses were adjusted for sex, age, tobacco smoking, body mass index, SZ-PRS and five ancestry principal components. In the patient group, we additionally adjusted for the duration of pharmacological treatment.

To correct for multiple comparisons, we used the False Discovery Rate (FDR), Benjamin–Hochberg (5%) method, computed using R p.adjust function.

Schizophrenia Polygenic Risk Score (SZ-PRS)

To evaluate mean differences in SZ-PRS across the groups, values were standardized (z-scored), and we used a One-Way Analysis of Covariance (ANCOVA), including five ancestry principal components as covariates. To account for potential confounding, we additionally adjusted for age, sex, tobacco smoking, and BMI. All analyses concerning SZ-PRS were considered exploratory, given the limited sample size.

Exploratory analysis: Schizophrenia Polygenic Risk Score contribution to associations between dimensions of psychopathology and immune proteins

In the event of significant associations between clinical and subclinical dimensions of psychopathology with immune proteins, we explored how the associations would vary according to polygenic liability to schizophrenia. Study participants were stratified into terciles of SZ-PRS (top = high-risk group, middle = no genetic risk group, bottom = low genetic risk group), and the generalized linear models described before were re-run in each group.

Main analyses were performed using SPSS v.28 and R v1.3.1093, and all results were considered significant at $p \leqslant 0.05$ (two-sided).

Results

Sample characteristics

Differences among the groups on socio-demographic data are detailed in Table 1.

The median of pharmacological treatment in the FEP group was thirteen weeks, and the patients were relatively stable at the time of assessment (BPRS mean [S.D.]: 8.8 [6.8]).

The Community Assessment of Psychic Experiences: group comparison

Unaffected siblings and community controls did not differ in any of the four CAPE dimensions ($p > 0.05$ for all). These results are detailed in online Supplementary Table 1.

Exploratory analysis: Schizophrenia Polygenic Risk Score group comparison

We found that FEP participants and their unaffected siblings did not differ in their SZ-PRS mean values. However, both FEP participants and their unaffected siblings had higher SZ-PRS than community controls. The results remained similar after including sex, age, tobacco smoking, and BMI in the model (Fig. 1).

Subclinical and clinical dimensions of psychopathology by immune proteins

Unaffected siblings

High IFN-γ (B [S.E.] = 0.84 [0.25]; FDR = 0.008) and low IL-4 levels (B [S.E.] = −0.28 [0.09] FDR = 0.008) were associated with the CAPE general dimension. Low IL-6 (B [S.E.] = −0.20 [0.08]; FDR = 0.044) and high TNF-α (B [S.E.] = 0.29 [0.11]; FDR = 0.044) were associated with the CAPE positive dimension. In addition, both low IL-6 (B [S.E.] = −0.22 [0.08]; FDR = 0.021) and IL-1β (B [S.E.] = −0.30 [0.09]; FDR = 0.008), but high IFN-γ levels (B [S.E.] = 0.54 [0.15]; FDR = 0.008) were related to the CAPE depressive dimension. There was a marginal association between low IL-10 levels and the CAPE negative dimension, but this did not survive FDR correction (B [S.E.] = −0.07 [0.11]; $p = 0.052$; FDR = 0.416). These results are presented in Figs 2A-D and online Supplementary Table S2.

Community controls

Similar to unaffected siblings, the CAPE general dimension was associated with high IFN-γ levels (B [S.E.] = 0.19 [0.07]; FDR = 0.024) in community controls. We also observed that IL-1β was negatively related to the general dimension, although this

https://doi.org/10.1017/S0033291724000199 Published online by Cambridge University Press

Table 1. Socio-demographic and clinical variables ($n = 435$)

Variables	FEP ($n = 134$)	Siblings ($n = 66$)	Controls ($n = 235$)	p
Males, n (%)[1]	89 (66.4)	21 (31.8)	126 (53.6)	**<0.001**[a,b,c]
Age, mean (s.d.)[2]	29.9 (11.9)	31.7 (10.7)	31.6 (11.4)	0.131
Self-reported ethnicity (white), n (%)[1]	67 (50.0)	33 (50.0)	153.0 (65.1)	**0.006**[b,c]
Years of study (⩾9 years), n (%)[1]	59 (44.0)	47 (71.2)	182 (77.4)	**<0.001**[a,b]
Body mass index (kg/m^2), mean (s.d.)[2]	24.3 (4.3)	25.3 (4.9)	26.0 (5.2)	**0.012**[b]
Tobacco smoking (yes), n (%)[1]	50 (37.3)	11 (16.7)	42 (17.9)	**<0.001**[a,b]
Psychosis onset age, mean (s.d.)	28.9 (11.8)	-	-	-
DUP (weeks), median (min-max)	10.0 (0–1292)	-	-	-
Pharmacological treatment (weeks), median (min-max)	13.0 (0–155)	-	-	-
Duration of psychosis (weeks), median (min-max)	34.0 (2–1394)	-	-	-
BPRS, mean (s.d.)[2]	8.8 (6.8)	0.9 (2.2)	0.8 (1.9)	**<0.001**[a,b]
Antipsychotics (AP)	57 (42.5)	-	-	-
Antidepressants (AD)	1 (0.8)	-	-	-
Mood stabilizers (MS)	2 (1.5)	-	-	-
AP + AD	22 (16.4)	-	-	-
AP + MS	35 (26.1)	-	-	-
AP + AD + MS	8 (6.0)	-	-	-
None	9 (6.7)	-	-	-
Type of antipsychotics, n (%)				
First generation				
Haloperidol	55 (41.0)	-	-	-
Chlorpromazine	5 (3.7)	-	-	-
Haloperidol decanoate	1 (0.7)	-	-	-
Second generation				
Risperidone	33 (24.6)	-	-	-
Olanzapine	18 (13.4)	-	-	-
Quetiapine	8 (6.0)	-	-	-
Clozapine	1 (0.7)	-	-	-
Ziprasidone	1 (0.7)	-	-	-
No antipsychotics	12 (8.96)	-	-	-

[1]Pearson's Chi-square test; [2]Kruskal–Wallis (with Bonferroni post-hoc when appropriate).
Pairwise comparison: [a]FEP *v.* Siblings; [b]FEP *v.* Controls; [c]Siblings *v* Controls.
SD, Standard deviation; FEP, First-episode psychosis; BPRS, Brief Psychiatric Rating Scale.
Significant results are highlighted in bold.

association did not survive FDR correction (B [s.e.] = −0.18 [0.08]; FDR = 0.124). In addition, low TGF-β related to the positive dimension (B [s.e.] = −0.14 [0.05]; FDR = 0.048). No other significant results were found in community controls. These results are presented in Figs 2A-D and online Supplementary Table S3.

First episode psychosis

We found that higher IFN-γ levels were associated with the manic symptom dimension (B [s.e.] = 0.29 [0.09]; FDR = 0.008) and lower TNF-α levels were associated with the depressive symptom dimension (B [s.e.] = −0.31 [0.10]; FDR = 0.008). Other associations did not survive the FDR correction, including a positive trend between IL-1β and the negative symptom dimension (B [s.e.] = 0.25 [0.10]; $p = 0.013$; FDR = 0.117), a positive and negative trend between TNF-α (B [s.e.] = 0.23 [0.11]; $p = 0.031$; FDR = 0.093) and IL-10 (B [s.e.] = −0.23 [0.10]; $p = 0.017$; FDR = 0.077) with the manic symptom dimension, respectively, and a positive trend between IL-6 and the depressive dimension (B [s.e.] = 0.17 [0.08]; $p = 0.032$; FDR = 0.144). These results are presented in Figs 3A-G and online Supplementary Table S4.

https://doi.org/10.1017/S0033291724000199 Published online by Cambridge University Press

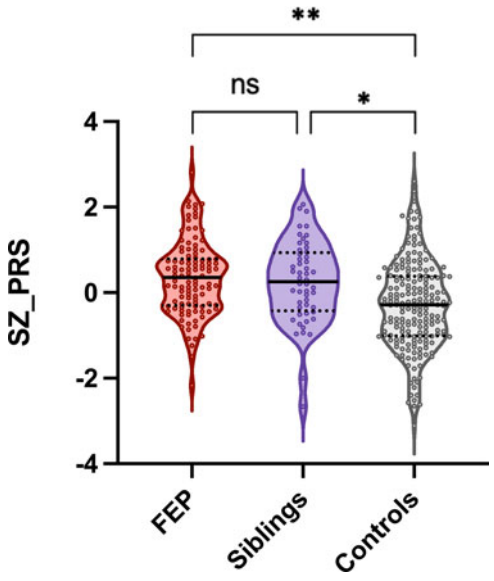


Figure 1. Group differences in schizophrenia polygenic risk score (SZ-PRS).Univariate analysis of covariance with Bonferroni post-hoc, adjusted for five ancestry principal components. Values were standardized (z-scored).FEP, first episode psychosis.Adjusted for ancestry principal components: $^{**}p < 0.001$; $^{*}p = 0.035$; ns: non-significant ($p > 0.05$).Adjusted for ancestry principal components, age, sex, tobacco smoking, and BMI: $^{**}p < 0.001$; *0.047; ns: non-significant ($p > 0.05$).

Exploratory analyses: Variability of associations by Schizophrenia Polygenic Risk Score

Previous associations that survived FDR correction were evaluated according to participants' SZ-PRS terciles and are detailed in online Supplementary Table 5.

Unaffected siblings

More than a third of siblings were classified with high polygenic liability ($n = 18$; 34.6%) and around the same proportion with low polygenic liability ($n = 17$; 32.7%).

Regarding the general dimension of PEs, we observed that the negative association with IL-4 only occurred in individuals at the top tercile of SZ-PRS (B [S.E.] = −0.21 [0.08]; $p = 0.005$) but not in those at the middle ($p > 0.05$) and bottom ($p > 0.05$) terciles. The IFN-γ association was significant and positively related to the general dimension in both those at the top (B [S.E.] = 0.53 [0.25]; $p = 0.032$) and bottom (B [S.E.] = 1.42 [0.57]; $p = 0.012$) terciles.

Regarding the positive dimension of PEs, associations with IL-6 differed according to the degree of SZ-PRS. Individuals at the top tercile presented a positive association (B [S.E.] = 0.18 [0.08]; $p = 0.030$), while a negative association was observed for those at the bottom tercile (B [S.E.] = −0.28 [0.14]; $p = 0.048$). Concerning TNF-α, significant positive associations were seen in those at the top tercile of SZ-PRS only (B [S.E.] = 0.59 [0.13]; $p < 0.01$).

Regarding the depressive dimension of PEs, associations with IFN-γ differed according to the degree of SZ-PRS. Those at the top tercile presented a positive association (B [S.E.] = 0.46 [0.21]; $p = 0.029$), while a negative association was observed for those at the bottom tercile (B [S.E.] = −1.73 [0.50]; $p < 0.01$). The IL-6 and IL-β associations with the depressive dimension were irrespective of the degree of SZ-PRS.

Community controls

More than half of community controls were classified as having a low polygenic liability to schizophrenia ($n = 110$; 55%), and the minority with high polygenic liability ($n = 32$; 16%).

In community controls, the previously observed association between IFN-γ and CAPE general dimension was only significant in those at the top tercile of SZ-PRS (B [S.E.] = 0.66 [0.14]; $p < 0.01$) but not in those in the middle or bottom terciles ($p > 0.05$ for both).

However, the previously negative association observed for TGF-β and the positive dimension was irrespective of the degree of SZ-PRS.

First-episode psychosis

More than a third of patients were classified with high polygenic liability ($n = 38$; 34.5%), and around the same proportion with low polygenic liability ($n = 33$; 30%).

The observed association between IFN-γ and manic symptoms dimension was significant and positive for those at the top (B [S.E.] = 0.29 [0.10]; $p = 0.003$) and bottom (B [S.E.] = 0.26 [0.13]; $p = 0.040$) terciles. TNF-α association with the OPCRIT depressive dimension was irrespective of the degree of SZ-PRS.

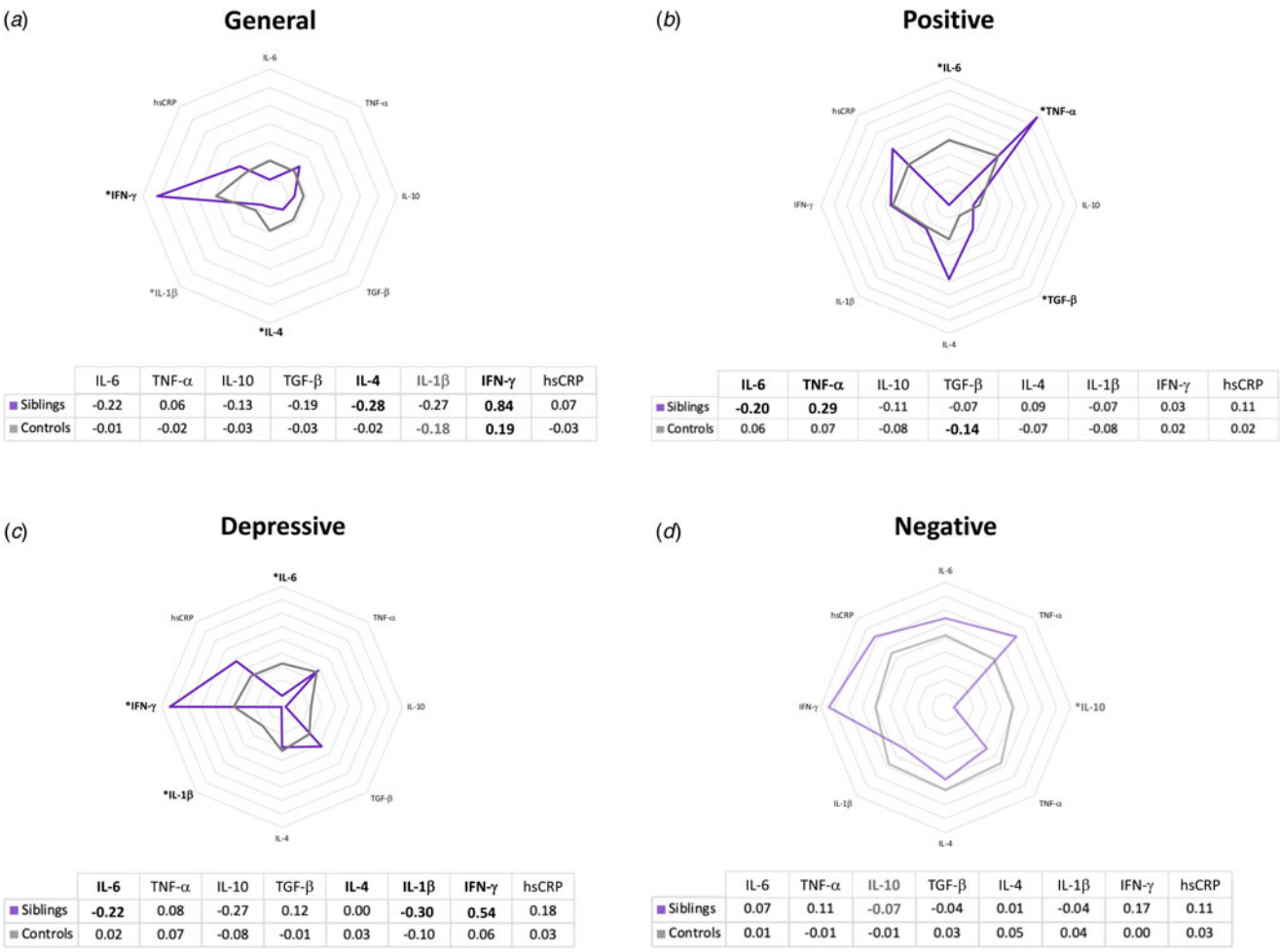
Discussion

Our study sought to investigate the involvement of immune proteins in the multidimensional expression of psychosis and the contribution of schizophrenia polygenic liability in the associations. We provide evidence that both inflammatory and regulatory immune proteins map onto dimensions of psychopathology in both clinical and community samples with some variability by polygenic liability to schizophrenia. We also noticed that among non-clinical samples, most associations were seen in first-degree relatives of patients, supporting a role for familial liability. The results align with the view that psychosis exists on a *continuum* and that PEs experienced by the general population have similar biological substrates to clinical disorders. Our findings also reinforce that immune dysregulation goes beyond the traditional nosology by impacting the pathogenesis of symptom domains that cut across diagnostic categories, as reflected in associations between immune proteins with the depressive dimension in FEP patients and unaffected siblings and manic dimension in patients.

Immune dysfunction in the continuity of psychosis

Meta-analyses of cross-sectional studies have demonstrated elevated levels of cytokines and other inflammatory proteins in the blood of patients with psychosis and depression, compared with controls (Çakici et al., 2020; Goldsmith et al., 2016). Large prospective cohort studies indicate that heightened concentrations of IL-6 during childhood or adolescence precede the onset of symptoms and are associated with an increased risk for both disorders in adulthood (Giollabhui, Ng, Ellman, & Alloy, 2021; Khandaker, Pearson, Zammit, Lewis, and Jones, 2014). Nevertheless, there is scarce evidence regarding the association between a immune protein profile and specific patterns of symptomatology across the psychosis spectrum. Our bifactorial model allowed us to capture for the first time that alterations in IL-6 and immune proteins upstream the IL-6 pathway (e.g. IL-1β and TNF-α) extend to subclinical positive and depressive symptoms, particularly in vulnerable individuals such as first-degree relatives,

https://doi.org/10.1017/S0033291724000199 Published online by Cambridge University Press



	IL-6	TNF-α	IL-10	TGF-β	IL-4	IL-1β	IFN-γ	hsCRP
Siblings	-0.22	0.06	-0.13	-0.19	**-0.28**	-0.27	**0.84**	0.07
Controls	-0.01	-0.02	-0.03	-0.03	-0.02	-0.18	**0.19**	-0.03

	IL-6	**TNF-α**	IL-10	TGF-β	IL-4	IL-1β	IFN-γ	hsCRP
Siblings	**-0.20**	**0.29**	-0.11	-0.07	0.09	-0.07	0.03	0.11
Controls	0.06	0.07	-0.08	**-0.14**	-0.07	-0.08	0.02	0.02

	IL-6	TNF-α	IL-10	TGF-β	**IL-4**	**IL-1β**	**IFN-γ**	hsCRP
Siblings	**-0.22**	0.08	-0.27	0.12	0.00	**-0.30**	**0.54**	0.18
Controls	0.02	0.07	-0.08	-0.01	0.03	-0.10	0.06	0.03

	IL-6	TNF-α	IL-10	TGF-β	IL-4	IL-1β	IFN-γ	hsCRP
Siblings	0.07	0.11	-0.07	-0.04	0.01	-0.04	0.17	0.11
Controls	0.01	-0.01	-0.01	0.03	0.05	0.04	0.00	0.03

Figure 2. Association between CAPE (**a**) general, (**b**) positive, (**c**) depressive, and (**d**) negative dimensions with immune proteins in unaffected siblings of patients (purple; $n = 52$) and community-based controls (gray; $n = 200$).The spider plot exhibits a distinct spoke for each cytokine, with the spokes evenly dispersed around the wheel. As the spike extends towards the outer edge, the standardized B coefficients increase in magnitude.The table displays the standardized B coefficient values of the generalized linear model. **Significant results (false discovery rate, Benjamin–Hochberg 5%) are depicted in bold.** The faint bold color indicates significance before FDR correction.

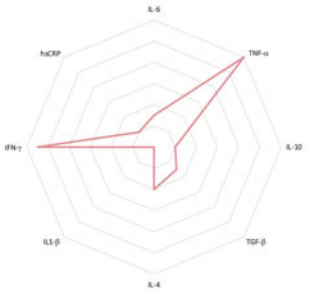
confirming a transdiagnostic role for IL-6 and its pathways along the *continuum*.

Siblings of patients may represent endophenotypes of the disease because they can display biological dysfunction similar to the probands and subclinical psychiatric symptoms without fulfilling the diagnostic criteria (Lichtenstein et al., 2009; Noyan et al., 2021). One important consideration is that, in our study, the unaffected siblings did not differ from community controls in the mean scores for general or specific dimensions of PEs. A hypothetical explanation is that the recruited siblings were the caregivers and, therefore, healthy relatives. However, our findings are consistent with a study showing that rates of PEs do not significantly differ between relatives and non-relatives of probands (Landin-Romero et al., 2016). On the other hand, our SCZ-PRS findings confirm a significant polygenic liability to schizophrenia among siblings, evidenced by higher means in patients and their siblings compared to controls, consistent with prior research (Ahangari et al., 2022a; Ahangari et al., 2022b; Ohi et al., 2020, 2022).

The only previous study that simultaneously assessed clinical and subclinical symptom dimensions and their association with immune proteins found elevated IL-1β levels associated with the severity of psychotic symptoms in established schizophrenia, with a similar trend in their siblings. Different from our study, these measurements were obtained through total scores of the Comprehensive Assessment of Symptoms, for evaluation of clinical symptoms in patients, and the History and the Structured Interview for Schizotypy-Revised, for the evaluation of subclinical symptoms in siblings (Noyan et al., 2021). In our study, the negative association between IL-1β with the subclinical depressive dimension, and between IL-6 with the subclinical positive and depressive dimensions in vulnerable siblings may offer distinct yet complementary interpretations. One is that IL-1β and IL-6 are designated state immune markers (Capuzzi et al., 2017; Miller et al., 2011). Hence, their levels are not stable and may fluctuate along the *continuum*, with associations turning positive only when transiting to full-blown psychosis or during acute states. In fact, we identified positive associations between IL-6 levels and depressive symptoms and between IL-1β and negative symptoms in FEP (although these did not survive FDR correction). One important limitation in our patient sample is that, although these were early-stage psychosis, they were not free of antipsychotic treatment. Meta-analyses show that levels of state markers such as IL-6 and IL-1β tend to decrease with antipsychotic

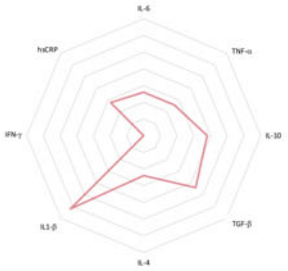
https://doi.org/10.1017/S0033291724000199 Published online by Cambridge University Press

(*a*) **General**



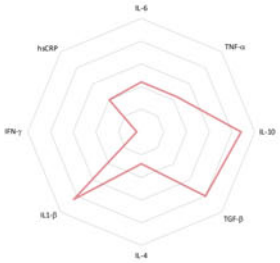
	IL-6	TNF-α	IL-10	TGF-β	IL-4	IL-1β	IFN-γ	hsCRP
General	0.01	0.10	0.00	0.01	0.02	-0.02	0.09	0.00

(*b*) **Delusion**



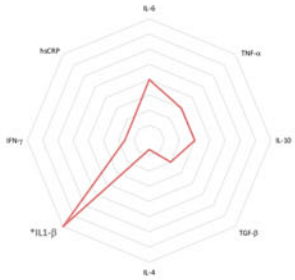
	IL-6	TNF-α	IL-10	TGF-β	IL-4	IL-1β	IFN-γ	hsCRP
Delusion	-0.02	-0.02	0.04	0.07	-0.03	0.16	-0.15	-0.01

(*c*) **Hallucination**



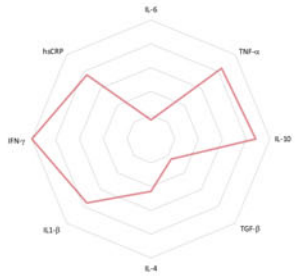
	IL-6	TNF-α	IL-10	TGF-β	IL-4	IL-1β	IFN-γ	hsCRP
Hallucination	0.01	0.01	0.12	0.1	-0.03	0.11	-0.09	0.00

(*d*) **Negative**



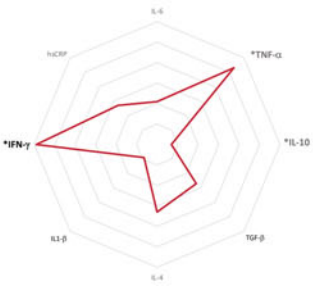
	IL-6	TNF-α	IL-10	TGF-β	IL-4	IL-1β	IFN-γ	hsCRP
Negative	0.05	0.00	0.00	-0.05	-0.12	-0.25	-0.07	-0.07

(*e*) **Disorganisation**



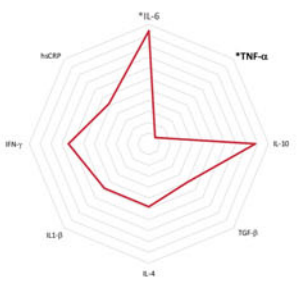
	IL-6	TNF-α	IL-10	TGF-β	IL-4	IL-1β	IFN-γ	hsCRP
Disorganisation	-0.11	0.06	0.07	-0.09	-0.04	0.04	0.10	0.04

(*f*) **Manic**



	IL-6	TNF-α	IL-10	TGF-β	IL-4	IL-1β	**IFN-γ**	hsCRP
Mania	-0.09	0.23	-0.23	-0.03	0.03	-0.21	**0.29**	-0.03

(*g*) **Depressive**



	IL-6	**TNF-α**	IL-10	TGF-β	IL-4	IL-1β	IFN-γ	hsCRP
Depression	0.17	**-0.31**	0.14	-0.10	-0.06	-0.06	0.02	-0.09

Figure 3. Association between OPCRIT (**a)** general, (**b)** delusion, (**c)** hallucination, (**d)** negative, (**e)** disorganization, (**f)** manic, and (**g)** depressive dimensions with inflammatory proteins in first episode psychosis patients ($n = 110$).The spider plot exhibits a distinct spoke for each cytokine, with the spokes evenly dispersed around the wheel. As the spike extends towards the outer edge, the standardized B coefficients increase in magnitude.The table displays the standardized B coefficient values of the generalized linear model. **Significant results (false discovery rate, Benjamin–Hochberg 5%) are depicted in bold.** The faint bold color indicates significance before FDR correction.

https://doi.org/10.1017/S0033291724000199 Published online by Cambridge University Press

treatment (Capuzzi et al., 2017; Miller et al., 2011). The other interpretation may relate to different actions and pathways of these immune proteins. For example, IL-6 *'trans-signalling'* involves IL-6 binding to its soluble receptor and is responsible for most of its pathogenic actions (Rose-John, Winthrop, & Calabrese, 2017). However, it is widely known that IL-6 has physiological roles for neuronal development and function mediated mainly through its protective membrane-bound *'classic signalling'* (Kummer, Zeidler, Kalpachidou, & Kress, 2021). The negative associations in siblings could, therefore, reflect a failure in the protective IL-6 pathway, which may function as a gateway for future dysregulation of the pathogenic *'trans-signalling'* pathway and subsequent manifestation of full-blown psychosis (Hartwig, Borges, Horta, Bowden, & Davey Smith, 2017).

Different from previous studies, we were also able to evaluate the contribution of other immune proteins along the *continuum*. An interesting discovery was the positive association between the general dimension with IFN-γ in both unaffected siblings and community controls. This association was stronger for first-degree relatives, expanding to the depressive dimension in this group. The general dimension is the covariance among all items and can be a useful representation of the mood-psychosis spectrum (Quattrone et al., 2019). Our findings seem to align with a hypothesis that IFN-γ may be a potential trait marker for psychosis, as longitudinally evaluated in drug-naïve FEP and acute exacerbations (Capuzzi et al., 2017; Miller et al., 2011). TNF-α, which we found to be positively associated with the positive dimension in siblings, has also been designated as a trait marker for psychosis when evaluated in drug-naïve FEP and acute exacerbations (Capuzzi et al., 2017; Miller et al., 2011). Interestingly, in our minimally treated and relatively stable FEP patients, only the two previously described trait markers remained significant after FDR correction, IFN-γ with the manic dimension and TNF-α with the depressive dimension. These significant findings between cytokines and affective dimensions in FEP align with evidence that psychotic disorders, MDD, and BD share commonalities in genetic, inflammatory and clinical features that converge in a transdiagnostic conceptualization (Wei et al., 2022).

Finally, we found a negative association between IL-4 and the general dimension in siblings, in addition to a negative association between TGF-β and the positive dimension in controls. These findings would align with a T-cell imbalance hypothesis of psychosis, which claims that T helper lymphocytes type 2 (Th-2)-producing anti-inflammatory IL-4 (Kim et al., 2004) and protective regulatory T cells producing TGF-β (Corsi-Zuelli & Deakin, 2021; Corsi-Zuelli et al., 2021) fail to counteract the inflammatory actions of pathogenic Th1 cells and monocytes, resulting in disinhibited production of trait cytokines such as IFN-γ and TNF-α, and state cytokines such as IL-6 and IL-1β.

Altogether, our results indicate that innate immune proteins related to the IL-6 pathway (IL-6, TNF-α, IL-1β) and adaptive T cell-related proteins (IFN-γ, IL-4, TGF-β) may be biological contributors to the multidimensional mood-psychosis spectrum. Our hypothetical model is summarized in Fig. 4.

Polygenic threshold and the immune-psychosis spectrum

Our exploratory analyses suggested that associations between immune proteins and symptom dimensions significantly varied according to the degree of polygenic liability to schizophrenia across the three studied subgroups. This variability occurred for both innate and adaptive cytokines but was mainly observed for the psychotic dimension, in which most of the significant associations occurred primarily in those at the top tercile of SZ-PRS. Intriguing, in the sibling group, those at the highest genetic risk displayed a positive association between the positive dimension and both IL-6 and TNF-α, whereas those at the lowest genetic risk had a negative association with IL-6 in this dimension. These different directions of associations across the genetic groups – with positive associations only seen in the highest genetic group – support our previously discussed hypothesis of positive associations reflecting dysregulation in cytokines' pathogenic pathways only in those at higher risk for the disease. Longitudinal studies are needed to clarify if siblings with high SZ-PRS and raised immune proteins are those who later transition to psychosis.

Associations with the affective dimensions tended to be irrespective of SZ-PRS, particularly between the depressive dimension and innate cytokines (IL-6, IL-1β, and TNF-α). These findings suggest that positive and general dimensions of psychosis may have a greater genetic and familial basis in their association with both innate and adaptive immune proteins than affective dimensions. The independence of the depressive dimension from SZ-PRS in its association with innate cytokines may indicate the influence of other but still unknown factors that may be shared across disorders and impact the functioning of the innate immune system (e.g. environmental factors such as stress) (Corsi-Zuelli et al., 2022a, 2022b).

Finally, we noted an interdependency of the adaptive cytokine IFN-γ to SZ-PRS in its positive association with the general dimension (community controls and siblings) and affective dimension (particularly manic in FEP and depression in siblings). Noteworthy, in the control group, for which the sample size (n = 200) was slightly greater compared to FEP patients (n = 110) and siblings (n = 52), significant associations were only found for those at the top tercile of SZ-PRS, but not in those in the middle or bottom terciles. In addition, in the FEP group, associations for those in the top tercile were slightly greater than those at the bottom tercile. While these findings are exploratory, they appear to align with the concept of IFN-γ being a trait marker in psychosis, irrespective of the stage of illness. Our study now offers novel evidence that extends to the transdiagnostic continuity spectrum.

Altogether, our exploratory results suggest that genetic liability to schizophrenia influences the immune phenotype of transdiagnostic dimensions in psychosis.

Strengths and limitations

Our study is the first to investigate associations between immune proteins along the extended psychosis phenotype using multidimensional models to help unravel the heterogeneity of the psychotic phenomena. Instead of relying on total scores, our item response modeling and factor analysis enabled us to generate one general factor representing the mood-psychosis spectrum, and a set of specific factors to estimate the transdiagnostic expression of psychosis. Many of the generated factors had not been evaluated in their associations with immune proteins before. In addition, previous studies were mainly focused on CRP and IL-6. We expanded that by including both regulatory and inflammatory cytokines. Moreover, we examined for the first time the contribution of polygenic liability to schizophrenia in the immune-psychosis spectrum. Finally, our community controls were recruited based on the representativeness of the catchment

https://doi.org/10.1017/S0033291724000199 Published online by Cambridge University Press

area's population at risk, and we additionally recruited unaffected siblings of patients to investigate disease endophenotypes.

Important limitations should be acknowledged. First, although we considered first-stage individuals with psychosis to minimize the masking effects of long-term treatment and illness duration, the patients were not free of pharmacological treatment. The inclusion of their first-degree siblings was an advantage to that limitation, although we recognize that our sibling sample was smaller. Furthermore, even though we used transdiagnostic dimensional approaches, we recognize limitations. For example, we could not capture the full extent of the negative symptom dimension with the OPCRIT and CAPE. The structure of negative symptoms comprises at least two subdomains of diminished (a) expressivity and (b) motivation and pleasure, each encompassing distinct mechanisms (Strauss et al., 2013), and that would require more specific assessment scales. Finally, we treated the SZ-PRS analyses as exploratory because our total sample size was not extensive. There are several important considerations for future research. Firstly, the findings from this study should be replicated and validated in larger samples. Item response modeling and factor analysis have proven valuable in our investigation, and their application in future studies could help establish the robustness and generalizability of the observed associations. Moreover, longitudinal studies are essential to shed light on the progression of psychosis and the potential transition from non-clinical to clinical states.

Conclusions and future perspectives

Our study delves into the intricate relationship between the immune system and the multidimensional expression of psychosis. By examining both clinical and non-clinical samples, we have identified significant associations between innate and adaptive inflammatory and regulatory immune proteins with the transdiagnostic multidimensional expression of psychosis, observing some variability by polygenic liability to schizophrenia. Our research contibutes to the understanding of the extended psychosis phenotype, oppening new avenues for further exploration.

Comprehending the trajectory of individuals with high polygenic risk scores and specific immune profiles could be an important step in predicting and preventing the onset of psychosis. Understanding the immune system, particularly at early stages or before illness onset, may shed light on mechanisms of

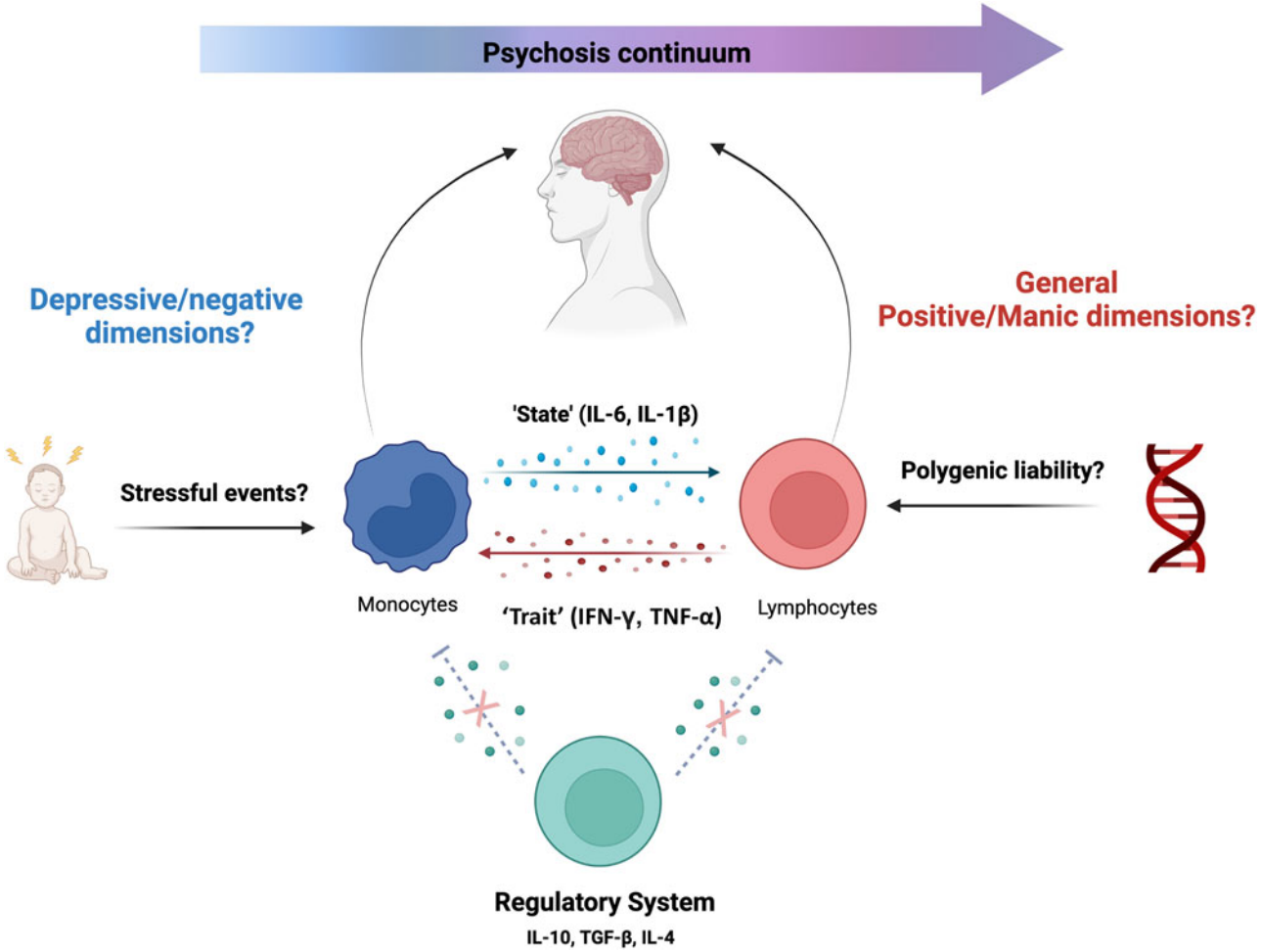


Figure 4. Hypothetical model and summary of main findings. A heightened polygenic predisposition to psychosis may activate the adaptive immune system (e.g. lymphocytes in red), contributing to the release of trait markers such as IFN-γ and TNF-α that associate with psychotic dimensions along the *continuum*. The substantial crosstalk between both arms of the immune system (innate and adaptive) releases the activity of innate immune cells (e.g. monocytes in blue) that produce 'state' markers such as IL-6 and IL-1β that are relevant to negative, depressive, and other transdiagnostic dimensions. Early-life stressors (not investigated in our study) may exacerbate the hidden genetic liability to immune deregulation. Failure in the regulatory immune system (green), producing anti-inflammatory and regulatory cytokines (e.g. IL-4, IL-10, TGF-β), sustains the inflammatory disinhibition.

https://doi.org/10.1017/S0033291724000199 Published online by Cambridge University Press

disease pathophysiology to improve diagnosis, prognosis and development of novel personalized treatments.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724000199.

Acknowledgements. We acknowledge Giuliana Bertozi for the technical support during cytokine measurement.

Authors' contributions. F.C.Z. interpreted critically all the results of the study for important intellectual content to write a first draft of the manuscript; revised the manuscript critically; performed statistical analyses; measured cytokines in human plasma with technical supervision; created the figures and tables and responded to reviewers' questions. D.Q revised the manuscript critically, generated clinical and subclinical dimensions and computed the SZ-PRS for statistical analyses. C.M.L. and T.C.C.R. critically revised the manuscript and participated in data collection. R.S. contributed to the management of data collected and ethical aspects. P.R.M., P.L.J., and C.M.D.B. conceptualized the clinical work and critically revised the manuscript.

Funding statement. This work received financial support from the São Paulo Research Foundation – FAPESP, Brazil (grant number 2012/05178-0), the National Council for Scientific and Technological Development – CNPq, Brazil (grant number 476945/2012-7), and the Center for Research in Inflammatory Diseases (CRID grant number 2013/08216-2). P.L.-J., C.M.D-B., and P.R.M. are recipients of fellowships from CNPq; F.C-Z, C.M.L, and R.S. acknowledge fellowships from FAPESP (21/07448-3 and 19/13229-2, 20/15752-1, and 2013/11167-3 respectively). DQ is a recipient of a grant from MRC/UKRI (MRC CARP grant MR/W030608/1).

Competing interests. None.

References

Ahangari, M., Gentry, A. E., Irish Schizophrenia Genomics Consortium, Nguyen, T.-H., Kirkpatrick, R., Verrelli, B. C., & … Riley, B. P. (2022a). Evaluating the role of common risk variation in the recurrence risk of schizophrenia in multiplex schizophrenia families. *Translational Psychiatry*, *12*(1), 291. https://doi.org/10.1038/s41398-022-02060-3

Ahangari, M., Kirkpatrick, R., Nguyen, T.-H., Gillespie, N., Kendler, K. S., Bacanu, S.-A., … Riley, B. P. (2022b). Examining the source of increased bipolar disorder and major depressive disorder common risk variation burden in multiplex schizophrenia families. Schizophrenia (Heidelberg, *Germany)*, *8*(1), 106. https://doi.org/10.1038/s41537-022-00317-w

American Psychiatric Association, & American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed). Washington, D.C: American Psychiatric Association.

Borovcanin, M., Jovanovic, I., Radosavljevic, G., Djukic Dejanovic, S., Bankovic, D., Arsenijevic, N., & Lukic, M. L. (2012). Elevated serum level of type-2 cytokine and low IL-17 in first episode psychosis and schizophrenia in relapse. *Journal of Psychiatric Research*, *46*(11), 1421–1426. https://doi.org/10.1016/j.jpsychires.2012.08.016

Çakici, N., Sutterland, A. L., Penninx, B. W. J. H., Dalm, V. A., de Haan, L., & van Beveren, N. J. M. (2020). Altered peripheral blood compounds in drug-naïve first-episode patients with either schizophrenia or major depressive disorder: A meta-analysis. *Brain, Behavior, and Immunity*, *88*, 547–558. https://doi.org/10.1016/j.bbi.2020.04.039

Capuzzi, E., Bartoli, F., Crocamo, C., Clerici, M., & Carrà, G. (2017). Acute variations of cytokine levels after antipsychotic treatment in drug-naïve subjects with a first-episode psychosis: A meta-analysis. *Neuroscience & Biobehavioral Reviews*, *77*, 122–128. https://doi.org/10.1016/j.neubiorev.2017.03.003

Corsi-Zuelli, F., & Deakin, B. (2021). Impaired regulatory T cell control of astroglial overdrive and microglial pruning in schizophrenia. *Neuroscience and Biobehavioral Reviews*, *125*, 637–653. https://doi.org/10.1016/j.neubiorev.2021.03.004

Corsi-Zuelli, F., Deakin, B., de Lima, M. H. F., Qureshi, O., Barnes, N. M., Upthegrove, R., … Del-Ben, C. M. (2021). T regulatory cells as a potential therapeutic target in psychosis? Current challenges and future perspectives. Brain, Behavior, *&* *Immunity - Health*, *17*, 100330. https://doi.org/10.1016/j.bbih.2021.100330

Corsi-Zuelli, F., Loureiro, C. M., Shuhama, R., Fachim, H. A., Menezes, P. R., Louzada-Junior, P., … Del-Ben, C. M. (2020). Cytokine profile in first-episode psychosis, unaffected siblings and community-based controls: The effects of familial liability and childhood maltreatment. *Psychological Medicine*, *50*(7), 1139–1147. https://doi.org/10.1017/S0033291719001016

Corsi-Zuelli, F., Marques, L., da Roza, D. L., Loureiro, C. M., Shuhama, R., Di Forti, M., … Del-Ben, C. M. (2022a). The independent and combined effects of cannabis use and systemic inflammation during the early stages of psychosis: Exploring the two-hit hypothesis. *Psychological Medicine*, *52*(16), 3874–3884. https://doi.org/10.1017/S0033291721000726

Corsi-Zuelli, F., Schneider, A. H., Santos-Silva, T., Loureiro, C. M., Shuhama, R., Menezes, P. R., … Del-Ben, C. M. (2022b). Increased blood neutrophil extracellular traps (NETs) associated with early life stress: Translational findings in recent-onset schizophrenia and rodent model. *Translational Psychiatry*, *12*(1), 1–11. https://doi.org/10.1038/s41398-022-02291-4

Crippa, J. A., Sanches, R. F., Hallak, J. E., Loureiro, S. R., & Zuardi, A. W. (2001). A structured interview guide increases Brief Psychiatric Rating Scale reliability in raters with low clinical experience. *Acta Psychiatrica Scandinavica*, *103*(6), 465–470. https://doi.org/10.1034/j.1600-0447.2001.00185.x

Cross-Disorder Group of the Psychiatric Genomics Consortium. Electronic address: plee0@mgh.harvard.edu & Cross-Disorder Group of the Psychiatric Genomics Consortium. (2019). Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. *Cell*, *179*(7), 1469-1482.e11. https://doi.org/10.1016/j.cell.2019.11.020

Del-Ben, C. M., Shuhama, R., Loureiro, C. M., Ragazzi, T. C. C., Zanatta, D. P., Tenan, S. H. G., … Menezes, P. R. (2019). Urbanicity and risk of first-episode psychosis: Incidence study in Brazil. *British Journal of Psychiatry*, *215*(6), 726–729. https://doi.org/10.1192/bjp.2019.110

Del-Ben, C. M., Vilela, J. A. A., Crippa, J. A. de S., Hallak, J. E. C., Labate, C. M., & Zuardi, A. W. (2001). Confiabilidade da 'Entrevista Clínica Estruturada para o DSM-IV - Versão Clínica' traduzida para o português. *Revista Brasileira de Psiquiatria*, *23*(3), 156–159. https://doi.org/10.1590/S1516-44462001000300008

Fernandes, B. S., Steiner, J., Bernstein, H.-G., Dodd, S., Pasco, J. A., Dean, O. M., … Berk, M. (2016). C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: Meta-analysis and implications. *Molecular Psychiatry*, *21*(4), 554–564. https://doi.org/10.1038/mp.2015.87

First, M. (1997). Structured Clinical Interview for DSM-IV Axis I Disorders (Structured Clinical Interview for DSM-IV Axis I Disorders: Clinician Version (SCID-CV)) - First, Michael B.; Etc.; Gibbon, Miriam; Sptizer, Robert L.; Williams, Janet B.W: 9780880489324 - AbeBooks. Retrieved 14 April 2023, from https://www.abebooks.co.uk/9780880489324/Structured-Clinical-Interview-DSM-IV-Axis-0880489324/plp

Gayer-Anderson, C., Jongsma, H. E., Di Forti, M., Quattrone, D., Velthorst, E., de Haan, L., … Morgan, C. (2020). The European network of national schizophrenia networks studying gene-environment interactions (EU-GEI): Incidence and first-episode case–control programme. *Social Psychiatry and Psychiatric Epidemiology*, *55*(5), 645–657. https://doi.org/10.1007/s00127-020-01831-x

Giollabhui, N., Ng, T. H., Ellman, L. M., & Alloy, L. B. (2021). The longitudinal associations of inflammatory biomarkers and depression revisited: Systematic review, meta-analysis, and meta-regression. *Molecular Psychiatry*, *26*(7), 3302–3314. https://doi.org/10.1038/s41380-020-00867-4

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. *Molecular Psychiatry*, *21*(12), 1696–1709. https://doi.org/10.1038/mp.2016.3

Hancock, G. R., & Mueller, R. O. (2001). Rethinking construct reliability within latent variable systems. In R. Cudek, S. Du Toit, & D. Sorbom (Eds.), *Structural Equation Modeling: Present and Future: A Festschrift in Honor of Karl Jöreskog* (pp. 195–216). Linconlnwood, IL: Scientific Software International, Inc.

Hartwig, F. P., Borges, M. C., Horta, B. L., Bowden, J., & Davey Smith, G. (2017). Inflammatory biomarkers and risk of schizophrenia: A 2-sample

Mendelian randomization study. *JAMA Psychiatry*, *74*(12), 1226–1233. https://doi.org/10.1001/jamapsychiatry.2017.3191

Heslin, M., Lomas, B., Lappin, J. M., Donoghue, K., Reininghaus, U., Onyejiaka, A., … Doody, G. A. (2015). Diagnostic change 10 years after a first episode of psychosis. *Psychological Medicine*, *45*(13), 2757–2769. https://doi.org/10.1017/S0033291715000720

Khandaker, G. M., Pearson, R. M., Zammit, S., Lewis, G., & Jones, P. B. (2014). Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: A population-based longitudinal study. *JAMA Psychiatry*, *71*(10), 1121–1128. https://doi.org/10.1001/jamapsychiatry.2014.1332

Khandaker, G. M., Stochl, J., Zammit, S., Lewis, G., Dantzer, R., & Jones, P. B. (2021). Association between circulating levels of C-reactive protein and positive and negative symptoms of psychosis in adolescents in a general population birth cohort. *Journal of Psychiatric Research*, *143*, 534–542. https://doi.org/10.1016/j.jpsychires.2020.11.028

Kim, Y.-K., Myint, A.-M., Lee, B.-H., Han, C.-S., Lee, H.-J., Kim, D.-J., & Leonard, B. E. (2004). Th1, Th2 and Th3 cytokine alteration in schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *28*(7), 1129–1134. https://doi.org/10.1016/j.pnpbp.2004.05.047

Krynicki, C. R., Dazzan, P., Pariante, C. M., Barnes, N. M., Vincent, R. C., & Roberts, A., … BeneMin Study team. (2021). Deconstructing depression and negative symptoms of schizophrenia; differential and longitudinal immune correlates, and response to minocycline treatment. *Brain, Behavior, and Immunity*, *91*, 498–504. https://doi.org/10.1016/j.bbi.2020.10.026

Kummer, K. K., Zeidler, M., Kalpachidou, T., & Kress, M. (2021). Role of IL-6 in the regulation of neuronal development, survival and function. *Cytokine*, *144*, 155582. https://doi.org/10.1016/j.cyto.2021.155582

Landin-Romero, R., McKenna, P. J., Romaguera, A., Álvarez-Moya, E., Sarró, S., Aguirre, C., … Pomarol-Clotet, E. (2016). Examining the continuum of psychosis: Frequency and characteristics of psychotic-like symptoms in relatives and non-relatives of patients with schizophrenia. *Schizophrenia Research*, *178*(1), 6–11. https://doi.org/10.1016/j.schres.2016.07.015

Laursen, T. M., Agerbo, E., & Pedersen, C. B. (2009). Bipolar disorder, schizoaffective disorder, and schizophrenia overlap: A new comorbidity index. *The Journal of Clinical Psychiatry*, *70*(10), 1432–1438. https://doi.org/10.4088/JCP.08m04807

Lichtenstein, P., Yip, B. H., Björk, C., Pawitan, Y., Cannon, T. D., Sullivan, P. F., & Hultman, C. M. (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: A population-based study. *The Lancet*, *373*(9659), 234–239. https://doi.org/10.1016/S0140-6736(09)60072-6

Linscott, R. J., & van Os, J. (2010). Systematic reviews of categorical versus continuum models in psychosis: Evidence for discontinuous subpopulations underlying a psychometric continuum. Implications for DSM-V, DSM-VI, and DSM-VII. *Annual Review of Clinical Psychology*, *6*(1), 391–419. https://doi.org/10.1146/annurev.clinpsy.032408.153506

Linscott, R. J., & van Os, J. (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: On the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological Medicine*, *43*(6), 1133–1149. https://doi.org/10.1017/S0033291712001626

Mallet, R. (1997). MRC Sociodemographic schedule. Retrieved 14 April 2023, from https://scholar.google.com/scholar_lookup?title=Sociodemographic+Schedule&author=R+Mallett&publication_year=1997&

McGuffin, P., Farmer, A., & Harvey, I. (1991). A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. *Archives of General Psychiatry*, *48*(8), 764–770. https://doi.org/10.1001/archpsyc.1991.01810320088015

Miller, B. J., Buckley, P., Seabolt, W., Mellor, A., & Kirkpatrick, B. (2011). Meta-analysis of cytokine alterations in schizophrenia: Clinical status and antipsychotic effects. *Biological Psychiatry*, *70*(7), 663–671. https://doi.org/10.1016/j.biopsych.2011.04.013

Monshouwer, K., ten Have, M., Tuithof, M., van Dorsselaer, S., Bak, M., Gunter, N., … de Graaf, R. (2022). Prevalence, incidence, and persistence of psychotic experiences in the general population: Results of a 9-year follow-up study. *Psychological Medicine*, *53*(8), 3750–3761. https://doi.org/10.1017/S0033291722002690

Muthén, L. K., & Muthén, B. O. (2012). *Mplus: Statistical analysis with latent variables; user's guide; [version 7]* (7th ed). Los Angeles, CA: Muthén et Muthén. Retrieved from http://bvbr.bib-bvb.de:8991/F?func=service&doc_library=BVB01&local_base=BVB01&doc_number=027254870&line_number=0001&func_code=DB_RECORDS&service_type=MEDIA

Noto, C., Ota, V. K., Santoro, M. L., Ortiz, B. B., Rizzo, L. B., Higuchi, C. H., … Brietzke, E. (2015). Effects of depression on the cytokine profile in drug naïve first-episode psychosis. *Schizophrenia Research*, *164*(1–3), 53–58. https://doi.org/10.1016/j.schres.2015.01.026

Noto, M. N., Maes, M., Nunes, S. O. V., Ota, V. K., Rossaneis, A. C., Verri, W. A., … Noto, C. (2019). Activation of the immune-inflammatory response system and the compensatory immune-regulatory system in antipsychotic naive first episode psychosis. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *29*(3), 416–431. https://doi.org/10.1016/j.euroneuro.2018.12.008

Noyan, H., Erdağ, E., Tüzün, E., Yaylım, İ., Küçükhüseyin, Ö., Hakan, M. T., … Üçok, A. (2021). Association of the kynurenine pathway metabolites with clinical, cognitive features and IL-1β levels in patients with schizophrenia spectrum disorder and their siblings. *Schizophrenia Research*, *229*, 27–37. https://doi.org/10.1016/j.schres.2021.01.014

Ohi, K., Nishizawa, D., Shimada, T., Kataoka, Y., Hasegawa, J., Shioiri, T., … Ikeda, K. (2020). Polygenetic risk scores for major psychiatric disorders among schizophrenia patients, their first-degree relatives, and healthy participants. *The International Journal of Neuropsychopharmacology*, *23*(3), 157–164. https://doi.org/10.1093/ijnp/pyz073

Ohi, K., Nishizawa, D., Sugiyama, S., Takai, K., Fujikane, D., Kuramitsu, A., … Shioiri, T. (2022). Cognitive performances across individuals at high genetic risk for schizophrenia, high genetic risk for bipolar disorder, and low genetic risks: A combined polygenic risk score approach. *Psychological Medicine*, *53*(10), 4454–4463. https://doi.org/10.1017/S0033291722001271

Overall, J. E., & Gorham, D. R. (1962). The brief psychiatric rating scale. *Psychological Reports*, *10*(3), 799–812. https://doi.org/10.2466/pr0.1962.10.3.799

Perry, B. I., Zammit, S., Jones, P. B., & Khandaker, G. M. (2021). Childhood inflammatory markers and risks for psychosis and depression at age 24: Examination of temporality and specificity of association in a population-based prospective birth cohort. *Schizophrenia Research*, *230*, 69–76. https://doi.org/10.1016/j.schres.2021.02.008

Pillinger, T., Osimo, E. F., Brugger, S., Mondelli, V., McCutcheon, R. A., & Howes, O. D. (2019). A meta-analysis of immune parameters, variability, and assessment of modal distribution in psychosis and test of the immune subgroup hypothesis. *Schizophrenia Bulletin*, *45*(5), 1120–1133. https://doi.org/10.1093/schbul/sby160

Quattrone, D., Di Forti, M., Gayer-Anderson, C., Ferraro, L., Jongsma, H. E., Tripoli, G., … Reininghaus, U. (2019). Transdiagnostic dimensions of psychopathology at first episode psychosis: Findings from the multinational EU-GEI study. *Psychological Medicine*, *49*(8), 1378–1391. https://doi.org/10.1017/S0033291718002131

Quattrone, D., Ferraro, L., Tripoli, G., Cascia, C. L., Quigley, H., Quattrone, A., … Forti, M. D. (2021a). Daily use of high-potency cannabis is associated with more positive symptoms in first-episode psychosis patients: The EU-GEI case–control study. *Psychological Medicine*, *51*(8), 1329–1337. https://doi.org/10.1017/S0033291720000082

Quattrone, D., Reininghaus, U., Richards, A. L., Tripoli, G., Ferraro, L., Quattrone, A., … D'Andrea, G. (2021b). The continuity of effect of schizophrenia polygenic risk score and patterns of cannabis use on transdiagnostic symptom dimensions at first-episode psychosis: Findings from the EU-GEI study. *Translational Psychiatry*, *11*(1), 423. https://doi.org/10.1038/s41398-021-01526-0

Ragazzi, T. C. C., Shuhama, R., Sinval, J., Marôco, J., Corsi-Zuelli, F., Roza, D. L. da, … Del-Ben, C. M. (2020). Validation of the Portuguese version of the Community Assessment of Psychic Experiences and characterization of psychotic experiences in a Brazilian sample. Revista Brasileira De Psiquiatria (Sao Paulo, *Brazil*: 1999), *42*(4), 389–397. https://doi.org/10.1590/1516-4446-2019-0611

Robins, L. N., Wing, J., Wittchen, H. U., Helzer, J. E., Babor, T. F., Burke, J., … Regier, D. A. (1988). The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different

diagnostic systems and in different cultures. *Archives of General Psychiatry*, *45* (12), 1069–1077. https://doi.org/10.1001/archpsyc.1988.01800360017003

Rodriguez, A., Reise, S. P., & Haviland, M. G. (2016). Evaluating bifactor models: Calculating and interpreting statistical indices. *Psychological Methods*, *21*(2), 137–150. https://doi.org/10.1037/met0000045

Rose-John, S., Winthrop, K., & Calabrese, L. (2017). The role of IL-6 in host defence against infections: Immunobiology and clinical implications. *Nature Reviews Rheumatology*, *13*(7), 399–409. https://doi.org/10.1038/nrrheum.2017.83

Singh, S. P., Cooper, J. E., Fisher, H. L., Tarrant, C. J., Lloyd, T., Banjo, J., … Jones, P. (2005). Determining the chronology and components of psychosis onset: The Nottingham Onset Schedule (NOS). *Schizophrenia Research*, *80* (1), 117–130. https://doi.org/10.1016/j.schres.2005.04.018

Staines, L., Healy, C., Coughlan, H., Clarke, M., Kelleher, I., Cotter, D., & Cannon, M. (2022). Psychotic experiences in the general population, a review; definition, risk factors, outcomes and interventions. *Psychological Medicine*, *52*(15), 3297–3308. https://doi.org/10.1017/S0033291722002550

Stefanis, N. C., Hanssen, M., Smirnis, N. K., Avramopoulos, D. A., Evdokimidis, I. K., Stefanis, C. N., … Van Os, J. (2002). Evidence that three dimensions of psychosis have a distribution in the general population. *Psychological Medicine*, *32*(2), 347–358. https://doi.org/10.1017/s0033291701005141

Stojanovic, A., Martorell, L., Montalvo, I., Ortega, L., Monseny, R., Vilella, E., & Labad, J. (2014). Increased serum interleukin-6 levels in early stages of psychosis: Associations with at-risk mental states and the severity of psychotic symptoms. *Psychoneuroendocrinology*, *41*, 23–32. https://doi.org/10.1016/j.psyneuen.2013.12.005

Strauss, G. P., Horan, W. P., Kirkpatrick, B., Fischer, B. A., Keller, W. R., Miski, P., … Carpenter, W. T. (2013). Deconstructing negative symptoms of schizophrenia: Avolition–apathy and diminished expression clusters predict clinical presentation and functional outcome. *Journal of Psychiatric Research*, *47*(6), 783–790. https://doi.org/10.1016/j.jpsychires.2013.01.015

Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. *Archives of General Psychiatry*, *60*(12), 1187. https://doi.org/10.1001/archpsyc.60.12.1187

Trubetskoy, V., Pardiñas, A. F., Qi, T., Panagiotaropoulou, G., Awasthi, S., Bigdeli, T. B., … van Os, J. (2022). Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature*, *604*(7906), 502–508. https://doi.org/10.1038/s41586-022-04434-5

Upthegrove, R., Marwaha, S., & Birchwood, M. (2016). Depression and schizophrenia: Cause, consequence or trans-diagnostic issue? *Schizophrenia Bulletin*, *43*(2), 240–244. https://doi.org/10.1093/schbul/sbw097

van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P., & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: Evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychological Medicine*, *39*(2), 179–195. https://doi.org/10.1017/S0033291708003814

van Os, J., & Reininghaus, U. (2016). Psychosis as a transdiagnostic and extended phenotype in the general population. *World Psychiatry: Official Journal of the World Psychiatric Association* (*WPA*), *15*(2), 118–124. https://doi.org/10.1002/wps.20310

Wei, Y., Womer, F. Y., Sun, K., Zhu, Y., Sun, D., Duan, J., … Wang, F. (2022). Applying dimensional psychopathology: Transdiagnostic prediction of executive cognition using brain connectivity and inflammatory biomarkers. *Psychological Medicine*, *53*(8), 3557–3567. https://doi.org/10.1017/S0033291722000174

Yuan, N., Chen, Y., Xia, Y., Dai, J., & Liu, C. (2019). Inflammation-related biomarkers in major psychiatric disorders: A cross-disorder assessment of reproducibility and specificity in 43 meta-analyses. *Translational Psychiatry*, *9*, 233. https://doi.org/10.1038/s41398-019-0570-y

https://doi.org/10.1017/S0033291724000199 Published online by Cambridge University Press