*Supplementary Material*

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

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**Running title:** Immune dysregulation in the extended psychosis phenotype

**Methods**

*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. Further best-guess imputation was performed in the Michigan Imputation Server, using the Haplotype Reference Consortium reference panel (Quattrone *et al.*, 2021).

We used Plink 1.9 to calculate ancestry principal components based on the pruned single nucleotide polymorphisms (SNPs). We used PRS-CS for Bayesian (posterior) estimation of each SNPs effect size (subsequently summed into the PRS) using summary statistics from the latest wave of the schizophrenia GWAS (PGC3), from which the effect of overlapping samples was removed.

*Blood immune proteins*

Cytokines and high-sensitivity CRP (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 (#HCYTOMAG-60K; #HTH17MAG-14K; #TGFBMAG-64K-01; EDM Millipore, Billerica, MA, USA).The results were analysed on a Luminex-200 System (Luminex, Austin, TX, USA) and reported on xPOTENT software. Cytokines’ concentrations were calculated using the five-parameter logistic curve-fitting method considering the median fluorescence intensity, and all data were corrected using Milliplex Analyst software.

**Results**

*The Community Assessment of Psychic Experiences: group comparison*

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| --- | --- | --- | --- |
| **STable 1: CAPE scores in unaffected siblings and community controls (n=301)** | | | |
| **CAPE dimension, mean (SD)** | **Siblings** | **Controls** | **p** |
| **(n=66)** | **(n=235)** |
| General | -0.51 (1.13) | -0.44 (0.83) | 0.614 |
| Positive | -0.12 (0.62) | 0.04 (0.70) | 0.090 |
| Negative | 0.07 (0.60) | 0.01 (0.53) | 0.416 |
| Depressive | 0.17 (0.68) | 0.12 (0.62) | 0.616 |

1 One-way Analysis of Variance with Bonferroni post-hoc. Values are Z-scored.

SD: Standard Deviation; CAPE: Community Assessment of Psychic Experiences

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| **STable 2: Association between CAPE dimensions and immune proteins in unaffected siblings of patients with psychosis (n=52)** | | | | | | | | | | | | | | | | |
|  | **General** | | | | **Positive** | | | | **Depressive** | | | | **Negative** | | | |
|  | **B (SE)** | **95% CI** | **p** | **FDR** | **B (SE)** | **95% CI** | **p** | **FDR** | **B (SE)** | **95% CI** | **p** | **FDR** | **B (SE)** | **95% CI** | **p** | **FDR** |
| **IL-6** | -0.22 (0.12) | -0.46; 0.02 | 0.078 | 0.156 | **-0.20 (0.08)** | **-0.35; -0.05** | **0.011** | **0.044** | **-0.22 (0.08)** | **-0.38; -0.06** | **0.008** | **0.021** | 0.07(0.09) | -0.11; 0.26 | 0.449 | 0.718 |
| **TNF-α** | 0.06 (0.18) | -0.28; 0.41 | 0.720 | 0.720 | **0.29 (0.11)** | **0.08; 0.50** | **0.008** | **0.044** | 0.08 (0.10) | -0.12; 0.29 | 0.434 | 0.496 | 0.11 (0.10) | -0.09; 0.30 | 0.275 | 0.698 |
| **IL-10** | -0.13 (0.27) | -0.67; 0.41 | 0.639 | 0.720 | -0.11 (0.18) | -0.45; 0.24 | 0.550 | 0.629 | -0.27 (0.15) | -0.57; 0.03 | 0.075 | 0.131 | **-0.07 (0.11)** | **-0.43; 0.00** | **0.052** | 0.416 |
| **TGF-β** | -0.19 (0.13) | -0.44; 0.06 | 0.128 | 0.205 | -0.07 (0.08) | -0.22; 0.08 | 0.364 | 0.580 | 0.12 (0.08) | -0.04; 0.28 | 0.143 | 0.191 | -0.04 (0.09) | -0.21; 0.14 | 0.693 | 0.792 |
| **IL-4** | **-0.28 (0.09)** | **-0.46; -0.10** | **0.002** | **0.008** | 0.09 (0.07) | -0.04; 0.22 | 0.184 | 0.476 | 0.00 (0.08) | -0.15; 0.15 | 0.979 | 0.979 | 0.01 (0.06) | -0.01; 0.13 | 0.872 | 0.872 |
| **IL-1β** | -0.27 (0.15) | -0.56; 0.03 | 0.074 | 0.156 | -0.07 (0.09) | -0.26; 0.11 | 0.435 | 0.580 | **-0.30 (0.09)** | **-0.48; -0.11** | **0.002** | **0.008** | -0.04 (0.09) | -0.23; 0.14 | 0.658 | 0.792 |
| **IFN-γ** | **0.84 (0.25)** | **0.36; 1.32** | **<0.001** | **0.008** | 0.03 (0.19) | -0.34; 0.39 | 0.880 | 0.880 | **0.54 (0.15)** | **0.23; 0.84** | **<0.001** | **0.008** | 0.17 (0.16) | -0.14; 0.49 | 0.281 | 0.698 |
| **hsCRP** | 0.07 (0.16) | -0.25; 0.38 | 0.686 | 0.720 | 0.11 (0.09) | -0.07; 0.03 | 0.238 | 0.476 | 0.18 (0.10) | -0.02; 0.39 | 0.082 | 0.131 | 0.11 (0.12) | -0.12; 0.35 | 0.349 | 0.698 |

*Subclinical and clinical dimensions of psychopathology and immune proteins*

Generalised Linear model with robust estimator, adjusted for sex, age, tobacco smoking, body mass index, schizophrenia polygenic risk score, and five ancestry clusters

Cytokines and hsCRP were natural log transformed before standardisation

CAPE: Community Assessment of Psychic Experiences; B: standardised estimates; SE: Standard Error; 95% CI: 95% Confidence Interval

FDR: False discovery rate, Benjamini-Hochberg (5%) adjustment, computed using R p.adjust function

**Significant results are highlighted in bold**

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| **STable 3: Association between CAPE dimensions and inflammatory proteins in community-based controls (n=200)** | | | | | | | | | | | | | | | | |
|  | **General** | | | | **Positive** | | | | **Depression** | | | | **Negative** | | | |
|  | **B (SE)** | **95% CI** | **p** | **FDR** | **B (SE)** | **95% CI** | **p** | **FDR** | **B (SE)** | **95% CI** | **p** | **FDR** | **B (SE)** | **95% CI** | **p** | **FDR** |
| **IL-6** | -0.01 (0.04) | -0.09; 0.08 | 0.847 | 0.847 | 0.06 (0.04) | -0.02; 0.13 | 0.156 | 0.430 | 0.02 (0.04) | -0.06; 0.11 | 0.582 | 0.752 | 0.01 (0.03) | -0.05; 0.06 | 0.755 | 0.972 |
| **TNF-α** | -0.02 (0.06) | -0.14; 0.11 | 0.814 | 0.847 | 0.07 (0.07) | -0.06; 0.20 | 0.269 | 0.430 | 0.07 (0.06) | -0.04; 0.18 | 0.233 | 0.466 | -0.01 (0.05) | -0.09; 0.08 | 0.911 | 0.972 |
| **IL-10** | -0.03 (0.06) | -0.15; 0.09 | 0.650 | 0.847 | -0.08 (0.06) | -0.19; 0.03 | 0.162 | 0.430 | -0.08 (0.05) | -0.18; 0.02 | 0.101 | 0.466 | -0.01 (0.04) | -0.09; 0.07 | 0.841 | 0.972 |
| **TGF-β** | -0.03 (0.07) | -0.17; 0.10 | 0.628 | 0.847 | **-0.14 (0.05)** | **-0.24; -0.04** | **0.006** | **0.048** | -0.01 (0.05) | -0.12; 0.09 | 0.814 | 0.814 | 0.03 (0.04) | -0.05; 0.11 | 0.408 | 0.972 |
| **IL-4** | -0.02 (0.09) | -0.19; 0.15 | 0.824 | 0.847 | -0.07 (0.07) | -0.20; 0.07 | 0.337 | 0.449 | 0.03 (0.07) | -0.10; 0.16 | 0.658 | 0.752 | 0.05 (0.05) | -0.06; 0.15 | 0.370 | 0.972 |
| **IL-1β** | **-0.18 (0.08)** | **-0.34; -0.02** | **0.031** | 0.124 | -0.08 (0.07) | -0.22; 0.06 | 0.623 | 0.430 | -0.10 (0.07) | -0.23; 0.04 | 0.151 | 0.466 | 0.04 (0.06) | -0.08; 0.15 | 0.520 | 0.972 |
| **IFN-γ** | **0.19 (0.07)** | **0.06; 0.32** | **0.003** | **0.024** | 0.02 (0.06) | -0.10; 0.14 | 0.744 | 0.744 | 0.06 (0.05) | -0.04; 0.16 | 0.227 | 0.466 | 0.00 (0.05) | -0.10; 0.10 | 0.972 | 0.972 |
| **hsCRP** | -0.03 (0.06) | -0.16; 0.09 | 0.616 | 0.847 | 0.02 (0.05) | -0.08; 0.13 | 0.654 | 0.744 | 0.03 (0.05) | -0.07; 0.12 | 0.600 | 0.752 | 0.03 (0.05) | -0.07; 0.12 | 0.585 | 0.972 |

Generalised Linear model with robust estimator, adjusted for sex, age, tobacco smoking, body mass index, schizophrenia polygenic risk score, and five ancestry clusters

Cytokines and hsCRP were natural log transformed before standardisation

CAPE: Community Assessment of Psychic Experiences; B: standardised estimates; SE: Standard Error; 95% CI: 95% Confidence Interval

FDR: False discovery rate, Benjamini-Hochberg (5%) adjustment, computed using R p.adjust function

**Significant results are highlighted in bold**

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| **STable 4: Association between OPCRIT dimensions and inflammatory proteins in FEP (n=110)** | | | | | | | | | | | | | | | | |
|  | **General** | | | | **Delusion** | | | | **Hallucination** | | | | **Negative** | | | |
|  | **B (SE)** | **95% CI** | **p** | **FDR** | **B (SE)** | **95% CI** | **p** | **FDR** | **B (SE)** | **95% CI** | **p** | **FDR** | **B (SE)** | **95% CI** | **p** | **FDR** |
| **IL-6** | 0.01 (0.09) | -0.18; 0.19 | 0.959 | 0.995 | -0.02 (0.09) | -0.191; 0.151 | 0.818 | 0.878 | 0.01 (0.09) | -0.17; 0.19 | 0.900 | 0.986 | 0.05 (0.09) | -0.13; 0.23 | 0.610 | 0.813 |
| **TNF-α** | 0.10 (0.10) | -0.09; 0.29 | 0.294 | 0.995 | -0.02 (0.09) | -0.204; 0.160 | 0.815 | 0.878 | 0.01 (0.10) | -0.18; 0.21 | 0.909 | 0.986 | 0.00 (0.08) | -0.17; 0.16 | 0.988 | 0.988 |
| **IL-10** | 0.00 (0.09) | -0.17; 0.17 | 0.995 | 0.995 | 0.04 (0.08) | -0.125; 0.200 | 0.652 | 0.878 | 0.12 (0.10) | -0.08; 0.32 | 0.234 | 0.568 | 0.00 (0.08) | -0.16; 0.15 | 0.960 | 0.988 |
| **TGF-β** | 0.01 (0.07) | -0.13; 0.16 | 0.854 | 0.995 | 0.07 (0.06) | -0.051; 0.197 | 0.246 | 0.656 | 0.10 (0.08) | -0.06; 0.25 | 0.213 | 0.568 | -0.05 (0.07) | -0.19; 0.09 | 0.454 | 0.726 |
| **IL-4** | 0.02 (0.09) | -0.16; 0.20 | 0.818 | 0.995 | -0.03 (0.10) | -0.226; 0.163 | 0.753 | 0.878 | -0.03 (0.11) | -0.24; 0.18 | 0.757 | 0.986 | -0.12 (0.09) | -0.29; 0.05 | 0.176 | 0.704 |
| **IL-1β** | -0.02 (0.10) | -0.21; 0.18 | 0.867 | 0.995 | 0.16 (0.10) | -0.040; 0.358 | 0.117 | 0.468 | 0.11 (0.10) | -0.09; 0.31 | 0.268 | 0.568 | **0.25 (0.10)** | **0.05; 0.45** | **0.013** | 0.104 |
| **IFN-γ** | 0.09 (0.07) | -0.06; 0.23 | 0.236 | 0.995 | -0.15 (0.08) | -0.307; 0.017 | 0.080 | 0.468 | -0.09 (0.09) | -0.26; 0.08 | 0.284 | 0.568 | -0.07 (0.08) | -0.22; 0.08 | 0.366 | 0.726 |
| **hsCRP** | 0.00 (0.08) | -0.16; 0.17 | 0.961 | 0.995 | -0.01 (0.07) | -0.155; 0.132 | 0.878 | 0.878 | 0.00 (0.08) | -0.16; 0.16 | 0.986 | 0.986 | -0.07 (0.07) | -0.21; 0.08 | 0.364 | 0.726 |

Generalised Linear model with robust estimator, adjusted for sex, age, tobacco smoking, body mass index, duration of antipsychotic treatment, schizophrenia polygenic risk score, and five ancestry clusters

Cytokines and hsCRP were natural log transformed before standardisation

OPCRIT: Operational Criteria Checklist for Psychotic Illness and Affective Illness; B: standardised estimates; SE: Standard Error; 95% CI: 95% Confidence Interval

FDR: False discovery rate, Benjamini-Hochberg (5%) adjustment, computed using R p.adjust function

**Significant results are highlighted in bold**

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| **STable 4 (continuation): Association between OPCRIT dimensions and inflammatory proteins in FEP (n=110)** | | | | | | | | | | | | |
|  | **Disorganisation** | | | | **Manic** | | | | **Depressive** | | | |
|  | **B (SE)** | **95% CI** | **p** | **FDR** | **B (SE)** | **95% CI** | **p** | **FDR** | **B (SE)** | **95% CI** | **p** | **FDR** |
| **IL-6** | -0.11 (0.06) | -0.22; 0.01 | 0.068 | 0.269 | -0.09 (0.10) | -0.29; 0.12 | 0.398 | 0.637 | **0.17 (0.08)** | **0.02; 0.33** | **0.032** | 0.128 |
| **TNF-α** | 0.06 (0.06) | -0.07; 0.18 | 0.354 | 0.548 | **0.23 (0.11)** | **0.02; 0.45** | **0.031** | 0.083 | **-0.31 (0.10)** | **-0.50; -0.12** | **0.001** | **0.008** |
| **IL-10** | 0.07 (0.06) | -0.06; 0.19 | 0.285 | 0.548 | **-0.23 (0.10)** | **-0.42; -0.04** | **0.017** | 0.068 | 0.14 (0.08) | -0.01; 0.30 | 0.071 | 0.176 |
| **TGF-β** | -0.09 (0.05) | -0.20; 0.01 | 0.077 | 0.269 | -0.03 (0.08) | -0.19; 0.14 | 0.753 | 0.813 | -0.10 (0.06) | -0.20; 0.01 | 0.088 | 0.176 |
| **IL-4** | -0.04 (0.07) | -0.18; 0.09 | 0.548 | 0.548 | 0.03 (0.10) | -0.16; 0.22 | 0.763 | 0.813 | -0.06 (0.11) | -0.27; 0.16 | 0.598 | 0.683 |
| **IL-1β** | 0.04 (0.07) | -0.09; 0.17 | 0.545 | 0.548 | -0.21 (0.12) | -0.44; 0.02 | 0.067 | 0.134 | -0.06 (0.11) | -0.26; 0.15 | 0.581 | 0.683 |
| **IFN-γ** | 0.10 (0.06) | -0.02; 0.22 | 0.101 | 0.269 | **0.29 (0.09)** | **0.12; 0.46** | **0.001** | **0.008** | 0.02 (0.09) | -0.15; 0.20 | 0.781 | 0.781 |
| **hsCRP** | 0.04 (0.06) | -0.07; 0.15 | 0.476 | 0.548 | -0.03 (0.11) | -0.23; 0.18 | 0.813 | 0.813 | -0.09 (0.07) | -0.23; 0.05 | 0.208 | 0.333 |

Generalised Linear model with robust estimator, adjusted for sex, age, tobacco smoking, body mass index, duration of antipsychotic treatment, schizophrenia polygenic risk score and five ancestry clusters

Cytokines and hsCRP were natural log transformed before standardisation

OPCRIT: Operational Criteria Checklist for Psychotic Illness and Affective Illness; B: standardised estimates; SE: Standard Error; 95% CI: 95% Confidence Interval

FDR: False discovery rate, Benjamini-Hochberg (5%) adjustment, computed using R p.adjust function

**Significant results are highlighted in bold**

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| **STable 5: Dimensions of psychopathology and immune proteins by SZ-PRS** | | | | | | | | | | | |
| **Unaffected siblings** | | | | | | | | | | | |
|  | **Top (n=18)** | | | **Middle (n=17)** | | | | **Bottom (n=17)** | | | |
|  | **B (SE)** | **95% CI** | **p** | **B (SE)** | **95% CI** | **p** | | **B (SE)** | **95% CI** | | **p** |
| **CAPE general** | | | | | | | | | | | |
| **IL-4** | **-0.21 (0.08)** | **-0.36; -0.07** | **0.005** | -0.38 (0.21) | -0.78; 0.02 | | 0.065 | -0.28 (0.43) | | -1.12; 0.56 | 0.516 |
| **IFN-γ** | **0.53 (0.25)** | **0.05; 1.02** | **0.032** | -0.34 (0.19) | -0.72; 0.04 | | 0.078 | **1.42 (0.57)** | | **0.31; 2.53** | **0.012** |
| **CAPE positive** | | | | | | | | | | | |
| **IL-6** | **0.18 (0.08)** | **0.02; 0.35** | **0.030** | 0.04 (0.13) | 0.13; -0.20 | | 0.731 | **-0.28 (0.14)** | | **-0.56; -0.00** | **0.048** |
| **TNF-α** | **0.59 (0.13)** | **0.34; 0.85** | **<0.001** | 0.21 (0.16) | -0.10; 0.52 | | 0.180 | 0.06 (0.14) | | -0.23; 0.34 | 0.702 |
| **CAPE depressive** | | | | | | | | | | | |
| **IL-6** | -0.16 (0.21) | -0.57; 0.24 | 0.431 | -0.18 (0.09) | -0.35; 0.00 | | 0.056 | 0.07 (0.16) | | -0.25; 0.39 | 0.684 |
| **IL-1β** | -0.55 (0.30) | -1.13; 0.04 | 0.067 | 0.17 (0.17) | -0.17; 0.51 | | 0.319 | -0.06 (0.20) | | -0.45; 0.33 | 0.765 |
| **IFN-γ** | **0.46 (0.21)** | **0.05; 0.87** | **0.029** | -0.07 (0.22) | -0.49; 0.36 | | 0.767 | **-1.73 (0.50)** | | **-2.70; -0.76** | **<0.001** |
| **Community controls** | | | | | | | | | | | |
| **CAPE general** | | | | | | | | | | | |
|  | **Top (n=32)** | | | **Middle (n=58)** | | | | **Bottom (n=110)** | | | |
|  | **B (SE)** | **95% CI** | **p** | **B (SE)** | **95% CI** | | **p** | **B (SE)** | | **95% CI** | **p** |
| **IFN-γ** | **0.66 (0.14)** | **0.39; 0.94** | **<0.001** | -0.07 (0.07) | -0.20; 0.07 | | 0.319 | 0.01 (0.07) | | -0.04; 0.23 | 0.162 |
| **FEP #** | | | | | | | | | | | |
| **OPCRIT Manic** | | | | | | | | | | | |
|  | **Top (n=38)** | | | **Middle (n=39)** | | | | **Bottom (n=33)** | | | |
|  | **B (SE)** | **95% CI** | **p** | **B (SE)** | **95% CI** | | **p** | **B (SE)** | | **95% CI** | **p** |
| **IFN-γ** | **0.29 (0.10)** | **0.10; 0.49** | **0.003** | 0.35 (0.20) | -0.05; 0.75 | | 0.085 | **0.26 (0.13)** | | **0.01; 0.51** | **0.040** |
| **OPCRIT Depressive** | | | | | | | | | | | |
| **TNF-α** | -0.04 (0.13) | -0.31; 0.22 | 0.749 | -0.09 (0.13) | -0.33; 0.16 | | 0.488 | -0.23 (0.13) | | -0.48; 0.01 | 0.064 |

Generalised Linear model with robust estimator, adjusted for sex, age, tobacco smoking, body mass index, and five ancestry clusters

# For FEP analyses, duration of pharmacological treatment was additionally included as covariate

Cytokines were natural log transformed before standardisation

FEP: First-episode psychosis; SZ-PRS: schizophrenia polygenic risk score; CAPE: Community Assessment of Psychic Experiences; OPCRIT: Operational Criteria System; B: standardised estimates; SE: Standard Error; 95% CI: 95% Confidence Interval

**Significant results are highlighted in bold**

**References**

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