**Supplementary table 1: Bivariate correlation with Pearson coefficients between DDD of medication and inflammatory markers revealing no significant correlations**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Inflammatory marker** | **Antipsychotics**  **(n=636)** | **Lithium**  **(n=61)** | **Mood Stabilizers**  **(n=182)** | **Antidepressants**  **(n=269)** |
| **CXCL16** | 0.01 | -0.02 | 0.01 | -0.02 |
| **sIL-2R** | -0.05 | 0.02 | -0.03 | -0.06 |
| **MIF** | 0.03 | -0.01 | -0.12 | -0.12 |
| **sCD14** | -0.04 | 0.04 | 0.01 | -0.01 |
| **ALCAM** | -0.02 | -0.05 | 0.01 | -0.06 |

sIL-2R= soluble interleukin-2 receptor, sCD14= soluble CD14, MIF= macrophage inhibitory factor, ALCAM= activated leukocyte cell adhesion molecule, n= number

**Supplementary table 2: Bivariate correlation with Pearson or Spearman coefficients between core symptoms and inflammatory markers**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Inflammatory marker** | **GAF-S**  **(n=874)** | **GAF-F**  **(n=874)** | **PANSS total**  **(n=861)** | **CDSS**  **(n=666)** | **YMRS**  **(n=737)** |
| **CXCL16** | -0.01 | -0.03 | 0.01 | 0.03 | 0.003 |
| **sIL-2R** | -0.07\* | -0.06 | 0.05 | -0.04 | 0.09\* |
| **MIF** | -0.05 | -0.06 | 0.03 | 0.002 | -0.02 |
| **sCD14** | 0.03 | 0.03 | -0.02 | -0.02 | -0.01 |
| **ALCAM** | 0.02 | 0.01 | -0.04 | -0.08\* | 0.01 |

\*p≤0.05, PANSS=Positive and Negative Syndrome Scale, CDSS= Calgary Depression Scale for Schizophrenia, GAF-F= Global Assessment of Functioning- functions, GAF-S= Global Assessment of Functioning-symptoms, YMRS= Young Mania Rating Scale, sIL-2R= soluble interleukin-2 receptor, sCD14= soluble CD14, MIF= macrophage inhibitory factor, ALCAM= activated leukocyte cell adhesion molecule, n=number

**Supplementary table 3: Clinical characteristics of follow-up patients at 1 year**

|  |  |  |  |
| --- | --- | --- | --- |
| Total  n=216 | **ALL**  **(n=124)** | **HC**  **(n=92)** | P-value |
| **Clinical parameters** | % (n) | % (n) |  |
| Gender (male) | 56 (69) | 57 (52) | 0.90 |
| Ethnicity (European) | 67 (83) | 98 (90) | 0.002 |
| Smoking status (daily day) | 27 (33) | N/A\* | N/A |
| Illicit substances (use/2 weeks) | 7 (8) | 0(0) | N/A |
| Medicated | 69 (85) | 0(0) | N/A |
|  | **Mean (SD)** | **Mean (SD)** |  |
| Age (years) | 32.1 (9.9) | 31.6 (7.2) | 0.85 |
| Alcohol (use/2 weeks) | 11.3 (26.3) | N/A\* | N/A |
| **Cardiometabolic risk factors** |  |  |  |
| BMI (kg/m2) | 25.8 (3.8) | 25.5 (3.6) | 0.65 |
| Glucose (mmol/L) | 5.0 (0.6) | 5.1 (0.8) | 0.75 |
| HDL (mmol/L) | 1.3 (0.4) | 1.5 (0.4) | 0.02 |
| Triglycerides (mmol/L) | 1.4 (0.7) | 1.5 (1.3) | 0.98 |
| Total cholesterol (mmol/L) | 5.0 (1.1) | 4.9 (0.9) | 0.91 |
| **Symptom scores** | **Baseline** | **1 year** |  |
| PANSS total | 55.1 (16.6) | 47.6 (14.5) | <0.0001 |
| CDSS total | 5.2 (4.1) | 3.3 (3.9) | 0.01 |
| GAF-F | 47.5 (12.1) | 59.0 (15.5) | <0.0001 |
| GAF-S | 48.3 (12.2) | 59.0 (15.7) | <0.0001 |
| YMRS total | 5.2 (5.8) | 3.3 (4.3) | 0.01 |

Analysed with ANOVA for continuous variables and chi-square test for categorical variables. IU= international units, n=number, SD= standard deviation, SCZ= schizophrenia, AFF= affective, HC= healthy controls, ALL= all patients, N/A= not applicable, n.s.= not significant, PANSS=Positive and Negative Syndrome Scale, CDSS= Calgary Depression Scale for Schizophrenia, YMRS= Young Mania Rating Scale, GAF-F= Global Assessment of Functioning- functions, GAF-S= Global Assessment of Functioning-symptoms, HDL=high density lipoprotein cholesterol, LDL= low density lipoprotein cholesterol, BMI= body mass index, mmol= millimoles per liter

**Supplementary table 4: Inflammatory markers at 1 year in follow-up sample after controlling for cardiometabolic risk factors (ANCOVA)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Inflammatory Marker** | **ALL**  **(n=124)** | **SCZ**  **(n=67)** | **AFF**  **(n=57)** | **HC**  **(n=92)** |
|  | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** |
| **CXCL161** | 17.4 (11.6) | 19.4 (14.5) | 15.0 (6.1) | 15.4 (8.1) |
| **sIL-2R1** | 0.8 (2.9) | 0.9 (3.0) | 0.7 (2.7) | 0.8 (2.7) |
| **sCD141** | 1739 (377.0)\* | 1727 (426.1)\* | 1753 (309.6) | 1888 (410.4) |
| **MIF1** | 31.8 (41.7) | 33.1 (50.4) | 30.2 (28.1) | 31.8 (50.7) |
| **ALCAM2** | 38.4 (9.8) | 39.8 (10.4) | 36.9 (8.9) | 38.1 (7.9) |

\*p<0.05= statistical significant difference between patients and healthy controls analysed with analysis of covariance (ANCOVA). sIL-2R= soluble interleukin-2 receptor, sCD14= soluble CD14, MIF= macrophage inhibitory factor, ALCAM= activated leukocyte cell adhesion molecule, SD= standard deviation, n=number, ALL= All patients SCZ= schizophrenia, AFF= affective, HC= healthy controls, 1= adjusted for age, gender, total cholesterol, 2= adjusted for age, gender, BMI, glucose, total cholesterol.

**Supplementary table 5: Table representing inflammatory makers in patients using antipsychotics versus those not using antipsychotics**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Antipsychotics  (n=636)  Mean +/- SD | Not using antipsychotics  (n=235)  Mean +/- SD | p-value |
| CXCL16 | 19.6 (14.2) | 17.7 (10.4) | 0.15 |
| sIL-2R | 1.0 (3.3) | 0.7 (2.7) | 0.03 |
| MIF | 55.7 (107.2) | 62.5 (120.6) | 0.21 |
| sCD14 | 1928.2 (374.3) | 1961.7 (372.0) | 0.24 |
| ALCAM | 38.8 (9.5) | 38.9 (10.5) | 0.92 |

sIL-2R= soluble interleukin-2 receptor, sCD14= soluble CD14, MIF= macrophage inhibitory factor, ALCAM= activated leukocyte cell adhesion molecule, n=number, SD= standard deviation

**Supplementary table 6: Table representing inflammatory markers in participants who are smokers versus non-smokers**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| SMOKING | Patients |  |  | HC |  |  |
|  | No  Mean (+/-SD) | Yes  Mean (+/-SD) | p-value | No  Mean (+/-SD) | Yes  Mean (+/-SD) | p-value |
| CXCL16 | 18.6 (13.7) | 18.9 (12.2) | 0.28 | 18.9 (13.9) | 17.3 (6.8) | 0.91 |
| sIL-2R | 1.0 (3.5) | 1.0 (3.0) | 0.10 | 1.1 (3.8) | 0.4 (0.7) | 0.80 |
| MIF | 52.9 (112.1) | 61.0 (111.9) | 0.20 | 89.4 (208.6) | 121.6 (289.9) | 0.41 |
| sCD14 | 1923.1 (350.1) | 1938.2 (388.8) | 0.56 | 2057.5 (334.7) | 2018.8 (363.8) | 0.50 |
| ALCAM | 39.0 (9.1) | 38.4 (10.2) | 0.37 | 39.3 (9.8) | 39.7 (6.6) | 0.80 |

sIL-2R= soluble interleukin-2 receptor, sCD14= soluble CD14, MIF= macrophage inhibitory factor, ALCAM= activated leukocyte cell adhesion molecule, HC= healthy controls, SD= standard deviation

**Supplementary table 7: Table representing inflammatory markers in those who had used illicit drugs or not in the previous two weeks before inclusion to the study**

|  |  |  |  |
| --- | --- | --- | --- |
| ILLICIT DRUGS | Patients |  |  |
|  | Yes  Mean (+/-SD) | No  Mean (+/-SD) | p-value |
| CXCL16 | 19.0 (14.8) | 18.7 (13.2) | 0.87 |
| sIL-2R | 1.1 (3.3) | 0.9 (3.2) | 0.61 |
| MIF | 78.6 (146.5) | 51.5 (98.1) | 0.30 |
| sCD14 | 1958.1 (378.4) | 1931.2 (366.2) | 0.54 |
| ALCAM | 38.0 (8.1) | 39.0 (9.6) | 0.36 |

sIL-2R= soluble interleukin-2 receptor, sCD14= soluble CD14, MIF= macrophage inhibitory factor, ALCAM= activated leukocyte cell adhesion molecule, SD= standard deviation

**Supplementary Table 8: Table representing main findings excluding those participants (n=44) with CRP >10mmol/L.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Inflammatory marker** | **Covariates** | **F** | **p-value** |
| **CXCL16** | Age | 0.06 | 0.80 |
|  | Gender | 0.08 | 0.78 |
| Total cholesterol | 5.5 | 0.02 |
| Patient vs HC | 1.9 | 0.16 |
| **sIL-2R** | Age | 8.5 | 0.004 |
|  | Gender | 22.2 | 3.0x10-6 |
| Total cholesterol | 0.36 | 0.55 |
| Patient vs HC | 10.9 | 0.001 |
| **sCD14** | Age | 5.9 | 0.02 |
|  | Gender | 1.2 | 0.30 |
| Total cholesterol | 4.2 | 0.04 |
| Patient vs HC | 8.2 | 0.004 |
| **MIF** | Age | 0.10 | 0.75 |
|  | Gender | 20.7 | 6.0x10-6 |
| Total cholesterol | 4.9 | 0.03 |
| Patient vs HC | 1.5 | 0.22 |
| **ALCAM** | Age | 1.7 | 0.20 |
|  | Gender | 12.4 | 4.4x10-4 |
| BMI | 11.8 | 0.001 |
| Glucose | 2.5 | 0.12 |
| Total cholesterol | 8.2 | 0.004 |
| Patient vs HC | 4.2 | 0.04 |

sIL-2R= soluble interleukin-2 receptor, sCD14= soluble CD14, MIF= macrophage inhibitory factor, ALCAM= activated leukocyte cell adhesion molecule, BMI= body mass index, HC= healthy controls, F=F-test

**Supplementary table 9: ROC curve analysis of the inflammatory markers with area under the curve:**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Inflammatory marker | Area | Standard Error | p-value | 95% Confidence interval |
| CXCL16 | 0.54 | 0.02 | 0.02 | 0.51-0.56 |
| sIL-2R | 0.59 | 0.01 | 1.4x10-4 | 0.56-0.62 |
| MIF | 0.52 | 0.02 | 0.11 | 0.50-0.55 |
| sCD14 | 0.47 | 0.02 | 0.04 | 0.44-0.50 |
| ALCAM | 0.48 | 0.02 | 0.28 | 0.46-0.51 |

sIL-2R= soluble interleukin-2 receptor, sCD14= soluble CD14, MIF= macrophage inhibitory factor, ALCAM= activated leukocyte cell adhesion molecule

**Supplementary table 10: Bivariate correlation analysis between illness duration and inflammatory markers:**

|  |  |  |
| --- | --- | --- |
|  | Illness duration  Pearson correlation | p-value |
| CXCL16 | 0.10 | 0.02 |
| sIL-2R | 0.02 | 0.69 |
| MIF | 0.02 | 0.69 |
| sCD14 | -0.01 | 0.83 |
| ALCAM | 0.07 | 0.14 |

sIL-2R= soluble interleukin-2 receptor, sCD14= soluble CD14, MIF= macrophage inhibitory factor, ALCAM= activated leukocyte cell adhesion molecule