**SUPPLEMENTARY MATERIAL**

**Supplementary Table S1. List of peripheral biomarkers for bipolar disorder examined for available meta-analysis**. Each biomarker was entered as a search term in the MEDLINE database to identify specific meta-analyses.

|  |  |
| --- | --- |
| **Biomarker name** | **Eligible Meta-analysis** |
| Adrenocorticotropic hormone (ACTH) | **No** |
| Cortisol | **Yes** |
| Corticotropin-releasing hormone (CRH) | **No** |
| Dexamethasone/CRH suppression test | **No** |
| Post-dexamethasone cortisol levels | **No** |
| Platelet 3H-imipramine binding | **No** |
| Brain-derived neurotrophic factor | **Yes** |
| Glial cell-derived neurotrophic factor | **No** |
| Vascular endothelial growth factor | **No** |
| Nerve growth factor (NGF) | **No** |
| Neurotrophin-3 (NT-3) | **No** |
| Neurotrophin-4 (NT-4/5) | **No** |
| Interleukin-1 beta | **No** |
| Interleukin-1 receptor antagonist (IL-1RA) | **No** |
| Interleukin-2 | **No** |
| Interleukin-6 | **No** |
| Interleukin-8 | **No** |
| Interferon gamma | **No** |
| Interleukin-1 receptor antagonist | **No** |
| Interleukin-2 | **No** |
| Interleukin**-**4 | **Yes** |
| Interleukin-5 | **No** |
| Interleukin-6 | **No** |
| Soluble IL-6 receptor | **No** |
| Interleukin-8 | **No** |
| Interleukin-10 | **Yes** |
| Interleukin-12 | **No** |
| Soluble interleukin-2 receptor | **Yes** |
| Tumor necrosis factor (TNF)-α | **Yes** |
| Tumor necrosis factor receptor-1 | **No** |
| Tumor necrosis factor receptor-2 | **No** |
| Soluble tumor necrosis factor receptor-1 | **No** |
| Soluble tumor necrosis factor receptor-2 | **No** |
| Interleukin-13 | **No** |
| Chemokine (C-C motif) ligand 2 (CCL2) | **No** |
| Chemokine (C-C motif) ligand 3 (CCL3) | **No** |
| Chemokine (C-X-C motif) ligand 8 (CXCL8) | **No** |
| Chemokine (C-X-C motif) ligand 10 (CXCL10) | **No** |
| Chemokine (C-X-C motif) ligand 11 (CXCL11) | **No** |
| Chemokine (C-X-C motif) ligand 24 (CLXL24) | **No** |
| C-reactive protein | **Yes** |
| Apolipoprotein A1 | **No** |
| Protein S100-Beta | **No** |
| Transforming growth factor beta-1 | **No** |
| Melatonin | **No** |
| Adiponectin | **No** |
| Resistin | **No** |
| Thyroid-stimulating hormone | **No** |
| Thyroxin (T4) | **No** |
| Thyrotropin-releasing hormone (TRH) | **No** |
| Leptin | **No** |
| Lipid peroxidation | **Yes** |
| Superoxide dismutase (SOD) activity | **Yes** |
| Nitric oxide (NO) | **Yes** |
| Glutathione peroxidase (GPx) activity | **Yes** |
| Catalase (CAT) activity | **Yes** |

**Supplementary Table S2. Evaluated meta-analyses of bipolar disorder peripheral biomarkers. (A)** Biomarkers fromstudies that did not separate the data sets by mood state (n = 11). **(B)** Biomarkers from studies that provided data sets separated by each mood state (n = 3).

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Biomarker** | **StudyDataSets,N** | **Cases/Controls,N** | **Meta-analysis ES(95% CI)** | **95% Prediction Interval** | ***P* Valuea** | **Largest Study ES(95% CI)** | **I2,%** | **Egger’s Test*P* Value** |
|
| **A. STUDIES THAT COMBINED MOOD STATES** |  |
| ([Dargel *et al.*, 2015](#_ENREF_2)) | **C-Reactive Protein (CRP)** | 11 | 730 / 888 |  0.39 (0.24 ̶ 0.55) |  0.04 ̶ 0.74 | **< 0.001** |  0.22 (0.03 ̶ 0.41) | 48 | **0.006** |
| ([Brown *et al.*, 2014](#_ENREF_1)) | **Catalase** | 5 | 200 / 154 |  -1.57 (-3.47 ̶ 0.32) |  -7.06 ̶ 3.92 | 0.104 |  -2.02 (-2.51 ̶ -1.52) | 98 | 0.459 |
| ([Brown *et al.*, 2014](#_ENREF_1)) | **Gluthatione peroxidase** | 7 | 258 / 262 |  0.04 (-0.38 ̶ 0.47) |  -1.06 ̶ 1.15 | 0.837 |  -0.44 (-0.80 ̶ -0.07) | 80 | 0.799 |
| ([Brown *et al.*, 2014](#_ENREF_1)) | **Lipid peroxidation** | 10 | 486 / 388 |  1.93 (1.23 ̶ 2.62) |  -0.17 ̶ 4.03 | **< 0.001** |  0.22 (-0.11 ̶ 0.55) | 94 | **0.058** |
| ([Brown *et al.*, 2014](#_ENREF_1)) | **Nitric oxide** | 6 | 203 / 153 |  0.94 (0.06 ̶ 1.83) |  -1.52 ̶ 3.40 | **0.037** |  1.16 (0.66 ̶ 1.66) | 93 | 0.987 |
| ([Brown *et al.*, 2014](#_ENREF_1)) | **Superoxide dismutase** | 11 | 412 / 344 |  0.11 (-0.94 ̶ 1.16) |  -3.25 ̶ 3.47 | 0.838 |  3.24 (2.65 ̶ 3.83) | 97 | **0.088** |
| ([Girshkin *et al.*, 2014](#_ENREF_3)) | **Cortisol (morning)** | 18 | 358 / 300 |  0.21 (0.06 ̶ 0.36) |  0.07 ̶ 0.35 | **0.008** |  0.01 (-0.42 ̶ 0.45) | 0 | 0.240 |
| ([Modabbernia *et al.*, 2013](#_ENREF_5)) | **IL-10** | 8 | 399 / 311 |  0.28 (0.06 ̶ 0.50) |  -0.18 ̶ 0.74 | **0.013** |  0.21 (-0.08 ̶ 0.49) | 45 | 0.438 |
| ([Modabbernia *et al.*, 2013](#_ENREF_5)) | **IL-4** | 9 | 482 / 376 |  0.24 (-0.28 ̶ 0.77) |  -1.29 ̶ 1.78 | 0.363 |  -0.02 (-0.31 ̶ 0.27) | 92 | 0.771 |
| ([Modabbernia *et al.*, 2013](#_ENREF_5)) | **TNF-α** | 13 | 561 / 439 |  0.91 (0.42 ̶ 1.40) |  -0.66 ̶ 2.48 | **< 0.001** |  -0.04 (-0.33 ̶ 0.24) | 92 | **0.001** |
| ([Modabbernia *et al.*, 2013](#_ENREF_5)) | **sIL-2R** | 9 | 359 / 257 |  0.40 (0.19 ̶ 0.60) |  0.03 ̶ 0.76 | **< 0.001** |  0.54 (0.26 ̶ 0.82) | 27 | 0.518 |
|  |  |  |  |  |  |  |  |  |
| **B. STUDIES THAT SEPARATED MOOD STATES** |
| ([Polyakova *et al.*, 2015](#_ENREF_6)) | **BDNF** |  |  |  |  |  |  |  |  |
|  | Depression | 7 | 117 / 161 |  -1.16 (-1.85 ̶ -0.48) |  -2.99 ̶ 0.66 | **0.001** |  -2.32 (-2.93 ̶ -1.71) | 83 | 0.723 |
|  | Euthymia | 10 | 426 / 457 |  0.00 (-0.41 ̶ 0.42) |  -1.20 ̶ 1.21 | 0.984 |  -0.25 (-0.50 ̶ -0.00) | 88 | 0.469 |
|  | Mania | 8 | 148 / 204 |  -0.77 (-1.10 ̶ -0.44) |  -1.49 ̶ -0.05 | **< 0.001** |  -0.29 (-0.76 ̶ 0.18) | 50 | 0.517 |
| ([Dargel *et al.*, 2015](#_ENREF_2)) | **C-Reactive Protein (CRP)** |  |  |  |  |  |  |  |  |
|  | Depression | 4 | 107 / 297 |  0.28 (-0.17 ̶ 0.73) |  -0.93 ̶ 1.48 | 0.224 |  -0.08 (-0.37 ̶ 0.20) | 60 | **0.091** |
|  | Euthymia | 6 | 399 / 735 |  0.26 (0.01 ̶ 0.51) |  -0.32 ̶ 0.83 | **0.042** |  0.22 (0.03 ̶ 0.41) | 65 | 0.657 |
|  | Mania | 7 | 188 / 557 |  0.73 (0.44 ̶ 1.02) |  0.10 ̶ 1.36 | **< 0.001** |  0.46 (-0.04 ̶ 0.95) | 53 | **0.023** |
| ([Looney and el-Mallakh, 1997](#_ENREF_4)) | **Na,K-ATPase activity** |  |  |  |  |  |  |  |  |
|  | Depression | 5 | 55 / 99 |  -0.65 (-1.36 ̶ 0.06) |  -2.39 ̶ 1.09 | 0.075 |  -0.09 (-0.48 ̶ 0.31) | 72 | 0.125 |
|  | Euthymia | 9 | 182 / 237 |  0.26 (-0.07 ̶ 0.58) |  -0.44 ̶ 0.96 | 0.118 |  1.02 (0.54 ̶ 1.50) | 51 | 0.868 |
|  | Mania | 6 | 98 / 174 |  0.44 (-0.17 ̶ 1.04) |  -1.13 ̶ 2.00 | 0.159 |  0.11 (-0.27 ̶ 0.49) | 84 | 0.207 |

**Abbreviations:** **BDNF** = brain-derived neurotrophic factor; **ES** = effect size; **CI** = confidence interval; **sIL-2R** = soluble IL-2 receptor1

a *P* value in test of overall effect (z).