**Supplementary Materials**

**Supplemental Method**

*Substance Use Exclusionary Criteria*

• Any current drug use as assessed by a urine drug test (covering cocaine, cannabinoids, opiates, amphetamines, methamphetamines, phencyclidine, MDMA, benzodiazepines, methadone, oxycodone, tricyclic antidepressants, and barbiturates);

• Any alcohol-induced blackouts within the past year, or more than 3 lifetime blackouts;

• History of moderate or severe alcohol or substance use disorder;

• History of regular use (5-7x per week) of marijuana before the age of 15;

• Lifetime history of other recreational drug use beyond the following limits:

 > 10 uses: Mushrooms

 > 5 uses: Anxiolytics, cocaine, other hallucinogens (LSD, Ecstasy), opioids, or stimulants

 (this includes prescribed stimulants such as methylphenidate). Prescribed opioids for a limited period (e.g., post-surgery) is OK if not in the past 3 months.

 > 1 use: Inhalants, IV drugs, crack cocaine, or crystal methamphetamine

• Use of any other drug or herbal supplement with well-characterized psychotropic effects (such as prednisone or St. John's Wort) within the past three weeks;

• Use of any medication in the past 24 hours (including antibiotics, asthma inhalants, pain relievers, antihistamines, or over-the-counter medications);

• Recent use (within 3 weeks) or any medication that affects blood flow or blood pressure, or which is vasodilating/vasoconstricting (for participants undergoing neuroimaging).

*Participants*

Among the 88 participants, 75 completed the neuroimaging session. Since collection of blood sample was added midway, only 63 participants had usable IL-6 data. In addition, only 66 had useable neuroimaging data after exclusion for artifacts, yielding a total of 53 participants with both IL-6 and structural MRI data.

*Procedure*

Upon arrival for session 1, participants were informed about the procedures, offered the opportunity to ask questions and asked to provide written informed consent to a protocol approved by the Partners Institutional Review Board. Next, participants completed a structured clinical interview (First et al., 2002) with a PhD or Masters-level clinician

*Plasma Collection and IL-6 Analysis*

Participants had an 18-gauge intravenous catheter positioned in a major vein in the antecubital fossa of their non-dominant arm. The catheter was connected to a 3-way stopcock valve using a sterile procedure, which in turn was connected to a normal saline drip on the one port and a Vacutainer holder assembly on the other port and. For each blood draw, the 3-way stopcock valve was used to turn off the saline drip and allow for blood to be drawn using Vacutainer blood collection tubes. Approximately 6mL of whole blood was collected from each participant. Each blood draw was preceded by a “waste” tube collection of 6-8mL to clear saline from the proximal line and IV catheter before blood collection. Between draws, the saline drip rate was kept at circa 20cc/hr. in order to maintain patency of the intravenous line to allow sequential blood draws. Samples were collected in EDTA tubes and centrifuged within 20 min of collection at 1300G for 10 min at room temperature in a Vanguard V6500 centrifuge model (Hamilton Bell), yielding approximately 3 mL of plasma sample. Using a pipette, plasma was then transferred in aliquots of 1mL into two 2mL clean cryovials, and immediately stored in a –80°C freezer (1mL was used for hormonal assays reported in Treadway et al., 2017).

*High Sensitivity C-Reactive Protein (hsCRP)*

The concentration of CRP was determined using an immunoturbidimetric assay on the Roche Cobas 6000 system (Roche Diagnostics - Indianapolis, IN), using reagents and calibrators from Roche. In this assay, an antigen-antibody reaction occurs between CRP in the sample and an anti-CRP antibody that has been sensitized to latex particles, and agglutination results. This antigen-antibody complex causes a decrease in transmitted light, which is detected spectrophotometrically, with the magnitude of the change being proportional to the concentration of CRP in the sample. This assay is approved by the Food and Drug Administration for clinical use. This high-sensitivity assay has a limit of detection of 0.03 mg/L. The day-to-day variabilities of the assay was 3.0% on average.

**Table S1: Characteristics of Study 1 sample**

|  |  |
| --- | --- |
| N = 53, all female |   |
| Age (mean, M; standard deviation, SD) | 25.6 (5.0) |
| Years of education (M, SD) | 16.1 (2.4) |
| Beck Depression Inventory score (M, SD) | 1.3 (1.7) |
| Race (N, % of total) |  |
| *Asian* | 3 (6%) |
| *Black/ African American* | 7 (13%) |
| *White* | 43 (81%) |
| Interleukin 6 (IL6) mg/L (M, SD) | 1.15 (0.85) |
| C-Reactive protein (CRP) mg/L (M, SD) | 2.28 (3.22) |

**Table S2: Characteristics of Study 2 biobank sample**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | Probable MDD | Probable non-MDD | Total |
| Sex (N, % total): |  |  |  |
|  *Female* | 1,656 (20.2%) | 6,557 | 8,213 |
|  *Male* | 885 (20.2%) | 3,491 | 4,376 |
| Race (N, % total): |  |  |  |
|  *Asian* | 12 (5.9%) | 190 | 202 |
|  *Black* | 135 (20.2%) | 532 | 667 |
|  *White* | 2,144 (19.9%) | 8,639 | 10,783 |
|  *Other* | 118 (33.4%) | 235 | 353 |
|  *Unknown* | 132 (22.6%) | 452 | 584 |
| Body mass index (median): | 28.3 | 29.7  | 28.6 |
| Count of CRP labs (median) | 2 | 1 | 1 |
| Education (N, % total) \*: |  |  |  |
|  *Grade school* | 8 (32.0%) | 17 | 25 |
|  *Some high school* | 19 (24.7%) | 58 | 77 |
|  *Finished high school* | 110 (21.6%) | 399 | 509 |
|  *Some college* | 132 (26.7%) | 494 | 626 |
|  *Vocational school* | 123 (25.6%) | 358 | 481 |
|  *Four-year college* | 227 (16.7%) | 1,133 | 1,360 |
|  *Postgraduate degree* | 241 (15.2%) | 1,346 | 1,587 |

\* Educational information only available for 37.1% (N = 4665) of the total sample (N = 12,589)

**Table S3: Model definition with features and betas for depressive phenotype**

|  |  |  |
| --- | --- | --- |
| Feature ID | Beta(weight) | Feature Description |
| Intercept | -2.539 | Model Intercept |
| Depression | 2.018 | Count of coded diagnosis of depression or MDD |
| Mental health disorders | 0.175 | Count of coded diagnosis of any mental health disorder |
| Bipolar disorder | -0.813 | Count of coded diagnosis of bipolar disorder |
| Antidepressants | 1.096 | Count of prescriptions for an antidepressant |
| Antipsychotics | -0.395 | Count of prescriptions for an antipsychotic |
| Anticonvulsants | -0.323 | Count of prescriptions for an anticonvulsant |
| Patient diagnosis count | -0.515 | Total number of visits with a coded diagnosis |

**Table S4: Gold standard criteria used for phenotyping of biobank data**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Definite Criteria | Possible Criteria | Not criteria | Rule out diagnosis | Reference |
| 2 or more mentions of depression diagnosis occurring > than 2 weeks apartANDmention of antidepressant prescribed OR psychotherapy initiated OR ECT treatmentANDno mention of a rule out diagnosis | 2 or more mentions of depression diagnosis occurring > than 2 weeks apartANDno mention of a rule out diagnosis | No mention of Depression OR only 1 mention of depression | Bipolar, Postpartum Depression, Schizophrenia, Schizo-affective Disorder or Mania | www.nami.org |

**Supplemental Results**

**Table S5. Incidence of lifetime chronic inflammatory medical conditions in biobank sample**

|  |  |  |
| --- | --- | --- |
| Medical condition | N cases (MDD) | % total (% total, MDD only) |
| Chronic obstructive pulmonary disease | 196 (54) | 1.6% (2.1%)\* |
| Asthma | 1,828 (595) | 14.5% (23.4%) |
| Coronary artery disease | 1,094 (258) | 8.6% (10.1%) |
| Chronic heart failure | 343 (80) | 2.7% (3.1%) |
| Crohn’s disease | 616 (111) | 4.8% (4.3%) |
| Hypertension | 6,864 (1676) | 54.5% (65.9%) |
| Rheumatoid arthritis | 736 (146) | 5.8% (5.7%) |
| Type I diabetes | 139 (38) | 1.1% (1.5%) |
| Type II diabetes | 1,551 (489) | 12.3% (19.2%) |
| TOTAL with at least one of the above | 8,441 (1,981) | 67.1% (77.9%) |

\* % of total is (n cases)/ (total n); e.g. 196/12,589, values in parentheses indicate (n MDD cases/ total MDD n); e.g. 54/2541.

**Table S6. Correlation of voxel-based morphometry calculated grey matter volume with C-reactive protein (CRP)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Region of interest | Pearson Correlation | Sig | SpearmanCorrelation | Sig |
| Hippocampus | -0.39 | 0.004\* | -0.33 | 0.02 |
| Amygdala | -0.29 | 0.03 | -0.30 | 0.03 |
| Anterior cingulate cortex | -0.23 | 0.10 | -0.18 | 0.20 |
| Caudate nucleus | -0.20 | 0.15 | -0.19 | 0.18 |
| Nucleus accumbens | -0.16 | 0.25 | -0.10 | 0.47 |
| Putamen | -0.28 | 0.05 | -0.28 | 0.04 |

Pearson correlation calculated for log transformed data. All regions of interest bilateral. \* meets Bonferroni correction for multiple comparisons (threshold for α < 0.05 and 6 tests = 0.008). N = 53.