**Supplementary Methods**

**Cognitive Testing**: *Episodic memory* was measured using CERAD Word List Memory, Recall, and Recognition, immediate and delayed recall of the East Boston Story, and Story A from Logical Memory. *Semantic memory* was measured using a 20-item version of the Boston Naming Test, a 15-item version of Extended Range Vocabulary, a 20-item reading recognition test from the National Adult Reading Test, and Verbal Fluency which involves naming animals and fruits/vegetables in 1-minute epochs. *Working memory* was measured using Digit Span Forward, Digit Span Backward and Digit Ordering. *Perceptual speed* was measured with the oral version of the Symbol Digit Modalities Test, Stroop Test, and Number Comparison. *Visuospatial ability* was assessed with a 15-item version of Judgment of Line Orientation and a 17-item version of Standard Progressive Matrices. Summary measures of these five cognitive domains were formed based in part on a principal-components factor analysis. Raw scores on each test were converted to *z* scores (based on all CEDHA participants at baseline) and then the average z score among tests in a given domain was computed. A global cognitive score was formed by averaging z scores of all tests.

**Serum immune activation and inflammatory markers:** Testing was performed following the manufacturer’s procedures. Standards and experimental samples were tested in duplicate. Milliplex results were acquired on a Labscan 200 analyzer (Luminex, Austin, Tx) using Bio-Plex manager software 6.1 (Bio-Rad, Hercules, CA). A 5-point logistic curve was used to calculate the concentration from the fluorescence intensity of the bead measurements. Samples that were below the level of detection were assigned one-half the lowest detectable value for that analyte.

**Brain image acquisition and processing:** T1-weighted high-resolution anatomical data was collected with a 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence and the following parameters: TE=3.7 ms, TR=8 ms, preparation time=955 ms, flip angle 8°, 181 sagittal slices, acquired voxel-size of 1 mm3. The T1-weighted data from each subject was processed using FreeSurfer version 5.3 extended atlas (http://surfer.nmr.mgh.harvard.edu). Gray matter was segmented into 81 cortical (per hemisphere) and 15 subcortical regions (both hemispheres), and the hippocampus was further segmented into subfields. The results were reviewed by a research engineer with extensive experience in FreeSurfer post-processing, and any errors were corrected manually. Regional brain volumes were calculated from the Freesurfer segmentation. Tissue probability maps were generated for each subject using SPM12 and the volumes of gray matter, white matter and cerebrospinal fluid were added to obtain the total intracranial volume (ICV)18.

**Supplementary Tables**

**Table e1. Correlations of the immune markers**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Neopterin** | **IL1** | **IL6** | **TNF** | **CRP** |
| **Neopterin** | 1.0 | 0.119 | 0.080 | 0.204- | -0.013 |
| **CRP** | -0.013 | -0.26\* | -0.138 | -0.101 | 1.0 |
| **IL1** | 0.119 | 1.0 | 0.687\*\* | 0.551\*\* | -0.26\* |
| **IL6** | 0.079 | 0.687\*\* | 1.0 | 0.734\*\* | -0.138 |
| **TNF** | 0.204 | 0.551\*\* | 0.734\*\* | 1.0 | -0.101 |

\* p < .05

\*\*p < .01

**Table e2. Full models for association of neopterin with total hippocampus outcome**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Model 1** | | | **Model 2** | | | **Model 3** | | | |
| **Terms** | **Est.** | **SE** | **p** | **Est.** | **SE** | **p** | **Est.** | **SE** | | **p** |
| R2 | 0.084 | | | 0.119 | | | 0.230 | | | | |
| **Intercept** | 0.275 | 0.308 |  | 0.175 | 0.306 |  | 0.510 | | 0.306 |  | |
| **Age at scan** | -0.301 | 0.119 | 0.014 | -0.252 | 0.120 | 0.040 | -0.238 | | 0.112 | 0.038 | |
| **Sex (male)** | -0.352 | 0.272 | 0.200 | -0.284 | 0.269 | 0.296 | -0.466 | | 0.258 | 0.076 | |
| **Education** | 0.162 | 0.140 | 0.250 | 0.126 | 0.138 | 0.365 | 0.133 | | 0.129 | 0.309 | |
| **Race (black)** | -0.028 | 0.293 | 0.923 | 0.046 | 0.290 | 0.875 | -0.250 | | 0.287 | 0.387 | |
| **CD4** |  |  |  | 0.231 | 0.124 | 0.068 | 0.048 | | 0.131 | 0.714 | |
| **Neopterin** |  |  |  |  |  |  | 0.398 | | 0.182 | 0.003 | |

All coefficients of determination (R2) shown are adjusted for degrees of freedom. Estimates (SEs) are coefficients (and their standard errors) from a regression model in which the outcome is standardized and all continuous outcomes are also standardized. Each band of 3 columns represents a separate model, showing only the estimates for the terms included.

**Table e3. Full models for associations of neopterin and hippocampal volume with episodic memory outcome**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table e3, part 1** | **Model 1** | | | **Model 2** | | | **Model 3** | | | **Model 4** | | |
| **Models** | **Est.** | **SE** | **p** | **Est.** | **SE** | **p** | **Est.** | **SE** | **P** | **Est.** | **SE** | **p** |
| **R2** | 0.115 | | | 0.181 | | | 0.262 | | | 0.226 | | |
| **Intercept** | 0.423 | 0.295 |  | 0.334 | 0.296 |  | 0.626 | 0.300 |  | 0.289 | 0.288 |  |
| **Age at scan** | 0.060 | 0.114 | 0.601 | 0.104 | 0.116 | 0.372 | 0.116 | 0.110 | 0.296 | 0.169 | 0.116 | 0.152 |
| **Sex (male)** | -0.415 | 0.261 | 0.117 | -0.354 | 0.259 | 0.177 | -0.513 | 0.253 | 0.047 | -0.281 | 0.254 | 0.274 |
| **Education** | 0.408 | 0.134 | 0.003 | 0.376 | 0.113 | 0.006 | 0.382 | 0.126 | 0.004 | 0.344 | 0.130 | 0.011 |
| **Race (black)** | -0.178 | 0.281 | 0.529 | -0.112 | 0.280 | 0.689 | -0.371 | 0.281 | 0.192 | -0.124 | 0.272 | 0.650 |
| **CD4** |  |  |  | 0.205 | 0.120 | 0.093 | 0.045 | 0.128 | 0.724 | 0.146 | 0.120 | 0.230 |
| **Neopterin** |  |  |  |  |  |  | -0.347 | 0.125 | 0.008 |  |  |  |
| **Hippo volume** |  |  |  |  |  |  |  |  |  | 0.257 | 0.121 | 0.038 |
| **Neop x Hippo Int** |  |  |  |  |  |  |  |  |  |  |  |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table e3 (cont.)** | **Model 5** | | | **Model 6** | | |
| **Models** | **Est.** | **SE** | **p** | **Est.** | **SE** | **p** |
| **Adjusted R2** | 0.269 | | | 0.264 | | |
| **Intercept** | 0.546 | 0.305 |  | 0.538 | 0.306 |  |
| **Age at scan** | 0.153 | 0.113 | 0.182 | 0.168 | 0.115 | 0.151 |
| **Sex (male)** | -0.440 | 0.258 | 0.094 | -0.442 | 0.259 | 0.094 |
| **Education** | 0.361 | 0.127 | 0.006 | 0.378 | 0.130 | 0.005 |
| **Race (black)** | -0.331 | 0.282 | 0.244 | -0.261 | 0.298 | 0.385 |
| **CD4** | 0.038 | 0.127 | 0.768 | 0.034 | 0.128 | 0.789 |
| **Neopterin** | -0.284 | 0.135 | 0.039 | -0.256 | 0.140 | 0.074 |
| **Hippo volume** | 0.157 | 0.127 | 0.220 | 0.156 | 0.127 | 0.227 |
| **Neop x Hippo Int** |  |  |  | 0.100 | 0.135 | 0.456 |

All coefficients of determination (R2) shown are adjusted for degrees of freedom. Estimates (SEs) are coefficients (and their standard errors) from a regression model in which the outcome is standardized and all continuous outcomes are also standardized. Each band of 3 columns represents a separate model, showing only the estimates for the terms included.