877 FHS Offspring participants who attended exam 7 between 1998 and 2001 and had an available plasma sample for biomarker profiling

8 Were excluded due to missing APOE genotype

869 Participants with protein panel and complete APOE status

161 Were excluded due to no neuropsychological tests within 5 years after Exam 7

32 Were excluded:

17 with prevalent stroke and

15 with missing covariate or outcome data

837 Participants in incident dementia, AD, and MCI sample

708 Participants with cross-sectional neuropsychological testing outcomes and cognitive factor scores

Figure S1: Study sample inclusion and exclusion description.

Note: FHS = Framingham Heart Study; AD = Alzheimer’s Disease; MCI = mild cognitive impairment, APOE = Apolipoprotein E.

Table S1: Full list of proteins showing the corresponding LOD and proportion with missing values or values below LOD

|  |  |  |
| --- | --- | --- |
| Protein | LOD | Missing Proportion |
| 4E-BP1 | 1.857 | 0.001 |
| ADA | 1.472 | 0.002 |
| ARTN | 1.677 | 0.956 |
| AXIN1 | 1.421 | 0.026 |
| Beta-NGF | -0.231 | 0.990 |
| CASP-8 | 1.577 | 0.034 |
| CCL11 | 2.118 | 0.001 |
| CCL19 | 2.100 | 0.001 |
| CCL20 | 2.531 | 0.001 |
| CCL23 | 2.391 | 0.002 |
| CCL25 | 2.324 | 0.001 |
| CCL28 | 1.284 | 0.001 |
| CCL3 | 1.650 | 0.001 |
| CCL4 | 1.904 | 0.001 |
| CD244 | 2.450 | 0.001 |
| CD40 | 3.540 | 0.001 |
| CD5 | 1.575 | 0.001 |
| CD6 | 2.178 | 0.001 |
| CD8A | 2.679 | 0.002 |
| CDCP1 | 0.335 | 0.001 |
| CSF-1 | 2.270 | 0.001 |
| CST5 | 0.337 | 0.001 |
| CX3CL1 | 1.946 | 0.002 |
| CXCL1 | 2.674 | 0.001 |
| CXCL10 | 2.806 | 0.001 |
| CXCL11 | 1.569 | 0.001 |
| CXCL5 | 2.138 | 0.001 |
| CXCL6 | 2.031 | 0.002 |
| CXCL9 | 1.965 | 0.002 |
| DNER | 0.969 | 0.001 |
| EN-RAGE | 1.881 | 0.003 |
| FGF-19 | 1.825 | 0.001 |
| FGF-21 | 2.436 | 0.004 |
| FGF-23 | 2.174 | 0.942 |
| FGF-5 | 1.617 | 0.727 |
| Flt3L | 2.962 | 0.001 |
| GDNF | 2.377 | 0.913 |
| HGF | 2.144 | 0.001 |
| IFN-gamma | 3.610 | 0.002 |
| IL-1 alpha | -0.437 | 0.971 |
| IL-10RA | 1.512 | 0.695 |
| IL-10RB | 2.616 | 0.001 |
| IL-12B | 1.433 | 0.001 |
| IL-15RA | 1.814 | 0.348 |
| IL-17A | 2.839 | 0.537 |
| IL-17C | 2.316 | 0.054 |
| IL-18R1 | 2.390 | 0.001 |
| IL-20 | 1.557 | 0.970 |
| IL-20RA | 1.913 | 0.908 |
| IL-22 RA1 | 3.381 | 0.977 |
| IL-24 | 3.052 | 0.936 |
| IL-2RB | 1.802 | 0.939 |
| IL10 | 1.741 | 0.002 |
| IL13 | 1.729 | 0.941 |
| IL18 | 2.346 | 0.001 |
| IL2 | 2.413 | 0.996 |
| IL33 | 2.372 | 0.989 |
| IL4 | 1.754 | 0.862 |
| IL5 | 2.406 | 0.867 |
| IL6 | 2.580 | 0.140 |
| IL7 | 1.371 | 0.013 |
| IL8 | 1.023 | 0.001 |
| LAP TGF-beta-1 | 1.434 | 0.001 |
| LIF | 1.048 | 0.981 |
| LIF-R | 1.737 | 0.001 |
| MCP-1 | 3.542 | 0.001 |
| MCP-2 | 2.838 | 0.001 |
| MCP-3 | 1.945 | 0.698 |
| MCP-4 | 4.943 | 0.001 |
| MMP-1 | 3.402 | 0.002 |
| MMP-10 | 2.072 | 0.001 |
| NRTN | 1.658 | 0.944 |
| NT-3 | 2.263 | 0.112 |
| OPG | 2.405 | 0.001 |
| OSM | 0.874 | 0.001 |
| PD-L1 | 2.723 | 0.001 |
| SCF | 2.442 | 0.001 |
| SIRT2 | 3.273 | 0.886 |
| SLAMF1 | 2.410 | 0.233 |
| ST1A1 | 1.114 | 0.544 |
| STAMBP | 1.238 | 0.001 |
| TGF-alpha | 0.493 | 0.003 |
| TNF | 1.040 | 0.001 |
| TNFB | 1.428 | 0.001 |
| TNFRSF9 | 2.048 | 0.001 |
| TNFSF14 | 2.301 | 0.002 |
| TRAIL | 1.687 | 0.001 |
| TRANCE | 1.565 | 0.001 |
| TSLP | 1.654 | 0.889 |
| TWEAK | 1.196 | 0.001 |
| uPA | 2.632 | 0.001 |
| VEGFA | 3.300 | 0.003 |

Note: LOD = limit of detection.

Table S2 (a): The mean and SD of the 68 proteins in the full, NP/factor score, and dementia samples

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Protein | Full Sample  n=869 | | NP/Factor Score Sample n=708 | | Dementia Sample  n=837 | |
|  | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** |
| 4E-BP1 | 6.507 | 0.692 | 6.501 | 0.694 | 6.504 | 0.698 |
| ADA | 5.262 | 0.337 | 5.258 | 0.338 | 5.257 | 0.334 |
| AXIN1 | 2.991 | 0.759 | 2.973 | 0.746 | 2.976 | 0.743 |
| CASP-8 | 2.147 | 0.336 | 2.143 | 0.319 | 2.143 | 0.314 |
| CCL11 | 7.552 | 0.476 | 7.553 | 0.471 | 7.551 | 0.477 |
| CCL19 | 8.710 | 0.914 | 8.715 | 0.913 | 8.711 | 0.908 |
| CCL20 | 6.994 | 1.014 | 6.989 | 1.009 | 6.982 | 1.012 |
| CCL23 | 10.196 | 0.469 | 10.187 | 0.465 | 10.195 | 0.466 |
| CCL25 | 6.487 | 0.585 | 6.480 | 0.582 | 6.489 | 0.585 |
| CCL28 | 2.385 | 0.386 | 2.378 | 0.358 | 2.382 | 0.358 |
| CCL3 | 5.919 | 0.552 | 5.906 | 0.547 | 5.919 | 0.554 |
| CCL4 | 5.918 | 0.615 | 5.913 | 0.603 | 5.927 | 0.617 |
| CD244 | 5.985 | 0.316 | 5.989 | 0.322 | 5.986 | 0.317 |
| CD40 | 10.772 | 0.354 | 10.772 | 0.332 | 10.774 | 0.339 |
| CD5 | 6.069 | 0.399 | 6.058 | 0.382 | 6.067 | 0.381 |
| CD6 | 5.741 | 0.469 | 5.742 | 0.473 | 5.739 | 0.462 |
| CD8A | 9.301 | 0.678 | 9.266 | 0.665 | 9.294 | 0.674 |
| CDCP1 | 2.858 | 0.592 | 2.839 | 0.581 | 2.858 | 0.590 |
| CSF-1 | 9.501 | 0.233 | 9.502 | 0.234 | 9.503 | 0.230 |
| CST5 | 5.628 | 0.473 | 5.625 | 0.478 | 5.629 | 0.477 |
| CX3CL1 | 3.860 | 0.416 | 3.855 | 0.391 | 3.855 | 0.387 |
| CXCL1 | 7.856 | 1.014 | 7.871 | 1.022 | 7.858 | 1.014 |
| CXCL10 | 9.144 | 0.848 | 9.169 | 0.872 | 9.151 | 0.857 |
| CXCL11 | 6.853 | 0.748 | 6.851 | 0.744 | 6.856 | 0.755 |
| CXCL5 | 8.454 | 1.411 | 8.459 | 1.410 | 8.449 | 1.416 |
| CXCL6 | 7.574 | 0.772 | 7.569 | 0.781 | 7.566 | 0.759 |
| CXCL9 | 6.948 | 0.834 | 6.943 | 0.831 | 6.952 | 0.843 |
| DNER | 8.082 | 0.312 | 8.091 | 0.258 | 8.088 | 0.255 |
| EN-RAGE | 2.760 | 0.567 | 2.745 | 0.525 | 2.756 | 0.529 |
| FGF-19 | 7.956 | 0.943 | 7.932 | 0.924 | 7.946 | 0.927 |
| FGF-21 | 5.751 | 1.174 | 5.736 | 1.164 | 5.754 | 1.174 |
| Flt3L | 8.838 | 0.434 | 8.830 | 0.444 | 8.833 | 0.432 |
| HGF | 8.711 | 0.457 | 8.714 | 0.452 | 8.717 | 0.456 |
| IFN-gamma | 6.291 | 0.934 | 6.286 | 0.934 | 6.295 | 0.937 |
| IL-10RB | 6.907 | 0.293 | 6.907 | 0.292 | 6.908 | 0.291 |
| IL-12B | 7.189 | 0.627 | 7.198 | 0.622 | 7.193 | 0.629 |
| IL-15RA | 1.936 | 0.342 | 1.925 | 0.243 | 1.925 | 0.253 |
| IL-17C | 3.235 | 0.703 | 3.222 | 0.682 | 3.231 | 0.692 |
| IL-18R1 | 7.757 | 0.426 | 7.761 | 0.420 | 7.756 | 0.423 |
| IL10 | 3.428 | 0.644 | 3.427 | 0.640 | 3.425 | 0.617 |
| IL18 | 8.869 | 0.562 | 8.862 | 0.562 | 8.870 | 0.560 |
| IL6 | 3.367 | 0.808 | 3.355 | 0.809 | 3.362 | 0.803 |
| IL7 | 2.151 | 0.529 | 2.155 | 0.516 | 2.146 | 0.516 |
| IL8 | 3.892 | 0.610 | 3.882 | 0.609 | 3.888 | 0.606 |
| LAP TGF-beta-1 | 6.641 | 0.346 | 6.637 | 0.339 | 6.641 | 0.344 |
| LIF-R | 3.466 | 0.296 | 3.458 | 0.230 | 3.461 | 0.232 |
| MCP-1 | 11.493 | 0.419 | 11.485 | 0.404 | 11.495 | 0.419 |
| MCP-2 | 8.824 | 0.586 | 8.833 | 0.584 | 8.826 | 0.586 |
| MCP-4 | 12.563 | 0.629 | 12.562 | 0.639 | 12.563 | 0.629 |
| MMP-1 | 11.819 | 1.034 | 11.853 | 1.046 | 11.821 | 1.035 |
| MMP-10 | 8.903 | 0.662 | 8.910 | 0.661 | 8.910 | 0.652 |
| NT-3 | 2.598 | 0.322 | 2.594 | 0.290 | 2.597 | 0.299 |
| OPG | 10.064 | 0.400 | 10.062 | 0.393 | 10.065 | 0.390 |
| OSM | 2.811 | 0.840 | 2.833 | 0.851 | 2.814 | 0.842 |
| PD-L1 | 5.365 | 0.377 | 5.357 | 0.350 | 5.361 | 0.353 |
| SCF | 9.038 | 0.464 | 9.046 | 0.454 | 9.041 | 0.467 |
| SLAMF1 | 2.680 | 0.438 | 2.675 | 0.377 | 2.675 | 0.390 |
| STAMBP | 3.500 | 0.480 | 3.492 | 0.471 | 3.491 | 0.471 |
| TGF-alpha | 2.270 | 0.413 | 2.259 | 0.405 | 2.264 | 0.389 |
| TNF | 3.859 | 0.496 | 3.857 | 0.496 | 3.858 | 0.491 |
| TNFB | 4.553 | 0.468 | 4.554 | 0.474 | 4.556 | 0.468 |
| TNFRSF9 | 5.811 | 0.519 | 5.807 | 0.523 | 5.813 | 0.520 |
| TNFSF14 | 3.675 | 0.456 | 3.676 | 0.449 | 3.672 | 0.450 |
| TRAIL | 7.410 | 0.290 | 7.416 | 0.286 | 7.413 | 0.288 |
| TRANCE | 4.464 | 0.598 | 4.472 | 0.587 | 4.464 | 0.581 |
| TWEAK | 8.197 | 0.323 | 8.203 | 0.304 | 8.201 | 0.305 |
| uPA | 9.928 | 0.334 | 9.932 | 0.326 | 9.933 | 0.325 |
| VEGFA | 10.306 | 0.305 | 10.306 | 0.293 | 10.308 | 0.294 |

Note: NP = Neuropsychological, SD = standard deviation.

Table S2 (b): The summary of Neuropsychological (NP) test and dementia-related outcomes in NP/factor score and dementia sample

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **NP/Factor Score Sample**  **n=708** | | | | | | | | | |
| **NP Tests** | | **E2 carriers**  **n=87** | | **E4 carriers**  **n=133** | | **E3E3**  **n=468** | | **All**  **n=708** | |
|  | | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** |
| **EF domain factor score** | | 0.319 | 0.498 | 0.368 | 0.548 | 0.382 | 0.512 | 0.368 | 0.519 |
| **SIM** | | 16.678 | 3.276 | 16.857 | 3.786 | 16.773 | 3.675 | 16.772 | 3.638 |
| **TRAILSBA** | | 0.992 | 1.243 | 0.829 | 0.577 | 0.796 | 0.676 | 0.842 | 0.813 |
| **LAN domain factor score** | | 0.512 | 0.515 | 0.549 | 0.540 | 0.548 | 0.554 | 0.543 | 0.548 |
| **BNT30** | | 27.264 | 2.517 | 27.654 | 2.290 | 27.482 | 2.528 | 27.481 | 2.481 |
| **MEM domain factor score** | | 0.574 | 0.437 | 0.559 | 0.457 | 0.571 | 0.430 | 0.563 | 0.435 |
| **LMD** | | 11.230 | 3.691 | 10.602 | 3.699 | 10.646 | 3.442 | 10.674 | 3.532 |
| **VRD** | | 7.782 | 3.408 | 8.308 | 3.351 | 8.260 | 3.270 | 8.203 | 3.318 |
| **PASD** | | 8.310 | 1.520 | 8.323 | 1.444 | 8.280 | 1.429 | 8.291 | 1.435 |
| **VP score HVOT** | | 24.856 | 3.378 | 25.167 | 2.826 | 24.983 | 3.012 | 25.014 | 3.001 |
| **Dementia Sample**  **n=837** | | | | | | | | | |
| **Dementia-related Outcomes** | **Follow-up Time** | **E2 carriers**  **n=102** | | **E4 carriers**  **n=164** | | **E3E3**  **n=551** | | **All**  **n=837** | |
| **Incident dementia** | **10 years** | 4 | | 16 | | 20 | | 40 | |
| **Full** | 7 | | 27 | | 50 | | 84 | |
| **Incident AD** | **10 years** | 2 | | 11 | | 15 | | 28 | |
| **Full** | 4 | | 20 | | 37 | | 61 | |
| **MCI** | **10 years** | 8 | | 27 | | 53 | | 88 | |
| **Full** | 10 | | 39 | | 85 | | 134 | |

Note: SIM = Similarities subtest, TRAILSBA = Trails Making test B - Trails Making test A, BNT30 = 30 - item Boston Naming Test, LMD = Logical Memory - delayed recall, VRD = Visual Reproduction - delayed recall, PASD = Paired Association learning - delayed recall, HVOT = Hooper Visual Organization Test, SD = standard deviation, AD = Alzheimer’s Disease, MCI= mild cognitive impairment, EF = executive function, LAN = language, MEM = memory, VP = visual perception.

Table S3: Summary of significant associations for cognitive function outcomes using Model 2

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Domain | Outcome | Full sample | E2 stratum | E4 stratum | E3E3 stratum |
| **Executive Function** | **Factor Score** | : 4 | : 1 |  |  |
| **Executive Function** | **SIM** |  |  |  |  |
| **Executive Function** | **TRAILBA** | : 1 | 1 |  |  |
| **Language** | **Factor Score** | : 3 | : 1 |  | : 1 |
| **Language** | **BNT30** | : 2 | : 1 |  | : 2 |
| Memory | **Factor Score** |  |  | : 1 |  |
| Memory | **LMD** |  |  |  |  |
| Memory | **VRD** |  | : 8 |  |  |
| Memory | **PASD** |  |  |  |  |
| Visual Perception | **HVOT** |  | 12 |  |  |

Note: The covariates adjusted in Model 2 included: sex, age, education level, time in years between exam 7 (blood sample) and cognitive testing date, a retest indicator, APOE genotype, indicators for prevalent cardiovascular diseases such as prevalent stroke, prevalent CVD, and prevalent atrial fibrillation (AF) at examination 7, and the CVD risk factors such as systolic and diastolic blood pressures (mmHg), diabetes status, treatment for hypertension, body-mass index (kg/m2), current smoking status, high-density lipoprotein cholesterol levels (HDL, measured in mg/dL), and use of lipid-lowering agents at examination 7.

APOE = Apolipoprotein E, SIM = Similarities subtest, TRAILSBA = Trails Making test B - Trails Making test A, BNT30 = 30 - item Boston Naming Test, LMD = Logical Memory - delayed recall, VRD = Visual Reproduction - delayed recall, PASD = Paired Association learning - delayed recall, HVOT = Hooper Visual Organization Test.

Table S4: Summary of significant associations for dementia-related outcomes using Model 2

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome | Follow-up time | Full sample | E4 stratum | E3E3 stratum |
| **Incident dementia** | **10 years** | : 1 |  |  |
| **Incident dementia** | **Full** | : 2 |  | : 2 |
| **Incident AD** | **10 years** |  |  |  |
| **Incident AD** | **Full** | : 1  : 1 |  |  |
| **MCI** | **10 years** | : 1  : 1 |  |  |
| **MCI** | **Full** | : 1 |  |  |

Note: The covariates adjusted in Model 2 included: sex, age, education level, APOE genotype, indicators for prevalent cardiovascular diseases (CVD) such as prevalent stroke, prevalent CVD, and prevalent atrial fibrillation (AF) at examination 7, and the CVD risk factors such as systolic and diastolic blood pressures (mmHg), diabetes status, treatment for hypertension, body-mass index (kg/m2), current smoking status, high-density lipoprotein cholesterol levels (HDL, measured in mg/dL), and use of lipid-lowering agents at examination 7.

APOE = Apolipoprotein E, AD = Alzheimer’s Disease, MCI = mild cognitive impairment.

Table S5: Cross-sectional associations of proteins with cognitive function outcomes for the combined and stratified analyses using Model 1(FDR 0.1)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Domain | Outcome | Stratum | Protein | Effect Size ± SE | p-value | FDR |
| Executive Function | **SIM** | **Combined** | LIF-R | -0.1040.034 | 0.002 | 0.080 |
| EN-RAGE | -0.1050.034 | 0.002 | 0.080 |
| **E4** | TGF-alpha | -0.2480.075 | <=0.001 | 0.062 |
| EN-RAGE | -0.2380.079 | 0.002 | 0.083 |
| IL-17C | -0.2000.069 | 0.004 | 0.091 |
| **TRAILBA** | **E3E3** | LIF-R | 0.1400.043 | 0.001 | 0.080 |
| Memory | **Factor Score** | **E4** | IL-17C | -0.0980.031 | 0.002 | 0.092 |
| TWEAK | 0.0930.031 | 0.003 | 0.092 |
| DNER | 0.0940.033 | 0.004 | 0.092 |
| **LMD** | **Combined** | FGF-21 | 0.1150.036 | 0.001 | 0.091 |
| **E3E3** | DNER | -0.1360.042 | 0.001 | 0.052 |
| AXIN1 | 0.1290.043 | 0.003 | 0.052 |
| HGF | 0.1350.046 | 0.003 | 0.052 |
| FGF-21 | 0.1220.042 | 0.004 | 0.052 |
| VEGFA | 0.1230.043 | 0.004 | 0.052 |
| STAMBP | 0.1170.044 | 0.008 | 0.079 |
| IL7 | 0.1110.042 | 0.008 | 0.079 |
| **VRD** | **E2** | IL10 | -0.3730.094 | <=0.001 | 0.005 |
| CCL19 | -0.3100.100 | 0.002 | 0.050 |
| CCL4 | -0.2660.087 | 0.002 | 0.050 |
| **PASD** | **E4** | IL-17C | -0.2090.064 | <=0.001 | 0.075 |
| Visual Perception | **HVOT** | **E2** | CCL11 | -0.4590.122 | <=0.001 | 0.012 |
| CCL19 | -0.4000.112 | <=0.001 | 0.012 |
| MCP-4 | -0.3390.117 | 0.004 | 0.084 |
| TWEAK | -0.2770.099 | 0.005 | 0.090 |

Note: The covariates adjusted in Model 1 included: sex, age, education level, time in years between exam 7 (blood sample) and cognitive testing date, a retest indicator, and APOE genotype.

LMD = Logical Memory - delayed recall, VRD = Visual Reproduction - delayed recall, PASD = Paired Association learning - delayed recall, TRAILSBA = Trails Making test B - Trails Making test A, HVOT = Hooper Visual Organization Test, APOE = Apolipoprotein E, SE = standard error, FDR = false discovery rate.

Table S6: Cross-sectional associations of proteins with cognitive function outcomes for the combined analysis using Model 2 (FDR 0.1)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Domain** | **Outcome** | **Protein** | **Effect Size**  **± SE** | **p-value** | **FDR** |
| **Executive Function** | **Factor Score** | IL7 | -0.049±0.017 | 0.003 | 0.093 |
| IL8 | -0.051±0.018 | 0.005 | 0.093 |
| LAP TGF-beta-1 | -0.051±0.018 | 0.005 | 0.093 |
| LIF-R | -0.050±0.018 | 0.005 | 0.093 |
| **TRAILBA** | SCF | 0.120±0.036 | 0.001 | 0.071 |
| **Language** | **Factor Score** | LIF-R | -0.069±0.021 | 0.001 | 0.035 |
| IL10 | -0.063±0.019 | 0.001 | 0.035 |
| TRANCE | -0.056±0.019 | 0.003 | 0.072 |
| **BNT30** | LIF-R | -0.116±0.035 | 0.001 | 0.059 |
| IL10 | -0.101±0.032 | 0.002 | 0.066 |

Note: The covariates adjusted in Model 2 included: sex, age, education level, time in years between exam 7 (blood sample) and cognitive testing date, a retest indicator, APOE genotype, indicators for prevalent cardiovascular diseases (CVD) such as prevalent stroke, prevalent CVD, and prevalent atrial fibrillation (AF) at examination 7, and the CVD risk factors such as systolic and diastolic blood pressures (mmHg), diabetes status, treatment for hypertension, body-mass index (kg/m2), current smoking status, high-density lipoprotein cholesterol levels (HDL, measured in mg/dL), and use of lipid-lowering agents at examination 7.

TRAILSBA = Trails Making test B - Trails Making test A, BNT30 = 30 - item Boston Naming Test, APOE = Apolipoprotein E, SE = standard error, FDR = false discovery rate.

Table S7: Cross-sectional associations of proteins with cognitive function outcomes for the stratified analyses using Model 2 (FDR 0.1)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Domain** | **Outcome** | **Stratum** | **Protein** | **Effect Size ± SE** | **p-value** | **FDR** |
| **Executive Function** | **Factor Score** | **E2** | PD-L1 | 0. 1450.043 | 0.001 | 0.052 |
| **TRAILBA** | **E2** | PD-L1 | -0. 4040.113 | <=0.001 | 0.025 |
| **Language** | **Factor Score** | **E2** | CCL19 | -0. 1930.055 | <=0.001 | 0.027 |
| **E3E3** | LIF-R | -0. 0830.026 | 0.001 | 0.089 |
| **BNT30** | **E2** | CCL19 | -0. 3880.099 | <=0.001 | 0.006 |
| **E3E3** | LIF-R | -0. 1360.043 | 0.002 | 0.066 |
| IL10 | -0. 1260.041 | 0.002 | 0.066 |
| **Memory** | **Factor Score** | **E4** | IL-17C | -0.1010.029 | <=0.001 | 0.031 |
| **VRD** | **E2** | IL10 | -0.4360.102 | <=0.001 | 0.001 |
| CCL19 | -0.3780.104 | <=0.001 | 0.010 |
| CCL4 | -0.3270.100 | 0.001 | 0.024 |
| ADA | -0.3120.106 | 0.003 | 0.036 |
| CD5 | -0.3960.134 | 0.003 | 0.036 |
| OSM | -0.3040.104 | 0.003 | 0.036 |
| CCL3 | -0.3480.120 | 0.004 | 0.036 |
| CCL11 | -0.3240.118 | 0.006 | 0.053 |
| **Visual Perception** | **HVOT** | **E2** | CCL11 | -0.5430.124 | <=0.001 | 0.001 |
| CCL19 | -0.4570.114 | <=0.001 | 0.002 |
| CD8A | -0.4090.114 | <=0.001 | 0.008 |
| MCP-1 | -0.3980.122 | 0.001 | 0.018 |
| MCP-4 | -0.3930.123 | 0.001 | 0.019 |
| IL18 | -0.3340.113 | 0.003 | 0.032 |
| LIF-R | -0.3310.113 | 0.003 | 0.032 |
| TWEAK | -0.3310.113 | 0.006 | 0.051 |
| CCL4 | -0.2990.113 | 0.008 | 0.061 |
| CXCL6 | -0.3040.116 | 0.009 | 0.061 |
| TNFSF14 | -0.2780.116 | 0.016 | 0.097 |
| TGF-alpha | -0.2930.123 | 0.017 | 0.097 |

Note: The covariates adjusted in Model 2 included: sex, age, education level, time in years between exam 7 (blood sample) and cognitive testing date, a retest indicator, indicators for prevalent cardiovascular diseases (CVD) such as prevalent stroke, prevalent CVD, and prevalent atrial fibrillation (AF) at examination 7, and the CVD risk factors such as systolic and diastolic blood pressures (mmHg), diabetes status, treatment for hypertension, body-mass index (kg/m2), current smoking status, high-density lipoprotein cholesterol levels (HDL, measured in mg/dL), and use of lipid-lowering agents at examination 7.

VRD = Visual Reproduction - delayed recall, TRAILSBA = Trails Making test B - Trails Making test A, HVOT = Hooper Visual Organization Test, BNT30 = 30 - item Boston Naming Test, APOE = Apolipoprotein E, SE = standard error, FDR = false discovery rate.

Table S8: Summary of significant associations for cognitive function outcomes using Model 1 for sensitivity analysis focusing on the participants who underwent NP tests within two years after examination 7 (FDR 0.1)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Domain | Outcome | Full sample | E2 stratum | E4 stratum | E3E3 stratum |
| **Executive Function** | **Factor Score** | : 9 |  | : 5 | : 7 |
| **Executive Function** | **SIM** |  |  | : 1 |  |
| **Executive Function** | **TRAILBA** |  |  |  | : 2 |
| **Language** | **Factor Score** | : 1 |  |  |  |
| **Language** | **BNT30** |  |  |  |  |
| Memory | **Factor Score** |  |  | : 1 |  |
| Memory | **LMD** |  |  |  | : 8  : 1 |
| Memory | **VRD** |  | : 3 | : 1 |  |
| Memory | **PASD** |  |  |  | : 1 |
| Visual Perception | **HVOT** | : 1 | : 4 |  |  |

Note: The covariates adjusted in Model 1 included: sex, age, education level, time in years between exam 7 (blood sample) and cognitive testing date, a retest indicator, and APOE genotype.

SIM = Similarities subtest, TRAILSBA = Trails Making test B - Trails Making test A, BNT30 = 30 - item Boston Naming Test, LMD = Logical Memory - delayed recall, VRD = Visual Reproduction - delayed recall, PASD = Paired Association learning - delayed recall, HVOT = Hooper Visual Organization Test, APOE = Apolipoprotein E, NP = Neuropsychological, FDR = false discovery rate.

Table S9: Cross-sectional associations of proteins with cognitive function outcomes under the combined analysis using Model 1 for sensitivity analysis focusing on the participants who underwent NP tests within two years after examination 7 (FDR 0.1)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Domain | Outcome | Protein | Effect Size ± SE | p-value | FDR |
| Executive Function | **Factor Score** | IL8 | -0.0630.018 | <=0.001 | 0.020 |
| LIF-R | -0.0580.017 | <=0.001 | 0.020 |
| IL7 | -0.0580.018 | 0.001 | 0.020 |
| LAP TGF-beta-1 | -0.0570.018 | 0.001 | 0.024 |
| IL6 | -0.0550.018 | 0.002 | 0.024 |
| MCP-4 | -0.0550.018 | 0.002 | 0.024 |
| TGF-alpha | -0.0510.017 | 0.003 | 0.030 |
| CXCL1 | -0.0470.017 | 0.007 | 0.059 |
| HGF | -0.0450.018 | 0.012 | 0.090 |
| Language | **Factor Score** | IL10 | -0.0630.020 | 0.001 | 0.094 |
| Visual Perception | **HVOT** | MCP-4 | -0.1350.039 | <=0.001 | 0.032 |

Note: The covariates adjusted in Model 1 included: sex, age, education level, time in years between exam 7 (blood sample) and cognitive testing date, a retest indicator, and APOE genotype.

HVOT = Hooper Visual Organization Test, SE = standard error, FDR= false discovery rate.

Table S10: Cross-sectional associations of proteins with cognitive function outcomes under the stratified analysis using Model 1 for sensitivity analysis focusing on the participants who underwent NP tests within two years after examination 7 (FDR 0.1)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Domain | Outcome | Stratum | Protein | Effect Size ± SE | p-value | FDR |
| Executive Function | **Factor Score** | **E4** | TGF-alpha | -0.1310.037 | <=0.001 | 0.032 |
| FGF-21 | -0.1230.043 | 0.004 | 0.087 |
| VEGFA | -0.1170.042 | 0.005 | 0.087 |
| Flt3L | -0.1050.038 | 0.005 | 0.087 |
| OSM | -0.1030.038 | 0.005 | 0.087 |
| **E3E3** | IL8 | -0.0780.023 | 0.001 | 0.036 |
| IL7 | -0.0690.022 | 0.002 | 0.036 |
| LAP TGF-beta-1 | -0.0670.022 | 0.002 | 0.036 |
| CXCL1 | -0.0640.021 | 0.002 | 0.036 |
| SLAMF1 | -0.0630.021 | 0.003 | 0.036 |
| LIF-R | -0.0580.021 | 0.006 | 0.071 |
| CXCL11 | -0.0580.022 | 0.009 | 0.091 |
| **SIM** | **E4** | TGF-alpha | -0.2570.076 | 0.001 | 0.047 |
| **TRAILBA** | **E3E3** | SLAMF1 | 0.1350.044 | 0.002 | 0.077 |
| LIF-R | 0.130.044 | 0.002 | 0.077 |
| Memory | **Factor Score** | **E4** | IL-17C | -0.1120.031 | <=0.001 | 0.021 |
| **LMD** | **E3E3** | DNER | -0.1580.044 | <=0.001 | 0.022 |
| VEGFA | 0.1360.044 | 0.002 | 0.039 |
| STAMBP | 0.1380.046 | 0.003 | 0.039 |
| HGF | 0.1420.048 | 0.003 | 0.039 |
| AXIN1 | 0.1330.045 | 0.003 | 0.039 |
| MCP-2 | 0.1300.044 | 0.003 | 0.039 |
| TNFSF14 | 0.1250.044 | 0.005 | 0.046 |
| IL7 | 0.1200.045 | 0.007 | 0.057 |
| FGF-21 | 0.1170.044 | 0.008 | 0.057 |
| **VRD** | **E2** | IL10 | -0.3770.105 | <=0.001 | 0.022 |
| CCL19 | -0.3470.112 | 0.002 | 0.057 |
| CCL4 | -0.2690.089 | 0.003 | 0.057 |
| **PASD** | **E3E3** | SLAMF1 | 0.1300.041 | 0.001 | 0.095 |
| Visual Perception | **HVOT** | **E2** | CCL11 | -0.4640.131 | <=0.001 | 0.020 |
| CCL19 | -0.4340.126 | <=0.001 | 0.020 |
| TWEAK | -0.3090.104 | 0.003 | 0.062 |
| MCP-4 | -0.3530.121 | 0.004 | 0.062 |

Note: The covariates adjusted in Model 1 included: sex, age, education level, time in years between exam 7 (blood sample) and cognitive testing date, a retest indicator, and APOE genotype.

SIM = Similarities subtest, TRAILSBA = Trails Making test B - Trails Making test A, LMD = Logical Memory - delayed recall, VRD = Visual Reproduction - delayed recall, PASD = Paired Association learning - delayed recall, HVOT = Hooper Visual Organization Test, FDR= false discovery rate.

Table S11: Summary of significant associations for cognitive function outcomes using Model 1 for sensitivity analysis focusing on the sample excluding participants with prevalent stroke, prevalent chronic leukemia or lymphoma, who reported use of glucocorticoids at examination 7, and who were identified as outliers (FDR 0.1)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Domain | Outcome | Full sample | E2 stratum | E4 stratum | E3E3 stratum |
| **Executive Function** | **Factor Score** | : 9 | : 1 | : 1  : 7 | : 6 |
| **Executive Function** | **SIM** | : 1 | : 1 | : 4 |  |
| **Executive Function** | **TRAILBA** |  | : 1 |  |  |
| **Language** | **Factor Score** |  |  |  |  |
| **Language** | **BNT30** |  |  |  |  |
| Memory | **Factor Score** |  |  | : 2  : 1 | : 1 |
| Memory | **LMD** | : 3 |  |  | : 5  : 1 |
| Memory | **VRD** |  | : 7 | : 1 |  |
| Memory | **PASD** |  |  | : 1 |  |
| Visual Perception | **HVOT** |  | : 3 |  |  |

Note: The covariates adjusted in Model 1 included: sex, age, education level, time in years between exam 7 (blood sample) and cognitive testing date, a retest indicator, and APOE genotype.

SIM = Similarities subtest, TRAILSBA = Trails Making test B - Trails Making test A, BNT30 = 30 - item Boston Naming Test, LMD = Logical Memory - delayed recall, VRD = Visual Reproduction - delayed recall, PASD = Paired Association learning - delayed recall, HVOT = Hooper Visual Organization Test, APOE = Apolipoprotein E, FDR = false discovery rate.

Table S12: Cross-sectional associations of proteins with cognitive function outcomes under the combined analysis using Model 1 for sensitivity analysis focusing on the sample excluding participants with prevalent stroke, prevalent chronic leukemia or lymphoma, who reported use of glucocorticoids at examination 7, and who were identified as outliers (FDR 0.1)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Domain | Outcome | Protein | Effect Size ± SE | p-value | FDR |
| Executive Function | **Factor Score** | IL8 | -0.0710.018 | <=0.001 | 0.008 |
| LIF-R | -0.0640.018 | <=0.001 | 0.012 |
| LAP TGF-beta-1 | -0.0630.018 | 0.001 | 0.013 |
| IL6 | -0.0610.018 | 0.001 | 0.013 |
| HGF | -0.0630.019 | 0.001 | 0.013 |
| MCP-4 | -0.0550.018 | 0.003 | 0.031 |
| TGF-alpha | -0.0500.018 | 0.005 | 0.047 |
| IL10 | -0.0440.018 | 0.013 | 0.099 |
| IL-17C | -0.0430.017 | 0.013 | 0.099 |
| **SIM** | EN-RAGE | -0.1220.038 | 0.001 | 0.079 |
| Memory | **LMD** | FGF-21 | 0.1330.038 | <=0.001 | 0.027 |
| CD40 | 0.1180.039 | 0.003 | 0.089 |
| AXIN1 | 0.1080.037 | 0.004 | 0.090 |

Note: The covariates adjusted in Model 1 included: sex, age, education level, time in years between exam 7 (blood sample) and cognitive testing date, a retest indicator, and APOE genotype.

SIM = Similarities subtest, LMD = Logical Memory - delayed recall, SE = standard error, FDR= false discovery rate.

Table S13: Cross-sectional associations of proteins with cognitive function outcomes under the stratified analysis using Model 1 for sensitivity analysis focusing on the sample excluding participants with prevalent stroke, prevalent chronic leukemia or lymphoma, who reported use of glucocorticoids at examination 7, and who were identified as outliers (FDR 0.1)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Domain | Outcome | Stratum | Protein | Effect Size ± SE | p-value | FDR |
| Executive Function | **Factor Score** | **E2** | PD-L1 | 0.1490.046 | 0.001 | 0.071 |
| **E4** | TGF-alpha | -0.1500.040 | <=0.001 | 0.011 |
| LAP TGF-beta-1 | -0.1350.046 | 0.003 | 0.074 |
| FGF-21 | -0.1210.043 | 0.005 | 0.074 |
| HGF | -0.1170.042 | 0.005 | 0.074 |
| IL-17C | -0.0990.036 | 0.006 | 0.074 |
| OSM | -0.1060.039 | 0.007 | 0.074 |
| TWEAK | 0.0970.037 | 0.008 | 0.077 |
| LIF-R | -0.1110.044 | 0.011 | 0.095 |
| **E3E3** | IL8 | -0.0800.024 | 0.001 | 0.040 |
| LAP TGF-beta-1 | -0.0620.022 | 0.005 | 0.086 |
| LIF-R | -0.0610.022 | 0.006 | 0.086 |
| HGF | -0.0650.024 | 0.006 | 0.086 |
| IL6 | -0.0600.022 | 0.007 | 0.086 |
| MCP-4 | -0.0600.022 | 0.008 | 0.086 |
| **SIM** | **E2** | ADA | -0.2670.081 | 0.001 | 0.070 |
| **E4** | IL-17C | -0.2460.075 | 0.001 | 0.049 |
| LAP TGF-beta-1 | -0.2940.094 | 0.002 | 0.049 |
| TGF-alpha | -0.2530.083 | 0.002 | 0.049 |
| EN-RAGE | -0.2540.085 | 0.003 | 0.049 |
| **TRAILBA** | **E2** | PD-L1 | -0.4520.117 | 0.001 | 0.007 |
| Memory | **Factor Score** | **E4** | DNER | 0.1210.034 | <=0.001 | 0.018 |
| IL-17C | -0.1120.032 | 0.001 | 0.018 |
| TWEAK | 0.1030.033 | 0.002 | 0.040 |
| **E3E3** | DNER | -0.0620.019 | 0.001 | 0.058 |
| **LMD** | **E3E3** | FGF-21 | 0.1450.043 | 0.001 | 0.050 |
| DNER | -0.1400.044 | 0.001 | 0.050 |
| AXIN1 | 0.1370.045 | 0.002 | 0.055 |
| VEGFA | 0.1260.045 | 0.005 | 0.086 |
| MCP-2 | 0.1210.045 | 0.007 | 0.089 |
| STAMBP | 0.1230.046 | 0.008 | 0.089 |
| **VRD** | **E2** | IL10 | -0.4160.104 | <=0.001 | 0.004 |
| CCL3 | -0.3350.106 | 0.002 | 0.035 |
| CCL4 | -0.2970.096 | 0.002 | 0.035 |
| CCL19 | -0.3220.104 | 0.002 | 0.035 |
| CD5 | -0.3890.129 | 0.003 | 0.035 |
| ADA | -0.2620.097 | 0.007 | 0.069 |
| IL18 | -0.2740.102 | 0.007 | 0.069 |
| **E4** | DNER | 0.2290.071 | 0.001 | 0.084 |
| **PASD** | **E4** | IL-17C | -0.2180.067 | <=0.001 | 0.080 |
| Visual Perception | **HVOT** | **E2** | CCL11 | -0.5120.128 | <=0.001 | 0.005 |
| CCL19 | -0.4200.118 | <=0.001 | 0.012 |
| MCP-4 | -0.4320.131 | 0.001 | 0.023 |

Note: The covariates adjusted in Model 1 included: sex, age, education level, time in years between exam 7 (blood sample) and cognitive testing date, a retest indicator, and APOE genotype.

SIM = Similarities subtest, TRAILSBA = Trails Making test B - Trails Making test A, LMD = Logical Memory - delayed recall, VRD = Visual Reproduction - delayed recall, PASD = Paired Association learning - delayed recall, HVOT = Hooper Visual Organization Test, SE = standard error, FDR= false discovery rate.

Table S14: Cross-sectional associations of proteins with dementia-related outcomes for the combined and stratified analyses using Model 2 (FDR 0.1)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | Follow-up Time | Stratum | Protein | Hazard Ratio | 95% CI | p-value | FDR |
| Incident dementia | **10 years** | **Combined** | TNFB | 1.86 | (1.33, 2.61) | <=0.001 | 0.022 |
| **Full** | **Combined** | TNFB | 1.65 | (1.33, 2.04) | <=0.001 | <=0.001 |
| CDCP1 | 1.67 | (1.27, 2.20) | <=0.001 | 0.009 |
| **E3E3** | CDCP1 | 1.84 | (1.32, 2.59) | <=0.001 | 0.032 |
| CX3CL1 | 1.54 | (1.17, 2.02) | 0.002 | 0.060 |
| Incident AD | **Full** | **Combined** | TNFB | 1.64 | (1.27, 2.12) | <=0.001 | 0.009 |
| TWEAK | 0.69 | (0.54, 0.88) | 0.003 | 0.097 |
| MCI | **10 years** | **Combined** | TNFB | 1.50 | (1.21, 1.87) | <=0.001 | 0.017 |
| FGF-19 | 0.69 | (0.54, 0.88) | 0.003 | 0.087 |
| **Full** | **Combined** | TNFB | 1.42 | (1.20, 1.69) | <=0.001 | 0.005 |

Note: The covariates adjusted in Model 2 included: sex, age, education level, APOE genotype, indicators for prevalent cardiovascular diseases (CVD) such as prevalent stroke, prevalent CVD, and prevalent atrial fibrillation (AF) at examination 7, and the CVD risk factors such as systolic and diastolic blood pressures (mmHg), diabetes status, treatment for hypertension, body-mass index (kg/m2), current smoking status, high-density lipoprotein cholesterol levels (HDL, measured in mg/dL), and use of lipid-lowering agents at examination 7.

FDR= false discovery rate, CI = confidence interval, AD = Alzheimer’s Disease, MCI = mild cognitive impairment.

Table S15: Cross-sectional associations of proteins with dementia-related outcomes for the combined and stratified analyses using Model 1 for sensitivity analysis on participants with age older than 60 years old (FDR 0.1)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | Follow-up Time | Stratum | Protein | Hazard Ratio | 95% CI | p-value | FDR |
| Incident dementia | **10 years** | **Combined** | TNFB | 1.80 | (1.32, 2.46) | <=0.001 | 0.014 |
| **Full** | **Combined** | TNFB | 1.59 | (1.29, 1.96) | <=0.001 | 0.001 |
| CDCP1 | 1.62 | (1.23, 2.15) | <=0.001 | 0.026 |
| TWEAK | 0.72 | (0.59, 0.89) | 0.002 | 0.042 |
| **E4** | TNF | 1.84 | (1.29, 2.61) | <=0.001 | 0.046 |
| **E3E3** | CX3CL1 | 1.63 | (1.23, 2.17) | 0.001 | 0.049 |
| CDCP1 | 1.83 | (1.25, 2.68) | 0.002 | 0.059 |
| Incident AD | **10 years** | **Combined** | TNFB | 1.72 | (1.23, 2.40) | 0.001 | 0.094 |
| **Full** | **Combined** | TNFB | 1.65 | (1.29, 2.12) | <=0.001 | 0.005 |
| TWEAK | 0.70 | (0.55, 0.88) | 0.003 | 0.095 |
| **E4** | TNFB | 1.95 | (1.32, 2.89) | <=0.001 | 0.054 |
| MCI | **10 years** | **Combined** | TNFB | 1.48 | (1.19, 1.84) | <=0.001 | 0.028 |
| **Full** | **Combined** | TNFB | 1.42 | (1.18, 1.70) | <=0.001 | 0.011 |
| **E3E3** | CX3CL1 | 1.52 | (1.17, 1.96) | <=0.001 | 0.095 |

Note: The covariates adjusted in Model 1 included: sex, age, education level, and APOE genotype.

FDR= false discovery rate, CI = confidence interval, AD = Alzheimer’s Disease, MCI = mild cognitive impairment.