**Supplementary Material**

**Neuropsychological Decline Improves Prediction of Dementia Beyond Alzheimer’s Disease Biomarker and Mild Cognitive Impairment Diagnoses**

**Supplementary Table 1.** All events by cognitive diagnosis and NP decline

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Group** | **Months of Follow-up** | **No Progression** | **Progression to Dementia** | **Total** |
| **CN NP-** | 12 | 24 | 0 | 24 |
|  | 18 | 2 | 0 | 2 |
|  | 24 | 81 | 4 | 85 |
|  | 36 | 98 | 4 | 102 |
|  | 48 | 144 | 5 | 149 |
|  | 60 | 40 | 3 | 43 |
|  | 72 | 18 | 4 | 22 |
|  | 84 | 10 | 1 | 11 |
|  | 96 | 14 | 3 | 17 |
|  | 108 | 28 | 3 | 31 |
|  | 120 | 34 | 3 | 37 |
| **CN NP+** | *Subtotal* | 493 | 30 | 523 |
|  | 12 | 8 | 0 | 8 |
|  | 18 | 2 | 3 | 5 |
|  | 24 | 12 | 9 | 21 |
|  | 36 | 19 | 7 | 26 |
|  | 48 | 31 | 6 | 37 |
|  | 60 | 17 | 2 | 19 |
|  | 72 | 5 | 3 | 8 |
|  | 84 | 0 | 1 | 1 |
|  | 96 | 6 | 2 | 8 |
|  | 108 | 6 | 1 | 7 |
|  | 120 | 5 | 0 | 5 |
| **MCI NP-** | *Subtotal* | 111 | 34 | 145 |
|  | 12 | 13 | 0 | 13 |
|  | 18 | 3 | 3 | 6 |
|  | 24 | 19 | 11 | 30 |
|  | 36 | 16 | 6 | 22 |
|  | 48 | 28 | 3 | 31 |
|  | 60 | 12 | 0 | 12 |
|  | 72 | 0 | 1 | 1 |
|  | 84 | 1 | 1 | 2 |
|  | 96 | 1 | 5 | 6 |
|  | 108 | 4 | 0 | 4 |
|  | 120 | 1 | 0 | 1 |
| **MCI NP+** | *Subtotal* | 98 | 30 | 128 |
|  | 12 | 18 | 0 | 18 |
|  | 18 | 7 | 25 | 32 |
|  | 24 | 23 | 47 | 70 |
|  | 36 | 40 | 27 | 67 |
|  | 48 | 28 | 15 | 43 |
|  | 60 | 12 | 4 | 16 |
|  | 72 | 3 | 3 | 6 |
|  | 84 | 2 | 0 | 2 |
|  | 96 | 2 | 2 | 4 |
|  | 108 | 3 | 1 | 4 |
|  | 120 | 3 | 1 | 4 |
| **All cases** | *Subtotal* | 141 | 125 | 266 |
|  | 12 | 63 | 0 | 63 |
|  | 18 | 14 | 31 | 45 |
|  | 24 | 135 | 71 | 206 |
|  | 36 | 173 | 44 | 217 |
|  | 48 | 231 | 29 | 260 |
|  | 60 | 81 | 9 | 90 |
|  | 72 | 26 | 11 | 37 |
|  | 84 | 13 | 3 | 16 |
|  | 96 | 23 | 12 | 35 |
|  | 108 | 41 | 5 | 46 |
|  | 120 | 43 | 4 | 47 |
|  | *Total* | 843 | 219 | 1062 |

**Supplementary Table 2.** Descriptive statistics for cognitive diagnosis x NP decline

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **N** | **CDR 0.5 (%)** | **MMSE (SD)** | **LM Story A delay recall (SD)** |
| **CN / NP-** | 521 | 198 (38.0%) | 28.9 (1.3) | 11.5 (4.0) |
| **CN / NP+** | 130 | 79 (60.8%) | 28.2 (1.7) | 8.5 (4.2) |
| **MCI / NP-** | 197 | 175 (88.8%) | 28.0 (1.7) | 6.5 (3.5) |
| **MCI / NP+** | 217 | 206 (94.9%) | 28.3 (1.7) | 4.9 (3.5) |

**Supplementary Table 3.** Cognitive diagnosis model for 48-month follow-up

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Wald** | ***p*** | **Odds Ratio** | **95% Confidence Interval** | |
|  |  |  |  | Lower | Upper |
| **Age** | 6.157 | 0.013 | 1.029 | 1.006 | 1.053 |
| **Sex** | 0.018 | 0.893 | 1.022 | 0.747 | 1.398 |
| **Education** | 0.527 | 0.468 | 1.019 | 0.968 | 1.073 |
| **APOE ε4** | 42.940 | <0.001 | 2.887 | 2.103 | 3.965 |
| **Cognitive Diagnosis** | 55.256 | <0.001 | 4.266 | 2.910 | 6.254 |
| **NP decline** | 67.440 | <0.001 | 3.103 | 2.368 | 4.066 |

**Supplementary Table 4.** Findings were replicated in two separate analyses wherein a random subsample of robustly normal participants was used to generate NP decline equations. The subsample used to generate the NP decline equations was removed from the test sample used in Cox regressions predicting future progression to dementia.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **1st Random Analysis** | **Wald** | ***p*** | **Odds Ratio** | **95% Confidence Interval** | |
|  |  |  |  | Lower | Upper |
| **Age** | 6.276 | 0.012 | 1.025 | 1.005 | 1.046 |
| **Sex** | 2.114 | 0.146 | 0.810 | 0.610 | 1.076 |
| **Education** | 3.177 | 0.075 | 1.044 | 0.996 | 1.095 |
| **APOE ε4** | 43.555 | <0.001 | 2.586 | 1.950 | 3.428 |
| **Cognitive Diagnosis** | 32.447 | <0.001 | 4.077 | 2.514 | 6.611 |
| **NP decline** | 74.904 | <0.001 | 2.685 | 2.147 | 3.358 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **2nd Random Analysis** | **Wald** | ***p*** | **Odds Ratio** | **95% Confidence Interval** | |
|  |  |  |  | Lower | Upper |
| **Age** | 6.777 | 0.009 | 1.026 | 1.006 | 1.047 |
| **Sex** | 1.668 | 0.197 | 0.829 | 0.624 | 1.102 |
| **Education** | 2.425 | 0.119 | 1.039 | 0.990 | 1.091 |
| **APOE ε4** | 44.674 | <0.001 | 2.620 | 1.975 | 3.475 |
| **Cognitive Diagnosis** | 35.739 | <0.001 | 4.370 | 2.695 | 7.087 |
| **NP decline** | 66.763 | <0.001 | 2.642 | 2.093 | 3.335 |

**Supplementary Table 5.** NP decline predicts progression to ADNI MCI or dementia in the ADNI cognitively normal subgroup.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Wald** | ***p*** | **Odds Ratio** | **95% Confidence Interval** | |
|  |  |  |  | Lower | Upper |
| **Age** | 1.997 | 0.158 | 0.965 | 0.918 | 1.014 |
| **Sex** | 0.333 | 0.564 | 1.18 | 0.673 | 2.066 |
| **Education** | 2.341 | 0.126 | 0.928 | 0.843 | 1.021 |
| **APOE ε4** | 6.782 | 0.009 | 2.059 | 1.196 | 3.545 |
| **NP decline** | 5.254 | 0.022 | 1.839 | 1.092 | 3.098 |

**Supplemental Table 6.** Simple difference scores z-transformed using the same robustly normal subgroup also predict progression to dementia.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Wald** | ***p*** | **Odds Ratio** | **95% Confidence Interval** | |
|  |  |  |  | Lower | Upper |
| **Age** | 14.95 | <0.001 | 1.041 | 1.02 | 1.063 |
| **Sex** | 0.511 | 0.475 | 0.902 | 0.681 | 1.196 |
| **Education** | 0.315 | 0.574 | 1.014 | 0.967 | 1.063 |
| **APOE ε4** | 65.832 | <0.001 | 3.228 | 2.432 | 4.284 |
| **Cognitive Diagnosis** | 106.171 | <0.001 | 4.977 | 3.668 | 6.754 |
| **NP decline** | 19.061 | <0.001 | 1.959 | 1.448 | 2.649 |

**Supplementary Table 7.** All events by cognitive diagnosis, biomarker profile and NP decline

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Months of Follow-up** | **No Progression** | **Progression to Dementia** | **Total** |
| **CN NP-** | *Aβ-Ptau-* | 12 | 8 | 0 | 8 |
|  |  | 24 | 35 | 0 | 35 |
|  |  | 36 | 32 | 0 | 32 |
|  |  | 48 | 58 | 0 | 58 |
|  |  | 60 | 17 | 0 | 17 |
|  |  | 72 | 7 | 0 | 7 |
|  |  | 84 | 4 | 0 | 4 |
|  |  | 96 | 3 | 0 | 3 |
|  |  | 108 | 5 | 0 | 5 |
|  |  | 120 | 7 | 0 | 7 |
|  |  | *Subtotal* | 176 | 0 | 176 |
|  | *Aβ+Ptau-* | 12 | 6 | 0 | 6 |
|  |  | 24 | 13 | 0 | 13 |
|  |  | 36 | 15 | 0 | 15 |
|  |  | 48 | 24 | 2 | 26 |
|  |  | 60 | 5 | 0 | 5 |
|  |  | 72 | 1 | 1 | 2 |
|  |  | 96 | 3 | 0 | 3 |
|  |  | 108 | 1 | 1 | 2 |
|  |  | 120 | 2 | 0 | 2 |
|  |  | *Subtotal* | 70 | 4 | 74 |
|  | *Aβ-Ptau+* | 12 | 2 | 0 | 2 |
|  |  | 24 | 8 | 1 | 9 |
|  |  | 36 | 8 | 0 | 8 |
|  |  | 48 | 25 | 0 | 25 |
|  |  | 60 | 8 | 0 | 8 |
|  |  | 72 | 2 | 0 | 2 |
|  |  | 96 | 1 | 1 | 2 |
|  |  | 108 | 2 | 0 | 2 |
|  |  | 120 | 5 | 0 | 5 |
|  |  | *Subtotal* | 61 | 2 | 63 |
|  | *Aβ+Ptau+* | 12 | 3 | 0 | 3 |
|  |  | 24 | 8 | 2 | 10 |
|  |  | 36 | 11 | 0 | 11 |
|  |  | 48 | 16 | 1 | 17 |
|  |  | 60 | 2 | 1 | 3 |
|  |  | 72 | 3 | 1 | 4 |
|  |  | 84 | 1 | 0 | 1 |
|  |  | 108 | 1 | 0 | 1 |
|  |  | 120 | 0 | 2 | 2 |
|  |  | *Subtotal* | 45 | 7 | 52 |
| **CN NP+** | *Aβ-Ptau-* | 12 | 3 | 0 | 3 |
|  |  | 24 | 4 | 1 | 5 |
|  |  | 36 | 5 | 0 | 5 |
|  |  | 48 | 10 | 0 | 10 |
|  |  | 60 | 7 | 0 | 7 |
|  |  | 72 | 2 | 0 | 2 |
|  |  | 96 | 2 | 1 | 3 |
|  |  | 108 | 2 | 0 | 2 |
|  |  | 120 | 1 | 0 | 1 |
|  |  | *Subtotal* | 36 | 2 | 38 |
|  | *Aβ+Ptau-* | 12 | 3 | 0 | 3 |
|  |  | 18 | 0 | 1 | 1 |
|  |  | 24 | 3 | 1 | 4 |
|  |  | 36 | 1 | 1 | 2 |
|  |  | 48 | 7 | 0 | 7 |
|  |  | 60 | 5 | 0 | 5 |
|  |  | 72 | 2 | 0 | 2 |
|  |  | 96 | 1 | 0 | 1 |
|  |  | 108 | 0 | 1 | 1 |
|  |  | *Subtotal* | 22 | 4 | 26 |
|  | *Aβ-Ptau+* | 18 | 1 | 0 | 1 |
|  |  | 36 | 2 | 1 | 3 |
|  |  | 48 | 5 | 0 | 5 |
|  |  | 60 | 3 | 0 | 3 |
|  |  | 72 | 1 | 1 | 2 |
|  |  | 108 | 1 | 0 | 1 |
|  |  | 120 | 1 | 0 | 1 |
|  |  | *Subtotal* | 14 | 2 | 16 |
|  | *Aβ+Ptau+* | 24 | 2 | 4 | 6 |
|  |  | 36 | 5 | 2 | 7 |
|  |  | 48 | 7 | 3 | 10 |
|  |  | 60 | 1 | 1 | 2 |
|  |  | 84 | 0 | 1 | 1 |
|  |  | 96 | 0 | 1 | 1 |
|  |  | *Subtotal* | 15 | 12 | 27 |
| **MCI NP-** | *Aβ-Ptau-* | 12 | 1 | 0 | 1 |
|  |  | 24 | 1 | 2 | 3 |
|  |  | 36 | 4 | 0 | 4 |
|  |  | 48 | 12 | 1 | 13 |
|  |  | 60 | 3 | 0 | 3 |
|  |  | 108 | 1 | 0 | 1 |
|  |  | *Subtotal* | 22 | 3 | 25 |
|  | *Aβ+Ptau-* | 12 | 2 | 0 | 2 |
|  |  | 18 | 0 | 1 | 1 |
|  |  | 24 | 3 | 0 | 3 |
|  |  | 36 | 4 | 0 | 4 |
|  |  | 48 | 4 | 0 | 4 |
|  |  | 60 | 4 | 0 | 4 |
|  |  | 72 | 0 | 1 | 1 |
|  |  | 96 | 1 | 0 | 1 |
|  |  | *Subtotal* | 18 | 2 | 20 |
|  | *Aβ-Ptau+* | 12 | 1 | 0 | 1 |
|  |  | 24 | 6 | 1 | 7 |
|  |  | 36 | 2 | 0 | 2 |
|  |  | 48 | 2 | 0 | 2 |
|  |  | 60 | 2 | 0 | 2 |
|  |  | 120 | 1 | 0 | 1 |
|  |  | *Subtotal* | 14 | 1 | 15 |
|  | *Aβ+Ptau+* | 12 | 3 | 0 | 3 |
|  |  | 18 | 0 | 2 | 2 |
|  |  | 24 | 5 | 5 | 10 |
|  |  | 36 | 2 | 3 | 5 |
|  |  | 48 | 4 | 2 | 6 |
|  |  | 60 | 2 | 0 | 2 |
|  |  | 84 | 0 | 1 | 1 |
|  |  | 96 | 0 | 2 | 2 |
|  |  | *Subtotal* | 16 | 15 | 31 |
| **MCI NP+** | *Aβ-Ptau-* | 12 | 2 | 0 | 2 |
|  |  | 18 | 0 | 1 | 1 |
|  |  | 24 | 3 | 0 | 3 |
|  |  | 36 | 6 | 0 | 6 |
|  |  | 48 | 12 | 2 | 14 |
|  |  | 60 | 4 | 0 | 4 |
|  |  | 72 | 2 | 0 | 2 |
|  |  | 96 | 0 | 1 | 1 |
|  |  | 108 | 0 | 1 | 1 |
|  |  | 120 | 1 | 0 | 1 |
|  |  | *Subtotal* | 30 | 5 | 35 |
|  | *Aβ+Ptau-* | 12 | 3 | 0 | 3 |
|  |  | 24 | 7 | 4 | 11 |
|  |  | 36 | 4 | 1 | 5 |
|  |  | 48 | 2 | 2 | 4 |
|  |  | 60 | 2 | 0 | 2 |
|  |  | 72 | 1 | 0 | 1 |
|  |  | 108 | 1 | 0 | 1 |
|  |  | *Subtotal* | 20 | 7 | 27 |
|  | *Aβ-Ptau+* | 12 | 2 | 0 | 2 |
|  |  | 18 | 1 | 2 | 3 |
|  |  | 24 | 1 | 2 | 3 |
|  |  | 36 | 4 | 3 | 7 |
|  |  | 48 | 5 | 0 | 5 |
|  |  | 60 | 2 | 0 | 2 |
|  |  | 96 | 2 | 0 | 2 |
|  |  | 108 | 1 | 0 | 1 |
|  |  | *Subtotal* | 18 | 7 | 25 |
|  | *Aβ+Ptau+* | 12 | 8 | 0 | 8 |
|  |  | 18 | 1 | 8 | 9 |
|  |  | 24 | 5 | 29 | 34 |
|  |  | 36 | 13 | 16 | 29 |
|  |  | 48 | 7 | 5 | 12 |
|  |  | 60 | 3 | 1 | 4 |
|  |  | 72 | 0 | 2 | 2 |
|  |  | 120 | 1 | 0 | 1 |
|  |  | *Subtotal* | 38 | 61 | 99 |
|  | *Total* | 12 | 47 | 0 | 47 |
|  |  | 18 | 3 | 15 | 18 |
|  |  | 24 | 104 | 52 | 156 |
|  |  | 36 | 118 | 27 | 145 |
|  |  | 48 | 200 | 18 | 218 |
|  |  | 60 | 70 | 3 | 73 |
|  |  | 72 | 21 | 6 | 27 |
|  |  | 84 | 5 | 2 | 7 |
|  |  | 96 | 13 | 6 | 19 |
|  |  | 108 | 15 | 3 | 18 |
|  |  | 120 | 19 | 2 | 21 |
|  |  | *Grand Total* | 615 | 134 | 749 |

**Supplementary Table 8.** Biomarker model for 48-month follow-up

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Wald** | ***p*** | **Odds Ratio** | **95% Confidence Interval** | |
|  |  |  |  | Lower | Upper |
| **Age** | 2.436 | 0.119 | 1.023 | 0.994 | 1.053 |
| **Sex** | 1.763 | 0.184 | 1.321 | 0.876 | 1.994 |
| **Education** | 0.238 | 0.626 | 1.017 | 0.950 | 1.089 |
| **APOE ε4** | 0.809 | 0.368 | 1.219 | 0.792 | 1.875 |
| **CSF Aβ1-42** | 19.637 | <0.001 | 1.002 | 1.001 | 1.002 |
| **CSF P-tau** | 0.724 | 0.395 | 0.974 | 0.918 | 1.035 |
| **CSF T-tau** | 2.812 | 0.094 | 1.006 | 0.999 | 1.013 |
| **Cognitive Diagnosis** | 22.974 | <0.001 | 3.263 | 2.012 | 5.292 |
| **NP decline** | 28.490 | <0.001 | 2.582 | 1.823 | 3.658 |

**Supplementary Table 9.** Cluster table for CN NP-/+ Analysis

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **cluster** | **cluster** | **peak** | **peak** | **peak** |  |  |  |  |
| **p(FWE-corr)** | **equivk** | **p(FWE-corr)** | **T** | **equivZ** | **x** | **y** | **z** | **Region** |
| <0.001 | 534 | 0.001 | 5.58 | 5.51 | 22 | 0 | -16 | R Entorhinal |
| <0.001 | 457 | 0.005 | 5.28 | 5.22 | -27 | -10 | -14 | L Hippocampus |
|  |  | 0.005 | 5.25 | 5.2 | -28 | 3 | -20 | L Entorhinal |
| 0.029 | 14 | 0.042 | 4.77 | 4.73 | -32 | -26 | -8 | L Hippocampus |

**Supplementary Table 10.** Cluster table for MCI NP-/+ analysis

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **cluster** | **cluster** | **peak** | **peak** | **peak** |  |  |  |  |
| **p(FWE-corr)** | **equivk** | **p(FWE-corr)** | **T** | **equivZ** | **x** | **y** | **z** | **Region** |
| <0.001 | 512 | 0 | 6.24 | 6.1 | -50 | -45 | -18 | L Inferior Temporal |
| <0.001 | 2523 | 0 | 6.22 | 6.08 | -27 | -26 | -8 | L Hippocampus |
|  |  | 0.002 | 5.5 | 5.4 | -14 | -36 | 2 |  |
| <0.001 | 396 | 0.001 | 5.78 | 5.66 | 63 | -21 | -8 | R Middle Temporal |
|  |  | 0.004 | 5.41 | 5.31 | 50 | -24 | 2 |  |
|  |  | 0.024 | 5 | 4.92 | 54 | -32 | -10 |  |
| <0.001 | 465 | 0.001 | 5.77 | 5.65 | -51 | -15 | -22 | L Middle Temporal |
|  |  | 0.016 | 5.09 | 5.01 | -50 | -3 | -30 |  |
| <0.001 | 3137 | 0.001 | 5.75 | 5.63 | 28 | -26 | -6 | R Hippocampus |
|  |  | 0.001 | 5.72 | 5.6 | 27 | -21 | -22 |  |
|  |  | 0.001 | 5.64 | 5.53 | 30 | -18 | -12 |  |
| <0.001 | 478 | 0.002 | 5.5 | 5.4 | 50 | -2 | -28 | R Middle Temporal |
|  |  | 0.006 | 5.3 | 5.21 | 44 | -3 | -36 |  |
|  |  | 0.02 | 5.04 | 4.96 | 56 | -2 | -20 |  |
| 0.002 | 160 | 0.003 | 5.48 | 5.38 | -14 | 30 | 26 | L Anterior Cingulate |
| 0.004 | 96 | 0.004 | 5.43 | 5.33 | 46 | -33 | 44 | R Supramarginal |
| 0.002 | 140 | 0.005 | 5.35 | 5.26 | -8 | -54 | 21 | L Precuneus |
| 0.012 | 44 | 0.009 | 5.21 | 5.13 | -50 | -56 | -6 | L Inferior Temporal  / Left Middle Temporal |
| 0.011 | 47 | 0.017 | 5.08 | 5 | -36 | -2 | -34 | L Inferior Temporal |
| 0.022 | 20 | 0.017 | 5.08 | 5 | 56 | -33 | -22 | R Inferior Temporal |
| 0.02 | 22 | 0.017 | 5.08 | 5 | -54 | -48 | -3 | L Middle Temporal |
| 0.028 | 12 | 0.017 | 5.07 | 4.99 | -12 | -88 | -9 | L Lingual |
| 0.018 | 26 | 0.021 | 5.03 | 4.95 | 4 | 2 | 8 |  |
| 0.027 | 13 | 0.024 | 5 | 4.92 | -33 | -86 | 14 |  |
| 0.034 | 6 | 0.026 | 4.98 | 4.9 | -42 | 4 | 0 |  |
| 0.017 | 30 | 0.027 | 4.97 | 4.89 | -60 | -32 | -6 |  |
| 0.026 | 14 | 0.03 | 4.94 | 4.87 | -38 | -78 | 21 |  |
| 0.045 | 1 | 0.05 | 4.82 | 4.75 | -8 | -28 | 14 |  |

**Supplementary Figure 1.**