**Supplementary Material C**

Supplementary Table C1.

Sample size estimates for the AD and MCI groups using a linear mixed-effects model for neuropsychological tests\*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Outcome measure | Annual change ± SE [95% CI] | $$σ\_{s}^{2}$$ | $$σ\_{ε}^{2}$$ | N/arm not controlling for normal aging [95% CI] | N/arm controlling for normal aging [95% CI] |
| CDR-SB |  |  |  |  |  |
|  | CN | 0.04 ± 0.02 [−0.01, 0.08] |  |  |  |  |
|  | All AD subjects | 1.52 ± 0.13 [1.26, 1.78] | 1.84 | 0.68 | 229 [168, 333] | 241 [176, 349] |
|  | *ApoE* ε4 non-carriers with AD | 1.70 ± 0.20 [1.31, 2.10] | 1.50 | 0.81 | 158 [105, 264] | 165 [110, 276] |
|  | *ApoE* ε4 carriers with AD | 1.37 ± 0.17 [1.03, 1.72] | 1.94 | 0.62 | 291 [187, 511] | 307 [198, 539] |
|  | All MCI subjects | 1.14 ± 0.09 [0.97, 1.32] | 1.55 | 0.49 | 336 [252, 470] | 358 [269, 501] |
|  | *ApoE* ε4 non-carriers with MCI | 0.90 ± 0.13 [0.64, 1.15] | 1.54 | 0.44 | 535 [326, 1037] | 581 [354, 1127] |
|  | *ApoE* ε4 carriers with MCI | 1.37 ± 0.12 [1.13, 1.61] | 1.47 | 0.54 | 226 [164, 332] | 238 [173, 351] |
| ADAS-Cog |  |  |  |  |  |
|  | CN | −0.18 ± 0.14 [−0.45, 0.08] |  |  |  |  |
|  | All AD subjects | 2.85 ± 0.34 [2.19, 3.52] | 8.44 | 8.32 | 363 [240, 611] | 320 [212, 539] |
|  | *ApoE* ε4 non-carriers with AD | 2.96 ± 0.51 [1.93, 4.00] | 6.76 | 9.97 | 307 [172, 698] | 272 [152, 619] |
|  | *ApoE* ε4 carriers with AD | 2.80 ± 0.44 [1.92, 3.68] | 9.65 | 7.20 | 401 [234, 839] | 353 [206, 738] |
|  | All MCI subjects | 2.75 ± 0.24 [2.29, 3.22] | 8.37 | 8.37 | 388 [284, 562] | 341 [250, 493] |
|  | *ApoE* ε4 non-carriers with MCI | 1.93 ± 0.33 [1.27, 2.58] | 7.64 | 8.13 | 736 [412, 1676] | 613 [343, 1396] |
|  | *ApoE* ε4 carriers with MCI | 3.50 ± 0.32 [2.86, 4.15] | 7.95 | 8.59 | 233 [167, 348] | 210 [151, 314] |
| MMSE |  |  |  |  |  |
|  | CN | 0.01 ± 0.06 [−0.11, 0.13] |  |  |  |  |
|  | All AD subjects | −1.44 ± 0.21 [−1.86, −1.02] | 3.53 | 3.20 | 582 [352, 1140] | 575 [348, 1125] |
|  | *ApoE* ε4 non-carriers with AD | −1.82 ± 0.35 [−2.52, −1.12] | 4.08 | 3.40 | 413 [218, 1057] | 409 [216, 1046] |
|  | *ApoE* ε4 carriers with AD | −1.19 ± 0.26 [−1.70, −0.67] | 3.06 | 3.05 | 761 [375, 2307] | 749 [368, 2269] |
|  | All MCI subjects | −1.51 ± 0.12 [−1.75, −1.27] | 2.09 | 2.72 | 351 [260, 498] | 346 [257, 491] |
|  | *ApoE* ε4 non-carriers with MCI | −1.05 ± 0.16 [−1.37, −0.73] | 1.56 | 2.50 | 586 [346, 1203] | 575 [339, 1180] |
|  | *ApoE* ε4 carriers with MCI | −1.93 ± 0.18 [−2.28, −1.58] | 2.22 | 2.91 | 228 [164, 339] | 226 [162, 335] |

\*The number of subjects per arm required to detect a 25% reduction in the mean rate of decline at the p < 0.05 level with 80% power, assuming a 24-month trial with neuropsychological examinations every 6 months (AD and CN participants did not undergo the examinations at 18 months), is shown before and after controlling for normal aging.

SE, standard error of the mean; CI, confidence interval; CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; CN, cognitively normal; AD, Alzheimer’s disease; MCI, mild cognitive impairment; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; MMSE, Mini-Mental State Examination; $σ\_{s}^{2}$, variance of the random slopes in the linear mixed-effects model; $σ\_{ε}^{2}$, variance of the residual errors in the linear mixed-effects model.

Supplementary Table C2.

Sample size estimates for the AD and MCI groups using a linear mixed-effects model for KN-BSI\*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Outcome measure | Annual % change ± SE [95% CI] | $$σ\_{s}^{2}$$ | $$σ\_{ε}^{2}$$ | N/arm not controlling for normal aging [95% CI] | N/arm controlling for normal aging [95% CI] |
| KN-BSI whole brain |  |  |  |  |  |
|  | CN | −0.41 ± 0.03 [−0.47, −0.34] |  |  |  |  |
|  | All AD subjects | −1.02 ± 0.05 [−1.13, −0.91] | 0.31 | 0.10 | 85 [70, 106] | 235 [193, 292] |
|  | *ApoE* ε4 non-carriers with AD | −0.92 ± 0.09 [−1.11, −0.73] | 0.39 | 0.10 | 130 [90, 204] | 416 [288, 653] |
|  | *ApoE* ε4 carriers with AD | −1.09 ± 0.07 [−1.22, −0.96] | 0.27 | 0.10 | 66 [53, 84] | 166 [133, 214] |
|  | All MCI subjects | −0.83 ± 0.04 [−0.91, −0.75] | 0.28 | 0.14 | 122 [102, 149] | 470 [392, 572] |
|  | *ApoE* ε4 non-carriers with MCI | −0.76 ± 0.06 [−0.88, −0.63] | 0.36 | 0.14 | 184 [135, 266] | 860 [631, 1238] |
|  | *ApoE* ε4 carriers with MCI | −0.90 ± 0.05 [−0.99, −0.80] | 0.20 | 0.14 | 79 [65, 99] | 263 [216, 329] |
| KN-BSI hipppocampus |  |  |  |  |  |
|  | CN | −0.77 ± 0.08 [−0.92, −0.61] |  |  |  |  |
|  | All AD subjects | −3.47 ± 0.17 [−3.81, −3.13] | 3.18 | 0.87 | 74 [61, 90] | 121 [101, 148] |
|  | *ApoE* ε4 non-carriers with AD | −2.93 ± 0.27 [−3.48, −2.38] | 3.32 | 0.75 | 106 [76, 158] | 194 [139, 290] |
|  | *ApoE* ε4 carriers with AD | −3.82 ± 0.21 [−4.24, −3.40] | 2.85 | 0.96 | 56 [45, 70] | 87 [71, 110] |
|  | All MCI subjects | −2.82 ± 0.14 [−3.09, −2.56] | 3.61 | 0.89 | 125 [104, 152] | 235 [196, 286] |
|  | *ApoE* ε4 non-carriers with MCI | −2.05 ± 0.19 [−2.43, −1.66] | 3.48 | 0.83 | 228 [163, 344] | 582 [415, 876] |
|  | *ApoE* ε4 carriers with MCI | −3.54 ± 0.16 [−3.86, −3.23] | 2.40 | 0.94 | 56 [47, 67] | 90 [76, 109] |

\*The number of subjects per arm required to detect a 25% reduction in the mean rate of decline at the p < 0.05 level with 80% power, assuming a 24-month trial with MRI scans every 6 months (AD and CN participants did not undergo MRI at 18 months), is shown before and after controlling for normal aging.

SE, standard error of the mean; CI, confidence interval; KN-BSI, k-means normalized boundary shift integral; CN, cognitively normal; AD, Alzheimer’s disease; MCI, mild cognitive impairment; $σ\_{s}^{2}$, variance of the random slopes in the linear mixed-effects model; $σ\_{ε}^{2}$, variance of the residual errors in the linear mixed-effects model.