**Supplemental Materials**

**APOE ε4 Gene Dose and Sex Effects on Alzheimer’s Disease MRI Biomarkers in Older Adults with Mild Cognitive Impairment**

**A detailed description of the MCI diagnostic criteria used in ADNI, NACC, and AIBL**

**ADNI**

An MCI diagnosis is determined by a study physician based on performance on a standardized neuropsychological battery according to consortium agreed criteria. Diagnostic uniformity is achieved across sites by a Central Review Committee. The criteria used for an MCI diagnosis is an MMSE score between 24-30. ADNI also follows Petersen’s criteria for MCI: subjective memory complaint, have objective memory loss measured by education adjusted scores (Wechsler Memory Scale Logical Memory II and CDR=0.5 are used), absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia, although ADNI has now begun distinguishing between subjective cognitive decline, early MCI, and late MCI.

**NACC**

A clinician or formal consensus panel determines an MCI diagnosis based on each annual visit. MCI criteria includes abnormal cognition (global CDR > 0 and/or neuropsychological testing outside of the normal range) and no diagnosis of clinical dementia. The NACC MCI diagnostic assessment also incorporates the Petersen criteria, similar to ADNI.

**AIBL**

AIBL closely follows the diagnostic criteria for MCI, as outlined in the ADNI general procedures manual. Similar to ADNI, MCI diagnoses in AIBL are determined according to a protocol based on Winblad criteria, which are informed by Petersen’s criteria. All participants classified with MCI had either personally, or through an informant, reported memory difficulties. Participants presenting with a clinical diagnosis of MCI (i.e., previously diagnosed by a clinician) were further required to demonstrate a score 1.5 SD or more below the age-adjusted mean on at least one neuropsychological task applied at the time of the AIBL assessment in order to be retained in the MCI category.

Overall, the MCI criteria used across the 3 cohorts are similar and follow related protocols.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Supplementary Table 1.** Sample Characteristics Stratified by *APOE* Genotypeand Cohort | | | | | | | | | | | |  | |  | |
|  | **ADNI** | | | **NACC** | | | | | **AIBL** | | | | | |
|  | **ε3/ε3** | **ε3/ε4** | **ε4/ε4** | **ε3/ε3** | **ε3/ε4** | | **ε4/ε4** | | **ε3/ε3** | | **ε3/ε4** | | **ε4/ε4** | |
|  | n = 343 | n = 293 | n = 87 | n = 56 | n = 52 | | n = 13 | | n = 40 | | n = 34 | | n = 12 | |
| Age, range | 55-89 | 55-88 | 55-87 | 59-92 | 56-89 | | 60-81 | | 61-96 | | 60-92 | | 64-83 | |
| Age, mean | 73.9 | 72.9 | 70.3 | 77.9 | 73.7 | | 71.9 | | 75.6 | | 76.5 | | 71 | |
| Education, group\* | 4.5 (0.8) | 4.4 (0.8) | 4.4 (0.8) | 4.2 (0.9) | 4.2 (1.0) | | 4.7 (0.9) | | 3.6 (1.1) | | 3.7 (1.1) | | 3.8 (1.2) | |
| Female, N (%) | 149 (43) | 113 (39) | 38 (44) | 21 (37) | 26 (50) | | 4 (29) | | 19 (48) | | 14 (41) | | 12 (50) | |
| Baseline Characteristics for the study population. Data are presented as mean (standard deviation) unless otherwise specified. | | | | | | | | | | | | | | | |
| \*Education groups are 1 = 7-8, 2 = 9-12, 3 = 13-15, 4 = 15+ | | | | | |  | |  | |  | |  | |  | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Supplementary Table 2.** Region of interest results | | | | | | | | |
|  |  |  | | |  | | |
| **Main effect of *APOE* ε4 across sex** | | |  | | |  | | | |
| **ROI** | **β*APOE* (SE; p)** | | | |  | | |
| Left hippocampus | **-392.6 – -166.4** (39-61; 0.0001) | | | |  | | |
| Right hippocampus | **-378.9 – -182.6** (41-63; 0.0001) | | | |  | | |
| Left amygdala | **-69.4 – -158.7** (19-30; 0.0001) | | | |  | | |
| Right amygdala | **-74.2 – -139.5** (22-33; 0.0001) | | | |  | | |
| Left entorhinal cortex | -0.05 – -0.09 (0.03-0.05; 0.135) | | | |  | | |
| Right entorhinal cortex | 0.06 – -0.08 (0.04-0.06; 0.153) | | | |  | | |
| Left inferior parietal cortex | **-0.04 – -0.06** (0.01-0.02; 0.002) | | | |  | | |
| Right inferior parietal cortex | **-0.03 – -0.04** (0.01-0.02; 0.019) | | | |  | | |
| Left middle temporal lobe | -0.02 – 0.01 (0.025-0.024; 0.108) | | | |  | | |
| Right middle temporal lobe | -0.03 – 0.001 (0.02-0.02; 0.086) | | | |  | | |
| Left medial orbitofrontal cortex | -0.01 – 0.02 (0.02-0.02; 0.152) | | | |  | | |
| Right medial orbitofrontal cortex | -0.02 – -0.02 (0.02-0.02; 0.71) | | | |  | | |
| Total gray | **-1584 – 7383** (4764-4715; 0.011) | | | |  | | |
|  |  |  | | |  | | |
| **APOE ε4 dose across sex** | | | | | | |
| **ROI** | **β 0 versus 1 allele (SE; p)** | | | **β 1 versus 2 alleles (SE; p)** | | |
| Left hippocampus | **-165.2** (40; 0.0001) | | | **-232.3** (61; 0.0001) | | |
| Right hippocampus | **-181.1** (42; 0.0001) | | | **-201.8** (64; 0.002) | | |
| Left amygdala | **-69.2** (19; 0.0001) | | | **-97.6** (30; 0.001) | | |
| Right amygdala | **-74** (22; 0.01) | | | **-77.4** (34; 0.025) | | |
| Left entorhinal cortex | -0.05 (0.03; 0.133) | | | -0.04 (0.05; 0.422) | | |
| Right entorhinal cortex | -0.06 (0.04; 0.105) | | | -0.03 (0.06; 0.568) | | |
| Left inferior parietal cortex | **-0.04** (0.01; 0.003) | | | -0.022 (0.02; 0.278) | | |
| Right inferior parietal cortex | **-0.03** (0.01; 0.015) | | | -0.01 (0.02; 0.624) | | |
| Left middle temporal lobe | **-0.03** (0.02; 0.037) | | | 0.02 (0.03; 0.526) | | |
| Right middle temporal lobe | **-0.03** (0.02; 0.039) | | | 0.03 (0.02; 0.212) | | |
| Left medial orbitofrontal cortex | -0.03 (0.01; 0.056) | | | 0.01 (0.02; 0.614) | | |
| Right medial orbitofrontal cortex | -0.002 (0.01; 0.884) | | | 0.02 (0.02; 0.437) | | |
| Total gray | **-8785** (3063; 0.004) | | | -238.4 (4736; 0.96) | | |

|  |  |  |  |
| --- | --- | --- | --- |
| **Main effect of sex by *APOE* ε4 allele** | | | |
| **ROI** | **β 0 alleles (SE; p)** | **β 1 allele (SE; p)** | **β 2 alleles (SE; p)** |
| Left hippocampus | -115.6 (66; 0.081) | **-300.6** (76; 0.0001) | -159.3 (113; 0.163) |
| Right hippocampus | **-141.2** (68; 0.039) | **-284.5** (80; 0.0001) | **-245.6** (120; 0.043) |
| Left amygdala | **-122.9** (31; 0.0001) | **-158.3** (37; 0.0001) | **-210.8** (59; 0.001) |
| Right amygdala | **-167.7** (35;0.0001) | **-196.5** (43; 0.0001) | **-209.3** (65; 0.002) |
| Left entorhinal cortex | **-0.12** (0.06; 0.029) | **-0.14** (0.07; 0.036) | -0.09 (0.09; 0.349) |
| Right entorhinal cortex | -0.05 (0.06; 0.384) | **-0.15** (0.07; 0.049) | -0.08 (0.11; 0.469) |
| Left inferior parietal cortex | **0.05** (0.02; 0.029) | -0.04 (0.03; 0.11) | 0.01 (0.04; 0.754) |
| Right inferior parietal cortex | 0.04 (0.02; 0.074) | **-0.07** (0.03; 0.009) | 0.003 (0.04; 0.942) |
| Left middle temporal lobe | -0.03 (0.03; 0.216) | -0.05 (0.03; 0.093) | -0.003 (0.05; 0.954) |
| Right middle temporal lobe | 0.001 (0.03; 0.955) | -0.04 (0.03; 0.165) | 0.004 (0.05; 0.922) |
| Left medial orbitofrontal cortex | -0.024 (0.02; 0.268) | -0.04 (0.03; 0.127) | -0.03 (0.04; 0.363) |
| Right medial orbitofrontal cortex | 0.003 (0.023; 0.907) | **-0.05** (0.03; 0.044) | -0.02 (0.04; 0.631) |
| Total gray | **-16509** (5014; 0.001) | **-19335** (5801; 0.001) | -17803 (9410; 0.062) |

|  |  |  |  |
| --- | --- | --- | --- |
| Region of interest results |  |  |  |
| ***APOE* ε4 dose in women** |  |  |  |
| **ROI** | **β 0 versus 1 allele (SE; p)** | **β 1 versus 2 alleles (SE; p)** |  |
| Left hippocampus | **-209.4** (62.9; 0.001) | **-217.5** (90; 0.016) |  |
| Right hippocampus | **-239** (63; 0.001) | **-244.7** (92; 0.009) |  |
| Left amygdala | **-72.7** (30; 0.016) | **-104.6** (44; 0.019) |  |
| Right amygdala | **-74.1** (33; 0.024) | -75.9 (49; 0.123) |  |
| Left entorhinal cortex | -0.05 (0.05; 0.339) | -0.02 (0.07; 0.77) |  |
| Right entorhinal cortex | -0.1 (0.06; 0.101) | -0.007 (0.09; 0.935) |  |
| Left inferior parietal cortex | **-0.06** (0.02; 0.003) | -0.02 (0.03; 0.596) |  |
| Right inferior parietal cortex | **-0.07** (0.02; 0.002) | 0.004 (0.03; 0.912) |  |
| Left middle temporal lobe | -0.03 (0.03; 0.335) | 0.02 (0.04; 0.567) |  |
| Right middle temporal lobe | **-0.05** (0.03; 0.05) | 0.04 (0.04; 0.25) |  |
| Left medial orbitofrontal cortex | -0.03 (0.02; 0.158) | 0.006 (0.03; 0.845) |  |
| Right medial orbitofrontal cortex | -0.02 (0.02; 0.358) | 0.03 (0.03; 0.32) |  |
| Total gray | **-10480** (4901; 0.033) | -3834 (7523; 0.611) |  |
|  |  |  |  |

|  |  |  |  |
| --- | --- | --- | --- |
| ***APOE* ε4 dose in men** | | |  |
| **ROI** | **β 0 versus 1 allele (SE; p)** | **β 1 versus 2 alleles (SE; p)** |  |
| Left hippocampus | **-34.3** (53; 0.011) | **-252.3** (84; 0.003) |  |
| Right hippocampus | **-138.5** (56; 0.014) | **-179** (91; 0.05) |  |
| Left amygdala | **-72** (25; 0.005) | -81.5 (42; 0.053) |  |
| Right amygdala | **-71.7** (29; 0.015) | -74 (49; 0.132) |  |
| Left entorhinal cortex | -0.05 (0.05; 0.306) | -0.05 (0.07; 0.504) |  |
| Right entorhinal cortex | -0.03 (0.05; 0.495) | -0.05 (0.08; 0.554) |  |
| Left inferior parietal cortex | -0.02 (0.02; 0.191) | -0.03 (0.025; 0.258) |  |
| Right inferior parietal cortex | -0.007 (0.02; 0.664) | -0.02 (0.03; 0.372) |  |
| Left middle temporal lobe | -0.04 (0.02; 0.053) | 0.004 (0.03; 0.899) |  |
| Right middle temporal lobe | -0.02 (0.02; 0.32) | 0.01 (0.03; 0.668) |  |
| Left medial orbitofrontal cortex | -0.02 (0.02; 0.18) | 0.008 (0.03; 0.772) |  |
| Right medial orbitofrontal cortex | 0.009 (0.02; 0.605) | 0.003 (0.03; 0.93) |  |
| Total gray | -6967 (3965; 0.08) | 977 (6107; 0.873) |  |