**eTable 2. Associations of *APOE* alleles with global and domain-specific cognitive outcomes excluding *APOE*ε4** **homozygotes**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **OUTCOME**  Contrast | **N** | **Model 1** | | | | **Model 2** | | | | **Model 3** | | | |
| **Estimate** | **SE** | **95% CI** | | **Estimate** | **SE** | **95% CI** | | **Estimate** | **SE** | **95% CI** | |
| **CDR-SOB** | 1,067 |  | | | | | | | | | | | |
| CERAD NP moderate vs none/sparse | N.A. | N.A. | N.A. | N.A. | **0.169** | **0.025** | **0.120** | **0.218** | **0.114** | **0.027** | **0.062** | **0.166** |
| Braak NFT III/IV vs 0/I/II | N.A. | N.A. | N.A. | N.A. | -0.020 | 0.022 | -0.063 | 0.023 | -0.038 | 0.022 | -0.081 | 0.004 |
| *APOE* genotype: |  | | | | | | | | | | | |
| ε2 vs ε3/ε3 | -0.004 | 0.026 | -0.056 | 0.047 | -0.025 | 0.029 | -0.082 | 0.032 | 0.000 | 0.009 | -0.017 | 0.017 |
| ε4 vs ε3/ε3 | **0.066** | **0.032** | **0.003** | **0.128** | **0.050** | **0.025** | **0.000** | **0.099** | **0.079** | **0.025** | **0.030** | **0.128** |
| ε2 vs ε4 | -0.070 | 0.038 | -0.144 | 0.004 | **-0.075** | **0.034** | **-0.141** | **-0.009** | **-0.079** | **0.026** | **-0.130** | **-0.028** |
| **MMSE** | 992 |  | | | | | | | | | | | |
| CERAD NP moderate vs none/sparse | N.A. | N.A. | N.A. | N.A. | **-0.136** | **0.039** | **-0.212** | **-0.060** | **-0.162** | **0.040** | **-0.241** | **-0.082** |
| Braak NFT III/IV vs 0/I/II | N.A. | N.A. | N.A. | N.A. | 0.006 | 0.032 | -0.057 | 0.069 | 0.025 | 0.032 | -0.038 | 0.088 |
| *APOE* genotype: |  | | | | | | | | | | | |
| ε2 vs ε3/ε3 | 0.003 | 0.049 | -0.094 | 0.100 | 0.004 | 0.042 | -0.079 | 0.088 | -0.034 | 0.044 | -0.121 | 0.053 |
| ε4 vs ε3/ε3 | **-0.176** | **0.040** | **-0.254** | **-0.098** | **-0.153** | **0.039** | **-0.230** | **-0.076** | **-0.138** | **0.041** | **-0.217** | **-0.058** |
| ε2 vs ε4 | **0.179** | **0.055** | **0.071** | **0.286** | **0.157** | **0.052** | **0.056** | **0.258** | 0.104 | 0.055 | -0.004 | 0.211 |
| **Memory** | 967 |  | | | | | | | | | | | |
| CERAD NP moderate vs none/sparse | N.A. | N.A. | N.A. | N.A. | 0.004 | 0.012 | -0.020 | 0.028 | 0.002 | 0.013 | -0.022 | 0.027 |
| Braak NFT III/IV vs 0/I/II | N.A. | N.A. | N.A. | N.A. | **-0.031** | **0.010** | **-0.051** | **-0.011** | **-0.029** | **0.010** | **-0.050** | **-0.009** |
| *APOE* genotype: |  | | | | | | | | | | | |
| ε2 vs ε3/ε3 | -0.002 | 0.013 | -0.027 | 0.024 | -0.003 | 0.013 | -0.029 | 0.022 | -0.001 | 0.013 | -0.028 | 0.025 |
| ε4 vs ε3/ε3 | -0.006 | 0.013 | -0.032 | 0.020 | -0.002 | 0.013 | -0.028 | 0.023 | -0.005 | 0.013 | -0.031 | 0.021 |
| ε2 vs ε4 | 0.004 | 0.017 | -0.029 | 0.037 | -0.001 | 0.016 | -0.033 | 0.031 | 0.004 | 0.017 | -0.029 | 0.036 |
| **Attention** | 970 |  | | | | | | | | | | | |
| CERAD NP moderate vs none/sparse | N.A. | N.A. | N.A. | N.A. | 0.002 | 0.012 | -0.022 | 0.026 | 0.001 | 0.012 | -0.023 | 0.025 |
| Braak NFT III/IV vs 0/I/II | N.A. | N.A. | N.A. | N.A. | **-0.023** | **0.010** | **-0.043** | **-0.004** | **-0.023** | **0.010** | **-0.042** | **-0.003** |
| *APOE* genotype: |  | | | | | | | | | | | |
| ε2 vs ε3/ε3 | -0.014 | 0.013 | -0.039 | 0.010 | 0.021 | 0.016 | -0.011 | 0.052 | 0.018 | 0.018 | -0.017 | 0.054 |
| ε4 vs ε3/ε3 | -0.016 | 0.012 | -0.039 | 0.008 | -0.020 | 0.012 | -0.044 | 0.003 | -0.021 | 0.012 | -0.045 | 0.003 |
| ε2 vs ε4 | 0.001 | 0.016 | -0.029 | 0.032 | **0.041** | **0.019** | **0.005** | **0.078** | 0.039 | 0.020 | -0.001 | 0.080 |
| **Executive** | 849 |  | | | | | | | | | | | |
| CERAD NP moderate vs none/sparse | N.A. | N.A. | N.A. | N.A. | **-0.021** | **0.011** | **-0.041** | **0.000** | -0.021 | 0.012 | -0.044 | 0.001 |
| Braak NFT III/IV vs 0/I/II | N.A. | N.A. | N.A. | N.A. | 0.005 | 0.009 | -0.013 | 0.022 | 0.006 | 0.009 | -0.012 | 0.024 |
| *APOE* genotype: |  | | | | | | | | | | | |
| ε2 vs ε3/ε3 | -0.006 | 0.012 | -0.029 | 0.017 | -0.005 | 0.012 | -0.028 | 0.019 | -0.003 | 0.013 | -0.029 | 0.022 |
| ε4 vs ε3/ε3 | -0.021 | 0.011 | -0.042 | 0.001 | -0.017 | 0.012 | -0.040 | 0.007 | -0.014 | 0.013 | -0.039 | 0.010 |
| ε2 vs ε4 | 0.015 | 0.014 | -0.014 | 0.043 | 0.012 | 0.015 | -0.018 | 0.042 | 0.011 | 0.017 | -0.021 | 0.043 |
| **Language** | 965 |  | | | | | | | | | | | |
| CERAD NP moderate vs none/sparse | N.A. | N.A. | N.A. | N.A. | **-0.022** | **0.009** | **-0.039** | **-0.005** | **-0.024** | **0.010** | **-0.043** | **-0.005** |
| Braak NFT III/IV vs 0/I/II | N.A. | N.A. | N.A. | N.A. | **-0.023** | **0.007** | **-0.036** | **-0.009** | **-0.019** | **0.008** | **-0.034** | **-0.005** |
| *APOE* genotype: |  | | | | | | | | | | | |
| ε2 vs ε3/ε3 | 0.012 | 0.009 | -0.007 | 0.030 | 0.010 | 0.010 | -0.009 | 0.029 | 0.007 | 0.010 | -0.013 | 0.028 |
| ε4 vs ε3/ε3 | -0.001 | 0.009 | -0.019 | 0.016 | 0.007 | 0.009 | -0.010 | 0.025 | 0.006 | 0.009 | -0.012 | 0.025 |
| ε2 vs ε4 | 0.013 | 0.012 | -0.010 | 0.036 | 0.003 | 0.012 | -0.020 | 0.026 | 0.001 | 0.013 | -0.024 | 0.026 |

Model 1 is adjusted by age, sex, and education. Model 2 is further adjusted by CERAD NP score (moderate vs. none/sparse) and Braak NFT stage (III/IV vs. 0/I/II). Model 3 is further adjusted by presence and severity of comorbid pathologies and the interaction between CERAD NP score and Braak NFT stage and the slope of cognitive trajectory. Estimates are in the forward time scale.