**Figure e-1. Flow diagram of patient selection**

Abbreviations: *APOE*=apolipoprotein E; MoCA=Montreal Cognitive Assessment; PASE=Physical Activity Scale of the Elderly.

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**Table e-1. Longitudinal change in LEDD**

|  |  |  |  |
| --- | --- | --- | --- |
| **LEDD, mg** | **Year 2** | **Year 3** | **Year 4** |
| Overall | 312.5 (302.0) | 439.1 (348.3) | 521.8 (375.5) |
| *APOE* ε4 (+) | 280.1 (253.7) | 409.8 (267.6) | 484.7 (369.8) |
| *APOE* ε4 (–) | 324.2 (317.8) | 449.0 (372.0) | 535.0 (378.2) |

Data are the mean (standard deviation).

Abbreviations: *APOE*=apolipoprotein E; LEDD=levodopa equivalent daily dose.

**Table e-2. Linear mixed effects models for the change in the MoCA score in patients with PD who were cognitively normal at year 2**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Model** | **Estimate (standard error)** | **95% confidence interval** | ***t* value** | ***p* value** |
| PA\**APOE* ε4\*Time | 0.006 (0.003) | 0.007 to 0.011 | 2.22 | **0.026** |
| PA\*Time | 0.002 (0.001) | 0.000 to 0.005 | 1.66 | 0.098 |
| *APOE* ε4\*Time | -1.11 (0.53) | -2.15 to -0.07 | -2.09 | **0.036** |
| Age\*time | -0.02 (0.01) | -0.04 to 0.00 | -2.01 | **0.045** |
| Disease duration\*Time | -0.001 (0.018) | -0.036 to 0.034 | -0.07 | 0.944 |
| Educational level\*Time | -0.04 (0.04) | -0.13 to 0.05 | -0.85 | 0.397 |
| Sex\*Time | -0.22 (0.20) | -0.62 to 0.18 | -1.08 | 0.280 |
| Baseline MoCA\*Time | -0.24 (0.07) | -0.39 to -0.10 | -3.38 | **0.001** |
| MDS-UPDRS part 3\*Time | 0.004 (0.010) | -0.016 to 0.024 | 0.46 | 0.646 |
| PA\**APOE* ε4 | 0.0003 (0.0037) | -0.0070 to 0.0075 | 0.07 | 0.945 |
| PA | 0.0006 (0.0021) | -0.0035 to 0.0046 | 0.27 | 0.787 |
| *APOE* ε4 | -0.04 (0.77) | -1.54 to 1.46 | -0.05 | 0.960 |
| Age | -0.003 (0.016) | -0.035 to 0.029 | -0.18 | 0.858 |
| Disease duration | -0.006 (0.025) | -0.056 to 0.044 | -0.25 | 0.801 |
| Educational level | -0.032 (0.060) | -0.150 to 0.098 | -0.40 | 0.686 |
| Sex | 0.03 (0.30) | -0.55 to 0.61 | 0.10 | 0.918 |
| Baseline MoCA | -0.05 (0.11) | -0.25 to 0.16 | -0.46 | 0.649 |
| MDS-UPDRS part 3 | -0.006 (0.014) | -0.033 to 0.021 | -0.43 | 0.665 |
| Time | 9.18 (2.38) | 4.51 to 13.85 | 3.85 | **<0.001** |

*APOE* ε4- and females were used as the reference group.

The significant values are in bold.

Abbreviations: *APOE*=apolipoprotein E; MDS-UPDRS=Movement Disorders Society Unified Parkinson’s Disease Rating Scale; MoCA=Montreal Cognitive Assessment; PA=physical activity.

**Table e-3. Linear mixed effects models for the change in the MoCA score after variables related to LEDD were included**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Model** | **Estimate (standard error)** | **95% confidence interval** | ***t* value** | ***p* value** |
| PA\**APOE* ε4\*Time | 0.007 (0.002) | 0.003 to 0.011 | 3.17 | **0.002** |
| PA\*Time | 0.001 (0.001) | -0.001 to 0.004 | 0.95 | 0.343 |
| *APOE* ε4\*Time | -1.31 (0.44) | -2.18 to -0.45 | -2.97 | **0.003** |
| Age\*time | -0.02 (0.01) | -0.04 to 0.00 | -1.53 | 0.126 |
| Disease duration\*Time | 0.002 (0.017) | -0.032 to 0.035 | 0.09 | 0.928 |
| Educational level\*Time | 0.04 (0.04) | -0.03 to 0.11 | 0.98 | 0.325 |
| Sex\*Time | 0.02 (0.20) | -0.38 to 0.42 | 0.11 | 0.916 |
| Baseline MoCA\*Time | -0.13 (0.04) | -0.21 to -0.05 | -3.27 | **0.001** |
| MDS-UPDRS part 3\*Time | -0.0003 (0.0090) | -0.0181 to 0.0174 | -0.04 | 0.971 |
| LEDD\*Time | 0.0002 (0.0003) | -0.0004 to 0.0007 | 0.59 | 0.556 |
| PA\**APOE* ε4 | -0.001 (0.003) | -0.007 to 0.005 | -0.37 | 0.709 |
| PA | 0.0010 (0.0018) | -0.0026 to 0.0045 | 0.55 | 0.586 |
| *APOE* ε4 | 0.12 (0.62) | -1.10 to 1.35 | 0.20 | 0.842 |
| Age | -0.01 (0.02) | -0.04 to 0.02 | -0.78 | 0.434 |
| Disease duration | 0.003 (0.024) | -0.043 to 0.049 | 0.13 | 0.895 |
| Educational level | -0.008 (0.050) | -0.106 to 0.090 | -0.16 | 0.875 |
| Sex | -0.05 (0.29) | -0.57 to 0.56 | -0.02 | 0.987 |
| Baseline MoCA | -0.09 (0.06) | -0.20 to 0.02 | -1.61 | 0.108 |
| MDS-UPDRS part 3 | -0.0004 (0.0125) | -0.0249 to 0.0240 | -0.04 | 0.971 |
| LEDD | -0.0001 (0.0004) | -0.0010 to 0.0007 | -0.32 | 0.752 |
| Time | 4.08 (1.48) | 1.19 to 6.98 | 2.76 | **0.006** |

*APOE* ε4- and females were used as the reference group.

The significant values are in bold.

Abbreviations: *APOE*=apolipoprotein E; MDS-UPDRS=Movement Disorders Society Unified Parkinson’s Disease Rating Scale; MoCA=Montreal Cognitive Assessment; PA=physical activity.

**Table e-4. Interactive association between high-intensity physical activity and *APOE* ε4 allele on the change in the MoCA score**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Model** | **Estimate (standard error)** | **95% confidence interval** | ***t* value** | ***p* value** |
| HIPA\**APOE* ε4\*Time | 0.018 (0.006) | 0.006 to 0.029 | 2.91 | **0.004** |
| HIPA\*Time | 0.003 (0.004) | -0.005 to 0.011 | 0.69 | 0.491 |
| *APOE* ε4\*Time | -0.77 (0.31) | -1.39 to -0.15 | -2.45 | **0.014** |
| Age\*time | -0.02 (0.01) | -0.04 to 0.00 | -1.70 | 0.089 |
| Disease duration\*Time | -0.001 (0.017) | -0.035 to 0.032 | -0.07 | 0.947 |
| Educational level\*Time | 0.04 (0.04) | -0.03 to 0.11 | 1.16 | 0.248 |
| Sex\*Time | 0.02 (0.21) | -0.38 to 0.43 | 0.10 | 0.921 |
| Baseline MoCA\*Time | -0.13 (0.04) | -0.21 to -0.05 | -3.27 | **0.001** |
| MDS-UPDRS part 3\*Time | -0.001 (0.009) | -0.019 to 0.016 | -0.14 | 0.892 |
| HIPA\**APOE* ε4 | -0.006 (0.009) | -0.023 to 0.011 | -0.71 | 0.476 |
| HIPA | 0.001 (0.006) | -0.010 to 0.012 | 0.22 | 0.830 |
| *APOE* ε4 | 0.15 (0.45) | -0.73 to 1.02 | 0.33 | 0.742 |
| Age | -0.010 (0.015) | -0.039 to 0.019 | -0.67 | 0.505 |
| Disease duration | 0.003 (0.024) | -0.044 to 0.050 | 0.12 | 0.905 |
| Educational level | -0.01 (0.05) | -0.11 to 0.09 | -0.20 | 0.841 |
| Sex | -0.03 (0.29) | -0.60 to 0.54 | -0.10 | 0.923 |
| Baseline MoCA | -0.09 (0.06) | -0.20 to 0.02 | -1.66 | 0.096 |
| MDS-UPDRS part 3 | 0.0007 (0.0125) | -0.0238 to 0.0253 | 0.06 | 0.953 |
| Time | 4.12 (1.43) | 1.32 to 6.93 | 2.88 | **0.004** |

*APOE* ε4- and females were used as the reference group.

The significant values are in bold.

Abbreviations: *APOE*=apolipoprotein E; HIPA=high-intensity physical activity; MDS-UPDRS=Movement Disorders Society Unified Parkinson’s Disease Rating Scale; MoCA=Montreal Cognitive Assessment.

**Table e-5. Interactive association between nonhigh-intensity physical activity and *APOE* ε4 allele on the change in the MoCA score**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Model** | **Estimate (standard error)** | **95% confidence interval** | ***t* value** | ***p* value** |
| NHIPA\**APOE* ε4\*Time | 0.007 (0.003) | 0.002 to 0.012 | 2.65 | **0.008** |
| NHIPA\*Time | 0.001 (0.002) | -0.002 to 0.004 | 0.96 | 0.339 |
| *APOE* ε4\*Time | -1.10 (0.44) | -1.97 to -0.24 | -2.51 | **0.012** |
| Age\*time | -0.02 (0.01) | -0.04 to 0.00 | -1.69 | 0.092 |
| Disease duration\*Time | 0.0009 (0.0172) | -0.0328 to 0.0346 | 0.05 | 0.957 |
| Educational level\*Time | 0.03 (0.04) | -0.04 to 0.11 | 0.96 | 0.338 |
| Sex\*Time | 0.05 (0.21) | -0.35 to 0.46 | 0.25 | 0.800 |
| Baseline MoCA\*Time | -0.14 (0.04) | -0.22 to -0.06 | -3.49 | **<0.001** |
| MDS-UPDRS part 3\*Time | -0.0002 (0.0091) | -0.0180 to 0.0176 | -0.02 | 0.983 |
| NHIPA\**APOE* ε4 | -0.0007 (0.0037) | -0.0079 to 0.0065 | -0.19 | 0.852 |
| NHIPA | 0.001 (0.002) | -0.0031 to 0.0052 | 0.51 | 0.614 |
| *APOE* ε4 | 0.02 (0.62) | -1.19 to 1.23 | 0.03 | 0.974 |
| Age | -0.01 (0.02) | -0.04 to 0.02 | -0.72 | 0.473 |
| Disease duration | 0.003 (0.024) | -0.044 to 0.050 | 0.13 | 0.900 |
| Educational level | -0.009 (0.050) | -0.107 to 0.089 | -0.18 | 0.855 |
| Sex | -0.005 (0.288) | -0.571 to 0.560 | -0.02 | 0.985 |
| Baseline MoCA | -0.09 (0.06) | -0.20 to 0.02 | -1.55 | 0.120 |
| MDS-UPDRS part 3 | -0.00005 (0.01253) | -0.02462 to 0.02451 | -0.01 | 0.997 |
| Time | 4.47 (1.46) | 1.61 to 7.33 | 3.07 | **0.002** |

*APOE* ε4- and females were used as the reference group.

The significant values are in bold.

Abbreviations: *APOE*=apolipoprotein E; MDS-UPDRS=Movement Disorders Society Unified Parkinson’s Disease Rating Scale; MoCA=Montreal Cognitive Assessment; NHIPA=nonhigh-intensity physical activity.