**Additional file 1.** Methods of neuroimaging

**MRI acquisition and analyses**

The acquisition protocol for brain MRI has been detailed elsewhere (Maltais et al., 2019; Vellas et al., 2014). In brief, the MRI scan was performed within the first 12 months of MAPT study enrollment and two years later, using a standardized protocol in each of the centers (Toulouse, Bordeaux, Montpellier, Limoges, Dijon, Lyon, Foix, Tarbes and Nice). In this study, we included MRI measurement for the total intracranial volume (cm3) and the hippocampus volume (cm3). Quality of each imaging data was assessed, and measures were excluded from our analysis if presenting poor or unreliable quality. The 3D T1-weighted sequence, derived by the SPM5 toolbox (fil.ion.ucl.ac.uk/spm), was used to compute the volumes.

**18-florbetapir PET acquisition and analysis**

PET scans were realized as close as possible to a clinical visit during the 3 years of follow-up of each patient, as previously described (Vellas et al., 2014)(Del Campo et al., 2016). Participants were examined using 5 different hybrid PET-CT scanners, including gone PET CT 690 (GE Healthcare), one Discovery RX VCT (GeneralElectric), 2 True Point HiRez (Siemens Medical Solutions), and one Biograph 4 Emission Duo LSO (Siemens Medical Solutions). All tomographs operated in 3D detection mode. All PET sinograms were reconstructed with an iterative algorithm, with corrections for randomness, scatter, photon attenuation, and decay, which pro-duced images with an isotropic voxel of 2 x 2 x2mm3 and a spatial resolution of approximately 5-mm full width at a half maximum at the field of view center. The acquisition data were processed using the standard package delivered with each acquisition system. All cerebral emission scans began 50 minutes after a mean injection of 4MBq/kg weight of F18-florbetapir. For each subject, 10- or 15-minuteframes were acquired to ensure movement-free image acquisition. A semiautomated quantitative analysis (cortical to cerebellar regional mean standardized uptake value ratio [SUVr]) was applied using the mean signal of 6 predefined anatomically relevant cortical regions of interest (frontal, temporal, parietal, precuneus, anterior cingulate, and posterior cingulate) with the whole cerebellum used as the reference region as previously described (Clark et al., 2011;Fleisher et al., 2011). In this procedure, the F18-florbetapir PET images were coregistered to the F18-florbetapir template provided by AVID company. Quality control based on the semiquantification process was also provided by AVID Lab. To acknowledge the fact that date of realization of PET scans did not matched, we included the difference between PET scan date and the baseline visit in the present study (12 month-follow up in MAPT) as a covariate in the linear regression models.

**Additional file 2.** Baseline differences in characteristics between included and non-included subjects in the present analyses.

|  |  |  |  |
| --- | --- | --- | --- |
| **Characterstics** | Whole MAPT Sample  (n=1680) | Included Subjects  (n=1097) | Non-included Subjects  (n=583) |
| **Women, No. (%)** |  |  |  |
| **Age, y** | 75.33 (4.22) | 75.30 (4.37) | 75.40 (4.53) |
| **Education, No. (%)** |  | | |
| No diploma | 85 (5.17) | 49 (4.54) | 36 (6.39) |
| Primary school certificate | 286 (17.41) | 179 (16.57) | 107 (19.01) |
| Secondary education | 553 (33.66) | 354 (32.78) | 199 (35.35) |
| High school diploma | 242 (14.73) | 168 (15.56) | 74 (13.14) |
| University level | 477 (29.03) | 330 (30.56) | 147 (26.11) |
| **Body Mass Indexc** | 26.27 (4.04) | 26.21 (4.06) | 26.49 (3.98) |
| **CDR Sum of boxes, range 0-18** | 0.39 (0.58) | 0.39 (0.58) | 0.41 (0.55) |
| **CDR status, No. (%)b** |  |  |  |
| No cognitive impairment,  CDR score, 0 | 716 (51.11) | 580 (52.97) | 136 (44.44) |
| Mild cognitive impairment,  CDR score, 0.5 | 677 (48.32) | 509 (46.48) | 168 (54.90) |
| Major cognitive impairment,  CDR score, ≥1 | 8 (0.57) | 6 (0.55) | 2 (0.65) |
| **MMSE score, range 0-30** | 28.03 (1.88) | 28.07 (1.81) | 27.90 (2.12) |
| **FCSRT Free Recall, range 0-48** | 30.38 (7.52) | 30.19 (7.56) | 29.52 (7.68) |
| **FCSRT Total Recall, range 0-48** | 45.69 (3.83) | 45.56 (3.96) | 45.72 (3.80) |
| **FCSRT Free Delayed Recall, range 0-16** | 11.42 (3.02) | 11.48 (2.99) | 11.20 (3.12) |
| **FCSRT Total Delayed Recall, range 0-16** | 15.50 (1.25) | 15.45 (1.36) | 15.52 (1.25) |
| **APOE ε4 genotype, No. (%)** |  |  |  |
| APOE ε4 carriers | 73 (23.32) | 226 (22.90) | 299 (23.00) |
| Non-APOE ε4 carriers | 240 (76.68) | 761 (77.10) | 1001 (77.00) |

Abbreviations: APOE, apolipoprotein E; CDR, Clinical Dementia Rating; FCSRT: Free and Cued Selective Reminding Test; MAPT: Multidomain Alzheimer Preventive Trial; MMSE, Mini-Mental State Examination.

a. High plasma MCP-1 defined as values in the 4th quartile.

b. P < .05 based on T-test or Pearson χ2 test.

c. Body mass index calculated as weight in kilograms divided by height in meters squared.

**Additional file 3.** Mixed-effect linear regression analysis for variation in overall cognitive outcomes, executive function and attention over time according to plasma MCP-1 status among community-dwelling older adults (excluding ApoE ε4 genotype)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Low plasma MCP-1a** | **High plasma MCP-1** | **Between-group Differenceb** |  |
|  | **Within-group evolution**  **Estimated mean**  **(95% CI)c** | **Within-group evolution**  **Estimated mean**  **(95% CI)** | **Estimated difference**  **(95%CI)** | **p-value** |
| **Cognitive Composite Scored, n=975** | | | | |
| 12 months | -0.08 (-0.17, 0.01) | -0.13 (-0.18, -0.08) | -0.05 (-0.14, 0.04) | 0.283 |
| 24 months | -0.08 (-0.17, 0.01) | -0.12 (-0.17, -0.06) | -0.04 (-0.14, 0.06) | 0.437 |
| 36 months | -0.16 (-0.26, -0.07) | -0.24 (-0.30, -0.17) | -0.07 (-0.18, 0.04) | 0.204 |
| **48 months** | -0.20 (-0.30, -0.11) | -0.31 (-0.39, -0.24) | -0.11 (-0.23, 0.01) | 0.064 |
| **MMSE, n=975** | | | | |
| 12 months | -0.15 (-0.40, 0.10) | -0.17 (-0.39, 0.04) | -0.02 (-0.28, 0.24) | 0.878 |
| 24 months | -0.18 (-0.43, 0.07) | -0.18 (-0.40, -0.04) | -0.001 (-0.28, 0.27) | 0.955 |
| 36 months | -0.33 (-0.59, -0.06) | -0.19 (-0.44, 0.07) | 0.15 (-0.16, 0.45) | 0.356 |
| **48 months** | -0.28 (-0.55, -0.01) | -0.33 (-0.60, -0.06) | -0.05 (-0.38, 0.28) | 0.770 |
| **CDR sum of boxes, n=975** | | | | |
| **12 months** | 0.10 (0.06, 0.15) | 0.20 (0.11, 0.30) | 0.10 (0.002, 0.20) | **0.045** |
| **24 months** | 0.13 (0.07, 0.18) | 0.28 (0.16, 0.40) | 0.15 (0.03, 0.28) | **0.015** |
| 36 months | 0.22 (0.15, 0.29) | 0.34 (0.19, 0.48) | 0.11 (-0.05, 0.27) | 0.165 |
| 48 months | 0.33 (0.25, 0.42) | 0.48 (0.31, 0.65) | 0.14 (-0.04, 0.33) | 0.132 |
| **Executive function composite scoree,n=871** | | | | |
| 12 months | -0.03 (-0.06, 0.00) | -0.04 (-0.14, 0.07) | -0.01 (-0.11, 0.09) | 0.908 |
| 24 months | -0.06 (-0.10, -0.03) | -0.09 (-0.20, 0.02) | -0.02 (-0.13, -0.09) | 0.658 |
| 36 months | -0.12 (-0.16, -0.08) | -0.17 (-0.28, -0.05) | -0.04 (-0.16, 0.07) | 0.463 |
| 48 months | -0.15 (-0.20, -0.11) | -0.20 (-0.32, -0.08) | -0.04 (-0.17, 0.08) | 0.507 |
| **Attention scoref, n=881** | | | | |
| 12 months | -0.03 (-0.07, 0.004) | -0.07 (-0.18, 0.04) | -0.04 (-0.15, 0.08) | 0.544 |
| 24 months | -0.07 (-0.11, -0.03) | -0.11 (-0.23, 0.004) | -0.05 (-0.17, 0.07) | 0.452 |
| 36 months | -0.12 (-0.17, -0.07) | -0.18 (-0.30, -0.05) | -0.06 (-0.19, 0.07) | 0.381 |
| 48 months | -0.15 (-0.19, -0.10) | -0.21 (-0.34, -0.08) | -0.06 (-0.20, 0.08) | 0.379 |

Significant associations in bold. Models were adjusted by sex, age, BMI, MAPT group, CDR status at baseline and GDS score

Abbreviations: MCP-1: Monocyte Chemoattractant Protein-1; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination.

a. High MCP-1 defined as values in the 4th quartile (> 251pg/mL).

b. Negative values for within-group differences mean cognitive decline, except for CDR sum of boxes (for which it is given by positive values).

c. Negative values for between-group differences indicate more pronounced cognitive decline among the high plasma MCP-1 group, except for CDR sum of boxes (for which it is given by positive values).

d. Based on the mean Z-score of 4 cognitive tests (free and total recall of the Free and Cued Selective Reminding test; 10 MMSE orientation items; Digit Symbol Substitution Test; and Category Naming Test) .

e. Based on the mean Z-score of 3 executive function tests (Controlled Oral Word Association Test, the Category Naming Test and the Trail Making Test-Part B) e Based on the mean Z-score of 2 attention tests (Digit-Symbol Test and the Trail Making Test-Part A)

**Additional file 4.** Mixed-effect linear regression analysis for variation in memory outcomes over time according to plasma MCP-1 status among community-dwelling older adults (excluding ApoE ε4 genotype).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Low plasma MCP-1a** | **High plasma MCP-1** | **Between-group Differenceb** |  |
|  | **Within-group evolution**  **Estimated mean**  **(95% CI)c** | **Within-group evolution**  **Estimated mean**  **(95% CI)** | **Estimated difference**  **(95%CI)** | **p-value** |
| **FCSRT Free Recall, n=881** | | | | |
| 12 months | -1.19 (-1.53, -0.84) | -1.76 (-2.75, -0.77) | -0.57 (-1.57, 0.44) | 0.268 |
| 24 months | -0.71 (-1.07, -0.34) | -1.31 (-2.34, -0.27) | -0.60 (-1.66, 0.45) | 0.262 |
| 36 months | -1.50 (-1.93, -1.08) | -2.66 (-3.77, -1.55) | -1.16 (-2.31, 0.001) | 0.054 |
| **48 months** | -1.70 (-2.16, -1.24) | -3.00 (-4.18, -1.82) | 1.30 (-2.54, -0.06) | **0.039** |
| **FCSRT Total Recall, n=881** | | | | |
| 12 months | -0.80 (-1.01, -0.59) | -1.36 (-1.94, -0.78) | -0.56 (-1.15, 0.03) | 0.062 |
| 24 months | -0.43 (-0.66, -0.20) | -0.86 (-1.48, -0.24) | -0.43 (-1.07, 0.22) | 0.192 |
| 36 months | -1.19 (-1.46, -0.91) | -1.60 (-2.29, -0.90) | -0.41 (-1.15, 0.33) | 0.275 |
| **48 months** | -1.17 (-1.48, -0.85) | -1.36 (-2.12, -0.59) | -0.20 (-1.01, 0.63) | 0.646 |
| **FCSRT Free Delayed Recall, n=881** | | | | |
| **12 months** | -0.13 (-0.28, 0.02) | -0.49 (-0.90, -0.08) | -0.26 (-0.66, 0.14) | 0.213 |
| **24 months** | -0.16 (-0.33, 0.001) | -0.44 (-0.87, -0.02) | -0.20 (-0.63, 0.22) | 0.349 |
| 36 months | -0.29 (-0.48, -0.10) | -0.79 (-1.25, -0.32) | -0.45 (-0.92, 0.02) | 0.062 |
| 48 months | -0.48 (-0.69, -0.28) | -1.08 (-1.57, -0.59) | -0.57 (-1.07, -0.06) | **0.028** |
| **FCSRT Total Delayed Recall, n=881** | | | | |
| 12 months | -0.12 (-0.19, -0.05) | -0.23 (-0.42, -0.05) | -0.12 (-0.31, 0.08) | 0.246 |
| 24 months | -0.12 (-0.20, -0.03) | -0.28 (-0.49, -0.07) | -0.16 (-0.38, 0.06) | 0.150 |
| 36 months | -0.31 (-0.41, -0.21) | -0.35 (-0.59, -0.11) | -0.04 (-0.30, 0.22) | 0.751 |
| 48 months | -0.36 (-0.47, -0.24) | -0.70 (-0.97, -0.42) | -0.34 (-0.63, -0.04) | **0.025** |

Significant associations in bold. Models were adjusted by sex, age, BMI, MAPT group, CDR status at baseline, GDS score and ApoE ε4 genotype

Abbreviations: MCP-1: Monocyte Chemoattractant Protein-1. FCSRT, Free and Cued Selective Reminding Test.

a. High MCP-1 defined as values in the 4th quartile (>251 pg/mL).

b. Negative values for within-group differences mean cognitive decline.

c. Negative values for between-group differences indicate more pronounced cognitive decline among the high plasma MCP-1 group.

**Additional file 5.** Mixed-Effect Linear Regression Analysis for Variation in Overall Cognitive Outcomes, Executive Function and Attention Over Time According to Combined Plasma MCP-1 and Aβ42/40 Status among Community-Dwelling Older Adults

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Aβ42/40-a/MCP1-b**  **n=195** | **Aβ42/40- /MCP1+**  **n=85** | **Aβ42/40+ /MCP1-**  **n=97** | **Aβ42/40+ /MCP1+**  **n=52** |
| **Period** | Estimated mean  (95% CI)c | Estimated mean  (95% CI) | Estimated mean  (95% CI) | Estimated mean  (95% CI) |
| **Cognitive Composite Scored** | | | | |
| 12 month | -0.09 (-0.12, -0.05) | -0.16 (-0.27, -0.06)\* | -0.33 (-0.48, -0.18)\*\*\* | -0.32 (-0.51, -0.13)\*\* |
| 24 month | -0.06 (-0.10, -0.03) | -0.14 (-0.25, 0.03) | -0.49 (-0.65, -0.33)\*\*\* | -0.34 (-0.54, -0.14)\*\* |
| 36 month | -0.16 (-0.20, -0.12) | -0.28 (-0.39, -0.16) | -0.54 (-0.72, -0.37)\*\*\* | -0.38 (-0.60, -0.17)\* |
| 48 month | -0.19 (-0.24, -0.15) | -0.32 (-0.45, -0.20) | -0.59 (-0.78, -0.41)\*\*\* | -0.60 (-0.83, -0.36)\*\*\* |
| **MMSE** | | | | |
| 12 month | -0.12 (-0.26, 0.01) | -0.21 (-0.50, -0.08) | -0.57 (-0.99, -0.16)\* | -0.63 (-1.15, -0.10) |
| 24 month | -0.06 (-0.20, 0.08) | -0.27 (-0.58, 0.03) | -1.05 (-1.48, -0.61)\*\*\* | -0.52 (-0.97, 0.14) |
| 36 month | -0.28 (-0.43, -0.13) | -0.27 (-0.60, 0.06) | -0.88 (-1.38, -0.38)\* | -0.70 (-1.18, -0.06) |
| 48 month | -0.21 (-0.37,-0.05) | -0.34 (-0.69, 0.01) | -0.90 (-1.43, -0.37)\* | -0.84 (-1.55, -0.20) |
| **CDR sum of boxes** | | | | |
| 12 month | 0.14 (0.08, 0.20) | 0.16 (0.06, 0.26) | 0.22 (0.04, 0.39) | 0.34 (0.14, 0.53)\* |
| 24 month | 0.13 (0.06, 0.20) | 0.22 (0.10, 0.34) | 0.24 (0.03, 0.46) | 0.48 (0.23, 0.73)\* |
| 36 month | 0.23 (0.15, 0.31) | 0.26 (0.11, 0.41) | 0.41 (0.13, 0.69) | 0.54 (0.23, 0.85) |
| 48 month | 0.33 (0.23, 0.43) | 0.37 (0.30, 0.54) | 0.75 (0.42, 1.08)\* | 0.83 (0.46, 1.20)\* |
| **Executive function composite scoree** | | | | |
| 12 month | -0.02 (-0.05, 0.02) | -0.07 (-0.19, 0.05) | -0.34 (-0.50, -0.17)\*\*\* | -0.15 (-0.36, 0.07) |
| 24 month | -0.04 (-0.08, -0.004) | -0.11 (-0.23, 0.01) | -0.39 (-0.56, -0.21)\*\*\* | -0.25 (-0.47, -0.02) |
| 36 month | -0.10 (-0.14, -0.05) | -0.17 (-0.30, -0.04) | -0.48 (-0.67, -0.29)\*\*\* | -0.33 (-0.58, -0.09) |
| 48 month | -0.12 (-0.17, -0.07) | -0.22 (-0.36, -0.08) | -0.53 (-0.74, -0.33)\*\*\* | -0.33 (-0.60, -0.07) |
| **Attention scoref** | | | | |
| 12 month | -0.03 (-0.05, 0.00) | -0.03 (-0.12, 0.06) | -0.14 (-0.27, -0.01) | -0.16 (-0.32, 0.01) |
| 24 month | -0.03 (-0.06, -0.01) | -0.05 (-0.14, 0.05) | -0.20 (-0.33, -0.06) | -0.25 (-0.41, -0.08)\* |
| 36 month | -0.10 (-0.13, -0.07) | -0.14 (-0.24, -0.04) | -0.22 (-0.37, -0.08) | -0.33 (-0.51, -0.15)\* |
| 48 month | -0.13 (-0.17, -0.10) | 0.17 (-0.27, -0.07) | -0.32 (-0.48, -0.18)\* | -0.42 (-0.61, -0.23)\*\* |

\*p-value <0.05; \*\* p-value <0.001; \*\*\* p-value <0.001: Significant differences in the evolution of the outcomes (Aβ42/40-/MCP1- as reference group)

#p-value <0.05; ## p-value <0.001; ### p-value <0.001: Significant difference in the evolution of the outcomes between Aβ42/40+ /MCP1- and Aβ42/40+/MCP1+ groups.

Models were adjusted by sex, age, BMI, MAPT group, CDR status at baseline, GDS score and ApoE ε4 genotype

Abbreviations: Aβ42/40: β-amyloid 42aa isoform/β-amyloid 40aa isoform ratio; MCP-1: Monocyte Chemoattractant Protein-1; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; MMSE.

a. Abnormal Aβ42/40 defined as values ≥ 107 pg/mL

b. Abnormal MCP-1 defined as values in the 4th quartile.

c. Negative values indicate worsening performance along follow-up, except for CDR sum of boxes (for which it is given by positive values).

d. Based on the z score of 4 cognitive tests (free and total recall of the Free and Cued Selective Reminding test; 10 MMSE orientation items; Digit Symbol Substitution Test;and Category Naming Test) .

e. Based on the z score of 3 executive function tests (Controlled Oral Word Association Test, the Category Naming Test and the Trail Making Test-Part B)

f. Based on the z score of 2 attention tests (Digit-Symbol Test and the Trail Making Test-Part A)

**Additional file 6.**  Mixed-Effect Linear Regression Analysis for Variation in Memory Endpoints Over Time According to Combined Plasma MCP-1 and Aβ42/40 Status Among Community-Dwelling Older Adults

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Aβ42/40-a/MCP1-b**  **n=195** | **Aβ42/40- /MCP1+**  **n=85** | **Aβ42/40+ /MCP1-**  **n=97** | **Aβ42/40+ /MCP1+**  **n=52** |
| **Period** | Estimated mean  (95% CI)c | Estimated mean  (95% CI) | Estimated mean  (95% CI) | Estimated mean  (95% CI) |
| **FCSRT Free Recall** | | | | |
| 12 month | -1.10 (-1.47, -0.72) | -1.71 (-2.84, -0.58) | -4.36 (-5.96, -2.75) \* | -3.84 (-5.85, -1.83)\*\* |
| 24 month | -0.46 (-0.86, -0.06) | -1.40 (-2.58, -0.23) | -4.70 (-6.39, -3.01) \*\*\* | -2.82 (-4.96, -0.68)\* |
| 36 month | -1.30 (-1.76, -0.84) | -2.89 (-4.16, -1.62)\* | -5.76 (-7.64, -3.88) \*\*\* | -3.12 (-5.45, -0.78) |
| 48 month | -1.47 (-1.97, -0.98) | -2.98 (-4.32, -1.64)\* | -5.69 (-7.71, -3.68) \*\*\* | -4.78 (-7.33, -2.23)\* |
| **FCSRT Total Recall** | | | | |
| 12 month | -0.60 (-0.84, -0.36) | -0.96 (-1.56, -0.36) | -3.42 (-4.42, -2.42)\*\*\* | -2.29 (-3.42, -1.52)\*\*\* |
| 24 month | -0.18 (-0.45, 0.08) | -0.53 (-1.17, 0.11) | -3.01 (-4.10, -1.92)\*\*\* | -1.89 (-3.15, 0.63)\*\* |
| 36 month | -0.92 (-1.24, -0.61) | -1.23 (-1.94, -0.52) | -3.92 (-5.21, -2.63)\*\*\* | -2. 92 (-4.34, 1.50)\*\* |
| 48 month | -0.81 (-1.17, -0.46) | -0.83 (-1.60, -0.06) | -4.75 (-6.19, -3.32)\*\*\* | -3.36 (-4.94, -1.77)\*\* |
| **FCSRT Free Delayed Recall** | | | | |
| 12 month | -0.10 (-0.27, 0.06) | -0.35 (-0.80, 0.10) | -1.22 (-1.86, -0.58)\*\*\* | -1.59 (-2.39, -0.79)\*\* |
| 24 month | -0.11 (-0.28, 0.07) | -0.38 (-0.85,-0.08) | -1.49 (-2.16, -0.81)\*\*\* | -1.25 (-2.11, -0.39)\* |
| 36 month | -0.24 (-0.44, -0.04) | -0.84 (-1.36, -0.33)\* | -1.61 (-2.38, -0.85)\*\*\* | -1.11 (-2.05, -0.16) |
| 48 month | -0.38 (-0.60, -0.17) | -1.07 (-1.61, -0.53)\* | -2.28 (-3.10, -1.46)\*\*\* | -1.66 (-2.70, -0.62)\* |
| **FCSRT Total Delayed Recall** | | | | |
| 12 month | -0.07 (-0.15, 0.01) | -0.29 ( -0.50, -0.09)\* | -0.64 (-0.94, -0.34)\*\*\* | -0.74 (-1.11, -0.36)\*\*\* |
| 24 month | -0.06 (-0.15, 0.03) | -0.38 (-0.61, 0.15)\*\* | -0.78 (-1.13, -0.44)\*\*\* | -0.57 (-1.00, -0.13)\* |
| 36 month | -0.25 (-0.36, -0.14) | -0.45 (-0.72, -0.18) | -1.25 (-1.66, -0.84)\*\*\* | -0.71 (-1.22, -0.19)\* |
| 48 month | -0.26 (-0.39 , -0.13) | -0.72 (-1.02, -0.41)\*\* | -1.46 (-1.93, -0.99)\*\*\* | -1.19 (-1.79, -0.59)\*\* |

\*p-value <0.05; \*\* p-value <0.001; \*\*\* p-value <0.001: Significant differences in the evolution of the outcomes (Aβ42/40-/MCP1- as reference group)

#p-value <0.05; ## p-value <0.001; ### p-value <0.001: Significant difference in the evolution of the outcomes between Aβ42/40+ /MCP1- and Aβ42/40+ /MCP1+ groups.

Models were adjusted by sex, age, BMI, MAPT group, CDR status at baseline, GDS score and ApoE ε4 genotype

Abbreviations: Aβ42/40: β-amyloid 42aa isoform/β-amyloid 40aa isoform ratio; FCSRT: Free and Cued Selective Reminding Test; MCP-1: Monocyte Chemoattractant Protein-1;

a. Abnormal Aβ42/40 defined as values ≥ 107 pg/mL

b. Abnormal MCP-1 defined as values in the 4th quartile.

c. Negative values indicate worsening performance along follow-up.

**Additional file 7.**  Mixed-Effect Linear Regression Analysis for Variation in Overall Cognitive Outcomes, Executive Function and Attention Over Time According to Combined Plasma MCP-1 and Aβ42/40 Status among Community-Dwelling Older Adults (excluding ApoE ε4 genotype)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Aβ42/40-/MCP1-** | **Aβ42/40- /MCP1+** | **Aβ42/40+ /MCP1-** | **Aβ42/40+ /MCP1+** |
| **Period** | **Estimated mean**  **(95% CI)c** | **Estimated mean**  **(95% CI)** | **Estimated mean**  **(95% CI)** | **Estimated mean**  **(95% CI)** |
| **Cognitive Composite Scored, n=429** | | | | |
| 12 month | -0.08 (-0.12, -0.05) | -0.05 (-0.16, 0.04) | -0.26 (-0.41, -0.12)\*\*\* | -0.19 (-0.37, -0.00)\* |
| 24 month | -0.07 (-0.10, -0.03) | -0.05 (-0.16, 0.06) | -0.43 (-0.59, -0.27)\*\*\* | -0.24 (-0.44, -0.04)\*\* |
| 36 month | -0.16 (-0.20, -0.12) | -0.09 (-0.21, 0.03) | -0.39 (-0.57, -0.22)\*\*\* | -0.20 (-0.42, -0.01) |
| 48 month | -0.20 (-0.24, -0.15) | -0.11 (-0.23, -0.02) | -0.41 (-0.60, -0.22)\*\*\* | -0.37 (-0.61, -0.13)\*\* |
| **MMSE, n=429** | | | | |
| 12 month | -0.08 (-0.21, 0.05) | 0.01 (-0.28, 0.29) | -0.49 (-0.91, -0.08)\* | -0.43 (-0.96, 0.09) |
| 24 month | -0.07 (-0.20, 0.07) | -0.07 (-0.37, 0.23) | -0.95 (-1.39, -0.51)\*\*\* | -0.24 (-0.80, 0.32) |
| 36 month | -0.25 (-0.40, -0.10) | 0.14 (-0.19, 0.48) | -0.60 (-1.12, -0.09)\* | -0.20 (-0.82, 0.43) |
| 48 month | -0.19 (-0.34, -0.04) | -0.03 (-0.38, 0.33) | -0.69 (-1.24, -0.14)\* | -0.57 (-1.25, 0.12) |
| **CDR sum of boxes, n=429** | | | | |
| 12 month | -0.1 (-0.05, 0.02) | 0.08 (-0.17, 0.06) | 0.06 (-0.10, 0.22) | 0.22 (0.02, 0.42)\* |
| 24 month | -0.05 (-0.08, -0.01) | 0.13 (-0.21, 0.02) | 0.10 (-0.10, 0.31) | 0.30 (0.04, 0.55)\* |
| 36 month | -0.10 (-0.14, -0.06) | 0.09 (-0.29, -0.04) | 0.19 (-0.07, 0.46) | 0.29 (-0.04, 0.62) |
| 48 month | -0.13 (-0.18, -0.08) | 0.11 (-0.34, -0.07) | 0.35 (0.03, -0.66)\* | 0.49 (0.10, 0.88)\* |
| **Executive function composite scoree, n=412** | | | | |
| 12 month | -0.02 (-0.05, 0.02) | -0.04 (-0.15, 0.07) | -0.30 (-0.47, -0.15)\*\*\* | -0.05 (-0.26, 0.16) |
| 24 month | -0.04 (-0.08, -0.004) | -0.05 (-0.17, 0.07) | -0.32 (-0.50, -0.17)\*\*\* | -0.12 (-0.35, 0.10) |
| 36 month | -0.10 (-0.14, -0.05) | -0.07 (-0.20, -0.06) | -0.37 (-0.56, -0.17)\*\*\* | -0.16 (-0.40, 0.08) |
| 48 month | -0.12 (-0.17, -0.07) | -0.07 (-0.21, -0.06) | -0.39 (-0.59, -0.18)\*\*\* | -0.12 (-0.39, 0.15) |
| **Attention scoref, n=429** | | | | |
| 12 month | -0.03 (-0.05, 0.01) | 0.01 (-0.07, 0.10) | -0.10 (-0.23, 0.03) | -0.08 (-0.24, 0.08) |
| 24 month | -0.04 (-0.06, -0.01) | 0.02 (-0.07, 0.10) | -0.15 (-0.29, -0.02)\* | -0.18 (-0.35, -0.01)\* |
| 36 month | -0.10 (-0.13, -0.07) | 0.02 (-0.08, 0.08) | -0.22 (-0.26, 0.03) | -0.20 (-0.38, -0.03)\* |
| 48 month | -0.13 (-0.17, -0.10) | -0.02 (-0.11, -0.06)\* | -0.32 (-0.33, -0.03)\* | -0.26 (-0.44, -0.07)\*\* |

\*p-value <0.05; \*\* p-value <0.001; \*\*\* p-value <0.001: Significant differences in the evolution of the outcomes (Aβ42/40-/MCP1- as reference group)

#p-value <0.05; ## p-value <0.001; ### p-value <0.001: Significant difference in the evolution of the outcomes between Aβ42/40+ /MCP1- and Aβ42/40+/MCP1+ groups.

Models were adjusted by sex, age, BMI, MAPT group, CDR status at baseline, GDS score and ApoE ε4 genotypeAbbreviations: Aβ42/40: β-amyloid 42aa isoform/β-amyloid 40aa isoform ratio; MCP-1: Monocyte Chemoattractant Protein-1; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; MMSE.

a. Abnormal Aβ42/40 defined as values ≥ 107 pg/mL

b. Abnormal MCP-1 defined as values in the 4th quartile.

c. Negative values indicate worsening performance along follow-up, except for CDR sum of boxes (for which it is given by positive values).

d. Based on the z score of 4 cognitive tests (free and total recall of the Free and Cued Selective Reminding test; 10 MMSE orientation items; Digit Symbol Substitution Test;and Category Naming Test) .

e. Based on the z score of 3 executive function tests (Controlled Oral Word Association Test, the Category Naming Test and the Trail Making Test-Part B)

f. Based on the z score of 2 attention tests (Digit-Symbol Test and the Trail Making Test-Part A)

**Additional file 8.** Mixed-Effect Linear Regression Analysis for Variation in Memory Outcomes Over Time According to Combined Plasma MCP-1 and Aβ42/40 Status Among Community-Dwelling Older Adults (excluding ApoE ε4 genotype)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Aβ42/40-a/MCP1-b**  **n=195** | **Aβ42/40- /MCP1+**  **n=85** | **Aβ42/40+ /MCP1-**  **n=97** | **Aβ42/40+ /MCP1+**  **n=52** |
| **Period** | Estimated mean  (95% CI)c | Estimated mean  (95% CI) | Estimated mean  (95% CI) | Estimated mean  (95% CI) |
| **FCSRT Free Recall, n=429** | | | | |
| 12 month | -1.05 (-1.43, -0.69) | -0.67 (-1.76, 0.42) | -3.36 (-4.96, -1.76)\*\*\* | -2.10 (-4.09, -0.12)\*\* |
| 24 month | -0.48 (-0.87, -0.10) | -0.84 (-1.98, 0.31) | -4.26 (-5.96, -2.57)\*\*\* | -2.05 (-4.17, 0.08) |
| 36 month | -1.26 (-1.70, -0.82) | -1.58 (-2.84, -0.32)\* | -4.55 (-6.45, -3.93)\*\*\* | -1.86 (-4.18, 0.46) |
| 48 month | -1.48 (-1.95, -0.99) | -1.50 (-2.84, -0.15)\* | -4.27 (-6.32, -3.74)\*\*\* | -2.91 (-5.44, -0.37)\* |
| **FCSRT Total Recall, n=429** | | | | |
| 12 month | -0.62 (-0.85, -0.40) | -0.68 (-1.33, -0.04)\* | -2.63 (-3.58, -1.67)\*\*\* | -2.77 (-3.97, -1.56) |
| 24 month | -0.27 (-0.51, -0.03) | -0.48 (-1.19, 0.21) | -2.56 (-3.62, -1.51)\*\*\* | -3.74 (-2.78, -1.06)\* |
| 36 month | -1.02 (-1.31, -0.73) | -0.43 (-1.23, 0.37) | -2.65 (-3.88, -1.43)\*\*\* | -4.89 (-4.34, -1.84)\* |
| 48 month | -0.92 (-1.25, -0.60) | -0.17 (-1.05, 0.72) | -3.44 (-4.81, -2.08)\*\*\* | -3.75 (-5.47, -2.03)\*\* |
| **FCSRT Free Delayed Recall, n=429** | | | | |
| 12 month | **-0.10 (-0.26, 0.06)** | -0.28 (-0.71, 0.16) | -1.27 (-1.91, -0.63)\*\*\* | -1.36 (-2.16, -0.57)\*\*\* |
| 24 month | -0.13 (-0.30, 0.04) | -0.34 (-0.79, 0.11) | -1.52 (-2.21, -0.84)\*\*\* | -1.14 (-1.99, -0.28)\*\* |
| 36 month | -0.24 (-0.43, -0.05) | -0.80 (-1.29, -0.30)\* | -1.66 (-2.42, -0.89)\*\*\* | -1.05 (-1.98, -0.10) |
| 48 month | -0.39 (-0.60, -0.18) | -1.04 (-1.57, -0.52)\* | -2.33 (-3.15, -1.50)\*\*\* | -1.62 (-2.65, -0.59)\* |
| **FCSRT Total Delayed Recall, n=429** | | | | |
| 12 month | -0.08 (-0.16, -0.004) | -0.10 (-0.32, 0.11) | -0.68 (-0.99, -0.37)\*\* | -0.54 (-0.93, -0.15)\*\* |
| 24 month | -0.07 (-0.16, 0.02) | -0.21 (-0.45, 0.03) | -0.79 (-1.15, -0.43)\*\* | -0.39 (-0.84, 0.06) |
| 36 month | -0.24 (-0.34, -0.13) | -0.10 (-0.39, 0.18) | -1.09 (-1.53, -0.66)\*\*\* | -0.35 (-0.88, 0.18) |
| 48 month | -0.27 (-0.39, -0.15) | -0.38 (-0.70, -0.06)\* | -1.28 (-1.77, -0.79)\*\*\* | -0.81 (-1.42, -0.20)\*\* |

\*p-value <0.05; \*\* p-value <0.001; \*\*\* p-value <0.001: Significant differences in the evolution of the outcomes (Aβ42/40-/MCP1- as reference group)

#p-value <0.05; ## p-value <0.001; ### p-value <0.001: Significant difference in the evolution of the outcomes between Aβ42/40+ /MCP1- and Aβ42/40+/MCP1+ groups.

Models were adjusted by sex, age, BMI, MAPT group, CDR status at baseline, GDS score and ApoE ε4 genotype

Abbreviations: Aβ42/40: β-amyloid 42aa isoform/β-amyloid 40aa isoform ratio; MCP-1: Monocyte Chemoattractant Protein-1; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; MMSE.

a. Abnormal Aβ42/40 defined as values ≥ 107 pg/mL

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c. Negative values indicate worsening performance along follow-up, except for CDR sum of boxes (for which it is given by positive values).

d. Based on the z score of 4 cognitive tests (free and total recall of the Free and Cued Selective Reminding test; 10 MMSE orientation items; Digit Symbol Substitution Test;and Category Naming Test) .

e. Based on the z score of 3 executive function tests (Controlled Oral Word Association Test, the Category Naming Test and the Trail Making Test-Part B)

f. Based on the z score of 2 attention tests (Digit-Symbol Test and the Trail Making Test-Part A)