Supplementary Table S1. Baseline characteristics of study subjects included in incident frailty investigation according to plasma amyloid-β status.

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | Total | Highplasma Aβ42/40 (>0.107) | Lowplasma Aβ42/40 (≤0.107) |
| N (%) | 377 | 249 (66.0) | 128 (34.0) |
| Age (years) | 76.6 (4.5) | 76.4 (4.4) | 77.1 (4.6) |
| Sex (female) | 223 (59.2) | 160 (64.3) | 63 (49.2)† |
| MAPT groups |  |  |  |
| Multidomain intervention + omega-3 | 106 (28.1) | 77 (30.9) | 29 (22.7) |
| Omega-3 | 87 (23.1) | 57 (22.9) | 30 (23.4) |
| Multidomain intervention | 91 (24.1) | 60 (24.1) | 31 (24.2) |
| Placebo | 93 (24.7) | 55 (22.1) | 38 (29.7) |
| Education |  |  |  |
| No diploma or primary school certificate | 104 (27.8) | 63 (25.6) | 41 (32.0)\* |
| Secondary education | 121 (32.4) | 73 (29.7) | 48 (37.5) |
| High school diploma | 52 (13.9) | 41 (16.7) | 11 (8.6) |
| University level | 97 (25.9) | 69 (28.0) | 28 (21.9) |
| Fried frailty phenotype |  |  |  |
| Robust (0/5) | 208 (55.2) | 130 (52.2) | 78 (60.9) |
| Pre-frail (1-2/5) | 169 (44.8) | 119 (47.8) | 50 (39.1) |
| Frail (≥3/5)  | 0 (0) | 0 (0) | 0 (0) |
| CDR |  |  |  |
| Score 0 | 167 (44.3) | 116 (46.6) | 51 (39.8) |
| Score 0.5 or 1 | 210 (55.7) | 133 (53.4) | 77 (60.2) |
| MMSE | 27.9 (1.8) | 28.0 (1.8) | 27.8 (1.8) |
| Body mass index (kg/m2) | 26.6 (4.0) | 26.8 (4.1) | 26.2 (3.7) |
| APOE ε4 carriers | 94 (27.1) | 48 (21.2) | 46 (38.3)† |
| Plasma Aβ42/40, median (IQR) | 0.110(0.100, 0.120) | 0.120(0.110, 0.130) | 0.100(0.090, 0.100)† |

Values presented in number (%) for categorical variables or mean (standard deviation) for continuous variables, unless otherwise indicated.

Aβ, amyloid-beta; APOE, Apolipoprotein E; CDR, Clinical Dementia Rating scale; MAPT, Multidomain Alzheimer Preventive Trial; MMSE, Mini-Mental State Examination (0-30, 0 is worse).

\*p<0.05; †p<0.01 between two groups determined by Student's t-test or by Chi-square/Fisher exact test.

Supplementary Table S2. Mixed-effect ordinal logistic regressions examining associations of frailty with plasma amyloid-β 42/40 as a continuous variable.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Unadjusted model†(N=477) | Adjusted model 1‡(N=466) | Adjusted model 2§(N=424) |
| OR | 95% CI | p-value | OR | 95% CI | p-value | OR | 95% CI | p-value |
| Plasma Aβ42/40\* | 0.97 | 0.90 – 1.04 | 0.414 | 0.97 | 0.91 – 1.04 | 0.429 | 1.00 | 0.93 – 1.08 | 0.959 |

OR, odds ratio of increasing frailty severity over time compared to reference group;

Aβ, amyloid-beta; CI, confidence interval;

\*Value of plasma amyloid-β 42/40 were multiplied 100 times before putting into the models; †Random slope on time and on participants only; ‡Adjustments for age, sex, Multidomain Alzheimer Preventive Trial (MAPT) groups, education, body mass index, Mini-Mental State Examination (MMSE) score, time and interaction between plasma Aβ42/40 group and time; excluding participants without data of education, body mass index or MMSE score; §Adjustments for age, sex, MAPT groups, education, body mass index, MMSE score, Apolipoprotein E (APOE) ε4 genotype, time and interaction between plasma Aβ42/40 group and time; excluding participants without data of education, body mass index, MMSE score or APOE ε4 genotype.

Supplementary Table S3. Mixed-effect ordinal logistic regressions examining associations between plasma amyloid-β 42/40 and frailty evolution over time among participants with APOE ε4 genotype measurement (N=424\*).

|  |  |
| --- | --- |
| Plasma Aβ42/40 | Adjusted model without adjustment for APOE ε4 genotype† |
| OR | 95% CI | p-value |
| Threshold 1: cutoff |  |  |  |
| High (>0.107) | ref. | - | - |
| Low (≤0.107) | 1.14 | 0.90 – 1.45 | 0.268 |
| Threshold 2: quartile |  |  |  |
| ≤25th percentile (≤0.103) | 1.18 | 0.86 – 1.63 | 0.299 |
| >25th-50th percentile (>0.103, ≤0.113) | 0.96 | 0.70 – 1.32 | 0.785 |
| >50th-75th percentile (>0.113, ≤0.123) | 1.06 | 0.78 – 1.44 | 0.718 |
| >75th percentile (>0.123) | ref. | - | - |

OR, odds ratio of increasing frailty severity over time compared to reference group;

Aβ, amyloid-beta; APOE, Apolipoprotein E; CI, confidence interval; ref, reference group;

\*42 subjects without measurement of APOE ε4 genotype, and 11 subjects without data of education, body mass index or Mini-Mental State Examination (MMSE) score were further excluded from adjusted models, respectively.

†Adjustments for age, sex, Multidomain Alzheimer Preventive Trial (MAPT) groups, education, body mass index, MMSE score, time and interaction between plasma Aβ42/40 group and time.

Supplementary Table S4. Cox proportional hazard models for incident frailty among participants with APOE ε4 genotype measurement (N=343\*).

|  |  |
| --- | --- |
| Plasma Aβ42/40 | Adjusted model without adjustment for APOE ε4 genotype† |
| HR | 95% CI | p-value |
| Threshold 1: cutoff |  |  |  |
| High (>0.107) | ref. | - | - |
| Low (≤0.107) | 1.48 | 0.76 – 2.86 | 0.249 |
| Threshold 2: quartile |  |  |  |
| ≤25th percentile (≤0.103) | 2.12 | 0.83 – 5.45 | 0.118 |
| >25th-50th percentile (>0.103, ≤0.113) | 0.83 | 0.28 – 2.44 | 0.733 |
| >50th-75th percentile (>0.113, ≤0.123) | 1.34 | 0.52 – 3.41 | 0.545 |
| >75th percentile (>0.123) | ref. | - | - |

Aβ, amyloid-beta; APOE, Apolipoprotein E; CI, confidence interval; HR, hazard ratio; ref, reference group;

\*30 subjects without measurement of APOE ε4 genotype, and 4 subjects without data of education, body mass index or Mini-Mental State Examination (MMSE) score were further excluded from adjusted models, respectively.

†Adjustments for age, sex, Multidomain Alzheimer Preventive Trial (MAPT) groups, education, body mass index and MMSE score.

Supplementary Table S5. Cox proportional hazard models for incident frailty, considering interaction between plasma Aβ42/40 and APOE ε4 genotype.

|  |  |  |
| --- | --- | --- |
| Plasma Aβ42/40 | Adjusted model 1\*(N=347) | Adjusted model 2†(N=343) |
| HR | 95% CI | p-value | HR | 95% CI | p-value |
| Threshold 1: cutoff (ref.: High (>0.107)) |  |  |  |  |  |  |
| Low (≤0.107) | - | - | 0.498‡ | - | - | 0.134‡ |
| Low at APOE ε4 non-carriers | 0.79 | 0.39 – 1.57 | 0.953§ | 0.57 | 0.27 – 1.19 | 0.849§ |
| Low at APOE ε4 carriers | 0.75 | 0.17 – 3.35 | 0.67 | 0.14 – 3.17 |
| Threshold 2: quartile (ref.: >75th percentile (>0.123)) |  |  |  |  |  |  |
| ≤25th percentile (≤0.103) | - | - | 0.073‡ | - | - | 0.023‡ |
| ≤25th percentile at APOE ε4 non-carriers | 2.48 | 0.92 – 6.71 | 0.224§ | 3.48 | 1.19 – 10.16 | 0.090§ |
| ≤25th percentile at APOE ε4 carriers | 0.73 | 0.13 – 3.99 | 0.59 | 0.10 – 3.56 |
| >25th-50th percentile (>0.103, ≤0.113) | - | - | 0.756‡ | - | - | 0.749‡ |
| >25th-50th percentile at APOE ε4 non-carriers | 1.20 | 0.39 – 3.71 | 0.262§ | 1.22 | 0.36 – 4.08  | 0.185§ |
| >25th-50th percentile at APOE ε4 carriers | 0.26 | 0.02 – 2.89 | 0.19 | 0.02 – 2.26 |
| >50th-75th percentile (>0.113, ≤0.123) | - | - | 0.121‡ | - | - | 0.211‡ |
| >50th-75th percentile at APOE ε4 non-carriers | 2.15 | 0.82 – 5.66 | 0.984§ | 1.94 | 0.69 – 5.50 | 0.986§ |
| >50th-75th percentile at APOE ε4 carriers | -|| | - | -|| | - |

Aβ, amyloid-beta; APOE, Apolipoprotein E; CI, confidence interval; HR, hazard ratio; ref, reference group;

\*Adjustments for APOE ε4 genotype and interaction between APOE ε4 genotype and plasma Aβ42/40; †Adjustments for age, sex, Multidomain Alzheimer Preventive Trial (MAPT) groups, education, body mass index, Mini-Mental State Examination (MMSE) score, APOE ε4 genotype and interaction between APOE ε4 genotype and plasma Aβ42/40; excluding participants without data of education, body mass index or MMSE score; ‡p-value for plasma Aβ42/40; §p-value for interaction between plasma Aβ42/40 and APOE ε4 genotype; ||There was no participant who fulfilled the criterion for incident frailty and had plasma Aβ42/40 in >50th-75th percentile.