**Supplementary content**

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**Controlled Trials.**

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# eTable 1. Baseline characteristics of the pooled sample per study

|  |  |  |  |
| --- | --- | --- | --- |
|  | **preDIVA**  **N=2818** | **MAPT**  **N=1344** | **P-value** |
| **Demographics** |  |  |  |
| Age y, median (IQR) | 74 (72-76) | 74 (72-78) | <0.001 |
| Female sex, n (%) | 1533 (54.4) | 870 (64.7) | <0.001 |
| Educational level, n (%) |  |  | <0.001 |
| * Low | 630 (22.6) | 292 (22.1) |  |
| * Intermediate | 1617 (57.9) | 453 (34.2) |
| * High | 546 (19.5) | 579 (43.7) |  |
| **Biological risk factors** |  |  |  |
| Systolic blood pressure (mmHg), mean (SD) | 154.8 (21.0) | 140.8 (19.6) | <0.001 |
| LDL cholesterol (mmol/L),  mean (SD) | 3.1 (1.0) | 3.2 (0.9) | <0.001 |
| BMI (kg/m2), mean (SD) | 27.5 (4.1) | 26.1 (4.0) | <0.001 |
| **Test scores** |  |  |  |
| MMSE, mean (SD)  (range 0-30) | 28.2 (1.7) | 28.2 (1.6) | 0.4 |
| Memory (MMSE item 5),  mean (SD) (range 0-3) | 2.2 (0.8) | 2.4 (0.8) | <0.001 |
| MMSE other, mean (SD)  (range 0-27) | 26.0 (1.4) | 26.0 (1.2) | <0.001 |
| GDS, mean (SD)  (range 0-15) | 1.5 (2.1) | 3.1 (2.5) | <0.001 |
| Subjective memory loss  (GDS15-Q10, n, % yes) | 473 (16.9) | 306 (22.8) | <0.001 |
| Apathy, mean (SD)  (range 0-3) | 0.7 (0.9) | 0.7 (0.9) | 0.2 |
| Depressive symptoms  (n, % GDS >5) | 144 (5.4) | 211 (15.8) | <0.001 |

Individuals with at least one follow-up visit with a test score for Mini-Mental State Examination or Geriatric Depression Scale. Abbreviations: BMI: Body Mass Index; GDS: Geriatric Depression Scale; GDS15-Q10: question 10 of the Geriatric Depression Scale: ‘Do you feel you have more problems with memory than most?’; IQR: interquartile range; LDL cholesterol: low-density lipoprotein cholesterol; SD: standard deviation; MMSE: Mini-Mental State Examination

# eTable 2. Baseline characteristics of individuals with at least a baseline and follow-up visit and individuals without any follow-up visits

|  |  |  |  |
| --- | --- | --- | --- |
|  | Included individuals\*  (n=4162) | Individuals without follow-up (n=1043) | P-value |
| **Study, n (%)** |  |  |  |
| * preDIVA | 2818 (67.7) | 708 (67.9) |  |
| * MAPT | 1344 (32.3) | 335 (32.1) |  |
| **Randomization, n (%)** |  |  | 0.3 |
| Intervention | 2166 (52.0) | 561 (53.8) |  |
| Control | 1996 (48.0) | 482 (46.2) |  |
| **Demographics** |  |  |  |
| Age y, median (IQR) | 74 (72, 76) | 75 (73, 77) | <0.001 |
| Female sex, n (%) | 2403 (57.7) | 603 (57.8) | 1.0 |
| Educational level, n (%) |  |  | 0.001 |
| * Low (max primary school) | 922 (22.4) | 285 (28.0) |  |
| * Intermediate | 2070 (50.3) | 461 (45.3) |  |
| * High (min high school) | 1125 (27.3) | 271 (26.6) |  |
| MMSE score, mean (SD)  (range 0-30) | 28.19 (1.7) | 27.76 (1.9) | <0.001 |
| **Biological risk factors** |  |  |  |
| Systolic blood pressure (mmHg), mean (SD) | 150.29 (21.6) | 152.53 (23.1) | 0.003 |
| LDL cholesterol, mean (SD) | 3.14 (1.0) | 3.09 (1.0) | 0.1 |
| BMI (kg/m2), mean (SD) | 27.0 (4.2) | 27.0 (4.3) | 1.0 |

**\***These individuals had at least one follow-up visit with a test score for Mini-Mental State Examination or Geriatric Depression Scale. Abbreviations: BMI: Body Mass Index; GDS: Geriatric Depression Scale; GDS15-Q10: question 10 of the Geriatric Depression Scale: ‘Do you feel you have more problems with memory than most?’; IQR: interquartile range; LDL cholesterol: low-density lipoprotein cholesterol; SD: standard deviation; MMSE: Mini-Mental State Examination

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Baseline MMSE <26 | | | | | Baseline MMSE ≥26 | | | | |
|  | **Baseline mean** | | **Mean difference baseline and follow-up** | | **Mean difference between intervention and control group** | **Baseline mean** | | **Mean difference baseline and follow-up** | | **Mean difference between intervention and control group** |
|  | Control | Intervention | Control | Intervention | MDc (95%CI) | Control | Intervention | Control | Intervention | MDc (95%CI) |
| Cognitive functioning |  |  |  |  |  |  |  |  |  |  |
| MMSE (range 0-30)\* | 24.20 | 24.08 | 0.65 | 1.58 | 0.84  (0.15 to 1.54) | 28.53 | 28.54 | -0.14 | -0.16 | -0.03  (-0.12 to 0.06) |
| Memory (MMSE item 5) (range 0-3)\* | 1.42 | 1.24 | 0.22 | 0.59 | 0.21  (-0.01 to 0.43) | 2.37 | 2.36 | 0.01 | 0.009 | -0.01  (-0.05 to 0.03) |
| Other (range 0-27)\* | 22.77 | 22.81 | 0.38 | 0.99 | 0.74  (0.26 to 1.21) | 26.16 | 26.17 | -0.16 | -0.18 | -0.02  (-0.09 to 0.05) |
| Subjective memory loss (GDS15-Q10, % yes)† | 0.34 | 0.33 | 1.48 | 1.86 | -1.83  (-10.86 to 7.21) | 0.17 | 0.19 | -0.07 | -0.97 | -0.37  (-2.42 to 1.67) |
| Depressive symptoms |  |  |  |  |  |  |  |  |  |  |
| GDS (range 0-15)† | 3.06 | 2.48 | 0.42 | 0.41 | -0.17  (-0.66 to 0.32) | 1.98 | 1.93 | 0.21 | 0.20 | -0.04  (-0.16 to 0.08) |
| Depressive symptoms (% GDS >5)† | 0.14 | 0.13 | 11.34 | 4.85 | -0.06  (-0.14 to 0.02) | 0.09 | 0.08 | 2.00 | 2.38 | -0.003  (-0.02 to 0.01) |
| Apathy (range 0-3)† | 0.88 | 0.77 | 0.14 | 0.22 | 0.03  (-0.16 to 0.21) | 0.69 | 0.68 | 0.12 | 0.11 | -0.01  (-0.06 to 0.04) |

# eTable 3. Mean difference in effect of multidomain interventions on cognition, symptoms of depression and apathy in subgroups by baseline cognition, after 3-4 years of follow-up

**\*** high score indicates better results; † low score indicates better results. Abbreviations: GDS: Geriatric Depression Scale; GDS15-Q10: question 10 of the Geriatric Depression Scale: ‘Do you feel you have more problems with memory than most?’; MDc: mean difference in change between the intervention and control group; MMSE: Mini-Mental State Examination; 95%CI: 95% confidence interval

# eTable 4. Mean difference in effect of multidomain interventions on cognition, symptoms of depression and apathy by study, after 3-4 years of follow-up

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Study | | | |
|  | **preDIVA**  MDc (95%CI) | **MAPT**  MDc (95%CI) | **P for interaction** |  |
| Cognitive functioning |  |  |  |  |
| MMSE (range 0-30)\* | -0.03  (-0.14 to 0.09) | 0.16  (-0.02 to 0.33) | 0.07 |  |
| Memory (MMSE item 5)  (range 0-3)\* | -0.007  (-0.06 to 0.04) | 0.03  (-0.05 to 0.11) | 0.43 |  |
| Other (range 0-27)\* | -0.03  (-0.12 to 0.06) | 0.13  (-0.006 to 0.27) | 0.0498 |  |
| Subjective memory loss (GDS15-Q10, % yes)† | -0.76  (-3.22 to 1.69) | -0.14  (-3.65 to 3.37) | 0.90 |  |
| Depressive symptoms |  |  |  |  |
| GDS (range 0-15)† | 0.02  (-0.11 to 0.15) | -0.15  (-0.38 to 0.08) | 0.21 |  |
| Depressive symptoms (% GDS >5)† | -0.0001  (-0.02 to 0.02) | -0.02  (-0.05 to 0.02) | 0.36 |  |
| Apathy (range 0-3)† | 0.02  (-0.03 to 0.08) | -0.06  (-0.14 to 0.03) | 0.14 |  |

\* high score indicates better results; † low score indicates better results. Abbreviations: GDS: Geriatric Depression Scale; GDS15-Q10: question 10 of the Geriatric Depression Scale: ‘Do you feel you have more problems with memory than most?’; MDc: mean difference in change between the intervention and control group; MMSE: Mini-Mental State Examination; 95%CI: 95% confidence interval

# eTable 5. Mean difference in effect of multidomain interventions on cognition for different baseline MMSE cutoff scores, after 3-4 years of follow-up

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Baseline MMSE cutoff score | N individuals | N observations | MMSE  MDc (95%CI) | P for interaction |
| <26 | 250 | 422 | 0.84  (0.15 to 1.54) | <0.001 |
| <27 | 492 | 840 | 0.29  (-0.15 to 0.72) | 0.11 |
| <28 | 963 | 1682 | 0.22  (-0.05 to 0.49) | 0.03 |
| <29 | 1798 | 3192 | 0.10  (-0.07 to 0.27) | 0.24 |
| <30 | 2864 | 5130 | 0.02  (-0.10 to 0.14) | 0.73 |

Abbreviations: MDc: mean difference in change between the intervention and control group; MMSE: Mini-Mental State Examination (range 0-30) ; 95%CI: 95% confidence interval

# eTable 6. Baseline characteristics according to baseline cognitive scores

|  |  |  |  |
| --- | --- | --- | --- |
|  | MMSE < 26  (n=250) | MMSE ≥ 26  (n=3454) | P-value |
| **Study, n (%)** |  |  | 0.1 |
| * preDIVA | 160 (64.0) | 2379 (68.9) |  |
| * MAPT | 90 (36.0) | 1075 (31.1) |  |
| **Demographics** |  |  |  |
| Age, y, mean (SD) | 74.82 (3.6) | 74.42 (3.2) | 0.07 |
| Female sex (%) | 149 (59.6) | 1991 (57.6) | 0.6 |
| Educational level , n (%) |  |  | <0.001 |
| - Low (max primary school) | 116 (47.0) | 708 (20.7) |  |
| - Intermediate | 92 (37.2) | 1739 (50.9) |  |
| - High (min high school) | 39 (15.8) | 967 (28.3) |  |
| **Biological risk factors** |  |  |  |
| Systolic blood pressure (mmHg) (mean (SD) | 150.11 (22.4) | 150.32 (21.6) | 0.9 |
| LDL cholesterol, mean (SD) | 3.1 (1.0) | 3.2 (1.0) | 0.3 |
| BMI (kg/m2), mean (SD) | 27.8 (4.2) | 26.9 (4.1) | 0.002 |

Abbreviations: BMI: Body Mass Index; LDL cholesterol: low-density lipoprotein cholesterol; MMSE: Mini-Mental State Examination (range 0-30)