

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Sensitivity Analyses for the Primary and Main Secondary Cognitive End Points From Baseline to 24 Months

Cognitive end point	APOE ε4	Difference between intervention and control groups per year		Difference between carriers and non-carriers per year (intervention x time x APOE)	
		Estimate (95% CI)	P value	Estimate (95% CI)	P value
ITT population (intention-to-treat, all randomized participants)					
NTB total score	Carrier	0.04 (0.001-0.07)	0.043	0.02 (-0.02-0.07)	0.30
	Non-carrier	0.01 (-0.01-0.04)	0.27		
Executive functioning	Carrier	0.04 (-0.004-0.09)	0.07	0.02 (-0.04-0.08)	0.49
	Non-carrier	0.02 (-0.01-0.05)	0.17		
Processing speed	Carrier	0.03 (-0.02-0.08)	0.18	0.01 (-0.05-0.07)	0.70
	Non-carrier	0.02 (-0.01-0.06)	0.21		
Memory	Carrier	0.04 (-0.02-0.10)	0.16	0.04 (-0.03-0.11)	0.27
	Non-carrier	0.002 (-0.04-0.04)	0.93		
Abbreviated Memory	Carrier	0.07 (0.005-0.13)	0.035	0.05 (-0.03-0.12)	0.24
	Non-carrier	0.02 (-0.02-0.07)	0.32		
Participants with all cognitive assessments					
NTB total score	Carrier	0.04 (0.005-0.08)	0.025	0.03 (-0.02-0.07)	0.20
	Non-carrier	0.01 (-0.01-0.04)	0.32		
Executive functioning	Carrier	0.04 (-0.01-0.09)	0.094	0.02 (-0.04-0.07)	0.56
	Non-carrier	0.02 (-0.01-0.06)	0.16		
Processing speed	Carrier	0.04 (-0.01-0.09)	0.14	0.02 (-0.04-0.08)	0.57
	Non-carrier	0.02 (-0.02-0.05)	0.26		
Memory	Carrier	0.05 (-0.01-0.11)	0.087	0.05 (-0.02-0.13)	0.16
	Non-carrier	0.00001 (-0.04-0.04)	1.00		
Abbreviated Memory	Carrier	0.08 (0.01-0.14)	0.021	0.06 (-0.02-0.14)	0.14
	Non-carrier	0.02 (-0.03-0.06)	0.46		

Mixed effects regression models with maximum likelihood estimation were used to analyse change in cognitive scores from baseline to 24 months as a function of randomization group, time, APOE genotype (ε4 allele carriers versus non-carriers), and their interactions (group x time, group x APOE, time x APOE, and group x time x APOE). In these models, the difference between carriers and non-carriers per year is indicated by the randomization group x time x APOE interaction. All other estimates were determined from the models using the *lincom* post-estimation command after *xtmixed* in Stata.

Scores on the NTB total score and memory, executive functioning and processing speed domain scores are estimated mean values (standard errors) of z scores of the cognitive tests included in each cognitive outcome with higher scores indicating better performance. A positive value of the estimate of differences between intervention and control groups indicates the effect is in favor of the intervention group.

eTable 2. Baseline Characteristics of Participants (ITT Population)

Characteristics	APOE ε4 carriers				ApoE ε4 non-carriers				p ³
	N*	Control	Intervention	p ¹	N*	Control	Intervention	p ²	
Demographic characteristics									
Age at baseline, years	200/189	68.80 (4.52)	69.18 (4.61)	0.42	385/401	69.44 (4.78)	69.66 (4.68)	0.51	0.051
Women, N (%)	200/189	101 (50.50%)	88 (46.56%)	0.44	385/401	182 (47.27%)	178 (44.39%)	0.42	0.37
Education, years	200/188	9.77 (3.20)	10.31 (3.91)	0.14	384/401	10.12 (3.52)	9.78 (3.27)	0.16	0.69
Married or cohabiting, N (%)	200/188	151 (75.50%)	146 (77.66%)	0.62	385/401	293 (76.10%)	284 (70.82%)	0.09	0.25
Vascular factors									
Systolic blood pressure, mmHg	197/188	139.87 (16.00)	141.63 (18.70)	0.32	382/399	139.48 (15.52)	139.46 (15.89)	0.99	0.21
Diastolic blood pressure, mmHg	197/188	79.17 (8.91)	81.12 (10.62)	0.052	382/399	80.57 (9.43)	80.19 (9.27)	0.57	0.67
Serum total cholesterol, mmol/l	200/189	5.27 (1.09)	5.31(1.01)	0.65	383/401	5.10 (0.99)	5.08 (0.99)	0.76	0.0015
Fasting plasma glucose, mmol/l	200/189	6.07 (0.83)	6.00 (0.78)	0.44	385/401	6.08 (1.06)	6.13 (0.84)	0.45	0.23
2h oral glucose tolerance test, mmol/l	171/164	7.11 (2.09)	6.79 (2.16)	0.18	332/341	6.93 (2.24)	7.14 (2.22)	0.21	0.55
BMI, kg/m ²	197/188	28.04 (4.92)	27.85 (4.37)	0.70	382/400	28.08 (4.61)	28.55 (4.57)	0.16	0.19
Other									
Hb A1C, %	200/188	5.54 (0.51)	5.54 (0.47)	0.87	383/396	5.58 (0.60)	5.59 (0.58)	0.77	0.19
CRP, mg/l	200/189	1.86 (2.84)	2.60 (5.99)	0.12	383/401	3.15 (10.40)	2.55 (5.59)	0.31	0.16
HDL-C, mmol/l	200/189	1.43 (0.40)	1.47 (0.39)	0.31	383/401	1.47 (0.37)	1.42 (0.38)	0.053	0.81
LDL-C, mmol/l	200/189	3.20 (0.98)	3.24 (0.89)	0.70	383/401	3.03 (0.83)	3.03 (0.84)	0.96	0.0004
Triglycerides, mmol/l	200/189	1.39 (0.63)	1.33 (0.59)	0.33	383/401	1.33 (0.60)	1.39 (0.64)	0.20	0.87
Lifestyle factors									
Physical activity at least twice/week, N (%)	197/186	140 (71.07%)	136 (73.12%)	0.66	381/398	273 (71.65%)	266 (66.83%)	0.15	0.32
Current smokers, N (%)	200/186	17 (8.50%)	18 (9.68%)	0.69	384/400	31 (8.07%)	43 (10.75%)	0.20	0.84
Alcohol drinking at least once/week, N (%)	199/187	84 (42.21%)	79 (42.25%)	0.99	381/400	173 (45.41%)	197 (44.75%)	0.85	0.36
Fish intake at least twice/week, N (%)	199/187	97 (48.74%)	96 (51.34%)	0.61	383/399	202 (52.74%)	214 (53.63%)	0.80	0.30

Daily intake of vegetables, N (%)	200/188	124 (62.00%)	121 (64.36%)	0.63	384/400	236 (61.46%)	242 (60.50%)	0.78	0.47
Self-reported medical conditions									
Hypertension, N (%)	198/188	127 (64.14%)	131 (69.68%)	0.25	380/397	252 (66.32%)	263 (66.25%)	0.98	0.85
Hypercholesterolemia, N (%)	199/187	141 (70.85%)	128 (68.45%)	0.61	382/399	260 (68.06%)	257 (64.41%)	0.28	0.23
Diabetes, N (%)	199/188	29 (14.57%)	26 (13.83%)	0.83	383/399	46 (12.01%)	59 (14.79%)	0.26	0.71
History of myocardial infarction, N (%)	199/189	11 (5.53%)	10 (5.29%)	0.92	383/399	19 (4.96%)	21 (5.26%)	0.85	0.83
History of stroke, N (%)	199/187	8 (4.02%)	11 (5.88%)	0.40	382/399	23 (6.02%)	20 (5.01%)	0.54	0.68
Cognition									
NTB total score, baseline	200/189	0.02 (0.59)	-0.07 (0.59)	0.15	384/401	0.02 (0.58)	-0.02 (0.55)	0.33	0.44
NTB total score, month 12	187/170	0.11 (0.67)	0.04 (0.66)	0.32	363/367	0.15 (0.66)	0.14 (0.61)	0.84	0.099
NTB total score, month 24	180/159	0.16 (0.70)	0.15 (0.72)	0.97	348/357	0.24 (0.68)	0.23 (0.65)	0.77	0.072
Executive functioning, baseline	199/189	-0.02 (0.70)	-0.05 (0.67)	0.72	384/401	0.02 (0.68)	-0.03 (0.66)	0.30	0.48
Executive functioning, month 12	186/168	0.04 (0.75)	-0.02 (0.68)	0.41	362/366	0.08 (0.74)	0.08 (0.68)	0.90	0.15
Executive functioning, month 24	179/159	0.04 (0.74)	0.09 (0.75)	0.53	345/356	0.14 (0.72)	0.11 (0.70)	0.57	0.20
Memory, baseline	200/189	0.07 (0.65)	-0.08 (0.74)	0.033	384/401	0.02 (0.66)	-0.01 (0.66)	0.66	0.77
Memory, month 12	187/170	0.21 (0.77)	0.09 (0.83)	0.16	363/368	0.24 (0.77)	0.21 (0.76)	0.66	0.12
Memory, month 24	181/159	0.29 (0.85)	0.25 (0.93)	0.72	348/357	0.40 (0.78)	0.40 (0.77)	0.90	0.018
Processing speed, baseline	200/189	0.01 (0.86)	-0.07 (0.83)	0.32	384/401	0.04 (0.83)	-0.02 (0.78)	0.35	0.45
Processing speed, month 12	187/170	0.05 (0.89)	0.03 (0.89)	0.86	363/367	0.08 (0.84)	0.06 (0.78)	0.78	0.58
Processing speed, month 24	179/159	0.07 (0.93)	0.06 (0.82)	0.94	348/357	0.11 (0.89)	0.10 (0.86)	0.87	0.53
Abbreviated memory, baseline	195/186	0.05 (0.75)	-0.08 (0.79)	0.12	376/396	0.03 (0.73)	-0.003 (0.79)	0.57	0.61
Abbreviated memory, month 12	175/167	0.08 (0.79)	0.02 (0.81)	0.51	353/354	0.10 (0.78)	0.12 (0.81)	0.70	0.24
Abbreviated memory, month 24	174/153	0.17 (0.87)	0.21 (0.92)	0.66	341/350	0.25 (0.79)	0.28 (0.80)	0.65	0.18

Values are means (SD) unless otherwise specified. * N is number of participants in control / intervention group. p^1 - p value for differences between intervention and control groups among APOE $\epsilon 4$ carriers; p^2 - p value for differences between intervention and control groups among APOE $\epsilon 4$ non-carriers; p^3 - p value for differences between all APOE $\epsilon 4$ carriers and non-carriers.

The number (%) of APOE $\epsilon 4$ carriers was 189 (32.0%) in the intervention group, and 200 (34.2%) in the control group ($p=0.43$).

Table 3. Assessment of Best-Fitting Model Using Bayesian Information Criterion (BIC)

Full model	NTB total score	Executive functioning	Processing speed	Memory	Abbreviated memory
	BIC				
- Randomization group - APOE4 - Time - Group x time - Group x APOE4 - Time x APOE4 - Group x time x APOE4	2728.36	4322.95	5093.39	5236.05	5726.04
Alternative models	BIC (*p-value for comparison with full model)				
Model 1 - Randomization group - APOE4 - Time - Group x time - Group x APOE4 - Time x APOE4	2721.34 (0.30)	4315.48 (0.44)	5085.48 (0.68)	5229.21 (0.27)	5719.45 (0.22)
Model 2 - Randomization group - APOE4 - Time - Group x time - Time x APOE4	2714.27 (0.35)	4307.41 (0.74)	5077.48 (0.88)	5223.34 (0.18)	5712.42 (0.29)
Model 3 - Randomization group - APOE4 - Time - Group x time - Group x APOE4	2724.45 (0.002)	4309.44 (0.27)	5078.29 (0.59)	5233.49 (0.001)	5713.70 (0.15)
Model 4 - Randomization group - APOE4 - Time - Group x time	2717.40 (0.004)	4301.37 (0.45)	5070.28 (0.77)	5227.63 (0.001)	5706.66 (0.19)

$BIC = -2 * \log\text{-likelihood} + \log(\text{number of observations}) * (\text{number of estimated parameters})$

The best fitting mixed effects regression model (lowest BIC, bold font) was determined by performing likelihood-ratio tests and comparing the full model with alternative models excluding non-significant interaction terms.

* p value from likelihood ratio test comparing each alternative model with the full model.

All analyses were conducted in the main population (mITT). All tested models included the main effects of randomization group, time, and APOE, as well as the intervention effect (randomization group x time interaction).

eTable 4. Results of the Best-Fitting Model

Best fitting model	NTB total score	Executive functioning	Processing speed	Memory	Abbreviated memory
	Estimate (95% CI), p-value				
Randomization group	-0.058 (-0.125-0.010) p=0.093	-0.055 (-0.134-0.024) p=0.171	-0.059 (-0.153-0.035) p=0.219	-0.063 (-0.142-0.015) p=0.115	-0.056 (-0.145-0.032) p=0.213
APOE4	-0.019 (-0.091-0.052) p=0.600	-0.047 (-0.130-0.036) p=0.266	-0.019 (-0.118-0.081) p=0.711	-0.003 (-0.086-0.081) p=0.947	-0.037 (-0.128-0.053) p=0.421
Time	0.093 (0.077-0.109) p<0.001	0.029 (0.010-0.047) p=0.003	0.018 (-0.001-0.038) p=0.068	0.178 (0.151-0.205) p<0.001	0.085 (0.059-0.111) p<0.001
Group x time	0.021 (0.001-0.042) p=0.042	0.030 (0.004-0.057) p=0.025	0.026 (-0.002-0.054) p=0.072	0.015 (-0.019-0.048) p=0.397	0.038 (0.001-0.075) p=0.041
Time x APOE4	-0.038 (-0.060- -0.016) p=0.001	N.A.	N.A.	-0.065 (-0.101- -0.029) p<0.001	N.A.

The best fitting mixed effects regression model is based on the lowest Bayesian Information Criterion (BIC) shown in Table S3. N.A. - not applicable.