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Effect of the Apolipoprotein E Genotype on Cognitive Change During a Multidomain Lifestyle Intervention
A Subgroup Analysis of a Randomized Clinical Trial

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IMPORTANCE The role of the apolipoprotein E (*APOE*) ε4 allele as an effect modifier in lifestyle interventions to prevent cognitive impairment is still unclear.

OBJECTIVE To examine whether the *APOE* ε4 allele modifies the previously reported significant cognitive benefits of a multidomain lifestyle intervention (prespecified subgroup analysis).

DESIGN, SETTING, AND PARTICIPANTS The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) was a randomized clinical trial in 6 centers across Finland (screening and randomization performed from September 7, 2009, through November 24, 2011; intervention duration, 2 years). Data analysis was performed from August 1, 2015, to March 31, 2016. The study population was at-risk older individuals from the general population. Inclusion criteria were age of 60 to 77 years; Cardiovascular Risk Factors, Aging, and Dementia risk score of at least 6 points; and cognition at a mean level or slightly lower than expected for age. Individuals with dementia or substantial cognitive impairment and conditions that prevented cooperation or safe engagement in the intervention were excluded. *APOE* genotype data were available for 1175 of the 1260 participants.

INTERVENTIONS Participants were randomly assigned in a 1:1 ratio to a multidomain intervention group (diet, exercise, cognitive training, and vascular risk management) or a control group (general health advice). Group allocation was not actively disclosed to participants, and outcome assessors were masked to group allocation.

MAIN OUTCOMES AND MEASURES Primary outcome was change in cognition measured through a comprehensive neuropsychological test battery. Analysis was based on modified intention to treat (participants with at least 1 postbaseline assessment).

RESULTS A total of 1109 participants (mean [SD] age, 69.3 [4.7] years; 514 [46.3%] female) were included in the analysis: 362 *APOE* ε4 allele carriers (173 intervention and 189 control) and 747 noncarriers (380 intervention and 367 control). The *APOE* ε4 carriers and noncarriers were not significantly different at baseline (except for serum cholesterol level). The difference between the intervention and control groups in annual neuropsychological test battery total score change was 0.037 (95% CI, 0.001 to 0.073) among carriers and 0.014 (95% CI, −0.011 to 0.039) among noncarriers. Intervention effect was not significantly different between carriers and noncarriers (0.023; 95% CI, −0.021 to 0.067).

CONCLUSIONS AND RELEVANCE Healthy lifestyle changes may be beneficial for cognition in older at-risk individuals even in the presence of *APOE*-related genetic susceptibility to dementia. Whether such benefits are more pronounced in *APOE* ε4 carriers compared with noncarriers should be further investigated. The findings also emphasize the importance of early prevention strategies that target multiple modifiable risk factors simultaneously.

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Dementia and Alzheimer disease (AD) are complex conditions that likely result from interactions between genetic and environmental factors.[1] The apolipoprotein E (*APOE*) ε4 allele is the strongest known genetic risk factor for sporadic AD.[2] Most available studies[2,3] have also linked *APOE* ε4 to an increased rate of late-life cognitive decline in individuals without dementia, although there is variability among the affected cognitive domains reported in different studies.[2,3] Several modifiable risk factors for dementia have been identified in population-based studies.[3,4] It is estimated that approximately one-third of all AD dementia cases worldwide could be attributable to low educational level, physical inactivity, obesity, hypertension, diabetes, smoking, and depression.[4] There is evidence that the *APOE* genotype interacts with modifiable risk factors, but variability in reported findings still precludes firm conclusions.[4,5] One prevailing hypothesis is that *APOE* ε4 carriers are more susceptible to the detrimental effects of environmental risk factors.[5] It remains unclear whether ε4 carriers are more likely to benefit from preventive interventions or whether the ε4 allele counteracts potential intervention benefits.

APOE with its 3 isoforms (ε2, ε3, and ε4) has key roles in lipid transport and metabolism, both systemically and in the brain.[6,7] The ε4 allele has been linked to cardiovascular and neurologic conditions, particularly AD.[6,7] The connections between the ε4 allele and AD pathophysiologic findings seem to involve a variety of amyloid-dependent (eg, related to amyloid-β production, aggregation, and clearance) and amyloid-independent (eg, effects on tau phosphorylation and neurofibrillary tangle formation, neuroinflammation, oxidative stress, synaptic plasticity and dendritic spine integrity, brain lipid metabolism, and blood-brain barrier permeability) mechanisms.[6,7] *APOE* ε4 carriers have brain structural and developmental features (eg, lower cortical gray matter volume in regions particularly affected by AD) that, together with functional features (eg, deficient neuronal maintenance and repair), increase vulnerability to neuropathologic changes and subsequent late-life cognitive decline.[5,7]

Previous randomized clinical trials (RCTs) that aimed to prevent cognitive impairment or dementia have yielded mainly negative results,[3] with some positive effects on cognition reported in smaller and/or shorter RCTs of physical activity and/or cognitive training.[8-13] The effect of the *APOE* genotype on response to intervention was investigated in some of these RCTs. Beneficial effects among *APOE* ε4 carriers were reported in patients with mild cognitive impairment treated with donepezil hydrochloride[14] or galantamine hydrobromide,[15] in an RCT of eicosapentaenoic acid and docosahexaenoic acid, in an RCT of docosahexaenoic acid supplementation,[16,17] and in a small 1-year weight loss RCT in elderly patients with obesity and mild cognitive impairment.[18] Some benefits for *APOE* ε4 carriers and noncarriers were observed in a trial of Mediterranean diet-based interventions,[19] whereas better effects among *APOE* ε4 noncarriers were found in a short physical activity RCT.[20] No effects of the *APOE* genotype on intervention response were found in trials of nonsteroidal anti-inflammatory drugs,[21] statins,[22] gingko biloba,[23] vitamin E,[14] or vitamin B_{12} supplementation.[24]

Key Points

Question Are the cognitive benefits of a 2-year multidomain lifestyle intervention affected by the apolipoprotein E ε4 allele?

Findings In the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability, a randomized clinical trial of 1260 at-risk elderly individuals from the general population, the cognitive benefits of a multidomain intervention (diet, exercise, cognitive training, and vascular risk management) were not significantly different between apolipoprotein E ε4 carriers and noncarriers (test of interaction). Within-group results by apolipoprotein E ε4 carrier status suggested beneficial effects, particularly among carriers.

Meaning Healthy lifestyle changes may be beneficial for cognition in older at-risk individuals even in the presence of apolipoprotein E–related genetic susceptibility to dementia.

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) was, to our knowledge, the first large, longer-term RCT to report beneficial effects on cognition for a 2-year multidomain lifestyle intervention in 1260 older at-risk individuals from the general population.[25] Herein, we report prespecified analyses of intervention effects on primary and secondary cognitive outcomes by *APOE* ε4 allele (carriers vs noncarriers).

Methods

Study Participants

The FINGER trial protocol,[26] baseline population characteristics,[27] and primary results[25] have been previously described in detail. The present study is a prespecified subgroup analysis by *APOE* genotype. Participants were recruited at 6 study sites across Finland from previous population-based observational studies.[28,29] Eligibility criteria were age of 60 to 77 years; Cardiovascular Risk Factors, Aging, and Dementia risk score of 6 points or higher[30]; the Consortium to Establish a Registry for Alzheimer Disease[31] word list memory task (10 words 3 times) score of 19 words or fewer; Consortium to Establish a Registry for Alzheimer Disease word list recall of 75% or less; or Mini-Mental State Examination score of 26 or fewer of 30 points. Exclusion criteria were previously diagnosed dementia, suspected dementia after clinical assessment by a study physician at the screening visit (individuals recommended for further investigations), Mini-Mental State Examination score of less than 20 points, and conditions that affect safe engagement in the intervention (eg, malignant tumor; major depression; symptomatic cardiovascular disease; revascularization within 1 year); severe vision, hearing, or communicative impairment; conditions that prevent cooperation as judged by the study physician; and coincident participation in another trial. FINGER and this subgroup analysis were approved by the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa. Participants gave written informed consent at screening and baseline visits. All data were deidentified.

Randomization

From September 7, 2009, through November 24, 2011, a total of 2654 individuals were screened for eligibility, and 1260 were randomized 1:1 to the intensive multidomain intervention or regular health advice (ie, control) group. Computer-generated allocation was performed in blocks of 4 (2 persons randomly allocated to each group) at each site. Outcome assessors were masked to allocation and not involved in the intervention. Group allocation was not actively disclosed to participants, and they were advised not to discuss the intervention during testing sessions. Data analysis was performed from August 1, 2015, to March 31, 2016.

Intervention

The control group received regular health advice. Both groups met the study nurse at screening, baseline, and 6, 12, and 24 months (for blood tests and blood pressure, weight, body mass index, and hip and waist circumference measurements) and the study physician at screening and 24 months (for medical history and physical examination). At baseline, the study nurse gave both groups oral and written information and advice on healthy diet and physical, cognitive, and social activities beneficial for vascular risk management and disability prevention. Blood test results were mailed to all participants, together with general written information about the significance of measurements and advice to contact a primary health care practitioner if needed.

The intervention group additionally received 4 intervention components.[26] The nutritional intervention was based on the Finnish Nutrition Recommendations[32] and conducted by study nutritionists (3 individual and 7-9 group sessions). Individual sessions included tailoring of the participant's diet. Group sessions provided discussions and practical exercises for facilitating lifestyle changes. The physical exercise training program followed international guidelines.[33,34] Training was guided by study physiotherapists and included aerobic and resistance training and balance exercises.[26] Cognitive training included psychologist-led group sessions and computer-based individual training. The training program was a web-based, in-house–developed program that focused on updating information on memory that was effective in shorter-term RCTs.[35-37] Social activities were stimulated through the group meetings of all intervention components. Management of metabolic and vascular risk factors was based on national evidence-based guidelines and included additional meetings with the study nurse (at 3, 9, and 18 months) and the study physician (at 3, 6, and 12 months).[26] Study physicians did not prescribe medication but strongly recommended participants to contact their own physician or clinic if needed.

Cognitive Outcomes

Standard neuropsychological tests (an extended version of the Neuropsychological Test Battery [NTB])[38] were administered at baseline and 12 and 24 months by study psychologists. Participants who dropped out during the study were invited to a final 24-month visit for outcome evaluation. Primary outcome was change in cognitive performance measured with NTB total score, including the 14 tests listed below (calculated on a standardized *z* scale, with higher scores indicating better performance).[38] Secondary outcomes included NTB domain *z* scores for executive functioning, processing speed, and memory. The executive functioning domain included Category Fluency, Digit Span, Concept Shifting Test (condition C), Trail Making Test (shifting score B-A), and a shortened 40-stimulus version of the original Stroop test (interference score 3-2). The processing speed domain included Letter Digit Substitution, Concept Shifting (condition A), and Stroop (condition 2). The memory domain included Visual Paired Associates, immediate and delayed recall, Logical Memory immediate and delayed recall, and Word List Learning and Delayed Recall. Post hoc analyses were conducted for an abbreviated memory domain that included 4 of 6 tests (2 associative memory and 2 logical memory tests), including longer recall delay (30 minutes instead of 5 minutes) and requiring more complex processing.

APOE Assessment

Genomic DNA was extracted from venous blood samples with Chemagic MSM1 (PerkinElmer) using magnetic beads. *APOE* genotyping was determined by polymerase chain reaction using TaqMan genotyping assays (Applied Biosystems) for 2 single-nucleotide polymorphisms (rs429358 and rs7412) and an allelic discrimination method on the Applied Biosystems 7500 platform.[39]

Statistical Analysis

Because of the small number of participants with the *APOE* ε4ε4 genotype (40 individuals, 16 in the control group and 24 in intervention group), participants were categorized as carriers of at least 1 ε4 allele vs noncarriers. For baseline comparisons between the intervention and control groups by *APOE* ε4 carrier status, the *t* test and χ^2 test were used as appropriate. Zero-skewness log transformation was applied to skewed NTB components. The *z* scores for tests at each time point were standardized to the baseline mean and SD. The NTB total score and domain scores for executive functioning, processing speed, and memory were obtained by calculating the mean of the individual NTB component *z* scores. The minimum number of necessary NTB components was set to 8 of 14 for calculating the NTB total score, 3 of 5 for executive functioning, 2 of 3 for processing speed, and 3 of 6 for memory.

Because data included repeated measurements from the same individuals, longitudinal analyses had to take into account within-person and between-person variability over time. Mixed effects regression models (*xtmixed* command in Stata [StataCorp]) with maximum likelihood estimation were thus used to analyze change in cognitive scores as a function of randomization group, time, *APOE* genotype (ε4 allele carriers vs noncarriers), and their interactions (group × time, group × *APOE*, time × *APOE*, and group × time × APOE). Following guidelines for subgroup analyses in clinical trials,[40] we report the coefficient (95% CI) for the group × time × *APOE* interaction as the main result (ie, estimated difference in intervention effects between ε4 carriers and noncarriers per year).

We also present the effect estimates (95% CI) within each *APOE* group using the *lincom* postestimation command after *xtmixed* in Stata.

Analyses were conducted according to the predefined primary efficacy analysis based on the modified intention-to-treat (mITT) population, including all randomized participants with at least 1 postbaseline observation (*APOE* genotype data available for 1109 of 1190 participants). Sensitivity analyses were conducted in the ITT population (all randomized participants; *APOE* genotype data available for 1175 of 1260 participants) and all randomized participants who completed all cognitive evaluations (*APOE* genotype data available for 1020 of 1094 participants). Level of significance was set to $P < .05$ in all analyses, and Stata software, version 14 (StataCorp), was used.

Results

Compared with participants without *APOE* genotype data, participants with available data included fewer physically active individuals (771 [70.2%] vs 66 [81.4%], $P = .03$) and more individuals with diabetes at baseline (146 [13.2%] vs 4 [5.0%], $P = .03$). No other significant differences in participants' baseline characteristics were found by availability of *APOE* data.

In the mITT population, the number of *APOE* ε4 carriers was 173 (31.3%) in the intervention group and 189 (33.9%) in the control group ($P = .34$). Comparisons of population characteristics between the intervention and control groups among ε4 carriers and noncarriers are given in **Table 1**. Among ε4 carriers, the intervention group had higher baseline diastolic blood pressure (81.08 vs 79.01 mm Hg, $P = .048$) and lower baseline memory performance (−0.07 vs 0.08, $P = .04$) compared with the control group (Table 1). Intervention and control groups were not significantly different among ε4 noncarriers.

As expected, *APOE* ε4 carriers had higher baseline total and low-density lipoprotein cholesterol levels compared with noncarriers (Table 1). No significant differences were found in baseline cognitive performance between ε4 carriers and noncarriers. However, memory performance at month 24 was significantly lower among ε4 carriers (0.27 vs 0.40, $P = .02$) (Table 1).

Table 2 gives the estimated mean 2-year cognitive change in the intervention and control groups by *APOE* ε4 carrier status and annual differences between groups (primary analysis, mITT population). Intervention effects (randomization group × time × *APOE* interaction) did not significantly differ between ε4 carriers and noncarriers for any cognitive domain. Within-group findings by ε4 carrier status indicated that the annual difference between intervention and control groups was significant among ε4 carriers for NTB total score (estimate, 0.037; 95% CI, 0.001 to 0.073; $P = .045$) and abbreviated memory (estimate, 0.070; 95% CI, 0.006 to 0.135; $P = .03$) but not among noncarriers (estimates, 0.014 [95% CI, −0.011 to 0.039; $P = .28$] for NTB total score and 0.022 [95% CI, −0.023 to 0.066; $P = .34$] for abbreviated memory) (Table 2).

Sensitivity analyses found results similar to the main analyses (eTable 1 in the Supplement). Population characteristics for sensitivity analyses are given in eTable 2 in the Supplement.

Given the complexity of the models, further analyses were conducted to assess the best-fitting model by performing likelihood ratio tests and comparing the Bayesian Information Criterion for the full model with alternative models that excluded nonsignificant interaction terms (eTable 3 in the Supplement). Detailed results of the best-fitting model for each cognitive outcome are given in eTable 4 in the Supplement. The randomization group × time interaction was similar to previously reported intervention effects.[25] The time × *APOE* interaction was significant for NTB total score and memory, indicating less overall improvement (intervention and control groups together) among ε4 carriers compared with noncarriers (eTable 4 in the Supplement).

Discussion

Results from the 2-year FINGER trial did not show significant differences between *APOE* ε4 carriers and noncarriers (test of interaction) regarding the previously reported positive intervention effects on cognition.[25] However, within-group findings by *APOE* ε4 status showed beneficial intervention effects, especially among *APOE* ε4 carriers for NTB total score and abbreviated memory score, including more complex memory tests. Baseline performance in these cognitive domains was not different between intervention and control or carrier and noncarrier groups.

The *APOE* ε4 allele is a key genetic risk factor for cognitive decline, AD, and dementia.[2,5] One of the main concerns regarding dementia prevention strategies is whether genetically susceptible individuals can still benefit from preventive lifestyle interventions. Thus, the current findings have positive practical implications because the *APOE* ε4 allele did not seem to hinder the intervention benefits.

Subgroup analyses in clinical trials are challenging.[40] Current reporting guidelines have emphasized between-group comparisons (ie, tests of interaction) as a more appropriate approach in assessing potential heterogeneity of intervention effects.[40] Guidelines have also cautioned against claims of heterogeneity based on only within-group results, which should not be overinterpreted.[40] Interpreting subgroup analyses in trials can be difficult for several reasons, including that statistical power for detecting significant interactions may be limited, dividing the trial population into smaller subgroups may also limit power and lead to nonsignificant within-group findings when the overall intervention effect is significant, and multiple subgroup analyses can increase the probability of false-positive findings.

Thus, given the nonsignificant tests of interaction, the promising within-group findings cannot be considered as definitive evidence that the FINGER intervention was significantly more effective among *APOE* ε4 carriers. However, the lack of significant interactions should be interpreted cautiously because they may result from statistical power limitations, especially if effect sizes are relatively small. Despite the

Table 1. Baseline Characteristics of FINGER Participants

Characteristic	*APOE* ε4 Carriers				*APOE* ε4 Noncarriers				
	Sample Size, Control/ Intervention	Control[a]	Intervention[a]	*P* Value[b]	Sample Size, Control/ Intervention	Control[a]	Intervention[a]	*P* Value[c]	*P* Value[d]
Demographic characteristics									
Age at baseline, y	189/173	68.74 (4.51)	69.21 (4.5)	.32	367/380	69.39 (4.8)	69.61 (4.7)	.52	.08
Women, No. (%)	189/173	94 (49.7)	81 (46.8)	.58	367/380	172 (46.9)	167 (44.0)	.42	.35
Education length, y	189/172	9.87 (3.2)	10.29 (3.8)	.25	366/380	10.12 (3.5)	9.81 (3.2)	.21	.62
Married or cohabiting, No. (%)	189/172	143 (75.7)	135 (78.5)	.52	367/380	281 (76.6)	273 (71.8)	.14	.31
Vascular factors									
Systolic blood pressure, mm Hg	186/172	139.50 (16.22)	141.06 (18.64)	.40	364/378	139.27 (15.45)	139.58 (15.95)	.79	.43
Diastolic blood pressure, mm Hg	186/172	79.01 (9.05)	81.08 (10.65)	.048	364/378	80.57 (9.43)	80.22 (9.23)	.62	.52
Serum total cholesterol level, mg/dL	189/173	204 (42)	205 (41)	.80	365/380	197 (38)	197 (37)	.79	.001
Fasting plasma glucose level, mg/dL	189/173	109 (15)	108 (13)	.26	367/380	110 (19)	111 (15)	.41	.15
2-h Oral glucose tolerance test, mg/dL	161/150	127 (37)	121 (33)	.10	318/327	125 (41)	128 (40)	.38	.33
BMI	186/172	28.07 (4.96)	28.05 (4.39)	.97	364/379	28.13 (4.63)	28.57 (4.63)	.19	.32
Other									
HbA_{1c} level, %	189/172	5.55 (0.51)	5.53 (0.48)	.70	365/375	5.58 (0.60)	5.59 (0.58)	.91	.28
CRP level, mg/L	189/173	1.84 (2.89)	2.29 (4.16)	.22	365/380	3.07 (10.32)	2.59 (5.70)	.43	.09
HDL-C level, mg/dL	189/173	55 (15)	56 (15)	.44	365/380	57 (14)	55 (14)	.01	.95
LDL-C level, mg/dL	189/173	125 (38)	125 (36)	.88	365/380	117 (32)	117 (32)	.96	<.001
Triglyceride level, mg/dL	189/173	124 (57)	120 (53)	.54	365/380	118 (51)	122 (55)	.24	.60
Lifestyle factors, No. (%)									
Physical activity at least twice per week	188/170	134 (71.3)	128 (75.3)	.39	364/377	259 (71.2)	250 (66.3)	.16	.13
Current smokers	189/170	17 (9.0)	15 (8.8)	.96	366/380	29 (7.9)	41 (10.8)	.18	.80
Alcohol intake at least once per week	188/171	80 (42.6)	73 (42.0)	.98	363/379	166 (45.7)	172 (45.38)	.92	.36
Fish intake at least twice per week	188/171	90 (47.9)	86 (50.3)	.65	365/378	191 (52.3)	208 (55.0)	.46	.15
Daily intake of vegetables	189/172	119 (63.0)	108 (62.8)	.97	366/379	226 (61.8)	231 (61.0)	.82	.62
Self-reported medical conditions, No. (%)									
Hypertension	187/172	120 (64.2)	123 (71.5)	.14	363/376	242 (66.7)	248 (66.0)	.84	.65
Hypercholesterolemia	188/171	136 (72.3)	120 (70.2)	.65	364/378	250 (68.7)	246 (65.1)	.30	.14
Diabetes	188/172	27 (14.4)	24 (14.0)	.91	365/378	43 (11.8)	52 (13.8)	.42	.53
History of myocardial infarction	188/173	11 (5.8)	9 (5.2)	.79	365/378	19 (5.2)	18 (4.8)	.78	.69
History of stroke	188/171	8 (4.3)	10 (5.8)	.49	364/378	22 (6.0)	20 (5.3)	.66	.66
Cognition									
NTB total score, baseline	189/173	0.04 (0.59)	−0.06 (0.58)	.10	367/380	0.03 (0.58)	−0.01 (0.55)	.37	.71
NTB total score, month 12	187/170	0.11 (0.67)	0.04 (0.66)	.32	362/367	0.15 (0.66)	0.14 (0.61)	.85	.10
NTB total score, month 24	180/159	0.16 (0.70)	0.15 (0.72)	.97	347/357	0.24 (0.68)	0.23 (0.65)	.76	.07
Executive functioning, baseline	188/173	0.01 (0.69)	−0.05 (0.67)	.36	367/380	0.03 (0.68)	−0.03 (0.66)	.23	.59
Executive functioning, month 12	186/168	0.04 (0.75)	−0.02 (0.68)	.41	361/366	0.08 (0.74)	0.08 (0.68)	.89	.15
Executive functioning, month 24	179/159	0.04 (0.74)	0.09 (0.75)	.53	344/356	0.14 (0.72)	0.11 (0.70)	.56	.20

(continued)

Table 1. Baseline Characteristics of FINGER Participants (continued)

Characteristic	*APOE* ε4 Carriers				*APOE* ε4 Noncarriers				
	Sample Size, Control/ Intervention	Control[a]	Intervention[a]	*P* Value[b]	Sample Size, Control/ Intervention	Control[a]	Intervention[a]	*P* Value[c]	*P* Value[d]
Memory, baseline	189/173	0.08 (0.65)	−0.07 (0.73)	.04	367/380	0.01 (0.66)	−0.002 (0.66)	.81	.96
Memory, month 12	187/170	0.21 (0.77)	0.09 (0.83)	.16	362/368	0.24 (0.77)	0.21 (0.76)	.66	.12
Memory, month 24	181/159	0.29 (0.85)	0.25 (0.93)	.72	347/357	0.40 (0.78)	0.40 (0.77)	.89	.02
Processing speed, baseline	189/173	0.05 (0.84)	−0.05 (0.80)	.27	367/380	0.04 (0.83)	−0.01 (0.77)	.42	.83
Processing speed, month 12	187/170	0.05 (0.89)	0.03 (0.89)	.86	362/367	0.08 (0.84)	0.06 (0.78)	.79	.58
Processing speed, month 24	179/159	0.07 (0.93)	0.06 (0.82)	.94	347/357	0.11 (0.89)	0.10 (0.86)	.87	.54
Abbreviated memory, baseline	184/171	0.06 (0.76)	−0.07 (0.79)	.10	359/375	0.02 (0.73)	0.002 (0.79)	.71	.79
Abbreviated memory, month 12	175/167	0.08 (0.79)	0.02 (0.81)	.51	352/354	0.10 (0.78)	0.12 (0.81)	.71	.24
Abbreviated memory, month 24	174/153	0.17 (0.87)	0.21 (0.92)	.66	340/350	0.25 (0.79)	0.28 (0.80)	.66	.18

Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CRP, C-reactive protein; FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NTB, Neuropsychological Test Battery.

SI conversion factors: To convert total cholesterol, HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259; CRP to nanomoles per liter, multiply by 9.524; HbA_{1c} to proportion of hemoglobin, multiply by 0.01; glucose to millimoles per liter, multiply by 0.0555; triglycerides to millimoles per liter, multiply by 0.0113.

[a] Data are presented as mean (SD) unless otherwise specified.

[b] *P* value for differences between intervention and control groups among *APOE* ε4 carriers.

[c] *P* value for differences between intervention and control groups among *APOE* ε4 noncarriers.

[d] *P* value for differences between all *APOE* ε4 carriers and noncarriers.

relatively large cohort and higher prevalence of the *APOE* ε4 allele in Finland compared with other European countries,[41] the sample size may still have limitations concerning interactions. In addition, the FINGER trial included several prespecified subgroup analyses besides *APOE*.[26] Findings reported here for 5 different cognitive outcomes were not adjusted for multiple testing because interactions were not significant.

Further studies are needed to clarify whether *APOE* ε4 carriers may benefit more from lifestyle interventions. In the FINGER trial, overall improvement in NTB total score and memory was less pronounced among ε4 carriers compared with noncarriers (intervention and control groups together). The extended 7-year FINGER follow-up will provide additional data for investigating whether the multidomain lifestyle intervention is effective for preventing dementia, whether this effect is modified by *APOE* genotype, and whether the cognitive change pattern observed among ε4 carriers persists for a longer period.

Strengths and Limitations

The main strengths of this study are the large sample size, longer duration than what is most common in previous dementia prevention trials, thorough randomization and masking, detailed outcome assessments, and choice of target population. The FINGER participants were at-risk older individuals from the general population without dementia or substantial cognitive impairment (cognitive performance <0.5 SD below the mean level for the cognitively normal Finnish population).[27] The multimodal lifestyle intervention thus started early, before the occurrence of significant clinical impairment. This early start date may be particularly important for *APOE* ε4 carriers, who have increased susceptibility to detrimental effects of unhealthy lifestyle factors through a variety of mechanisms.[5-7] The multidomain intervention targeted multiple modifiable risk factors simultaneously, thus potentially covering several of these mechanisms.

This study has some limitations. Despite the relatively large cohort, there may be statistical power limitations for tests of interaction. The exact mechanisms of the within-group effects for *APOE* ε4 carriers could not be determined. Findings may not necessarily apply to individuals who already have substantial cognitive impairment because they were excluded from the trial.

Conclusions

Results from the FINGER trial suggest that healthy lifestyle changes could be beneficial for cognition in older at-risk individuals even in the presence of *APOE*-related genetic susceptibility to dementia. Whether such benefits are more pronounced in *APOE* ε4 carriers compared with noncarriers should be further investigated. The findings also emphasize the importance of early prevention strategies that target multiple modifiable risk factors simultaneously.

Table 2. Primary and Secondary Cognitive End Points From Baseline to 24 Months

Cognitive End Point by *APOE* ε4 Carrier Status	Mean (SE) Change[a]		Difference Between Intervention and Control Groups per Year[b]		Difference Between Carriers and Noncarriers per Year (Intervention × Time × *APOE*)	
	Control	Intervention	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
NTB total score (primary end point)						
Carrier	0.096 (0.025)	0.170 (0.027)	0.037 (0.001 to 0.073)	.045	0.023 (−0.021 to 0.067)	.30
Noncarrier	0.194 (0.018)	0.222 (0.018)	0.014 (−0.011 to 0.039)	.28		
Executive functioning (secondary end point)						
Carrier	0.016 (0.032)	0.105 (0.034)	0.045 (−0.002 to 0.091)	.059	0.022 (−0.034 to 0.078)	.44
Noncarrier	0.079 (0.023)	0.123 (0.023)	0.022 (−0.010 to 0.054)	.17		
Processing speed (secondary end point)						
Carrier	0.010 (0.035)	0.077 (0.037)	0.034 (−0.015 to 0.083)	.18	0.013 (−0.047 to 0.073)	.68
Noncarrier	0.051 (0.025)	0.093 (0.024)	0.021 (−0.013 to 0.055)	.22		
Memory (secondary end point)						
Carrier	0.200 (0.042)	0.285 (0.044)	0.042 (−0.017 to 0.102)	.16	0.041 (−0.031 to 0.113)	.27
Noncarrier	0.370 (0.030)	0.373 (0.030)	0.001 (−0.040 to 0.043)	.95		
Abbreviated memory (post hoc end point)						
Carrier	0.099 (0.045)	0.239 (0.048)	0.070 (0.006 to 0.135)	.03	0.048 (−0.030 to 0.127)	.22
Noncarrier	0.207 (0.033)	0.250 (0.032)	0.022 (−0.023 to 0.066)	.34		

Abbreviations: *APOE*, apolipoprotein E; NTB, Neuropsychological Test Battery.

[a] A positive mean change indicates improvement.

[b] A positive value of the estimate of differences between intervention and control groups indicates the effect is in favor of the intervention group.

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