

# A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial



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## Summary

**Background** Modifiable vascular and lifestyle-related risk factors have been associated with dementia risk in observational studies. In the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a proof-of-concept randomised controlled trial, we aimed to assess a multidomain approach to prevent cognitive decline in at-risk elderly people from the general population.

**Methods** In a double-blind randomised controlled trial we enrolled individuals aged 60–77 years recruited from previous national surveys. Inclusion criteria were CAIDE (Cardiovascular Risk Factors, Aging and Dementia) Dementia Risk Score of at least 6 points and cognition at mean level or slightly lower than expected for age. We randomly assigned participants in a 1:1 ratio to a 2 year multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring), or a control group (general health advice). Computer-generated allocation was done in blocks of four (two individuals randomly allocated to each group) at each site. Group allocation was not actively disclosed to participants and outcome assessors were masked to group allocation. The primary outcome was change in cognition as measured through comprehensive neuropsychological test battery (NTB) Z score. Analysis was by modified intention to treat (all participants with at least one post-baseline observation). This trial is registered at ClinicalTrials.gov, number NCT01041989.

**Findings** Between Sept 7, 2009, and Nov 24, 2011, we screened 2654 individuals and randomly assigned 1260 to the intervention group (n=631) or control group (n=629). 591 (94%) participants in the intervention group and 599 (95%) in the control group had at least one post-baseline assessment and were included in the modified intention-to-treat analysis. Estimated mean change in NTB total Z score at 2 years was 0.20 (SE 0.02, SD 0.51) in the intervention group and 0.16 (0.01, 0.51) in the control group. Between-group difference in the change of NTB total score per year was 0.022 (95% CI 0.002–0.042, p=0.030). 153 (12%) individuals dropped out overall. Adverse events occurred in 46 (7%) participants in the intervention group compared with six (1%) participants in the control group; the most common adverse event was musculoskeletal pain (32 [5%] individuals for intervention vs no individuals for control).

**Interpretation** Findings from this large, long-term, randomised controlled trial suggest that a multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population.

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## Introduction

Late-life cognitive impairment and dementia have become serious human, social, and economic burdens.<sup>1</sup> WHO<sup>1</sup> and the G8 Dementia Summit (2013)<sup>2</sup> emphasised prevention as a key element to counteract the dementia epidemic. Findings from observational studies have linked several vascular and lifestyle-related risk factors with increased risk of late-life cognitive impairment and Alzheimer's disease, the most common cause of dementia.<sup>3</sup> A third of Alzheimer's disease cases worldwide are estimated to be

attributable to seven modifiable factors (low education, midlife hypertension, midlife obesity, diabetes, physical inactivity, smoking, and depression), providing prevention opportunities.<sup>3</sup> However, randomised controlled trials are desperately needed to confirm these associations and investigate strategies to maintain cognitive functioning and prevent cognitive impairment.<sup>4,5</sup>

Previous single-domain prevention trials for cognitive impairment and dementia have yielded mainly negative results.<sup>4</sup> Some positive associations with cognition were

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For the **National Institutes of Health report** see <http://www.ahrq.gov/research/findings/evidence-based-reports/alzcoqtp.html>

## Research in context

### Systematic review

We searched ClinicalTrials.gov and WHO's International Clinical Trial Registry Platform up to Jan 31, 2015, to identify larger multidomain randomised controlled trials. Search terms were "prevention of dementia OR prevention of Alzheimer disease". Further selection criteria included primary outcome cognitive impairment or dementia; at least two combined interventions (eg, physical exercise, cognitive training, social activities, dietary intervention, drug or dietary supplement); age 40 years or older; duration at least 1 year; and size 500 participants or greater. We based criteria on the 2010 National Institutes of Health Evidence Report on Preventing Alzheimer's Disease and Cognitive Decline. We identified two ongoing randomised controlled trials, the Multidomain Alzheimer Preventive Trial (MAPT; NCT00672685) and Prevention of Dementia by Intensive Vascular Care (Pre-DIVA; ISRCTN29711771). Results are not yet available.

### Added value of the study

To our knowledge, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is the first large, longer-term, and methodologically robust trial

showing that a multidomain intervention can improve or maintain cognitive functioning and reduce the risk of cognitive decline among older at-risk individuals. FINGER targeted the at-risk segment of the general elderly population, not patients in a clinical setting. Results are thus most appropriately interpreted in a public health context, where small long-term changes can have large effects. The FINGER extended follow-up will provide further knowledge about intervention effects on incidence of dementia and Alzheimer's disease.

### Interpretation

After many negative dementia trials, the focus has shifted to presymptomatic and predementia disease stages and at-risk states when intervention might not be too late. In these early stages, no other trials have so far provided references for expected cognitive effects, and these references cannot be simply extrapolated from dementia trials. FINGER provides a first reference, and also a novel and pragmatic model, for dementia prevention trials that can be tested and adapted in various other settings and populations.

reported for physical activity, cognitive training, or both in smaller and shorter intervention studies.<sup>6–11</sup> Cognitive impairment, dementia, and Alzheimer's disease are complex, multifactorial disorders, and multidomain interventions targeting several risk factors and disease mechanisms simultaneously could be needed for optimum preventive effects. Successful prevention trials for cardiovascular disease and type 2 diabetes have emphasised the importance of a multidomain approach.<sup>12,13</sup> Further, randomised controlled trials in individuals at risk of dementia have been recommended as an effective and feasible approach.<sup>4</sup>

In a proof-of-concept trial, we aimed to investigate the effects of a 2 year multidomain intervention on cognition in at-risk elderly people from the general population.

## Methods

### Study design and participants

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is a 2 year population-based multidomain randomised controlled trial done in six centres in Finland (Helsinki, Vantaa, Kuopio, Oulu, Seinäjoki, and Turku). The study protocol<sup>14</sup> and baseline population characteristics<sup>15</sup> have been published previously.

Participants were recruited from previous population-based non-interventional surveys.<sup>16,17</sup> To be eligible for participating in the trial, individuals were required to be 60–77 years old, and have a CAIDE (Cardiovascular Risk Factors, Aging and Dementia) Dementia Risk Score<sup>18</sup> of 6 points or higher (score based on age, sex, education, systolic blood pressure, body-mass index [BMI], total

cholesterol, and physical activity; range 0–15 points). Cognitive screening was done with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery,<sup>19</sup> and participants had to meet at least one of the following criteria: word list memory task (ten words three times) results of 19 words or fewer; word list recall of 75% or less; or mini mental state examination of 26 points or less out of 30 points. These criteria selected individuals with cognitive performance at the mean level or slightly lower than expected for age according to Finnish population norms.<sup>20</sup> Exclusion criteria were previously diagnosed dementia; suspected dementia after clinical assessment by study physician at screening visit (individuals recommended for further investigations); mini mental state examination less than 20 points; disorders affecting safe engagement in the intervention (eg, malignant disease, major depression, symptomatic cardiovascular disease, revascularisation within 1 year previously); severe loss of vision, hearing, or communicative ability; disorders preventing cooperation as judged by the study physician; and coincident participation in another intervention trial.

FINGER was approved by the coordinating ethics committee of the Hospital District of Helsinki and Uusimaa. Participants gave written informed consent at screening and baseline visits.

### Randomisation and masking

We randomly assigned participants into the intensive multidomain intervention or regular health advice group (referred to as control group) in a 1:1 ratio.

Computer-generated allocation was done in blocks of four (two individuals randomly allocated to each group) at each site after baseline by the study nurse. Double-blinding was pursued as much as possible: group allocation was not actively disclosed to participants, they were advised not to discuss the intervention during testing sessions, opportunities for between-group interactions were restricted, and outcome assessors were blinded to allocation and were not involved in intervention activities.

### Procedures

The control group received regular health advice. All participants (control and intervention group) met the study nurse at screening, baseline, and at 6, 12, and 24 months after randomisation for measurements of blood pressure, weight and BMI, and hip and waist circumference. All participants (control and intervention group) met the study physician at screening, and at 24 months for a detailed medical history and physical examination. At baseline, the study nurse gave all participants oral and written information and advice on healthy diet and physical, cognitive, and social activities beneficial for management of vascular risk factors and disability prevention. Blood samples were collected four times during the study at baseline and at 6, 12, and 24 months, and laboratory test results were mailed to all participants, together with general written information about the clinical significance of measurements, and advice to contact primary health care if needed.

The intervention group additionally received four intervention components previously described in detail.<sup>14</sup> The nutritional intervention was based on the Finnish Nutrition Recommendations<sup>21</sup> and was conducted by study nutritionists (three individual sessions and seven to nine group sessions). Individual sessions included tailoring of the participant's diet. Group sessions provided discussions and practical exercises for facilitating lifestyle changes. Participants were advised to consume a diet with 10–20% of daily energy from proteins, 25–35% daily energy from fat (<10% from saturated plus trans fatty acids, 10–20% from monounsaturated fatty acids, and 5–10% from polyunsaturated fatty acids [including 2.5–3 g/day of omega-3 fatty acids]), 45–55% daily energy from carbohydrates (<10% from refined sugar), 25–35 g/day of dietary fibre, less than 5 g/day of salt, and less than 5% daily energy from alcohol. Energy intake facilitating 5–10% reduction in bodyweight was recommended only if necessary after taking into account BMI, health status, age, and diet of the participant. These goals were achieved by recommendation of high consumption of fruit and vegetables, consumption of wholegrain cereal products and low-fat milk and meat products, limiting of sucrose intake to less than 50 g/day, use of vegetable margarine and rapeseed oil instead of butter, and fish consumption at least two portions per week.

The physical exercise training programme followed international guidelines<sup>22</sup> and represented a modified version of the Dose Responses to Exercise Training (DR's EXTRA) study protocol.<sup>23</sup> Training was guided by study physiotherapists at the gym and consisted of individually tailored programmes for progressive muscle strength training (1–3 times per week) and aerobic exercise (2–5 times per week), including exercises to improve postural balance. The strength training programme was standardised to include exercises for the eight main muscle groups (knee extension and flexion, abdomen and back muscles, rotation, upper back and arm muscles, and press bench for lower extremity muscles). Individual aerobic training included activities preferred by each participant. Aerobic group activities were also provided. Individualisation of strength and aerobic training was based on repetition maximum measurements (done at baseline and at 1, 3, 6, 9, 12, 18, and 24 months after the start of the exercise intervention).<sup>14</sup> Cognitive training included group and individual sessions. The ten group sessions were led by psychologists: six sessions with educational content on age-related cognitive changes, memory, and reasoning strategies applied to everyday activities, and four sessions for checking progress in individual computer-based training plus a visit to the local Alzheimer Association. Individual sessions consisted of computer-based training at home or at study site, conducted in two periods of six months each. Each period included 72 training sessions (three times per week, 10–15 min per session). The training programme was a web-based in-house developed computer program including several tasks adapted from protocols previously shown to be effective in shorter-term randomised controlled trials:<sup>24</sup> executive processes (updating spatial, updating letter, updating number, and mental set shifting tasks), working memory (maintenance task), episodic memory (relational and spatial tasks), and mental speed (shape match task). Social activities were stimulated through the numerous group meetings of all intervention components. Management of metabolic and vascular risk factors was based on national evidence-based guidelines.<sup>25–27</sup> It included additional meetings with the study nurse (at 3, 9, and 18 months), and the study physician (at 3, 6, and 12 months) for measurements of blood pressure, weight and BMI, and hip and waist circumference, physical examinations, and recommendations for lifestyle management. Study physicians did not prescribe medication, but strongly recommended participants to contact their own physician or clinic if needed.

### Outcomes

A thorough cognitive assessment with standard neuropsychological tests (an extended version of the neuropsychological test battery [NTB])<sup>28</sup> was done at baseline and at 12 and 24 months after randomisation by study psychologists. Participants who dropped out during the

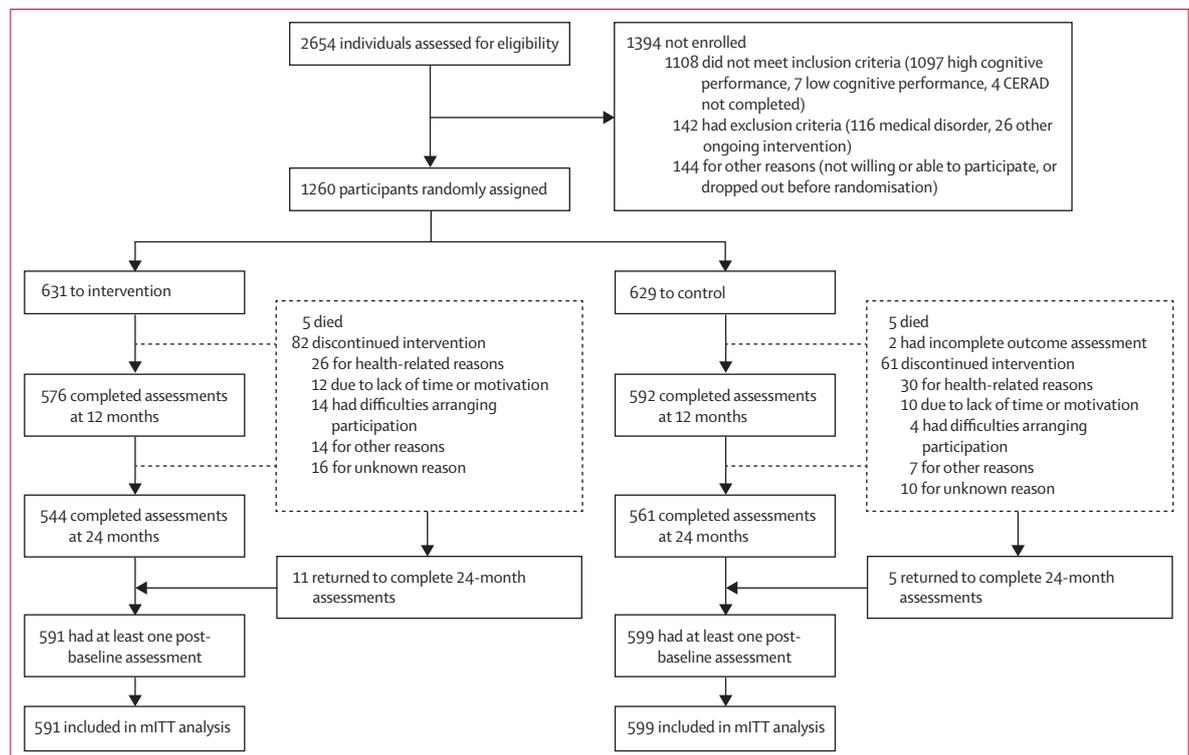
study were invited to a final visit at 24 months for outcome evaluation. The primary outcome was change in cognitive performance measured with NTB total score, a composite score based on results from 14 tests (calculated as Z scores standardised to the baseline mean and SD, with higher scores suggesting better performance).<sup>14</sup> Secondary outcomes included NTB domain Z scores for executive functioning, processing speed, and memory. The executive functioning domain included category fluency test,<sup>19</sup> 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 test, concept shifting test (condition A), and Stroop test (condition 2). The memory domain included visual paired associates test, immediate and delayed recall; logical memory immediate and delayed recall; and word list learning and delayed recall.<sup>19</sup> Post-hoc analyses were done for an abbreviated memory domain including four of six tests (two associative memory and two logical memory tests) including longer recall delay (30 min instead of 5 min) and requiring more complex processing. We defined cognitive decline as any decline compared with improvement or no decline on the NTB total score (overall decline) and NTB domain Z scores (decline per domain). Other secondary outcomes included vascular and lifestyle factors, depressive symptoms (Zung scale), and disability (short physical performance battery).

We assessed participation in intervention components with self-reports at 12 months and 24 months, and also recorded attendance in each component throughout the trial. We completed data verification for self-reported participation (yes or not at all per intervention component, and number of components in which the individual participated to at least some extent). Data verification is still in progress for recorded adherence; here, we report preliminary data on the proportion of participants who attended none or one or more sessions per intervention component.

We recorded adverse events as they occurred, and at the 24 month visit all participants were also asked if they had experienced any harm related to the study, such as stress or musculoskeletal pain. Vital status of dropout individuals was verified from the National Population Register. We linked participant data to nationwide registers, the Hospital Discharge Register, and Causes of Death Register (data up to Dec 31, 2011, available), to identify occurrence of myocardial infarction and stroke. An external safety committee regularly assessed safety-related issues.

### Statistical analyses

We based sample size calculations on the expected modified NTB score. In view of findings from previous studies in mild Alzheimer's disease,<sup>28</sup> an NTB decrease of roughly  $-0.21$  Z score with an SD of  $0.5$  was estimated in



the control group during 2 years (calculated as half of the decline in mild Alzheimer's disease, and with larger SD due to the more heterogeneous FINGER study group). With 5% significance level and 90% power, the required sample size was estimated to be roughly 500 participants per group to detect a 50% difference in change in NTB score between groups. On the basis of findings from earlier Finnish lifestyle interventions,<sup>9,20</sup> we assumed a dropout rate of 10%, and therefore calculated a starting size of 600 individuals per group as sufficient. An extended follow-up (7 years since enrolment for each participant) is planned to assess longer-term effects on incidence of dementia and Alzheimer's disease.

We applied zero-skewness log-transformation to skewed NTB components. Z scores for tests at each timepoint were standardised to the baseline mean and SD. We obtained NTB total score and domain scores for executive functioning, processing speed, and memory by averaging individual NTB component Z scores. The minimum number of necessary NTB components was set to eight of 14 for calculating NTB total score, three of five for executive functioning, two of three for processing speed, and three of six for memory. We used mixed-effects regression models with maximum likelihood estimation to analyse change in cognitive scores as a function of randomisation group, time, and group × time interaction. A small quadratic effect was observed for the mean change of NTB total score in both groups (ie, slightly more improvement from baseline to 12 months than from 12 to 24 months) and a model including a quadratic term was used. However, between-group difference for the quadratic effect was not significant. For the other cognitive outcomes, assumption of linearity was plausible and linear models were used.

We based the primary efficacy analysis on the modified intention-to-treat (mITT) population, including all randomly assigned participants with at least one post-baseline observation. Secondary and sensitivity analyses were done with intention-to-treat analyses (all randomly assigned participants, including those without post-baseline observations), all randomly assigned participants with a multiple imputation by chained equations approach with 20 repetitions, all randomly assigned participants who completed all cognitive evaluations, and binary logistic regression analyses with outcome defined as cognitive decline versus improvement or no change between assessments at baseline and 24 months.

We analysed other secondary outcomes in the mITT population using mixed-effects regression models with maximum likelihood estimation for all endpoints with three available measurements (at baseline, at 12 months, and at 24 months) for blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, plasma glucose (fasting and 2 h after glucose tolerance test), BMI, and depressive symptoms. For the short physical performance battery, only two measurements were available (baseline

and 24 months); mean change was adjusted for baseline level, and a linear regression model was used. For categorical variables (fish and vegetable intake, and physical activity), we calculated the change in percentage units between baseline and 24 months and used multinomial logistic models. We used a level of significance of less than 5% in all analyses. STATA 11.2 software was used for all calculations.

This trial is registered with ClinicalTrials.gov, number NCT01041989.

### Role of the funding source

The study funders had no role in study design, data collection, analysis, interpretation, writing of the report, or the decision to submit for publication. TN, JLe, EL, MP, and MK (the corresponding author) had full access to all

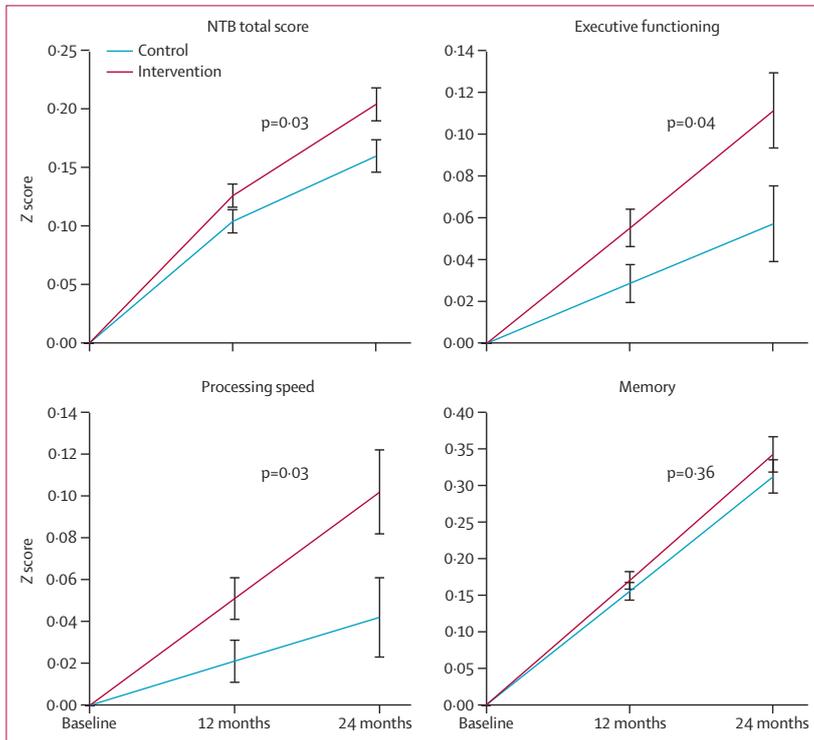
	Participants with information available	Intervention group (n=591)	Control group (n=599)
<b>Demographic characteristics</b>			
Age at the baseline visit, years	1190	69.5 (4.6)	69.2 (4.7)
Number of women	1190	267/591 (45%)	284/599 (47%)
Education, years	1179	10.0 (3.4)	10.0 (3.4)
Married or cohabiting	1189	436/590 (74%)	454/599 (76%)
<b>Vascular factors</b>			
Systolic blood pressure, mm Hg	1179	140.1 (16.7)	139.8 (15.7)
Diastolic blood pressure, mm Hg	1179	80.5 (9.6)	80.1 (9.3)
Serum total cholesterol, mmol/L	1186	5.2 (1.0)	5.2 (1.0)
Fasting plasma glucose, mmol/L	1188	6.1 (0.8)	6.1 (1.0)
2 h oral glucose tolerance test, mmol/L	1031	7.0 (2.1)	7.0 (2.2)
Body-mass index, kg/m <sup>2</sup>	1179	28.3 (4.5)	28.1 (4.9)
<b>Lifestyle factors</b>			
Physical activity two or more times per week	1180	410/585 (70%)	427/595 (72%)
Current smokers	1186	58/588 (10%)	48/598 (8%)
Alcohol drinking at least once per week	1182	265/588 (45%)	265/594 (45%)
Fish intake at least twice per week	1183	316/587 (54%)	304/596 (51%)
Daily intake of vegetables	1187	360/589 (61%)	374/598 (63%)
<b>Self-reported medical disorders</b>			
Hypertension	1177	392/585 (67%)	387/592 (65%)
Hypercholesterolaemia	1180	389/587 (66%)	414/593 (70%)
Diabetes	1180	76/586 (13%)	74/594 (12%)
History of myocardial infarction	1184	29/589 (5%)	31/595 (5%)
History of stroke	1181	32/587 (5%)	34/594 (6%)
<b>Cognition*</b>			
NTB total score	1190	-0.03 (0.55)	0.03 (0.59)
Executive functioning	1189	-0.03 (0.66)	0.03 (0.69)
Processing speed	1190	-0.02 (0.78)	0.05 (0.84)
Memory	1190	-0.03 (0.68)	0.03 (0.66)
Mini mental state examination	1187	26.7 (2.0)	26.8 (2.0)
Data are n, n/N (%), or mean (SD). Analysis was done in the modified intention-to-treat population (participants who underwent at least one post-baseline evaluation of the primary efficacy endpoint). NTB=neuropsychological test battery. *Scores on the NTB total score, and on executive functioning, processing speed, and memory are mean values of Z scores of the cognitive tests included in each cognitive outcome, with higher scores suggesting better performance.			
<b>Table 1: Baseline characteristics of participants</b>			

data in the study. The report was approved for submission by all authors. The corresponding author had final responsibility for the decision to submit for publication.

**Results**

Between Sept 7, 2009, and Nov 24, 2011, 2654 individuals were screened and 1260 were randomly assigned to the intensive intervention group (n=631) or control group (n=629; figure 1). 1168 (93%) participants completed the 12 month assessments, and 1105 (88%) participants

See Online for appendix



**Figure 2: Change in cognitive performance during the 2 year intervention**

Figure shows estimated mean change in cognitive performance from baseline until 12 and 24 months (higher scores suggest better performance) in the modified intention-to-treat population. Error bars are SEs. Mixed-model repeated-measures analyses were used to assess between-group differences (group × time interaction) in changes from baseline to 24 months based on data from all participants with at least one post-baseline measurement. NTB=neuropsychiatric test battery.

completed the 24 month assessments. 16 individuals who withdrew from the study came to the final cognitive evaluation. The intervention was completed in February, 2014. The mITT analyses included 1190 participants (94% of all enrolled participants). Dropout rates were similar in the intervention (87 [14%] participants) and control (66 [11%] participants) groups (p=0.07). The main reasons for dropout were health-related (56 [37%] participants), lack of time or motivation (22 [14%]), and difficulties in arranging participation (18 [12%]). Ten individuals died during the study.

Baseline characteristics have previously been described in detail.<sup>15</sup> The intervention and control groups were similar at baseline (table 1; baseline characteristics for intention-to-treat population are provided in the appendix). The mean age of the population was 69.3 years (SD 4.7), education 10.0 years (SD 3.4), and mini mental state examination score 26.8 points (SD 2.0). Mean cognitive performance was less than 0.5 SD below the average level for the cognitively normal Finnish population.<sup>15</sup> Several vascular and lifestyle risk factors were present.

We noted a significant beneficial effect of the intervention for the primary outcome (figure 2, appendix). Estimated mean change in NTB total Z score at 2 years was 0.20 (SE 0.01, SD 0.51) in the intervention group and 0.16 (0.01, 0.51) in the control group. The mean difference between groups (group × time interaction) in change of NTB total score per year was 0.022 (95%CI 0.002–0.042, p=0.030). Improvement in NTB total score after 24 months was 25% higher in the intervention group than in the control group. The results remained unchanged in sensitivity analyses, including intention-to-treat analyses (appendix).

We also noted a significant intervention effect for the secondary cognitive outcomes of executive functioning (p=0.039) and processing speed (p=0.029; figure 2, appendix). Improvement in executive functioning was 83% higher, and in processing speed 150% higher, in the intervention group than in the control group. The intervention was not associated with significant change in the prespecified memory domain.

Post-hoc abbreviated memory score analyses showed a significant between-group difference (p=0.036; appendix). NTB total score fell in 307 (28%) participants between the assessments at baseline and 24 months. Risk of cognitive decline was increased in the control group compared with intervention group for NTB total score (odds ratio 1.31, 95% CI 1.01–1.71), executive functioning, and processing speed (table 2).

We also noted significant intervention effects after 2 years for other secondary outcomes such as BMI, dietary habits, and physical activity (appendix).

Self-reported adherence (any vs no participation) to intervention domains was high: nutrition, 579 (100%) participants; physical exercise, 523 (90%) participants;

	Odds ratio (95% CI)		p value
	Intervention (n=554)	Control (n=565)	
<b>Overall cognitive decline</b>			
NTB total score	1 (reference)	1.31 (1.01-1.71)	0.04
<b>Cognitive decline per domain</b>			
NTB memory score	1 (reference)	1.23 (0.95-1.60)	0.12
NTB executive functioning score	1 (reference)	1.29 (1.02-1.64)	0.04
NTB processing speed score	1 (reference)	1.35 (1.06-1.71)	0.01

In post-hoc analyses, we defined cognitive decline as decrease in NTB total score (overall decline) and NTB domain scores (decline per domain) between the assessments at baseline and at 24 months. Logistic regression analyses were used to assess risk of cognitive decline in the control group compared with the intervention group. Analyses are based on all participants with data available at both baseline and 24 months. NTB=neuropsychological test battery.

**Table 2: Risk of cognitive decline from baseline to 24 months**

	Total (n=1260)	Intervention (n=631)	Control (n=629)
<b>Self-reported adverse events or negative experience of the study</b>			
All adverse events	52 (4%)	46 (7%)	6 (1%)
Musculoskeletal pain	32 (3%)	32 (5%)	0
Stress	8 (1%)	6 (1%)	2 (<1%)
Time-consuming	4 (<1%)	1 (<1%)	3 (<1%)
Other*	8 (1%)	7 (1%)	1 (<1%)
Death during the study	10 (1%)	5 (1%)	5 (1%)
<b>Health-care register information†</b>			
Myocardial infarction	6 (<1%)	1 (<1%)	5 (1%)
Stroke	8 (1%)	4 (1%)	4 (1%)

\*Other includes, in the intervention group, one lower limb oedema, one dizziness, one headache, one panic-attack-like experience, one undesired weight loss, one abdominal hernia, and one detachment of the retina; other includes, in the control group, one unknown adverse event. †Diagnoses occurring between the baseline visit and Dec 31, 2011.

**Table 3: Self-reported adverse events during the study and health-care register follow-up**

cognitive training, 491 (85%) participants; and recorded visits for monitoring of metabolic and vascular risk factors, 514 (87%) participants. Only eight (1%) individuals reported that they participated in one intervention domain, compared with 36 (6%) in two intervention domains, 121 (21%) in three intervention domains, and 416 (72%) in all four intervention domains. Information was missing for ten (2%) individuals. Preliminary recorded participation per intervention component is shown in the appendix.

Very few side-effects were reported during the study, the most common of which was slight exercise-related musculoskeletal pain (32 [5%] participants in the intervention group compared with no participants in the control group). No serious intervention-related adverse events were reported, and none of the events required hospitalisation (table 3).

## Discussion

To our knowledge, FINGER is the first large-scale, longer-term randomised controlled trial to assess a multidomain intervention for improvement or maintenance of cognitive functioning and reduction in the risk of cognitive decline in elderly at-risk individuals from the general population. The main hypothesis was that simultaneous changes in several risk factors (even of smaller magnitude) would lead to a protective effect on cognition. We noted significant intervention effects on the primary outcome (overall cognition), main cognitive secondary outcomes (executive functioning and processing speed), and other secondary outcomes (BMI, dietary habits, and physical activity). We noted no significant effect on memory, although post-hoc analyses showed an effect on more complex memory tasks (abbreviated memory score). There were also beneficial effects on risk of cognitive decline in post-hoc analyses.

The multidomain lifestyle-based intervention was feasible and safe. Dropout rates were low, and adherence to intervention domains was high.

Improvement in the primary and main secondary cognitive outcomes was 25% to 150% better in the intervention group than in the control group. However, our estimates of intervention effects could be considered to be conservative. Intervention adherence was not taken into account, and for ethical reasons advice and feedback on metabolic and vascular risk factors was also provided to the control group. The benefits of the multidomain intervention might thus be greater if compared with a do-nothing control group.

Although there is no gold standard for outcome measurements in trials of dementia prevention, use of compound batteries including several validated cognitive tests has been recommended.<sup>29</sup> The comprehensive outcome measurements in FINGER suggested beneficial effects on both global cognition and cognitive domains highly relevant for everyday activities (eg, executive functioning, processing speed, and complex memory tasks). Practice effects of repeated cognitive testing<sup>30</sup> might partly account for improvements in both the intervention and control groups. However, improvement was significantly greater in the intervention group, suggesting cognitive benefits beyond practice or placebo effects.

FINGER targeted the at-risk segment of the general elderly population, not patients in a clinical setting. Because of the long prodementia stage of neuropathological processes, we cannot exclude that some participants might already have had dementia-related brain changes. However, mean cognitive performance was less than 0.5 SD below the average level for the cognitively normal Finnish population. As previously described,<sup>15</sup> the frequency of several risk factors were quite similar to that in the age-equivalent general population. FINGER participants are thus representative of an important part of the general Finnish elderly population with several risk factors for dementia, but without pronounced cognitive impairment.<sup>15</sup> Intervention effects (Cohen's *d* 0.13 after 2 years) are thus most appropriately interpreted in a public health context, in which small long-term effects on common disorders could have high relevance. Meta-analyses of trials of previous cognitive training, physical activity, or both have shown effect sizes on cognition of roughly 0.20–0.30 (Hedges' *g*).<sup>8,10</sup> However, these studies were short (up to 16–18 weeks) and targeted mainly healthy elderly people (often volunteers), and many had substantial methodological limitations (eg, outcome assessments not blinded, no intention-to-treat analyses, or cognitive training effects assessed only on the trained tasks).<sup>8,10</sup>

Public health significance is not easily translated into clinical or personal significance. The clinical significance of observed positive intervention effects on cognition is less obvious in a population without dementia. However,

on the basis of findings from previous trials,<sup>31,32</sup> cognitive decline or lack of improvement could be classified as an indicator of further cognitive impairment, positive neuroimaging markers of  $\beta$ -amyloid, and neurodegeneration. A 7 year extended follow-up will be done to assess intervention effects on incidence of dementia and Alzheimer's disease and related functional outcomes. Postponing of the onset of Alzheimer's disease by 5 years has been estimated to decrease its prevalence by up to 50% in 50 years.<sup>33</sup> About a third of cases of Alzheimer's disease worldwide could be attributable to low education, physical inactivity (the highest population-attributable risk in the USA, Europe, and the UK), obesity, hypertension, diabetes, smoking, and depression.<sup>3</sup> The worldwide prevalence of Alzheimer's disease could be reduced by 8.3% by 2050 with relative reductions of 10% per decade in the prevalence of each of these factors. Such small changes imply large effects, and if the beneficial effects on cognition observed in FINGER will lead to even a modest delay in onset of dementia and Alzheimer's disease, it would have a huge effect on both individual and societal levels.

Findings from earlier observational studies have provided promising results linking several modifiable risk factors to cognitive impairment and dementia. FINGER, a proof-of-concept randomised controlled trial, supports the efficacy of multidomain prevention approaches. Intensity, type (eg, multidomain), long duration, and choice of target group (at-risk individuals) might account the observed beneficial effects on cognition. Possible mechanisms will be investigated in detail with use of the FINGER biomarker database. The multimodal intervention model needs to be investigated further, particularly with regard to the contribution of each component to the overall effect. FINGER provides a novel and pragmatic model for trials of cognitive decline prevention that can be tested and adapted in various other settings and populations.

#### Contributors

TN, AS, RA, TH, TL, JLi, TP, MP, RR, TS, JT, HS, and MK conceived and designed the trial. TN, JLe, SA, and MK coordinated the trial. JLe, JLi (nutrition), RR, SP, SA (physical exercise), TH, TN, LB, AS-N (cognitive training), TS, RA, JT, and AJ (vascular risk monitoring) designed and supervised intervention components. TN, JLe, EL, MP, and MK did the data analysis. TN, AS, FM, and MK interpreted the results and drafted the report. TN, AS, RA, TL, JLi, FM, MP, RR, TS, JT, HS, and MK obtained funding. All authors revised the Article for important intellectual content. MK is the principal investigator.

#### Declaration of interests

We declare no competing interests.

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