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


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 0·02·0·20 (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 0·02 (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.

Introduction Late-life cognitive impairment and dementia have become serious human, social, and economic burdens. WHO and the G8 Dementia Summit (2013) 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. 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. However, randomised controlled trials are desperately needed to confirm these associations and investigate strategies to maintain cognitive functioning and prevent cognitive impairment. Previous single-domain prevention trials for cognitive impairment and dementia have yielded mainly negative results. Some positive associations with cognition were

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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 was designed to investigate the effects of a 2 year multidomain intervention on cognition in at-risk elderly people from the general population. The intervention targeted several risk factors and disease mechanisms simultaneously and was therefore complex and multifactorial. The study design and results are discussed in this article.

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 and baseline population characteristics have been published previously.

Participants were recruited from previous population-based non-interventional surveys. 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 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, 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. 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. The randomisation was done centrally using a computer-generated randomisation schedule. Blinding was not possible for participants or study personnel; however, the study protocol and baseline population characteristics were published previously.

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 reported for physical activity, cognitive training, or both in smaller and shorter intervention studies. 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. Further, randomised controlled trials in individuals at risk of dementia have been recommended as an effective and feasible approach.

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.
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-blindning 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. The nutritional intervention was based on the Finnish Nutrition Recommendations 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 and represented a modified version of the Dose Responses to Exercise Training (DR’s EXTRA) study protocol. 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. Individualisation of strength and aerobic training was based on repetition maximum maximum measurements (done at baseline and at 1, 3, 6, 9, 12, 18, and 24 months after the start of the exercise intervention).

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: 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. 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]) 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). Secondary outcomes included NTB domain $Z$ scores for executive functioning, processing speed, and memory. The executive functioning domain included category fluency test, 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. 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, an NTB decrease of roughly $-0.21 Z$ score with an SD of 0.5 was estimated in

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**Figure 1: Trial profile**

CERAD=Consortium to Establish a Registry for Alzheimer’s Disease. mITT=modified intention-to-treat.
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, 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 cogntive 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 multinominal 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
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 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. 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. 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;
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. 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 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 predementia stage of neuro-pathological 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, 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. 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). 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).

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, cognitive decline or lack of improvement could be classified as an indicator of further cognitive impairment, positive neuroimaging markers of β-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. 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. 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 AT (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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