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The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): Study design and progress

Miia Kivipelto[a,b,c,d,*], Alina Solomon[a,c,d], Satu Ahtiluoto[b], Tiia Ngandu[b,d], Jenni Lehtisalo[b], Riitta Antikainen[e,f], Lars Bäckman[c], Tuomo Hänninen[g], Antti Jula[b], Tiina Laatikainen[b], Jaana Lindström[b], Francesca Mangialasche[c], Aulikki Nissinen[b], Teemu Paajanen[a], Satu Pajala[h], Markku Peltonen[b], Rainer Rauramaa[i], Anna Stigsdotter-Neely[j], Timo Strandberg[e,k], Jaakko Tuomilehto[l,m], Hilkka Soininen[a,g]

[a]*Department of Neurology, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland*
[b]*Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland*
[c]*Aging Research Center, Karolinska Institutet, Stockholm, Sweden*
[d]*Alzheimer's Disease Research Center, Karolinska Institutet, Stockholm, Sweden*
[e]*Institute of Health Sciences/Geriatrics, University of Oulu, and University Hospital, Oulu, Finland*
[f]*Oulu City Hospital, Oulu, Finland*
[g]*Department of Neurology, Kuopio University Hospital, Kuopio, Finland*
[h]*Department of Lifestyle and Participation, National Institute for Health and Welfare, Helsinki, Finland*
[i]*Kuopio Research Institute of Exercise Medicine, Kuopio, Finland*
[j]*Department of Psychology, Umeå University, Umeå, Sweden*
[k]*Department of Medicine, Geriatric Clinic, University of Helsinki and University Hospital, Helsinki, Finland*
[l]*Department of Public Health, University of Helsinki, Helsinki, Finland*
[m]*South Ostrobothnia Central Hospital, Seinäjoki, Finland*

Abstract

Background: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is a multi-center, randomized, controlled trial ongoing in Finland.

Materials: Participants (1200 individuals at risk of cognitive decline) are recruited from previous population-based non-intervention studies. Inclusion criteria are CAIDE Dementia Risk Score $\geq$6 and cognitive performance at the mean level or slightly lower than expected for age (but not substantial impairment) assessed with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery. The 2-year multidomain intervention consists of: nutritional guidance; exercise; cognitive training and social activity; and management of metabolic and vascular risk factors. Persons in the control group receive regular health advice. The primary outcome is cognitive performance as measured by the modified Neuropsychological Test Battery, Stroop test, and Trail Making Test. Main secondary outcomes are: dementia (after extended follow-up); disability; depressive symptoms; vascular risk factors and outcomes; quality of life; utilization of health resources; and neuroimaging measures.

Results: Screening began in September 2009 and was completed in December 2011. All 1200 persons are enrolled and the intervention is ongoing as planned. Baseline clinical characteristics indicate that several vascular risk factors and unhealthy lifestyle–related factors are present, creating a window of opportunity for prevention. The intervention will be completed during 2014.

Conclusions: The FINGER is at the forefront of international collaborative efforts to solve the clinical and public health problems of early identification of individuals at increased risk of late-life cognitive impairment, and of developing intervention strategies to prevent or delay the onset of cognitive impairment and dementia.

Keywords: Cognitive impairment; Dementia; Alzheimer's disease; Lifestyle; Intervention; Randomized trial

*Corresponding author. Tel.: +46-73-99-409-22; Fax: +46-86-90-59-54.
E-mail address: miia.kivipelto@ki.se

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1. Introduction

Cognitive impairment is one of the most frequent chronic conditions in the elderly [1], and the worldwide costs of dementia have been estimated to exceed those of other chronic diseases such as diabetes [2]. Alzheimer's disease (AD), the major cause of dementia, has reached epidemic proportions, with a large human, social, and economic burden [3]. However, postponing AD onset by only 5 years may halve the projected AD prevalence in the future [4,5].

The importance of finding methods to delay onset and/or modify progression of cognitive impairment/dementia was recently emphasized in a report of the National Institutes of Health (NIH) in USA [6]. Formulated by an independent panel of health professionals and public representatives from outside the AD research field, the report highlighted the need for high-quality, randomized, controlled trials (RCTs). As cognitive impairment/dementia has a multifactorial etiology, resulting from interactions between both genetic and environmental factors (Figure 1), the report recommended conducting RCTs with multidimensional interventions, combining interventions for multiple risk factors, and controlling for many other factors [6]. Conducting trials initially in individuals at high risk was also recommended as a more efficient approach.

Within the AD/dementia research field, a consensus has emerged that intervention strategies must be initiated as early as possible, even before significant symptoms begin to appear. This goal can be achieved, for example, by incorporating the classical clinical trial approach to disease into a public health model, with long-term longitudinal databases including large populations. Establishing comprehensive databases for studies on aging can create the opportunity to formulate and validate tools for early detection of people who are at increased risk of late-life cognitive impairment, to identify important targets (risk factors) for preventive interventions, and to test such interventions in RCTs.

The first initiatives with an international perspective have already been established, including the Leon Thal Symposia [7], Prevent Alzheimer's Disease by 2020 (PAD2020, http://www.pad2020.org), and the European Dementia Prevention Initiative (EDPI, http://www.edpi.org). It has been suggested that a worldwide database could be built by integrating and expanding already existing cohorts and registries [7]. The multidomain Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) has been at the forefront of these efforts, and the FINGER is actively planning collaborations and integrating efforts with other groups launching similar projects.

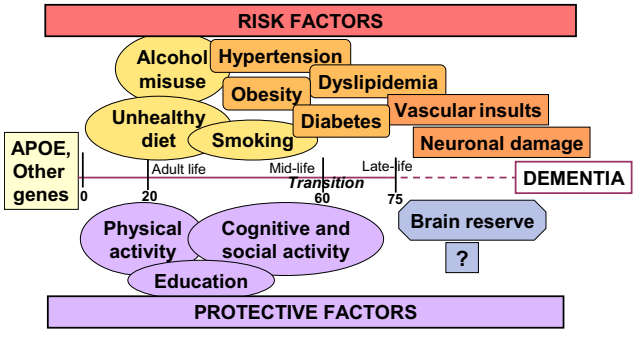

Fig. 1. Risk and protective factors for dementia.

The FINGER also provides a useful example of how a national dementia prevention research platform can be constructed using existing platforms for other chronic diseases. The study was initiated within the Academy of Finland Public Health Challenges Program, and is mainly based on the population of the FINRISK study, the Finnish survey database for monitoring of risk factors for chronic diseases. The FINRISK Study consists of large population-based surveys carried out since 1972 every 5 years using independent, random, and representative population samples from different parts of Finland [8]. The age range for the surveys is 25–74 years, and data are regularly linked to national hospital and drug registers. The first surveys were conducted within international cardiovascular disease prevention projects [9,10], but some cohorts were further investigated in the Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE) study [11]. FINGER participants are previous FINRISK participants screened with the CAIDE Dementia Risk Score (Table 1) [11].

Two earlier intervention trials in Finland were important sources of inspiration for the FINGER. The Diabetes Prevention Study (now completed) is a landmark RCT showing the effectiveness and feasibility of physical exercise and dietary interventions as preventive measures in people with impaired glucose tolerance [12]. It showed that trial participants can be motivated to make major longer term changes in their lifestyle. The ongoing 4-year exercise and the dietary intervention study Dose-Responses to Exercise Training (DRs EXTRA) had a drop-out rate of only 8% after 2 years, and its intervention protocol served as a model for the FINGER [13].

Table 1
CAIDE Dementia Risk Score: Probability of dementia in 20 years according to midlife risk score categories

Risk factor		Points		
Age	<47 years	0		
	47–53 years	3	Total score	Dementia risk
	>53 years	4	0–5	1.0%
Education	>10 years	0	6–7	1.9%
	7–9 years	2	8–9	4.2%
	<9 years	3	10–11	7.4%
Gender	Female	0	12–15	16.4%
	Male	1		
Blood pressure	<140 mm Hg	0		
	>140 mm Hg	2		
Body mass index	<30 kg/m^2	0		
	>30 kg/m^2	2		
Total cholesterol	<6.5 mmol/L	0		
	>6.5 mmol/L	2		
Physical activity	Yes	0		
	No	1		

The main objective of the FINGER is to investigate the extent to which a multidomain intervention can prevent/delay cognitive impairment in elderly at increased risk of cognitive decline. The 2-year intervention consists of nutritional guidance, exercise, cognitive training, and social stimulation, and intensive monitoring and management of metabolic and vascular risk factors. The aim of this article is to present the study design of the FINGER and describe some of the baseline characteristics of its participants.

2. Methods

2.1. Study design

The FINGER is a multicenter RCT (ClinicalTrials.gov identifier: NCT01041989) enrolling at least 1200 independently living persons from six cities (Helsinki, Vantaa, Kuopio, Oulu, Seinäjoki, Turku) in Finland. Each site is led by an experienced subgroup leader and run by a skilled study team. A monitoring committee ensures that the protocol of each intervention domain is followed carefully at each study site. Double blinding will be pursued as completely as possible, but in lifestyle interventions it may not be perfectly achieved. Participants in the FINGER are not actively told which group they belong to. Investigators evaluating outcome measures are blinded for the randomization group, and participants are also advised not to discuss the intervention during evaluation sessions. Cognitive testing and cognitive training sessions are conducted by different psychologists.

2.2. Selection of study participants: Inclusion and exclusion criteria

Participants in the FINGER are 60–77 years of age at the beginning of the study, recruited from previous random, population-based, nonintervention surveys (i.e., FINRISK). They are prescreened with the CAIDE Dementia Risk Score, and those scoring at least 6 points are further screened with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery [14]. For inclusion, at least one of the following criteria must be fulfilled: (1) Word List Memory Task (10 words × 3) ≤19 words; (2) Word List Recall ≤75%; or (3) Mini-Mental State Examination (MMSE) [15] ≤26/30 points. These criteria select persons with cognitive performance at the mean level or slightly lower than expected for age according to Finnish population norms [16], but without substantial cognitive decline. Exclusion criteria are conditions affecting safe engagement in the intervention (especially the exercise component): malignant diseases; major depression; dementia/substantial cognitive decline; MMSE <20; symptomatic cardiovascular disease; revascularization within 1 year; severe loss of vision, hearing, or communicative ability; conditions preventing cooperation [17] as judged by the study physician; as well as coincident participation in any intervention trial.

2.3. Intervention program

At baseline all participants receive oral and written information and advice on healthy diet and level of physical, cognitive, and social activities beneficial for vascular risk factors management and disability prevention from the study nurse. The study population is then randomized into two groups equal in size, to receive either an intensive multidomain intervention or regular health advice. Randomization was performed in blocks of four persons (two persons randomly allocated to each group) at each site by running a computer program that uses a linear congruential generator coded with a structured query language for random numbers. All participants (both the regular health advice group and the intensive multidomain intervention group) meet the study nurse three times after randomization and the physician at the final visit after 2 years. At each meeting with the study nurse, blood pressure, weight, and hip and waist circumference are measured. Blood samples are taken four times during the study and each time the participants receive their laboratory test results via mail, with general written information about the significance of these values together with advice for seeking medical care if needed.

In addition to what is given to both groups, the participants in the intensive intervention group receive all four components of the intervention: (1) nutritional guidance; (2) physical exercise; (3) cognitive training and social activity; and (4) intensive monitoring and management of metabolic and vascular risk factors (Figure 2). The different components of the multidomain intervention are initiated in a stepwise manner to facilitate adherence to each component.

The *nutritional intervention* includes individual counseling sessions (three meetings with the study nutritionist during the first year) and group sessions (six times during the first year and one to three times during the second year). Individual sessions include tailoring of the participant's daily diet. Group meetings provide more information and support for facilitating lifestyle changes, and include discussions and practical exercises, such as tools to assess one's own dietary behavior (e.g., tests to assess fat or fiber intake). The diet is based mainly on the Finnish Nutrition Recommendations [18]. Participants are advised to consume a diet with 10–20% of daily energy (E%) from proteins, 25–35E% from fat (<10E% from saturated plus transfatty acids, 10–20E% from monounsaturated fatty acids, 5–10E% from polyunsaturated fatty acids [including 2.5–3 g/day n-3 fatty acids]), 45–55E% from carbohydrates (<10E% refined sugar), 25–35 g/day dietary fiber, <5 g/day salt, and <5E% from alcohol.

These goals are achieved by recommending: high consumption of fruit and vegetables; whole grain in all cereal products; low-fat options in milk and meat products; sucrose intake <50 g/day; using vegetable margarine and rapeseed oil instead of butter; and consumption of fish in at least two portions per week. Because there is not sufficient evidence for the benefits of using dietary supplements (e.g., vitamins such as E or the B group related to cognitive

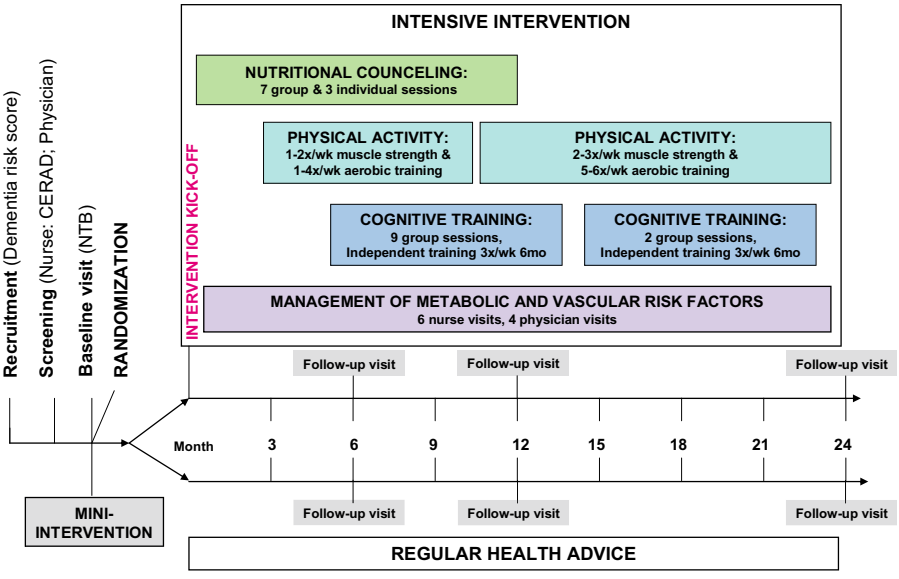

Fig. 2. FINGER protocol.

functioning in some studies) [6], the aim is to achieve an adequate intake with a balanced diet. However, vitamin D supplementation (10–20 μg/day) is advised [19], and fish oil supplements are recommended for participants not consuming fatty fish. Additional dietary measures can be taken according to individual needs related to disease history and medication. The need for weight loss is considered individually and energy intake that facilitates 5–10% of body weight reduction is recommended only if necessary. Food consumption and nutrient intake is assessed by 3-day food records at baseline, 12 months, and 24 months. Additional information on specific foods (i.e., fish) is assessed by a food frequency questionnaire.

The *physical exercise training program* is based on international guidelines [20] and represents a modified version of the Dose-Responses to Exercise Training (DR's EXTRA) study protocol [13]. Training is guided and supervised by study physiotherapists. The intervention comprises individually tailored, progressive muscle strength training and aerobic exercise programs, including exercises to maintain and improve postural balance (Table 2). The muscle strength training is conducted at the gym and guided by study physiotherapists during the first 6 months. The progressive strength training program is based on repetition maximum (RM) measurements at baseline and remeasurements at 1, 3, 6, 10, 15, and 20 months. The strength training program is standardized 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). Postural balance exercises are done during each training session at the gym. Individual aerobic training is planned together with each study participant and comprises activities preferred by the participant. Aerobic group activities, such as Nordic walking, aqua gym, jogging, and gymnastics, are also provided in the study. Muscle strength training and aerobic exercise are recorded in diaries throughout the intervention period.

Cognitive training targets cognitive domains most sensitive to aging and with a central role in everyday situations (episodic memory, executive function, mental speed, and working memory). The selection of the training was guided by a model that highlights three separate but related executive functions [21]. Training is done in group sessions and individually using a computer-based program that was specially adapted for the FINGER from protocols previously shown to be effective in shorter term RCTs [22]. Certain tasks were added to offer variation to this year-long training program. The cognitive training consists of 10 group sessions lead by a psychologist (approximately 60–90 minutes/session), when the computer program is introduced, and group discussions on memory-related themes are conducted. Discussions cover topics such as age-related changes in cognition, memory strategies, and every-day memory training. The computer-based training includes two periods of independent training of 6 months each, when participants train using the cognitive training program three times/week, 10–15 minutes/session, for a total of 72 training sessions per

Table 2
Progression of the resistance and aerobic training program

	0–1 mo	1–3 mo	3–6 mo	6–24 mo
Resistance exercise				
Exercise frequency per week	1–2	1–2	2	2–3
Duration of exercise (min)	30–45	30–60	45–60	60
Number of muscle groups	8–10	8–10	8–10	8–10
Repetitions/set	8–15	10–20	8–20	8–20
Load % 1RM	40–50	60	70	70–80
Number of sets	2	2–3	1–3	2–3
Aerobic exercise				
Exercise frequency per week	2	2–3	3–4	3–5
Duration of exercise (min)	30–45	30–45	30–60	45–60

period. Computer-based exercises enable an individual-adjusted increase in difficulty levels to facilitate a maximal effect of training. The effect of training is evaluated in testing sessions at the beginning, at 3 months and at the end of the independent training period. *Social activities* are stimulated through the numerous group meetings of all intervention components. A visit to the local Alzheimer Society offices is organized for each group. The participants are provided with information of the value of an active lifestyle and social connectedness. The amount of participation in social and cognitive activities, recorded in activity diaries, is evaluated at baseline, 1 year, and 2 years.

The *monitoring and maintenance of metabolic and vascular factors* begins with a risk factor assessment according to the latest national evidence-based guidelines [23–25]. The intensive intervention group members meet the study nurse every 3 months during the first year, and every 6 months during the second year for anthropometric measurements (weight, blood pressure, hip, and waist circumference). They also meet the study physician at 3, 6, 12, and 24 months for evaluation of laboratory test results, anthropometric measures, and cardiovascular and metabolic conditions. Participants in the intervention group are given oral and written information on the importance of reducing these risk factors. Motivating participants to make necessary lifestyle changes is an essential part of the meetings with the physician and nurse. When initiation or adjustment of pharmacologic treatment is necessary, participants are recommended to contact their own physician at the primary health care center.

2.4. Follow-up and outcome measurements

All participants meet the study nurse at screening, baseline, and months 6, 12, and 24, and the study physician at screening and month 24 for a general health evaluation. The cognitive status of each participant is assessed by a psychologist, and information on health status, socioeconomic factors, and lifestyles is gathered at baseline, 12 months, and 24 months.

The *primary outcome* of the FINGER is cognitive performance measured by modified Neuropsychological Test Battery (mNTB) composite z score evaluating several cognitive domains and Stroop test and Trail Making Test (A and B). The mNTB is an extended version of the original NTB and it is a sensitive measure for mild cognitive changes more typical for AD [26]. The additional tasks are used to detect executive dysfunctions more characteristic for vascular cognitive impairment [27].

Secondary outcomes are: (1) Incidence of dementia and AD. Final diagnoses will be made by a cognitive evaluation board according to standard criteria (DSM-IV [28] and NINCDS-ADRDA [29]). An extended follow-up of at least 7 years is needed to investigate the effect of the intervention on this outcome. (2) Cognition evaluated with mNTB domain z scores (memory, executive functioning, and cognitive speed), executive functioning z score (derived from the Stroop test and Trail Making Test), MMSE, CDR-SB, prospective memory [30], subjective memory, and memory problems perceived by a proxy [31]. (3) Vascular risk factors; (4) cardiovascular and cerebrovascular morbidity and mortality. (5) Dietary intake (food records, food frequency questionnaires). (6) Dietary markers (i.e., erythrocyte fatty acid composition, serum folate, S-B_{12}, homocysteine) and other biomarkers (i.e., inflammation, oxidative stress, lipid and glucose metabolism). (7) Disability (ADCS-ADL questionnaire completed by a proxy). Mobility limitations and the level of physical functioning are assessed with the Short Physical Performance Battery (SPPB; standing balance test, timed sit-to-stand test, 4-m comfortable walking time) [32], grip strength, and 10-m maximal walking time. For about 400 participants in the Helsinki and Vantaa cohorts postural balance is evaluated using force platform (Good Balance; Metitur, Ltd., Finland) measurements, and for 250 participants in Turku maximal isometric and dynamic knee extensor strength measurements are done using the leg extension/curl device (HURlabs, Ltd., Finland). (8) Falls (self-reported within the previous 12 months). (9) Cardiorespiratory fitness, measured for 400 participants by a maximal symptom-limited exercise test on a cycle ergometer. (10) Depressive symptoms (Zung scale) [33]. (11) Health-related quality of life (RAND-36/SF-36 and 15D instruments, [34,35]). (12) Utilization of health resources—questionnaire data [36] and register data. (13) Individuals' experience of participation in the study, inquired at 24 months. All scales have been selected according to recent recommendations (i.e., www.ema.europa.eu) and experiences in Finland.

Exploratory outcomes are brain magnetic resonance imaging (MRI) for about 100 participants in the cohorts from Kuopio, Oulu, Seinäjoki, and Turku, and for 60 participants in the Turku cohort also [^{11}C]PIB and [^{18}F]FDG positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) measures, enabling analyses of AD biomarkers and a study of the newly proposed AD criteria [37,38]. Echocardiography, ultrasound examination of the right carotid artery, measurement of pulse wave velocity, and collection of 24-hour urine for measurements of microalbumin are done for about 200 participants in the Turku cohort. The exploratory outcomes subsamples include the first consecutive participants randomized when imaging became available for the FINGER in the aforementioned centers (equal numbers from the control and intervention groups).

2.5. Statistical considerations

Sample size calculations were based on the expected modified NTB score. Considering previous studies in mild AD [26], an NTB decline of approximately −0.21 z score with an SD of 0.5 would be expected in the control group during 2 years (calculated as half of the decline in mild AD, and with larger SD due to the more heterogeneous FINGER participant group). With 5% significance level and

90% power, the sample size required at the end of the trial is approximately 500 persons per group to detect a 50% difference in change in NTB score between the two groups. In addition, this sample size will have >80% power to detect a smaller difference of 40% in change in NTB score between the two groups. Based on earlier Finnish lifestyle interventions, DR's EXTRA [13] and the Diabetes Prevention Study [12], a drop-out rate of 10% during the trial was assumed, and a starting size of 600 persons per group was therefore considered to be sufficient. During the intervention period, dementia incidence will still be low in this relatively young population (10 per 1000). An extended follow-up (7 years since enrollment for each participant) is planned to evaluate the longer term effects of the intervention on cognition (NTB and dementia/AD). Dementia incidence is estimated at 20 per 1000, giving, at 7 years, 95% power to detect differences expecting the intervention to decrease dementia incidence by 50%.

Preliminary *statistical analyses* will involve the univariate examination of the distribution of each covariate of interest to identify outliers and assess skewness. Besides the mNTB total composite *z* score, domain *z* scores will be created from mNTB components measuring memory, executive functioning, and cognitive speed. An additional *z* score for executive functioning will include: the score difference between Trail Making Test conditions B and A (a purer executive function measure of set shifting); and the score difference between various Stroop test conditions (a purer executive function measure of attention and inhibition). Primary and secondary outcomes will be analyzed using a multilevel model for change with level 1 estimating rate of individual change and level 2 estimating rate of between-person differences in change. The model may also be extended to predict nonlinear and discontinuous change of outcome. When the outcome of interest is binary, such as incidence of dementia/AD, a discrete time hazard regression model will be used. The model may be extended to polynomial effect of time on hazard. In these models, intervention group will be included as covariate. Other time-invariant and time-varying covariates may also be included as predictors. The effects of the intervention on primary and secondary outcomes will also be evaluated in subanalyses stratified by age, gender, baseline cognition, level of risk factors (including *APOE* ε4 genotype), and the level of adherence to the different domains of the intervention. The adherence to each domain will be defined based on the level of participation (divided into three groups: no participation; less than half of the proposed activities; and more than half of the proposed activities).

2.6. Ethics and safety aspects

The FINGER has been approved by the coordinating ethics committee of the hospital district for the Helsinki and Uusimaa region. Participants give their written informed consent before enrollment in the study. The principles of good clinical practice are applied in the intervention. The National Institute for Health and Welfare has patient insurance for all participants. Safety issues of the intervention (especially the exercise component) are carefully considered. The safety committee meets regularly for assessment of any occurring adverse events.

2.7. Data management process

A computerized logistics system created at the National Institute for Health and Welfare (THL) is used to schedule appointments and to follow-up the collected data, including forms and blood samples. The data are collected and sent to the THL without personal identifying information, using number-coded stickers that are unique for each visit. The link between the participant, visit, and code is kept in the logistics system at the THL. Data are analyzed (laboratory samples) or recorded (forms) and stored in the analysis database, where all changes can be tracked.

2.8. Study progress

Starting from September 2009, about 5500 individuals were invited to the FINGER screening examination. Of these, approximately 48% participated. The preliminary analyses show that the nonparticipants had lower education and were older than the participants.

The target of identifying and randomizing 1200 participants was achieved in December 2011. All four intervention domains have been initiated according to schedule for each wave of intervention groups, and the 2-year intervention period will end at the beginning of 2014. Electronic data entry and processing is currently ongoing.

Some baseline characteristics of the first 1118 participants are summarized in Table 3. The mean (SD) age was 68.6 (4.6) years, level of education 10.0 (3.4) years, and MMSE score 26.7 (2.1) points. Vascular risk factors were frequent, indicating a window of opportunity for the intervention: 53.3% of participants had systolic blood pressure (SBP) >140 mm Hg, and 16.1% had diastolic blood pressure (DBP) >90 mm Hg. Of the participants, 42.8% were overweight (body mass index [BMI] 25–30 kg/m^2) and 32.7% obese (BMI >30 kg/m^2). Serum total cholesterol level was >5.0 mmol/L in 53.9% of the participants, high-density lipoprotein (HDL) was <1 mmol/L in 10.3%, and low-density lipoprotein (LDL) was >3 mmol/L in 51.5% of the participants. Impaired fasting glucose (>6.1 mmol/L) was seen in 38.6%.

3. Discussion

The FINGER investigates whether a multidomain intervention can prevent or delay cognitive impairment in an older population at increased risk of cognitive decline. Risk and protective factors are chosen based on the best available knowledge, with focus on simultaneously addressing several such factors to obtain an optimal prevention

Table 3
Some initial characteristics based on the first 1118 randomized participants

	Baseline
Age (years)	68.6 (4.6)
Men/women (%)	53.4/46.6
Education (years)	10.0 (3.4)
MMSE	26.7 (2.1)
SBP (mm Hg)	141.2 (16.3)
DBP (mm Hg)	81.0 (9.3)
LDL-C (mmol/L)	3.09 (0.87)
HDL-C (mmol/L)	1.44 (0.38)
BMI (kg/m^2)	28.8 (4.4)
Fasting glucose (mmol/L)	6.1 (0.9)

effect [6]. An integrative, transdisciplinary approach is ensured by the inclusion of factors shared by AD and other major chronic diseases.

Some positive effects on cognition have been reported by single-domain lifestyle interventions [39,40], but large, long-term intervention studies combining different approaches have not been conducted so far for the prevention of cognitive decline and dementia. Disappointing results of previous trials with single agents in older patients or already cognitively impaired persons have pointed out several key issues, which the FINGER takes into account to the extent possible with the available resources [41]. Inclusion criteria select a population at increased risk of cognitive decline, but without substantial cognitive impairment. Given epidemiologic data linking midlife vascular risk factors to dementia and AD in late life [11], it would have been of interest to include even participants <60 years of age, but this would have required a much larger sample size and longer follow-up time. Recruiting participants from the FINRISK database ensures a truly population-based sample, offering the possibility of extrapolating the results to the general population. In addition, the information on earlier lifestyle and vascular factors from FINRISK offers detailed baseline data for the FINGER, which is very rare in RCTs. The clinical characteristics of the first participants indicate that several vascular risk factors and unhealthy lifestyle–related factors are present, creating a window of opportunity for the intervention. Preliminary findings also suggest that the participants in the FINGER are motivated to follow the study protocol. However, it seems that people in the oldest age groups and those with the highest values on dementia risk score are less likely to participate. A similar trend is often seen in RCTs. Further, cardiovascular disease prevention programs have led to a significant decrease in some vascular risk factors and raised awareness of a healthy lifestyle in Finland [9], and significant differences between intervention and regular health advice groups may be more difficult to detect.

Outcome measures in cognition-related RCTs have long been a matter of debate. Instead of focusing mainly on conversion to dementia, the FINGER uses, as primary outcomes, sensitive neuropsychological tests for mild changes in cognitive performance of both the Alzheimer and vascular types. Another major advantage in the FINGER is the possibility of investigating potential mechanisms behind the effects of the intervention, by detailed biomarker measurements (blood, CSF, MRI, PET) and analyses of patterns of change over time.

Because several chronic diseases among older people have overlapping risk and protective factors, conducting prevention RCTs raises major ethical issues. It is no longer possible to have a traditional control group where such factors (i.e., those known to increase the risk for cardiovascular or cerebrovascular conditions) are left untreated. The control group of the FINGER is given the health advice regularly offered by nurses and physicians in primary care settings. In addition, all participants are recommended to contact their regular physician in case initiation or adjustment of medication is considered necessary.

The FINGER design resulted from carefully balancing these key methodological issues with currently available resources. In theory, the study is powered to detect a 40–50% difference in change in cognitive scores between intervention and control groups. However, in everyday life even a smaller impact on cognitive decline may be important. Results from the FINGER can provide both high-quality scientific knowledge on the effects of a multidomain intervention in older people and some of the means to translate this knowledge into practice. The broad range of secondary outcomes enables the estimation of total benefit and cost-effectiveness of the intervention. Preliminary analyses in a Swedish/Finnish setting have already indicated that preventive interventions in dementia can be cost-effective [42], and similar analyses based on the FINGER data can provide useful information for health-policy decision-makers. Using experiences from the application of the diabetes prevention programs in several countries [43], findings from the FINGER could be extended beyond Finland as well. Lessons learned from this multidomain intervention trial will help in the planning and conducting of future larger interventions and in the implementation of preventive strategies in at-risk populations, while simultaneously facilitating international collaborations and future interoperability of data among researchers.

Together with two other large multidomain prevention RCTs (www.edpi.org), the FINGER is at one end of the current spectrum of intervention trials in AD/cognitive impairment. At the other end are treatment RCTs using disease-modifying drugs (i.e., anti-amyloid therapy) in genetically at-risk groups or those with an established biomarker burden [44]. The shift toward presymptomatic and pre-dementia stages of AD has brought prevention and treatment RCTs much closer to each other than before.

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RESEARCH IN CONTEXTTEXT

1. **Systematic review:** We identified larger multidomain randomized, controlled trials (RCTs) by searches of ClinicalTrials.gov and International Standard Randomized Controlled Trial Number Register. Search terms: "prevention of dementia OR prevention of Alzheimer disease." Further selection criteria: primary outcome dementia/cognitive impairment; at least two combined interventions (exercise, cognitive, or social activities; diet; drug/dietary supplement; etc.); age _40 years; duration _1 year; size _500 participants. Criteria were based on National Institutes of Health Q4 (NIH) report recommendations (6). We identified two ongoing studies, the Multidomain Alzheimer Preventive Trial (MAPT, NCT00672685) and Prevention of Dementia by Intensive Vascular Care (Pre-DIVA, ISRCTN29711771). Results are not yet available.
2. **Interpretation:** The population-based FINGER study addresses whether a multidomain intervention (nutritional guidance; exercise, cognitive and social activities; and vascular factors management) can prevent or delay cognitive impairment in the elderly at increased risk of cognitive decline.
3. **Future directions:** FINGER experiences can be used in planning and conducting larger, multinational dementia prevention RCTs.

FINGER study group

The FINGER study group is comprised of the following individuals: main investigator: Miia Kivipelto, MD, PhD; coordination: Satu Ahtiluoto, MD, and Tiia Ngandu, MD, PhD; subcohort leaders: Miia Kivipelto (Helsinki cohort), Tiina Laatikainen, MD, PhD (Vantaa cohort), Hilkka Soininen, MD, PhD (Kuopio cohort), Timo Strandberg, MD, PhD (Oulu cohort), Antti Jula, MD, PhD (Turku cohort), and Jaakko Tuomilehto, MD, PhD (Seinäjoki cohort); statistical analyses: Markku Peltonen, PhD, Risto Sippola, MSc, and Esko Levälahti, MSc; intervention supervision: Jaana Lindström, PhD, Jenni Lehtisalo, MSc (nutrition component), Rainer Rauramaa, MD, PhD, Satu Pajala, PhD (physical exercise component), Tuomo Hänninen, PhD, Tiia Ngandu (cognitive component), Timo Strandberg, Riitta Antikainen, MD, PhD, and Jaakko Tuomilehto (vascular risk factor component). The cognitive component was designed in collaboration with Lars Bäckman (Karolinska Institutet, Sweden) and Anna Stigsdotter-Neely (Umeå University, Sweden). Other study members and collaborators include: Raimo Sulkava, MD, PhD, Alina Solomon, MD, PhD, Teemu Paajanen, PhD, Marko Grönholm, MSc, Francesca Mangialasche, MD, PhD, and Juha Rinne MD, PhD.

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