



Featured Article

Multidomain lifestyle intervention benefits a large elderly population at risk for cognitive decline and dementia regardless of baseline characteristics: The FINGER trial

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Abstract

Introduction: The 2-year Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) multidomain lifestyle intervention trial (NCT01041989) demonstrated beneficial effects on cognition. We investigated whether sociodemographics, socioeconomic status, baseline cognition, or cardiovascular factors influenced intervention effects on cognition.

Methods: The FINGER recruited 1260 people from the general Finnish population (60–77 years, at risk for dementia). Participants were randomized 1:1 to multidomain intervention (diet, exercise, cognition, and vascular risk management) and regular health advice. Primary outcome was change in cognition (Neuropsychological Test Battery z-score). Prespecified analyses to investigate whether participants' characteristics modified response to intervention were carried out using mixed-model repeated-measures analyses.

Results: Sociodemographics (sex, age, and education), socioeconomic status (income), cognition (Mini-Mental State Examination), cardiovascular factors (body mass index, blood pressure, cholesterol, fasting glucose, and overall cardiovascular risk), and cardiovascular comorbidity did not modify response to intervention (*P*-values for interaction > .05).

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Conclusions: The FINGER intervention was beneficial regardless of participants' characteristics and can thus be implemented in a large elderly population at increased risk for dementia.

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

1. Introduction

Alzheimer's disease (AD) and dementia are a global public health priority [1], and prevention has been highlighted as a pivotal component to reduce the burden of AD and dementia [2,3]. It has been estimated that up to a third of all AD cases can be attributed to common modifiable risk factors, including midlife hypertension and obesity, low educational level, diabetes, low physical activity, depression, and smoking [4], and a reduction of these risk factors would have a significant impact on the disease prevalence [4]. The current generation of randomized controlled prevention trials recognizes this multifactorial nature of AD and dementia and focuses thus on multidomain interventions. Targeting several risk factors of AD and dementia simultaneously will likely lead to better preventive effects [2,5]. Recently, several large multidomain lifestyle-based trials aiming to prevent cognitive decline and dementia have been initiated [5–9], and some have already been completed [10–14]. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is the first large, long-term randomized controlled trial demonstrating that a multidomain lifestyle intervention consisting of nutritional guidance, exercise, cognitive training, and management of vascular risk factors has beneficial effects on cognition [10].

As recently emphasized by The Lancet Neurology Commission, immediate actions in dementia prevention need to be taken and up-to-date research knowledge as well as effective prevention programs must be put into practice promptly [2]. To facilitate the effective and feasible implementation of successful prevention programs, such as the FINGER trial, into clinical practice, it is of great importance to identify individuals most likely to benefit from the interventions and potentially tailor the interventions to different target populations with different characteristics [2,5]. However, considering the limited number of completed, large long-term dementia prevention trials, it is largely unknown, whether certain subgroups of trial participants are more or less prone to benefit from these types of interventions. The FINGER trial provides the first opportunity to explore whether the positive response to a multidomain lifestyle intervention is modified by characteristics of the trial participants. In this study, prespecified subgroup analyses were carried out to investigate specifically whether participants' sociodemographic characteristics, socioeconomic status, cognitive performance, and level of cardiovascular risk at baseline influenced the intervention effects on cognition.

2. Methods

2.1. Trial design and participants

FINGER is a 24-month multicenter randomized controlled trial (ClinicalTrials.gov identifier NCT01041989), which was completed in February 2014. The FINGER trial included 1260 individuals aged 60–77 years. Participants were screened from Finnish observational population-based studies and had a Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Dementia Risk Score [15] of ≥ 6 , indicating increased risk for dementia later in life. In addition, participants were required to meet at least one of the following criteria: Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [16], word list memory task result ≤ 19 words (maximum score 30), CERAD word list recall $\leq 75\%$ (maximum 100%), or Mini-Mental State Examination (MMSE) [17] score of 20–26 (maximum score 30). These selection criteria identified cognitively healthy older individuals whose cognitive abilities were at the mean level or slightly lower than expected based on age [18]. Exclusion criteria included diagnosed dementia, suspected dementia at screening visit, conditions affecting participation in the intervention including impaired vision, hearing or ability to communicate, other conditions as judged by the physician, and participation in another trial. The design of the trial and selection of trial participants have been described in detail elsewhere [19,20].

2.2. Trial protocol

Participants were randomized in a 1:1 ratio into the multidomain lifestyle intervention group or the control group receiving general health advice. Informed consent was obtained from all participants. To maintain double-blinding as much as possible, the randomization status was not disclosed to participants, participants were instructed not to discuss the intervention with each other, and the outcome evaluators were blinded. Both the intervention and the control group participants visited the study nurse at the screening and baseline visits and at 6, 12, and 24 months. In addition, all participants met the study physician at the screening visit and at 24 months. At baseline, both groups received information and advice on healthy diet and activities that support management of vascular risk factors. During the trial, the intervention group engaged additionally in a multidomain lifestyle intervention program focusing on four components: nutrition, exercise, cognitive training, and

management of vascular risk factors. Nutritional guidance was based on the national recommendations [21], and it was given by nutritionists both individually and in groups. The exercise program was based on international guidelines [22] and previous studies [23]. It involved muscle strength training and aerobic exercise, and it was led by physiotherapists. Cognitive training was based on protocols of previous trials [24] and targeted executive function, working memory, episodic memory, as well as mental speed. It consisted of group discussions and individual computer-based training sessions. For the management of vascular risk factors, national guidelines for hypertension [25], dyslipidemia [26], and diabetes [27] were followed. Participants in the intervention group met the nurse at 3, 9, and 18 months and the physician at 3, 6, and 12 months for measurements and further advice. Medications were not prescribed within the scope of this trial; however, participants were urged to seek medical attention if necessary. The detailed trial procedures have been described elsewhere [20].

2.3. Cognitive outcomes

Primary outcome of the trial was change in overall cognitive performance measured with a total score of an extended version of the Neuropsychological Test Battery (NTB) [28]. The NTB total score represents a composite score consisting of results from 14 cognitive tests (see below). Test results were calculated as standardized z-scores with higher scores demonstrating better performance. Secondary cognitive outcomes included domain-specific NTB z-scores for executive functioning, processing speed, and memory. The executive functioning domain included the following five test scores: Category Fluency Test, digit span, Concept Shifting Test (condition C), Trail Making Test (shifting score: time in part B – time in part A), and a 40-stimulus version of the Stroop test (interference score: time in part 3 – time in part 2). The processing speed domain consisted of three tests: Letter Digit Substitution Test, Concept Shifting Test (condition A), and Stroop test (condition 2). The memory domain included six test scores: visual-paired associates test (immediate and delayed recall), Logical Memory Test (immediate and delayed recall), and Word List Memory Test (learning and delayed recall). Cognitive assessments were performed by psychologists at baseline, 12, and 24 months. Dropped out participants were invited to the final assessment at 24 months.

2.4. Baseline measurements

Baseline characteristics of the trial participants investigated as modifiers of intervention efficacy included sociodemographic characteristics (age, sex, and years of education), socioeconomic status (annual gross household income), cognitive performance (MMSE score), cardiovascular risk factors (systolic and diastolic blood pressure, body mass index (BMI), total cholesterol, low-density lipo-

protein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose concentrations), overall cardiovascular risk, and presence of cardiovascular comorbidity. At baseline, information about participants' age and sex was obtained from registers, whereas the number of years of formal education and annual gross household income were self-reported data. Annual gross household income was an ordinal variable with nine categories: 0–10,000 €; 10,001–20,000 €; 20,001–30,000 €; 30,001–40,000 €; 40,001–50,000 €; 50,001–60,000 €; 60,001–70,000 €; 70,001–80,000 €; and >80,000 €. MMSE was performed by study nurses at the screening visit. Participants' height and weight as well as systolic and diastolic blood pressure were measured by the nurse at the baseline visit. BMI was calculated by dividing the weight in kilograms by the squared height in meters. Blood pressure was measured with a validated automatic device (Microlife WatchBP Office) twice in a sitting position using the right arm. Mean value of two measurements was calculated. The separated serum and plasma samples were frozen and sent to the laboratory of the National Institute for Health and Welfare in Finland where serum cholesterol and plasma glucose concentrations were determined enzymatically using commercial reagents from Abbott Laboratories on a clinical chemistry analyzer, Architect c8000 (Abbott Laboratories, Abbott Park, IL, USA).

Information about the presence of cardiovascular comorbidity was based on self-reported data collected by study physician at the screening visit, and it was defined as having at least one of the following: history of stroke, history of myocardial infarction, or diagnosis of any type of diabetes. An overall cardiovascular risk was calculated for the participants using the widely used FINRISK cardiovascular risk score developed for the Finnish population, including age, sex, serum total cholesterol, systolic blood pressure, HDL-C, smoking status, diabetes, and family history of infarction/stroke [29,30]. Family history was not taken into account, as this information was not available for the participants. Each participant's overall cardiovascular risk score was divided by the overall cardiovascular risk score calculated for a sex- and age-matched person without any cardiovascular risk factors, as defined by Vartiainen et al. (serum cholesterol 4.5 mmol/l, systolic blood pressure 120 mmHg, HDL-C 1.32 mmol/l, nonsmoker, no diabetes) [29,30].

2.5. Statistical analysis

Zero-skewness log-transformation was applied to all skewed NTB components, and z-scores for each test at each time point were standardized to the baseline mean and standard deviation. NTB total score and the domain-specific z-scores for executive functioning, processing speed, and memory were calculated by averaging z-scores of individual tests. To calculate the NTB total score, a minimum of 8/14 NTB components were required: at least 3/5 test scores for executive functioning, 3/6 test scores for

memory, and 2/3 test scores for processing speed. Mixed-model repeated-measures analyses with maximum likelihood estimation (xtmixed command in Stata) were used to analyze change in cognitive performance as a function of randomization group (dichotomous variable coded as 0 for control and 1 for intervention), time (continuous variable coded as 0 for baseline, 1 for 12-month visit, and 2 for 24-month visit), characteristic, and group \times time \times characteristic interaction. The characteristics were either dichotomous (sex, presence of cardiovascular comorbidity, and annual household income which was dichotomized based on median value) or continuous variables (age, education, MMSE, cardiovascular risk factors, and overall cardiovascular risk). Log-transformation was applied to skewed continuous variables.

Testing subgroup-treatment effect interactions is considered the most reliable statistical method to perform subgroup analyses [31]. In this study, P values for the coefficients for the group \times time \times characteristic interactions are reported as the main result. In addition, estimates for the difference between intervention and control groups (95% confidence interval) per year within each subgroup are presented. To determine these subgroup estimates for continuous variables, the variables were dichotomized based on median values, and a model with group \times time \times dichotomous variable with lincom postestimation command after xtmixed was used. Results are reported for the modified intention-to-treat (mITT) population (all randomized participants with at least one outcome assessment after the baseline visit). Sensitivity analyses were performed for the intention-to-treat (ITT) population (all randomized participants). Stata 14 software was used for all analyses, and the level of statistical significance was set at $<.05$. All analyses were prespecified [20] and adjusted for study site.

3. Results

Of the 2654 screened individuals, 1260 were randomized into the intervention group ($n = 631$) or the control group ($n = 629$). The 12- and 24-month assessments were completed by 93% and 88% of all randomized participants, respectively. In total, 1190 participants (94%) completed at least one assessment after the baseline visit (mITT population). 153 individuals dropped out during the trial. The mean age of the participants was 69.3 years, and 46.3% of them were women. On average, the participants had 10.0 years of education, and median income was 30,000 €. As expected based on the inclusion criteria, participants had an elevated risk for cardiovascular disease (CVD) and dementia. There were no significant differences between the intervention and control groups in the participants' characteristics at baseline (Table 1).

The previously published main results of the FINGER trial showed that the intervention had a significant beneficial effect on the primary cognitive outcome (change in NTB total score) ($P = .030$), as well as on most secondary cognitive outcomes,

including executive functioning ($P = .039$) and processing speed ($P = .029$) [10]. Fig. 1 shows that the intervention effects on the primary cognitive outcome do not vary by sociodemographic factors (age, sex, and education), socioeconomic status (household income), or baseline cognitive performance (MMSE score) (P -values for interaction $>.05$). Furthermore, neither the individual cardiovascular risk factors (blood pressure, BMI, cholesterol levels, and plasma glucose concentration) nor the overall cardiovascular risk modify the response to the intervention (P values for interaction $>.05$, Fig. 1). Beneficial intervention effects on the primary cognitive outcome were also observed regardless of the presence of cardiovascular comorbidity, defined as having history of either stroke, myocardial infarction, or diabetes (P value for interaction = .63, Fig. 1). Similar results were obtained in the sensitivity analysis for the ITT population (Supplementary Table A.1). Moreover, a similar pattern was observed for the secondary cognitive outcomes (Supplementary Table A.2). None of the participants' characteristics influenced the intervention effects on executive functioning, processing speed, or memory (P values for interaction $>.05$), apart from diastolic blood pressure that seemed to modify the intervention effects on processing speed so that the effect was more pronounced among those with lower diastolic blood pressure ($P = .03$) (Supplementary Table A.2).

4. Discussion

The aim of this study was to investigate whether sociodemographic characteristics, socioeconomic status, cognitive performance, or level of cardiovascular risk at baseline modify the effects of a multidomain lifestyle intervention on cognition in the FINGER trial. Results suggest that the previously reported beneficial intervention effects on cognition [10] do not seem to vary by age, sex, cognitive performance, level of education, household income, cardiovascular risk factors, or presence of cardiovascular comorbidity. Thus, the applicability of the FINGER intervention is not significantly limited by any of the abovementioned factors in an elderly general Finnish population at increased risk for CVD and dementia.

The choice of an at-risk target population for the FINGER trial might have accounted for the observed overall beneficial intervention effects on cognitive outcomes. Selection of the trial population was based on the CAIDE Dementia Risk Score [15] and CERAD [16] neuropsychological testing. These criteria selected older people from the general Finnish population with several risk factors common for CVD and dementia and cognitive performance at the mean level or slightly lower than expected for this age group [15,18]. Findings of this study suggest that no further stratification of this at-risk population is necessary to obtain beneficial intervention effects, which in turn indicates that the selection of the target population for the FINGER trial has been successful.

Table 1
Baseline characteristics of the trial population (mITT)

Characteristics	Participants with information available	Intervention group (n = 591)	Control group (n = 599)
Sociodemographic and socioeconomic characteristics			
Age at baseline, years	1190	69.5 (4.6)	69.2 (4.7)
Number of women	1190	267 (45.2)	284 (47.4)
Education, years	1188	10.0 (3.4)	10.0 (3.4)
Annual household income, €	1138		
0–20,000		135 (23.9)	125 (21.9)
20,001–30,000		139 (24.6)	153 (26.7)
30,001–40,000		120 (21.2)	121 (21.1)
40,001–50,000		71 (12.6)	67 (11.7)
>50,000		100 (17.7)	107 (18.6)
Vascular factors			
Systolic blood pressure, mmHg	1179	140.1 (16.7)	139.8 (15.7)
Diastolic blood pressure, mmHg	1179	80.5 (9.6)	80.1 (9.3)
Body mass index, kg/m ²	1179	28.3 (4.5)	28.1 (4.9)
Serum total cholesterol, mmol/L	1186	5.2 (1.0)	5.2 (1.0)
LDL-C, mmol/L	1186	3.1 (0.8)	3.1 (0.9)
HDL-C, mmol/L	1186	1.4 (0.4)	1.5 (0.4)
Fasting plasma glucose, mmol/L	1188	6.1 (0.8)	6.1 (1.0)
Overall cardiovascular risk	1164	1.4 [0.3–8.2]	1.4 [0.3–8.9]
Cardiovascular comorbidity			
Presence of cardiovascular comorbidity	1181	118 (20.1)	126 (21.2)
Cognition			
NTB total score	1190	−0.03 (0.55)	0.03 (0.59)
Executive functioning	1189	−0.03 (0.66)	0.03 (0.69)
Memory	1190	−0.03 (0.68)	0.03 (0.66)
Processing speed	1190	−0.02 (0.78)	0.05 (0.84)
MMSE score	1187	26.7 (2.0)	26.8 (2.0)

Abbreviations: CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; mITT, modified intention-to-treat; MMSE, Mini-Mental State Examination; NTB, Neuropsychological Test Battery; SD, standard deviation.

NOTE. Data are n (%), mean (SD), or median [range]. Baseline characteristics are shown for the mITT population (participants with at least one outcome assessment after the baseline visit). Overall cardiovascular risk is based on the FINRISK score and represents the risk of developing CVD compared to a person with the same age and sex but low risk. Presence of cardiovascular comorbidity is defined as having at least one of the following: history of stroke, history of myocardial infarction, or diabetes.

Contrary to the FINGER trial, the other two large long-term multidomain lifestyle-based dementia prevention trials completed so far did not specifically select a population at high risk for CVD and dementia. The Prevention of Dementia by Intensive Vascular Care trial recruited an unselected group of older people from general practices [11], whereas the Multidomain Alzheimer Preventive Trial targeted older individuals who were either frail or experienced subjective memory complaints [14]. Disappointingly, both trials failed to demonstrate a positive effect for the intervention: differences in neither incidence of dementia nor cognitive performance were observed between intervention and control groups [11,14]. However, post hoc analyses carried out in both trials revealed beneficial intervention effects in certain high-risk subgroups. In the Prevention of Dementia by Intensive Vascular Care trial, the intensive vascular care seemed to benefit particularly participants with untreated hypertension [11]. Similarly, the combination of multidomain lifestyle intervention and omega-3 polyunsaturated fatty acid supplementation administered in the Multidomain Alzheimer Preventive Trial had potentially positive effects on cognition among participants with a CAIDE Dementia Risk Score ≥ 6 , indicating an elevated risk for CVD and

dementia [14]. These findings indicate that cardiovascular risk burden is a potential effect modifier in multidomain lifestyle dementia prevention trials. Lifestyle-based prevention trials of other common chronic diseases, such as diabetes, further support the concept of selecting an at-risk population for prevention trials. In the Finnish Diabetes Prevention Study, the intervention seemed to be most effective among participants with a high Finnish Diabetes Risk Score [32]. Furthermore, results of the Diabetes Prevention Program conducted in the USA showed that the absolute risk reduction in diabetes was greater for high-risk participants compared with low-risk participants in the intervention group, even if there was no significant difference in the relative risk reduction [33]. Taken together, these findings and the results of this study support the notion that targeting at-risk individuals might be the optimal strategy for interventions aiming to prevent or postpone cognitive impairment and dementia. However, at the same time, considering the experiences from CVD prevention [34–36], a population-based strategy to change risk factor levels might have greatest impact on public health.

The strengths of the FINGER trial include the large sample size, longer duration than in most dementia

Baseline characteristics (N Intervention/ N Control)	Estimate for difference between intervention and control groups per year (95% CI)	P-value for interaction*	
Sex	Men (324/315) Women (267/284)	0.022 (-0.005 – 0.050) 0.022 (-0.007 – 0.051)	0.98
Age, years	< 70 (314/336) ≥ 70 (277/263)	0.016 (-0.009 – 0.043) 0.033 (0.004 – 0.062)	0.86
Education, years	< 9 (253/263) ≥ 9 (337/335)	0.016 (-0.014 – 0.046) 0.027 (0.001 – 0.053)	0.73
MMSE score	< 27 (260/244) ≥ 27 (329/354)	0.034 (0.003 – 0.065) 0.014 (-0.012 – 0.040)	0.41
Annual household income, €	< 30 000 (274/278) ≥ 30 000 (291/295)	0.014 (-0.015 – 0.043) 0.033 (0.005 – 0.061)	0.35
Body mass index, kg/m ²	< 27.4 (286/300) ≥ 27.4 (301/292)	0.038 (0.010 – 0.067) 0.004 (-0.024 – 0.032)	0.28
Systolic blood pressure, mmHg	< 140 (289/294) ≥ 140 (298/298)	0.005 (-0.023 – 0.033) 0.037 (0.008 – 0.065)	0.63
Diastolic blood pressure, mmHg	< 80 (277/296) ≥ 80 (310/296)	0.029 (0.0006 – 0.058) 0.012 (-0.016 – 0.040)	0.48
Serum total cholesterol, mmol/l	< 5.1 (303/296) ≥ 5.1 (288/299)	0.008 (-0.020 – 0.036) 0.037 (0.008 – 0.065)	0.25
LDL-C, mmol/l	< 3.04 (302/292) ≥ 3.04 (289/303)	0.015 (-0.013 – 0.043) 0.030 (0.001 – 0.058)	0.31
HDL-C, mmol/l	< 1.4 (304/300) ≥ 1.4 (287/295)	0.017 (-0.010 – 0.045) 0.028 (-0.001 – 0.056)	0.33
Fasting plasma glucose, mmol/l	< 5.9 (289/300) ≥ 5.9 (302/297)	0.013 (-0.015 – 0.041) 0.032 (0.004 – 0.060)	0.89
Presence of cardio- vascular comorbidity	No (469/468) Yes (118/126)	0.024 (0.001 – 0.046) 0.017 (-0.032 – 0.055)	0.63
Overall cardiovascular risk	< 1.4 (282/285) ≥ 1.4 (299/298)	0.015 (-0.013 – 0.044) 0.027 (-0.001 – 0.055)	0.60

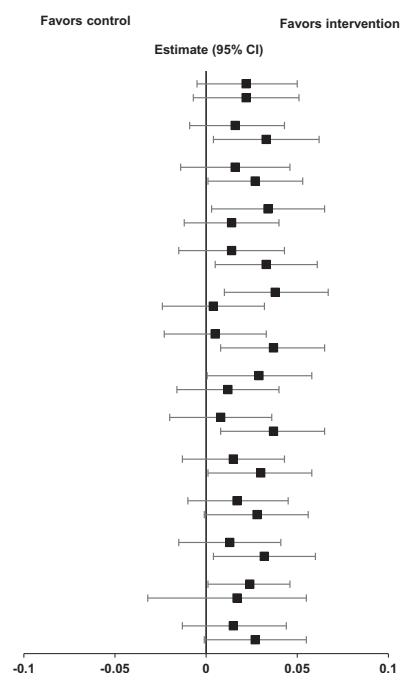


Fig. 1. Influence of sociodemographic factors, socioeconomic status, cognitive performance, and cardiovascular factors on intervention effects on the primary cognitive outcome (change in NTB total score). **P* values are shown for interactions where baseline characteristics are continuous variables (except for sex, household income, and presence of cardiovascular comorbidity). Mixed-model repeated-measures analyses were used to investigate whether the baseline characteristics of the participants influenced intervention effects on cognitive performance (group \times time \times characteristic interactions). Nonsignificant *P* values for interaction ($P > .05$) indicate that the intervention effects on cognition do not vary by baseline characteristics. Characteristics were either dichotomous (sex, presence of cardiovascular comorbidity, and annual household income that was dichotomized based on median value) or continuous variables (age, education, MMSE, cardiovascular risk factors, and overall cardiovascular risk). To determine estimates for the difference between intervention and control groups per year within each subgroup, the continuous variables were dichotomized based on median values and mixed-models repeated-measures analyses were performed (group \times time \times dichotomous variable). A positive value of the estimate for the difference between intervention and control groups indicates that the effect is in favor of the intervention group. Data are based on all participants with at least one postbaseline measurement (mITT population). Overall cardiovascular risk is based on the FINRISK score and represents the risk of developing CVD compared to a person with the same age and sex but low risk. Presence of cardiovascular comorbidity is defined as having at least one of the following: history of stroke, history of myocardial infarction, or diabetes. Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; mITT, modified intention-to-treat; MMSE, Mini-Mental State Examination; NTB, Neuropsychological Test Battery.

prevention trials, thorough randomization and blinding, detailed outcome assessments, and high-quality data collection. All variables investigated in this study as potential modifiers of intervention efficacy were available for more than 95% of the participants. All subgroup analyses conducted in this study were also prespecified [20]. The main limitation of this study is lack of statistical power, which is why the results should be interpreted with caution. The false negative rate for tests of subgroup-treatment effect interactions is often high, as only few trials are powered to detect subgroup effects reliably [31]. Furthermore, the subgroups investigated here are not independent. Thus, an impact of the participant's characteristics on the intervention effects cannot be fully excluded; however, it is likely that any clinically relevant heterogeneity of treatment effect would have been detected. As subgroup analyses often falsely suggest lack of treatment effect in certain subgroups when the trial shows overall benefit [31], the consistency of positive intervention effect across subgroups (positive estimates

for difference between intervention and control groups, even if sometimes nonsignificant) observed in this study supports the notion that lack of statistical power has not significantly distorted the results.

The fact that *P* values for subgroup-treatment interactions were statistically nonsignificant but significant estimates for difference between intervention and control groups were observed in some subgroups might suggest that while the intervention benefits a large elderly population, certain subgroups of people might be particularly responsive. This conclusion is in line with the initial hypothesis that people at highest risk for cognitive decline and dementia based on higher age, lower MMSE, and presence of vascular risk factors are likely to benefit most from the FINGER intervention [19]. Although the results of this study may seem contradictory for some vascular risk factors (e.g., significant estimates were observed for participants with higher systolic blood pressure and cholesterol but lower BMI and diastolic blood pressure), they might actually support this assumption, since the strength and

direction of association of several vascular and metabolic risk factors with increased risk of cognitive decline and dementia has been shown to vary across the lifespan [2]. However, this should be explored further in larger trials and meta-analyses to ensure sufficient statistical power.

The extended FINGER follow-up trial will provide additional information on the long-term effects of the intervention. It will also facilitate further analyses of responsiveness to the intervention by various participants' characteristics. However, there is an immediate need to put effective interventions and prevention programs into practice [2]. In addition to being safe, well tolerated, and feasible as previously shown [10], the present study demonstrates that the applicability of the FINGER intervention does not seem to be limited by age, sex, education, socioeconomic status, cognitive performance, or level of cardiovascular risk. Moreover, it is encouraging that not only older people with vascular risk factors but also those with history of CVD are likely to benefit from the multidomain lifestyle intervention. Considering that in terms of cardiovascular/dementia risk profile, the FINGER trial population is a fairly representative sample of the general elderly Finnish population [19], these results further underline the feasibility of the FINGER intervention and support its implementation in clinical practice.

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Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jalz.2017.09.006>.

RESEARCH IN CONTEXT

1. Systematic review: The authors searched PubMed for randomized controlled trials to prevent cognitive impairment or dementia, which target multiple lifestyle factors simultaneously. Several ongoing and completed trials were identified; however, only two large long-term dementia prevention trials have been conducted and reported subgroup analyses. These studies are appropriately cited.
2. Interpretation: Our findings suggest that the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability multidomain lifestyle intervention has beneficial effects on cognition regardless of participants' age, sex, education, socioeconomic status, baseline cognitive performance, and level of cardiovascular risk.
3. Future directions: Our manuscript proposes that a Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability–type intervention works among persons at risk for dementia from general population. Future research should investigate if the intervention works in other target groups (e.g., memory clinic patients) or cultural and geographical settings. Larger trials could help identify participants who may need a more tailored intervention approach based on their risk profile to achieve optimal effect.

References

- [1] World Health Organization and Alzheimer's Disease International. *Dementia: a public health priority*. Geneva: World Health Organization; 2012.
- [2] Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol* 2016;15:455–532.
- [3] Shah H, Albanese E, Duggan C, Rudan I, Langa KM, Carrillo MC, et al. Research priorities to reduce the global burden of dementia by 2025. *Lancet Neurol* 2016;15:1285–94.
- [4] Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol* 2014;13:788–94.
- [5] Andrieu S, Coley N, Lovestone S, Aisen PS, Vellas B. Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions. *Lancet Neurol* 2015;14:926–44.
- [6] Daly RM, Gianoudis J, Prosser M, Kidgell D, Ellis KA, O'Connell S, et al. The effects of a protein enriched diet with lean red meat combined with a multi-modal exercise program on muscle and cognitive health and function in older adults: study protocol for a randomised controlled trial. *Trials* 2015;16:339.
- [7] Rovner BW, Casten RJ, Hegel MT, Leiby BE. Preventing cognitive decline in older African Americans with mild cognitive impairment: design and methods of a randomized clinical trial. *Contemp Clin Trials* 2012;33:712–20.

- [8] Gregory MA, Gill DP, Shellington EM, Liu-Ambrose T, Shigematsu R, Zou G, et al. Group-based exercise and cognitive-physical training in older adults with self-reported cognitive complaints: The Multiple-Modality, Mind-Motor (M4) study protocol. *BMC Geriatr* 2016;16:17.
- [9] Hardman RJ, Kennedy G, Macpherson H, Scholey AB, Pipingas A. A randomised controlled trial investigating the effects of Mediterranean diet and aerobic exercise on cognition in cognitively healthy older people living independently within aged care facilities: the Lifestyle Intervention in Independent Living Aged Care (LIILAC) study protocol [ACTRN12614001133628]. *Nutr J* 2015;14:53.
- [10] Ngandu T, Lehtisalo J, Solomon A, Levalahti E, Ahtiluoto S, Antikainen R, et al. 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. *Lancet* 2015;385:2255–63.
- [11] Moll van Charante EP, Richard E, Eurelings LS, van Dalen JW, Ligthart SA, van Bussel EF, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet* 2016;388:797–805.
- [12] Lam LC, Chan WC, Leung T, Fung AW, Leung EM. Would older adults with mild cognitive impairment adhere to and benefit from a structured lifestyle activity intervention to enhance cognition? A cluster randomized controlled trial. *PLoS One* 2015;10:e0118173.
- [13] Lee KS, Lee Y, Back JH, Son SJ, Choi SH, Chung YK, et al. Effects of a multidomain lifestyle modification on cognitive function in older adults: an eighteen-month community-based cluster randomized controlled trial. *Psychother Psychosom* 2014;83:270–8.
- [14] Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol* 2017;16:377–89.
- [15] Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol* 2006;5:735–41.
- [16] Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* 1989;39:1159–65.
- [17] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
- [18] Hanninen T, Pulliainen V, Sotaniemi M, Hokkanen L, Salo J, Hietanen M, et al. Early detection of cognitive changes in memory diseases: new cut-off scores for the Finnish version of CERAD neuropsychological battery. *Duodecim* 2010;126:2013–21.
- [19] Ngandu T, Lehtisalo J, Levalahti E, Laatikainen T, Lindstrom J, Peltonen M, et al. Recruitment and baseline characteristics of participants in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)-a randomized controlled lifestyle trial. *Int J Environ Res Public Health* 2014;11:9345–60.
- [20] Kivipelto M, Solomon A, Ahtiluoto S, Ngandu T, Lehtisalo J, Antikainen R, et al. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): study design and progress. *Alzheimers Dement* 2013;9:657–65.
- [21] National Nutrition Council. Finnish nutrition recommendations: diet and physical activity in balance. Helsinki: Edita Publishing; 2005.
- [22] Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation* 2007;116:1094–105.
- [23] Komulainen P, Kivipelto M, Lakka T, Savonen K, Hassinen M, Kiviniemi V, et al. Exercise, fitness and cognition – a randomised controlled trial in older individuals: The DR's EXTRA study. *Eur Geriatr Med* 2010;1:266–72.
- [24] Dahlin E, Neely AS, Larsson A, Backman L, Nyberg L. Transfer of learning after updating training mediated by the striatum. *Science* 2008;320:1510–2.
- [25] Working group appointed by the Finnish Medical Society Duodecim and the Finnish Hypertension Society. Hypertension: Current care summary. Helsinki: The Finnish Medical Society Duodecim; 2009.
- [26] Working group set up by the Finnish Medical Society Duodecim and Finnish Society of Internal Medicine. Dyslipidaemias: Current care summary. Helsinki: The Finnish Medical Society Duodecim; 2009.
- [27] Working group appointed by the Finnish Medical Society Duodecim and the Medical Advisory Board of the Finnish Diabetes Society. Diabetes: Current care summary. Helsinki: The Finnish Medical Society Duodecim; 2007.
- [28] Harrison J, Minassian SL, Jenkins L, Black RS, Koller M, Grundman M. A neuropsychological test battery for use in Alzheimer disease clinical trials. *Arch Neurol* 2007;64:1323–9.
- [29] Vartiainen E, Laatikainen T, Peltonen M, Puska P. Predicting coronary heart disease and stroke: The FINRISK Calculator. *Glob Heart* 2016;11:213–6.
- [30] Vartiainen E, Laatikainen T, Salomaa V, Jousilahti P, Peltonen M, Puska P. Sydäninfarkti- ja aivohalvauksien arviointi FINRISKI-tutkimuksessa. *Suomen Lääkärilehti* 2007;62:4507–13.
- [31] Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. *Lancet* 2005;365:176–86.
- [32] Lindstrom J, Peltonen M, Eriksson JG, Aunola S, Hamalainen H, Ilanne-Parikka P, et al. Determinants for the effectiveness of lifestyle intervention in the Finnish Diabetes Prevention Study. *Diabetes Care* 2008;31:857–62.
- [33] Sussman JB, Kent DM, Nelson JP, Hayward RA. Improving diabetes prevention with benefit based tailored treatment: risk based reanalysis of Diabetes Prevention Program. *BMJ* 2015;350:h454.
- [34] Emberson J, Whincup P, Morris R, Walker M, Ebrahim S. Evaluating the impact of population and high-risk strategies for the primary prevention of cardiovascular disease. *Eur Heart J* 2004;25:484–91.
- [35] Jousilahti P, Vartiainen E, Pekkanen J, Tuomilehto J, Sundvall J, Puska P. Serum cholesterol distribution and coronary heart disease risk: observations and predictions among middle-aged population in eastern Finland. *Circulation* 1998;97:1087–94.
- [36] Jousilahti P, Laatikainen T, Peltonen M, Borodulin K, Mannisto S, Jula A, et al. Primary prevention and risk factor reduction in coronary heart disease mortality among working aged men and women in eastern Finland over 40 years: population based observational study. *BMJ* 2016;352:i721.