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CLINICAL RESEARCH
Clinical trials

Effect of a multi-domain lifestyle intervention on cardiovascular risk in older people: the FINGER trial

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Aims Joint prevention of cardiovascular disease (CVD) and dementia could reduce the burden of both conditions. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) demonstrated a beneficial effect on cognition (primary outcome) and we assessed the effect of this lifestyle intervention on incident CVD (pre-specified secondary outcome).

Methods and results FINGER enrolled 1259 individuals aged 60–77 years (ClinicalTrials.gov NCT01041989). They were randomized (1:1) to a 2-year multi-domain intervention with diet, physical and cognitive activity, and vascular monitoring ($n = 631$), or general health advice ($n = 628$). National registries provided data on CVD including stroke, transient ischaemic attack (TIA), or coronary heart event. During an average of 7.4 years, 229 participants (18%) had at least one CVD diagnosis: 107 in the intervention group and 122 in the control group. The incidence of cerebrovascular events was lower in the intervention than the control group: hazard ratio (HR) for combined stroke/TIA was 0.71 [95% confidence interval (CI): 0.51–0.99] after adjusting for background characteristics. Hazard ratio for coronary events was 0.84 (CI: 0.56–1.26) and total CVD events 0.80 (95% CI: 0.61–1.04). Among those with history of CVD ($n = 145$), the incidence of both total CVD events (HR: 0.50, 95% CI: 0.28–0.90) and stroke/TIA (HR: 0.40, 95% CI: 0.20–0.81) was lower in the intervention than the control group.

Conclusion A 2-year multi-domain lifestyle intervention among older adults was effective in preventing cerebrovascular events and also total CVD events among those who had history of CVD.

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Key question

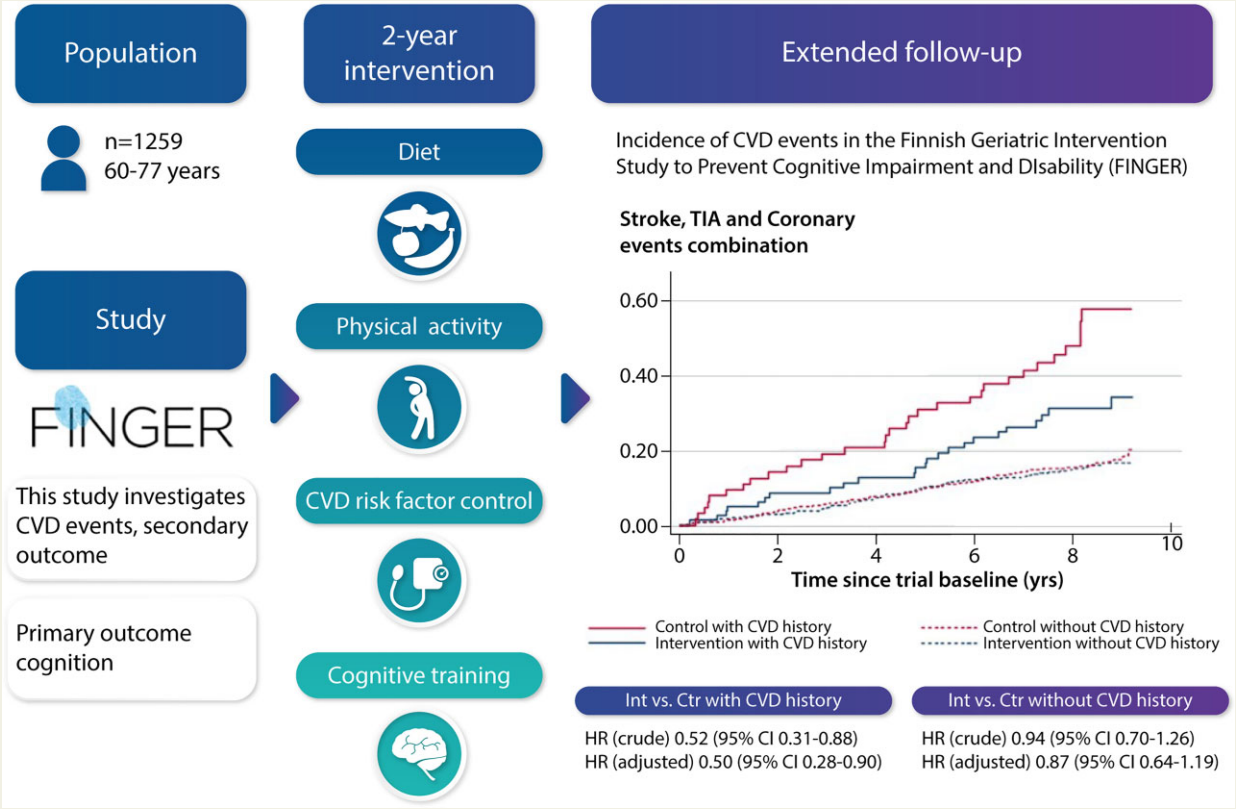
Can a 2-year multi-domain lifestyle intervention, primarily designed for prevention of cognitive impairment, prevent new cardiovascular events among older adults over an extended follow-up?

Key finding

Among the 1259 participants aged 60–77 years, the intervention resulted in 13–20% lower cardiovascular disease (CVD) event rates (unadjusted and adjusted analyses), but with large degree of uncertainty. Cerebrovascular event rates were lower but for total CVD only among those with earlier CVD events.

Take-home message

A 2-year multi-domain lifestyle intervention among older adults was effective in preventing cerebrovascular events and also total CVD events among those with a history of CVD.



Structured Graphical Abstract Incidence of cardiovascular events in the FINGER trial after a 2-year multidomain lifestyle intervention and extended follow-up stratified by the cardiovascular event history.

Keywords Cardiovascular disease • Coronary event • Stroke • Lifestyle • Prevention

Introduction

Both cardiovascular diseases (CVDs) and dementia are common among older individuals, and they share several risk and protective factors.[1] An estimated 40% of all dementia cases might be attributable to modifiable risk factors,[2] and for stroke, even an estimate of 90% has been proposed,[3] including lifestyle-related and CVD factors, such as hypertension, physical inactivity, unhealthy diet, obesity, smoking, and diabetes. Actions for the management of these risk factors and improvement in lifestyles might have a marked impact on the forecasted growth in the prevalence of both CVD and dementia due to population aging worldwide.

Healthy lifestyles are associated with a lower risk of both coronary heart disease (CHD) and stroke in epidemiological studies,[4] also among those using blood pressure or cholesterol-lowering medication.[5] Trials aiming to reduce CVD risk with lifestyle interventions have focused mainly on one lifestyle factor at the time. Drug treatment of hypertension to lower CVD risk is well established, and an intensive blood pressure management has been shown to decrease the risk of fatal and non-fatal CVD events also among older people.[6] A cholesterol-lowering treatment has been proven beneficial in decreasing the risk of CVD events also in at-risk older adults.[7] Data from larger-scale lifestyle intervention trials show benefit of Mediterranean dietary intervention in

primary CVD prevention[8] and secondary CHD[9] prevention, but no effect of moderate-activity exercise programme for primary prevention among an at-risk population[10] or in several secondary prevention studies.[11] Multifactorial preventive approaches, i.e. simultaneous management of multiple vascular and lifestyle risk factors, are generally recommended, but larger studies with longer term follow-up to assess the effect of multifactorial interventions on CVD outcomes are still scarce.[12]

A multifactorial approach combining several lifestyles and CVD risk factor management has been adopted in dementia prevention trials during the past decade, with the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) as the first to show benefit of a 2-year multi-domain lifestyle intervention for cognitive performance.[13] In the present study, we aimed at investigating whether the FINGER intervention reduces the risk of developing new CVD events, defined as coronary event, stroke, or transient ischaemic attack (TIA). All these analyses, as well as subgroup analyses, were pre-specified in the study protocol.

Methods

Setting and population

FINGER is a randomized, controlled trial in a population-based sample with the primary aim of investigating the efficacy of multi-domain lifestyle intervention in the prevention of cognitive impairment (ClinicalTrials.gov NCT01041989). CVD morbidity and mortality are pre-specified secondary outcomes. The study population has been described in detail before.[13] Briefly, persons aged 60–77 years were invited from earlier population-based surveys in six areas in Finland if they had elevated risk for dementia based on the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) dementia risk score, which represents presence of mostly CVD risk factors. Participants underwent screening with short neuropsychological testing and medical examination and were eligible if they had cognitive performance at average or slightly below expected but no diagnosed or suspected dementia. Other exclusion criteria included disorders affecting safe engagement in the intervention (e.g. malignant disease, major depression, symptomatic CVD, revascularization within last year); severe loss of vision, hearing, or communicative ability; disorders preventing cooperation; and coincident participation in another intervention trial. The study was approved by the Coordinating Ethics Committee of Helsinki and Uusimaa Hospital District, and all participants gave written informed consent. The flowchart is presented in Supplementary material online, *Figure S1*.

Randomization

Participants were randomly allocated (1:1) into intensive multi-domain lifestyle intervention or regular health advice (control) group for 2 years. The study nurse performed the randomization with a computerized algorithm in blocks of four (two individuals randomly allocated to each group) at each site, and the allocation was not actively told to the participants.

Interventions

All participants in the multi-domain group received all four intervention domains: dietary counselling, exercise training, cognitive training, and management of CVD and metabolic risk factors.

The dietary intervention included three individual counselling and six to eight group sessions during the first year with the study nutritionist. Guidance was based on national dietary recommendations including aims to e.g. increased consumption of fruits, berries, vegetables, whole grains, vegetable margarine and oil, and fish, with individually tailored goals for each participant.

The physical exercise intervention focused on individually tailored programmes for progressive muscle strength training (1–3 times per week), with exercises for the eight main muscle groups, complemented with exercises to improve balance. In addition, aerobic exercise (goal 2–5 times per week) was mainly individual, but self-guided activities were planned with the study physiotherapist. The intervention followed the international guidelines and experiences from previous Finnish trials.

The cognitive intervention consisted of 10 group sessions organized by the intervention psychologists and individual training with the computer programme. Six sessions contained education and guidance on using the computer programme. An individual web-based training programme was available at home or at the study site, two periods of 6 months each with 72 training sessions (3 times per week). Social activities were stimulated during the whole intervention through e.g. the group meetings in all domains.

Intensive management of metabolic and CVD risk factors was based on national guidelines with aims to improve blood pressure, lipids, blood glucose, and body weight with improving lifestyles and also medication if necessary. Study physicians did not prescribe medication, but strongly recommended contact with local healthcare facility if initiation or adjustment of pharmacologic treatment was needed. The intervention group had additional meetings with the study nurse (at 3, 9, and 18 months) for motivational discussion and assessment of anthropometrics, and the study physician (at 3, 6, and 12 months) for discussing their individual risk profile, including laboratory results and receiving personalized advice on vascular and metabolic factors. People in both groups received general feedback about their laboratory results by mail.

Covariate measurements

All participants met the study nurse at baseline and annually throughout the intervention period for assessment of CVD risk factors (blood samples, anthropometrics) and health status (self-reported questionnaires and interviews). *APOE* status (presence vs. absence of *APOE ε4* allele) was verified from the blood samples.

Cardiovascular morbidity

Data on CVD events were obtained from Finnish nationwide health registers (see details in Supplementary material online, *Table S1*). For the primary analyses, we used all available national health registers. Data on all patients discharged dead or alive from all public hospitals in Finland (covering most hospitals) have been recorded in a computerized Hospital Discharge Register since the year 1968. Since 1994 the Care Register for Health Care has additionally included information on day surgeries and outpatient visits at specialized health care at hospitals. The diagnoses (Supplementary material online, *Table S1*) were coded according to the International Classification of Diseases (ICD8–ICD10) and surgical procedures according to NOMESCO Classification of Surgical Procedures (NCSP). Data from primary health visit care were available starting from 2008 and were only used to identify events from the trial period but not pre-trial events. Primary healthcare diagnoses were coded according to ICD-10 or International Classification of Primary Care (ICPC-2) codes, depending on the healthcare provider. All registries were complete with information until the end of the year 2018, and dates and causes of death were obtained for all deceased participants from the Causes of Death register. A sensitivity analysis was conducted excluding primary healthcare diagnoses because the validity of the other registers is better known for both stroke[14] and coronary events.[15]

The outcomes of this study were incident coronary event (myocardial infarction, unstable angina pectoris, coronary revascularization,

and coronary bypass), stroke (ischaemic stroke, intracerebral haemorrhage, and subarachnoidal haemorrhage), TIA, and their combinations (see Supplementary material online, *Table S1* for codes and details).

We calculated a dichotomous variable to represent CVD history at the time of entering the trial as not having a previous condition or having at least one previous diagnosis (coronary event and/or stroke and/or TIA) any time earlier in life. Time-to-event was considered to start at the baseline of the FINGER trial, but the events during the first month of the study were considered as pre-trial because the interventions were initiated ~1 month after randomization. Sequelae of stroke contributed to the history of CVD before the trial, even if reported without initial stroke, but they were not considered if reported during the trial.

Statistical analyses

We used Cox proportional hazards models to estimate the first events during the study period. The main analysis was adjusted for age, sex, education, study site, baseline antihypertensive medication, and *APOE ε4* genotype. Sensitivity analyses were carried out without any adjustments. Analyses were run in the entire study population, and separately for those with and without history of CVD. The proportional hazards assumption was confirmed with Schoenfeld residuals. There was an indication of violation of the assumption in the sensitivity analysis of stroke incidence when excluding the primary healthcare data. In this model, we additionally present results from the analysis where the follow-up period was split, based on visual inspection of Kaplan–Meier curves, into the early (up to year 6) and late (6 years and after) periods, and analysis was run separately for each period. CVD morbidity and mortality are pre-specified secondary outcomes of the study. We also investigated modification by age, sex, *APOE ε4* (pre-specified subgroup analyses), or drug treatment for high blood pressure and cholesterol (*post hoc* exploratory analyses). As the present analyses were based on pre-specified secondary end points and subgroup analyses, no formal sample size estimation was conducted for these outcomes (trial sample size was based on calculations for the primary outcome, i.e. cognition).

Results

Altogether 2654 individuals were screened between 7 September 2009 and 24 November 2011, of whom 1260 met the cognition and other eligibility criteria and were randomly assigned to the intensive intervention group ($n = 631$) or control group ($n = 629$; 628 after one withdrawal of consent; Supplementary material online, *Figure S1*). Among the 1259 participants, 319 had at least one CVD diagnosis in the hospital or primary care registers, 145 (11%) before entering the trial, 229 (18%) during the trial and follow-up, and 55 (4%) during both time periods. Participants with CVD history were older, less educated, had higher body mass index, and were more likely to be men than those without CVD history (*Table 1*). They used blood pressure and cholesterol-lowering medication more often than participants without CVD history and consequently had lower blood pressure and cholesterol levels when entering the trial. There were no differences between the intervention and control groups in the whole population. Of participants with CVD history, the intervention group participants used antihypertensive medication more often ($n = 67$, 83%) than those in the control group ($n = 39$, 61%; $P = 0.003$), but there was no difference in cholesterol-lowering medication, combined medication (either antihypertensive or cholesterol-lowering), blood pressure levels, or other characteristics (Supplementary material online, *Table S2*).

Since the beginning of the trial, 99 incident coronary events, 105 strokes, and 68 TIAs emerged. Altogether, 23 participants (7 in the intervention, 16 in the control) had both coronary event and stroke/TIA diagnosis. Mean follow-up time was 7.4 years (range: 0.1–9.2) until diagnosis, death, or end of the year 2018 among all; and 4.3 (range: 0.1–9.1) until the first diagnosis among those who had one. Total of 128 participants died, and 15 deaths were related to coronary events or stroke (6 in the intervention and

Table 1 Characteristics of the participants according to intervention allocation and cardiovascular disease history

	All ($n = 1259$)	Intervention ($n = 631$)	Control ($n = 628$)	*P*-value[a]	No CVD ($n = 1114$)	History of CVD ($n = 145$)	*P*-value[b]
Age (years), mean ± SD	69.4 ± 4.7	69.5 ± 4.7	69.2 ± 4.7	0.271	69.1 ± 4.7	71.2 ± 4.5	0.000
Education (years), mean ± SD	10.0 ± 3.4	10.0 ± 3.5	10.0 ± 3.4	0.922	10.0 ± 3.5	9.6 ± 3.3	0.201
Men, *n* (%)	672 (53.4)	345 (54.7)	327 (52.1)	0.354	577 (51.8)	95 (65.5)	0.002
APOE ε4 carriers, *n* (%)	388 (33.0)	189 (32.0)	199 (34.1)	0.457	347 (33.3)	41 (30.8)	0.563
Smoking, *n* (%)	114 (9.4)	64 (10.6)	50 (8.3)	0.174	101 (9.4)	13 (9.4)	0.994
Weekly alcohol use, *n* (%)	556 (44.4)	280 (44.6)	276 (44.3)	0.989	496 (44.8)	60 (41.7)	0.007
Systolic blood pressure (mmHg), mean ± SD	140 ± 16	140 ± 17	140 ± 16	0.787	141 ± 16	137 ± 16	0.021
BMI (kg/m^2), mean ± SD	28.2 ± 4.7	28.3 ± 4.5	28.1 ± 4.9	0.456	28.1 ± 4.7	29.1 ± 4.9	0.011
LDL cholesterol (mmol/L), mean ± SD	3.1 ± 0.9	3.1 ± 0.9	3.1 ± 0.9	0.727	3.2 ± 0.9	2.5 ± 0.7	0.000
Fasting glucose (mmol/L), mean ± SD	6.1 ± 0.9	6.1 ± 0.8	6.1 ± 1.0	0.989	6.0 ± 0.8	6.3 ± 1.4	0.001
Use of antihypertensive medication, *n* (%)[c]	650 (52.6)	327 (52.7)	323 (52.5)	0.962	544 (49.9)	106 (73.1)	0.000
Use of cholesterol-lowering medication, *n* (%)[c]	535 (44.1)	256 (42.2)	279 (46.0)	0.184	419 (39.1)	116 (81.1)	0.000
History of CVD, *n* (%)	145 (11.5)	81 (12.8)	64 (10.2)	0.141			

CVD, cardiovascular disease; BMI, body mass index; LDL, low-density lipoprotein.
[a]Comparison between intervention and control groups; *t*-test for continuous variables and χ^2 test for categorized variables.
[b]Comparison between groups or not having history of CVD vs history; *t*-test for continuous variables and χ^2 test for categorized variables.
[c]Self-reported.

9 in the control group). When also deaths related to ischaemic heart disease or sequelae of stroke were taken into account, there was a total of 38 CVD-related deaths (20 in the intervention and 18 in the control). History of CVD was related to incident total CVD events with hazard ratio (HR) of 2.30 [95% confidence interval (CI): 1.66–3.18] after adjusting for age, sex, study area, and *APOE ε4*. This association was more evident for stroke/TIA (HR: 3.02, 95% CI: 2.07–4.42) than for coronary events (HR: 1.28, 95% CI: 0.74–2.22) after adjustments.

Numerically, lower estimates were observed in the intervention group in incident total CVD events and in all types of events (*Table 2*). After adjusting for age, education, sex, *APOE ε4* status, study area, and antihypertensive medication, difference in combined stroke/TIA (HR: 0.71, 95% CI: 0.51–0.99) was larger than in coronary events (HR: 0.84, 95% CI: 0.56–1.26). Separate analyses for those with and without CVD history showed fewer TIA, combined stroke/TIA, and total CVD events in the intervention compared with the control group among those with history of CVD. There was slightly lower CVD incidence in the intervention group but with large degree of uncertainty for those without CVD history (*Figure 1*, *Table 3*; number of cases in Supplementary material online, *Table S3*). Also for fatal CVD events (HR: 0.66, 95% CI: 0.23–1.85) and all-cause mortality (HR: 0.87, 95% CI: 0.62–1.23), lower incidence was observed in the intervention group, but given the large degree of uncertainty, this may have arisen by chance.

Results for crude models without any adjustment showed similar incidence estimates, but more uncertainty in the combined stroke/TIA difference between groups in the entire study population (Supplementary material online, *Table S4*). In addition, when analyses among those with CVD history were adjusted only for antihypertensive medication, which was different between groups, results remained unchanged. Sensitivity analyses restricted to hospital diagnoses only (Supplementary material online, *Table S5*) showed similar HRs as the main analysis, but the degree of uncertainty was greater. For stroke, there was an indication of the proportional hazards assumption not being met in these sensitivity analyses (proportional hazard test $P = 0.062$), and we ran the hospital-only analysis additionally by splitting the timeline at 6 years, showing no difference during the early period, and a somewhat lower estimate in stroke risk in the intervention group during the late period after 6 years with HR of 0.47 (95% CI: 0.20–1.11) among all.

We also tested modification of the intervention effect by age (dichotomized at the median 69.3 years), sex, *APOE ε4* carrier status, and drug treatment for high blood pressure and cholesterol in relation to total CVD events. Interactions were observed for age ($P = 0.008$) and antihypertensive medication ($P = 0.037$) in adjusted models, and in split analyses adjusted for background characteristics benefit of the intervention was most evident among older participants with age above the median (HR for intervention vs. control 0.61, 95% CI: 0.43–0.86), and among those without antihypertensive medication (HR for intervention 0.60, 95% CI: 0.40–0.90). These results remained similar after further adjustment for CVD history. No interactions with sex or *APOE ε4* were evident.

Discussion

These results showed that the FINGER multi-domain intervention reduced the risk of cerebrovascular events. Intervention was related to reduced risk of total CVD events (coronary event, stroke, or TIA) among those with a history of CVD and among older participants regardless of CVD history, indicating that in general those who are at higher risk of future events, also benefit from the intervention (*Structured Graphical Abstract*). At the same time, participants without previous antihypertensive medication appeared to benefit more, which could indicate more room for effect of multi-domain lifestyle intervention among them.

Multifactorial lifestyle intervention studies primarily designed for CVD primary prevention are scarce. Secondary analyses of successful diabetes prevention studies suggest no effect on CVD events for more than 10 years,[16] but a reduction in CVD-related mortality after 23 years of follow-up,[17] in markedly younger population than ours. A recent review summarizing multimodal randomized controlled trials for secondary prevention after stroke/TIA found no intervention effect on the recurrence of stroke or TIA, but a beneficial effect on the risk of coronary events,[18] and a significant heterogeneity across studies was noted. In addition, the multi-domain lifestyle intervention trial ASPIS with similar intervention as the one in FINGER reported no effect on CVD events among stroke survivors over a 2-year period.[19] The multi-domain dementia prevention trial preDIVA found no

Table 2 Incident cardiovascular disease events over the FINGER follow-up adjusted for age, education, sex, *APOE ε4* status, study site, and antihypertensive medication

	Intervention ($n = 631$)		Control ($n = 628$)		Intervention vs. control[a]		
	No events (%)	Time (py)	No events (%)	Time (py)	HR	95% CI	*P*-value
Coronary event	48 (7.6)	4901	51 (8.1)	4830	0.84	(0.56–1.26)	0.396
Stroke	48 (7.6)	4885	57 (9.1)	4866	0.80	(0.54–1.18)	0.264
TIA	27 (4.3)	4981	41 (6.5)	4888	0.63	(0.38–1.03)	0.064
Stroke and TIA	66 (10.5)	4819	87 (13.9)	4758	0.71	(0.51–0.99)	0.043
Total CVD events (coronary events, stroke, and TIA)	107 (17.0)	4667	122 (19.4)	4608	0.80	(0.61–1.04)	0.098

HR, hazard ratio; CI, confidence interval; py, person years; CVD, cardiovascular disease; TIA, transient ischaemic attack.
[a]Models adjusted for age, education, sex, *APOE ε4* status, study site, and blood pressure medication at baseline. Unadjusted models presented in Supplementary material online, *Table S5*.

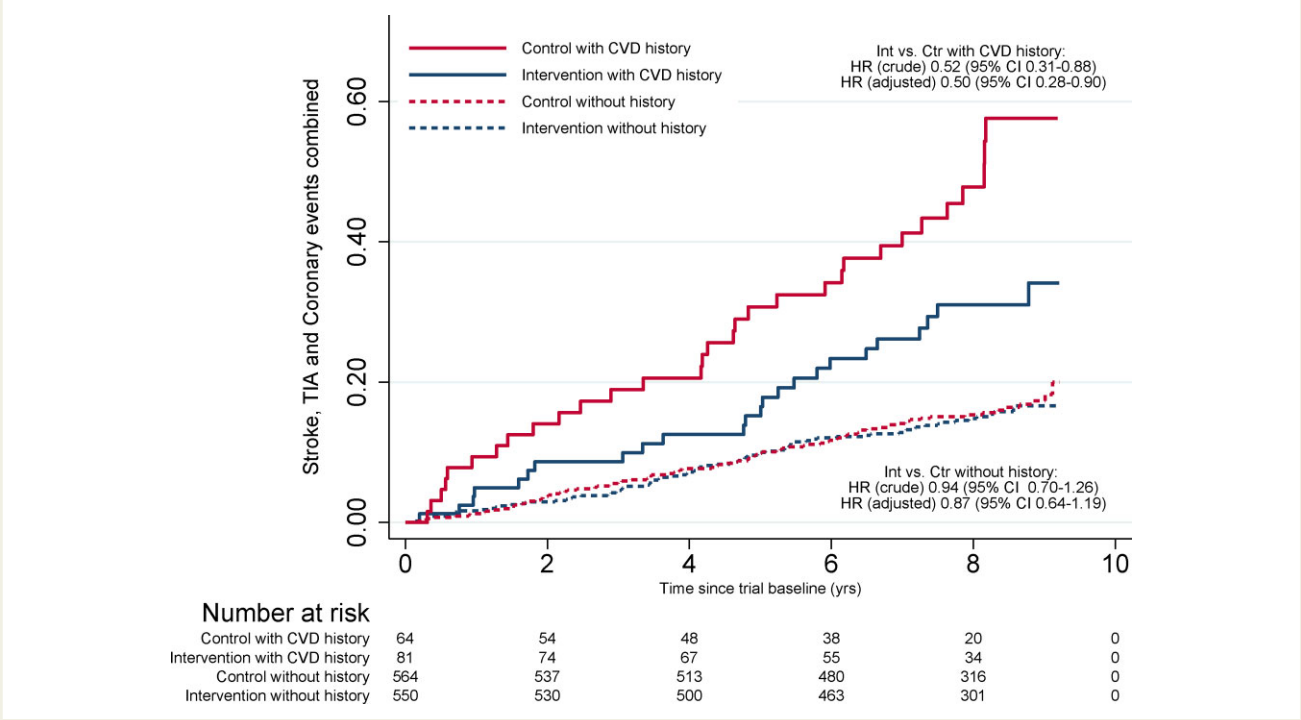


Figure 1 Incidence of total cardiovascular disease events including coronary events, stroke, and transient ischaemic attack according to intervention allocation and cardiovascular disease history.

Table 3 Incident cardiovascular disease events over the FINGER follow-up stratified by cardiovascular disease history adjusted for age, education, sex, *APOE ε4* status, study site, and antihypertensive medication

	Intervention ($n = 550$) vs. control ($n = 564$) among those without CVD history			Intervention ($n = 81$) vs. control ($n = 64$) among those with CVD history		
	HR	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Coronary event	0.81	(0.51–1.28)	0.362	0.92	(0.30–2.81)	0.890
Stroke	0.86	(0.54–1.36)	0.510	0.50	(0.21–1.16)	0.107
TIA	0.78	(0.44–1.38)	0.397	0.31	(0.10–0.96)	0.042
Stroke and TIA	0.82	(0.56–1.20)	0.305	0.40	(0.20–0.81)	0.011
Total CVD events (coronary events, stroke, and TIA)	0.87	(0.64–1.19)	0.391	0.50	(0.28–0.90)	0.022

All models adjusted for age, education, sex, *APOE ε4* status, study site, and blood pressure medication at baseline.
Absolute number of participants by CVD history groups is presented in Supplementary material online, *Table S3*.
HR, hazard ratio; CI, confidence interval; py, person years; CVD, cardiovascular disease; TIA; transient ischaemic attack.

differences in the incidence of stroke or cardiac events over 6 years.[20] While many of these previous trials reporting no difference in CVD risk resulted in improvement in CVD risk factors, our results show the opposite: a reduction in CVD risk without an immediate difference in CVD risk factor levels.[13] This could imply that not all pathways of e.g. dietary intervention and physical activity are mediated by the traditional risk factors, at least in older adults, where their role is in general less clear.

The intervention effect was mainly observed among those who had a history of CVD, a small group of participants but with a markedly higher risk especially for stroke/TIA when compared with persons without prior CVD. Reduction in stroke/TIA incidence in the whole intervention group was more clear after adjustment for confounders, and it is possible that our study was underpowered or too short in follow-up to detect an intervention effect on CVD events among those without an established CVD history. Timing of previous events in the CVD history group ranged from decades-old to recent ones, and thus the population was slightly different from traditional secondary prevention trials, which typically are initiated soon after the initial event. The internet-based multi-domain lifestyle intervention trial HATICE demonstrated a lower incidence of stroke already at 18 months,

although it lacked an effect on total CVD.[21] Power issues may also explain the attenuation of statistical significance when primary healthcare diagnoses were excluded from the analysis; the HRs remained numerically similar but there were fewer cases and thus less power to detect the differences.

The intervention-related benefit for total CVD events was observed especially among older participants, who are more prone to having CVD events and have more frequently CVD history. However, the benefit of the intervention was evident among those without antihypertensive medication, who in turn had a lower probability of events. It is possible that there is more room for the effect of lifestyle changes among those without initial medication, and there also have been new medications initiated in this group.

Means of prevention of CVD are well established, although the latest guidelines identified some gaps related to e.g. effective interventions for diet and physical activity.[22] Recently, the importance of joint primary prevention of stroke and dementia has also been emphasized,[23] and observational evidence linking these conditions with each other and with the shared risk factors is extensive. Lack of trial evidence showing efficacy, however, hinders the consideration of the best available strategies. The evidence is more consistent for antihypertensive treatment,[24,25] although few studies have reported both outcomes in the same cohort, and also modelling of hypothetical joint prevention suggested potential only for prevention of stroke but not dementia.[26] In the earlier Syst-Eur trial, however, the risk of both stroke[27] and dementia[28] was reduced with antihypertensive treatment. The more recent SPRINT trial showed benefits of intensive antihypertensive treatment on both total CVD incidence[29] and cognitive impairment but not particularly on stroke.[30] The dietary intervention trial PREDIMED was beneficial for combined CVD and stroke incidence,[8] and on cognitive test results in a subsample,[31] but no data for dementia have been reported to the best of our knowledge. Our trial showed cognitive benefits over the 2-year intervention period,[13] but a follow-up for dementia outcome is still ongoing. While the WSO declaration emphasizes primary prevention and population-wide strategies, our results suggest that joint secondary prevention might be a feasible part of the strategy.

The present study has several strengths. Although CVD was a secondary outcome of the trial, the utilized intervention creates a plausible rationale for CVD prevention as well. The sample was a population-based at-risk group, and despite the intensive intervention the dropout rate was low and adherence to the intervention was high.[32] The use of Finnish comprehensive health register data available for the ascertainment of the CVD diagnoses provided a virtually complete follow-up. However, register-based diagnoses were not ascertained by the study personnel from medical records, which may result in some vague diagnoses, even if the registers have been validated for CVD outcomes.[14,15] Some other limitations need to be addressed too. First, the trial was designed to prevent cognitive impairment and participants were selected based on cognitive performance and risk of dementia. The CAIDE dementia risk score is likely to represent increased CVD risk as well, and the cognitive screening process was more likely to screen out those with high cognitive performance, thus likely resulting in an at-risk population for both dementia and CVD. Second, because of the design of the study, we cannot ascertain the effect of single intervention components. The majority of our participants had at least some vascular risk factors, most often hypercholesterolemia or hypertension, and many used medication for these disorders already when entering the study. Given that majority of the CVD history cohort was initially using drug therapies, at least some proportion of the intervention effect was likely due to changes in diet and physical exercise, in addition to increased monitoring and motivating the participants to take their medication. This highlights the importance of continuous support also for those using medication. Third, the sample size was relatively small, and initial power calculations were based on the cognitive outcome. Particularly the group with CVD history was small, and we were thus not able to investigate the type of pre-trial events, or the time since the earlier event, which would have given more insight to comparison with other secondary prevention cohorts. As the present analyses consider secondary outcomes and subgroup analyses of the FINGER trial, these analyses should be interpreted with caution. The registers do not cover all hospitals and healthcare providers, although diagnoses are primarily lacking from private hospitals, which are rarely used for acute CVD care in Finland.

Based on these results, the benefits of the FINGER multidomain intervention appear to extend beyond cognitive impairment to prevention of CVD events, particularly among those who have a history of CVD. This suggests that secondary prevention measures should be emphasized among individuals who have had events earlier in life. A 2-year lifestyle intervention may have latency effects for risk of stroke/TIA also among people without prior CVD, but detecting those effects takes many years after the intervention and may thus be more evident among older individuals who have a higher risk of the events. Multifactorial prevention approaches have already been recommended for the prevention of CVD, but randomized controlled trial evidence regarding the efficacy of such interventions has been limited. It might be effective to target more resource-demanding preventive actions to people who, in addition to presence of risk factors, also already have a history of CVD.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

Public deposition of the deidentified data set is not possible due to legal and ethical reasons, and complete deidentification is not possible as this investigation is part of an ongoing study. The study participants gave informed consent which includes data use only under confidentiality agreement. Further, the data contain large amount of sensitive information, and public data deposition may pose privacy concerns. Data dictionary relevant for the present study can be shared upon request to

the corresponding author or by addressing request to the Finnish Institute for Health and Welfare: kirjaamo@thl.fi. Pseudonymized personal data relevant for the present study can be made available only for those fulfilling the requirements for viewing confidential data as required by the Finnish law and the Finnish Institute for Health and Welfare. Data will be made available only for the purpose of research that is in alignment with informed consent, with investigator support and after approval of a proposal and completion of material transfer agreement.

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Conflict of interest: Outside this work, T.S. reports consulting fees from Orion Pharma, Novartis, Sanofi, Amgen, Boehringer, Sankyo; J.T. reports consulting fees from Eli Lilly and Aktivolabs; J.T. reports stocks from Orion Pharma and Aktivolabs; H.S. reports consulting fees from ACImmune and Novo Nordisk; M.K. reports consulting fees from Biogen, Roche, and Nutricia; M.K. reports membership of advisory boards for Combinostics, Swedish Care International, Roche, and Biogen. The other authors have no relationships with industry pertinent to this work.

References

1. Leszek J, Mikhaylenko EV, Belousov DM, Koutsouraki E, Szczechowiak K, Kobusiak-Prokopowicz M, *et al.* The links between cardiovascular diseases and Alzheimer's disease. *Curr Neuropharmacol* 2021;**19**:152–169.
2. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, *et al.* Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 2020;**396**:413–446.
3. Hankey GJ. Population impact of potentially modifiable risk factors for stroke. *Stroke* 2020;**51**:719–728.
4. Barbaresko J, Rienks J, Nöthlings U. Lifestyle indices and cardiovascular disease risk: a meta-analysis. *Am J Prev Med* 2018;**55**:555–564.
5. Chiuve SE, McCullough ML, Sacks FM, Rimm EB. Healthy lifestyle factors in the primary prevention of coronary heart disease among men: benefits among users and nonusers of lipid-lowering and antihypertensive medications. *Circulation* 2006;**114**:160–167.
6. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, *et al.* Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. *JAMA* 2016;**315**:2673–2682.
7. Cholesterol Treatment Trialists' Collaboration, Armitage J, Baigent C, Barnes E, Betteridge DJ, Blackwell L, *et al.* Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet* 2019;**393**:407–415.
8. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, *et al.* Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med* 2018;**378**:e34.
9. de Lorgeril M, Renaud S, Mamelle N, Salen P, Martin JL, Monjaud I, *et al.* Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;**343**:1454–1459.
10. Newman AB, Dodson JA, Church TS, Buford TW, Fielding RA, Kritchevsky S, *et al.* Cardiovascular events in a physical activity intervention compared with a successful aging intervention: the LIFE study randomized trial. *JAMA Cardiol* 2016;**1**:568–574.
11. Deijle IA, Van Schaik SM, Van Wegen EEH, Weinstein HC, Kwakkel G, Van den Berg-Vos RM. Lifestyle interventions to prevent cardiovascular events after stroke and transient ischemic attack: systematic review and meta-analysis. *Stroke* 2017;**48**:174–179.
12. US Preventive Services Task Force, Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, *et al.* Behavioral counseling interventions to promote a healthy diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: US preventive services task force recommendation statement. *JAMA* 2020;**324**:2069–2075.
13. Ngandu T, Lehtisalo J, Solomon A, Levälahti 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**:2255–2263.
14. Tolonen H, Salomaa V, Torppa J, Sivenius J, Immonen-Räihä P, Lehtonen A, *et al.* The validation of the Finnish Hospital Discharge Register and Causes of Death Register data on stroke diagnoses. *Eur J Cardiovasc Prev Rehabil* 2007;**14**:380–385.
15. Pajunen P, Koukkunen H, Ketonen M, Jerkkola T, Immonen-Raiha P, Karja-Koskenkari P, *et al.* The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease. *Eur J Cardiovasc Prev Rehabil* 2005;**12**:132–137.
16. Uusitupa M, Peltonen M, Lindström J, Aunola S, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, *et al.* Ten-year mortality and cardiovascular morbidity in the Finnish Diabetes Prevention Study—secondary analysis of the randomized trial. *PLoS One* 2009;**4**:e5656.
17. Li G, Zhang P, Wang J, An Y, Gong Q, Gregg EW, *et al.* Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. *Lancet Diabetes Endocrinol* 2014;**2**:474–480.
18. Lawrence M, Pringle J, Kerr S, Booth J, Govan L, Roberts NJ. Multimodal secondary prevention behavioral interventions for TIA and stroke: a systematic review and meta-analysis. *PLoS One* 2015;**10**:e0120902.
19. Matz K, Teuschl Y, Firlinger B, Dachenhausen A, Keindl M, Seyfang L, *et al.* Multidomain lifestyle interventions for the prevention of cognitive decline after ischemic stroke: randomized trial. *Stroke* 2015;**46**:2874–2880.
20. van Charante EPM, Richard E, Eurelings LS, van Dalen J-W, 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.
21. Richard E, Moll van Charante EP, Hoevenaar-Blom MP, Coley N, Barbera M, van der Groep A, *et al.* Healthy ageing through internet counselling in the elderly (HATICE): a multinational, randomised controlled trial. *Lancet Digit Health* 2019;**1**:e424–e434.
22. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, *et al.* 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227–3337. https://doi.org/10.1093/eurheartj/ehab484.
23. Brainin M, Feigin VL, Norrving B, Martins SCO, Hachinski V, World Stroke Organization Board of Directors. Global prevention of stroke and dementia: the WSO Declaration. *Lancet Neurol* 2020;**19**:487–488.
24. Hughes D, Judge C, Murphy R, Loughlin E, Costello M, Whiteley W, *et al.* Association of blood pressure lowering with incident dementia or cognitive impairment: a systematic review and meta-analysis. *JAMA* 2020;**323**:1934–1944.
25. Salam A, Atkins E, Sundstrom J, Hirakawa Y, Ettehad D, Emdin C, *et al.* Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of blood pressure lowering on cardiovascular events, in the context of regression to the mean: a systematic review of randomized trials. *J Hypertens* 2019;**37**:16–23.
26. Rojas-Saunero LP, Hilal S, Murray EJ, Logan RW, Ikram MA, Swanson SA. Hypothetical blood-pressure-lowering interventions and risk of stroke and dementia. *Eur J Epidemiol* 2021;**36**:69–79.
27. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, *et al.* Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997;**350**:757–764.
28. Forette F, Seux M-L, Staessen JA, Thijs L, Birkenhager WH, Babarskiene M-R, *et al.* Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 1998;**352**:1347–1351.
29. SPRINT Research Group, Wright JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, *et al.* A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103–2116.
30. SPRINT MIND Investigators for the SPRINT Research Group, Williamson JD, Pajewski NM, Auchus AP, Bryan N, Chelune G, *et al.* Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA* 2019;**321**:553–561.
31. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martinez-Gonzalez MA, *et al.* Mediterranean diet and age-related cognitive decline: a randomized clinical trial. *JAMA Intern Med* 2015;**175**:1094–1103.
32. Ngandu T, Lehtisalo J, Korkki S, Solomon A, Coley N, Antikainen R, *et al.* The effect of adherence on cognition in a multidomain lifestyle intervention (FINGER). *Alzheimers Dement*; https://doi.org/10.1002/alz.12492. Published online ahead of print 20 October 2021.