Multi-domain preventive interventions: experiences from Finland

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From cardiovascular-related conditions to dementia prevention

Cardiovascular conditions and dementia have more in common that it was previously thought (1). Dementia-related disorders (i.e. Alzheimer disease, AD) are often multifactorial, resulting from interactions between genetic and environmental factors (such as modifiable vascular or lifestyle-related factors). The traditional late-life perspective is presently being replaced by a life-course approach, with more focus on windows of opportunity for prevention.

The step towards the multi-domain Finnish Geriatric Intervention Study to prevent cognitive impairment and disability (FINGER) was taken on a research platform that has been developing in Finland over several decades. Some of the main components of this platform are:

1. The nearly 40 years long experience in countrywide risk factors monitoring and effective prevention of cardiovascular conditions, which started with the community-based North Karelia Project in the 1970s and the WHO-MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) Project in the 1980s (2). Such projects were extended over the years beyond the field of Cardiology, developing into the current **FINRISK** system (Finnish national system for monitoring of risk factors for chronic non-communicable diseases) (3). FINRISK is a large population survey carried out since 1972 every five years using independent, random and representative population samples from different parts of Finland. Work is at present ongoing to integrate dementia-related diseases into FINRISK. The FINRISK database is regularly linked to several national registers, such as the Population Register, Hospital Discharge Register, Drug Reimbursement Register, and Causes of Death Register. Because a large amount of information is already available on the survey participants, the decision was made to select the FINGER study participants from FINRISK.

2. **The Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE) study,** partly based on FINRISK, is one of the few studies in the world with a large and representative population-based cohort including both males and females, long follow-up times (up to three decades), and measurements of several risk factors and health-related outcomes from several time points (midlife and late-life). Based on CAIDE results, the first tool was formulated for estimating dementia risk based on risk factor profiles (4). The CAIDE Dementia Risk Score includes modifiable risk factors such as hypertension, hypercholesterolemia, obesity, physical inactivity, and has been validated in a population from USA (Kaiser Permanente of Northern California). This tool is now being used to select participants in the FINGER study.

3. Two intervention studies in Finland have shown that trial participants can be motivated to make major changes in their lifestyle. The **Diabetes Prevention Study** (now completed) is a landmark randomized controlled trial (RCT) showing the effectiveness and feasibility of physical exercise and dietary interventions as preventive measures in general populations (ref). The ongoing exercise and dietary 4-year intervention study **Dose-Responses to Exercise Training (DRs EXTRA)** had a drop-out rate of only 8% after two years, and its intervention protocol served as a model for FINGER.

The FINGER study

The Finnish Geriatric Intervention Study to prevent cognitive impairment and disability (FINGER) is a multicenter (6 sites) RCT currently ongoing in Finland. The main objective is to investigate to what extent a multi-domain intervention can reduce the risk of cognitive impairment and dementia in an elderly population at increased risk of cognitive decline. FINGER involves 1200 participants, aged 60-77 years, who previously participated in population-based non-intervention surveys (i.e. FINRISK). Participant selection is done according to the CAIDE Dementia Risk Score and CERAD cognitive test battery performance. Inclusion criteria are meant to select elderly who are at risk of cognitive decline/dementia, and who are most likely to benefit from the intervention. Persons with dementia/substantial cognitive decline are excluded. In the intervention group, each subject receives all four components: nutrition; physical activity; cognitive and social activity; monitoring/treatment of metabolic and vascular risk factors (Figure). Intervention programs follow a detailed and cautiously planned and monitored protocol, but are at the same time individually tailored according to participants' needs and health status. Subjects in the reference group are given general public health advice on lifestyle and vascular risk factors.

The four components of the 2-year multi-domain intervention are:

1) Dietary intervention, supervised by nutritionists, and formulated according to current guidelines for cardiovascular disease prevention, studies on diet and dementia risk, and Finnish nutrition recommendations. The dietary intervention is also adjusted to the needs of an elderly population. Nutrient intake in all participants is periodically assessed.

2) Exercise training program, supervised by physiotherapists, and based on international guidelines. Subjects participate in a supervised, individually prescribed strength training and aerobic exercise program. Compliance to training and physical performance is periodically evaluated by a validated questionnaire and standardized tests.

3) Cognitive training, supervised by psychologists, is organized into group sessions and individual training. Several cognitive domains are targeted by the intervention. *Social activities* are stimulated via group meetings of the other interventions within the treatment arm, and also arranged with local offices of the Finnish Alzheimer Association. Participation in social and cognitive activities is monitored during the study, and participants are asked to keep diaries.

4) Intensive monitoring and management of metabolic and vascular risk factors (i.e. hypertension, dyslipidemia, waist/hip ratio, impaired glucose tolerance). At baseline all participants are evaluated by the study physicians according to the latest evidence-based guidelines. The treatment group meets periodically the study physicians for evaluation of laboratory test results, anthropometric measures (height, weight, blood pressure, hip and waist circumference) and cardiovascular/metabolic morbidity. Participants in the intervention arm receive oral and written information on their laboratory analyses, on the risks associated with these values, on the importance of management of metabolic/vascular risk factors, and are motivated to adhere to adequate lifestyle changes and pharmacological treatment. If initiation/adjustment of pharmacological treatment is necessary, participants are strongly recommended to visit their own physician.

The primary outcome is cognitive impairment, diagnosed using accurate and validated neuropsychological tests (Neuropsychological Test Battery, Trail Making and Stroop Tests). Secondary outcomes are depressive symptoms, cardiovascular and cerebrovascular morbidity and mortality, quality of life, disability, and utilization of health resources, measured using validated scales selected according to recent recommendations (e.g. European Medicines Agency). Brain MRI is performed in a sub-group of participants at baseline and at month 24 to evaluate vascular lesions and hippocampal and total brain atrophy. An extended 7 years follow-up is planned to fully analyse the effect of the intervention on dementia incidence and secondary outcomes.

Addressing current problems in cognitive impairment/dementia prevention trials: contributions of the FINGER study

Robust evidence on prevention of dementia/AD is missing, and many studies done so far are limited by methodological problems. Recent recommendations for AD research include use of a life-course approach, with combination of retrospective and prospective data, use of standardized and well-validated neuropsychological batteries, comprehensive approach in outcome assessment and biomarkers validation and implementation (5). The FINGER study follows these suggestions. This

RCT targets risk/protective factors chosen based on the best available knowledge; focus is on simultaneously addressing several common modifiable risk factors to obtain an optimal prevention effect. The attention is on vascular and lifestyle-related risk factors shared by AD, vascular dementias and other major chronic diseases common in the elderly, with an integrative approach including several secondary outcomes and estimation for cost/effectiveness and total benefit.

Disappointing results of previous trials with single agents in elderly or already cognitively impaired persons pointed out some key issues, which have been taken into account in the FINGER study design:

1) Balancing the timing of the intervention and the selection of the target group: starting the intervention earlier may lead to better effects, but a healthy, too young target population would require long follow-up times, large sample sizes and considerable financial resources. FINGER inclusion criteria select thus a population at increased risk of cognitive decline, but without advanced cognitive impairment.

2) Representative target group: recruiting FINGER participants from FINRISK ensures a truly population-based sample.

3) Baseline data: the information on earlier lifestyle and vascular factors from FINRISK offers detailed baseline data for FINGER, which is very rare in RCTs.

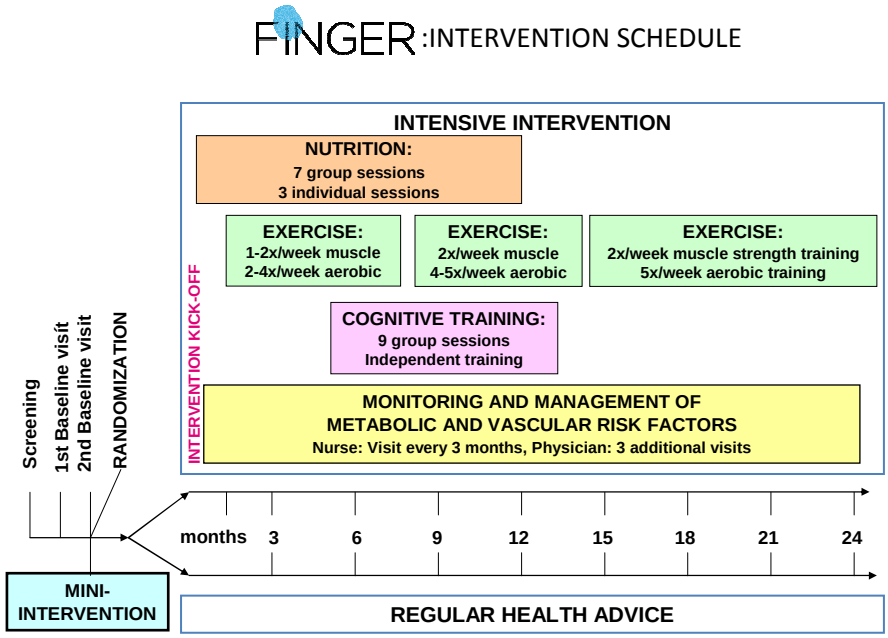
4) Outcome measures: cognitive impairment may be a better outcome than just conversion to dementia.

5) Ethical issues: it is no longer possible to have a traditional placebo group where risk factors for cardio/cerebrovascular conditions are not treated.

4) Investigating potential mechanisms of action: collecting blood samples at baseline, month 12 and month 24 allows detailed biomarker measurements (i.e. inflammation, redox status, lipid and glucose metabolism, NMR metabonomics). In addition, MRI and PET measurements are planned for a subsample of the participants.

The lessons learned from this multi-domain intervention will help in planning and conducting future interventions and in the implementation of preventive measures for the whole population at risk in the future.

Figure



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