RE-inventing Strategies for Healthy Ageing; Recommendations and Tools (RESTART) - a Randomized Controlled Trial Testing a Complex Lifestyle Intervention in Older Adults at Increased Risk for Cardiometabolic Disease

Study protocol and statistical analysis plan

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Project overview

The goal of the RESTART RCT is to examine whether a complex lifestyle intervention, coordinated with municipal and non-government organizations (NGO), can establish and preserve improvements in risk factors and functional capacity among older adults at high risk of cardiometabolic disease. The main objectives to investigate are whether a complex lifestyle intervention, compared to an active control group, will at 24 months have:

- Produced a clinically relevant increase in cardiorespiratory fitness (primary endpoint)
- Increased muscle strength and power, physical activity and reduced adiposity
- Improved body composition, health-related quality of life and cognitive function

All participants (Control and Intervention Groups) are provided with wrist-worn activity trackers at baseline and access to national recommendations on physical activity. The intervention group additionally advances through a comprehensive lifestyle program including high-intensity aerobic and strength exercise, dietary and behavioral counselling. Intervention participants are gradually transitioned into exercise activities organized by Tromsø Municipaity and local NGO:s. Testing of outcomes are performed at baseline, 6, 12 and 24 months. Primary endpoint (VO2max) is assessed at 24 months.

Detailed description

The proportion of older individuals worldwide is growing, posing a significant challenge to western societies. To address the health challenges of the aging population, primary prevention efforts should focus on various lifestyle factors simultaneously. However, many interventions fail to maintain improved lifestyle habits among participants, highlighting the need for novel and complex approaches to ensure healthy aging among older adults.

The RESTART randomized controlled trial aims to investigate whether participants undergoing a complex lifestyle intervention improve their cardiorespiratory fitness, muscle strength, physical activity, adiposity and body composition, quality of life and cognitive function at 24 months, compared to active controls.

The study and data collection will occur in Tromsø, Norway (pop. 77,000). Participants will receive the intervention at a local community exercise center near the University of Tromsø campus area. Testing of physical performance will take place at the UiT Faculty of Health Sciences research laboratory for sports, physical activity, and public health. The Clinical Trial Unit (CTU) at the local university hospital will additionally oversee clinical examinations, collection of questionnaire data, and blood sampling.

At baseline, both the Control and Intervention Groups are given wrist-worn activity trackers and access to national physical activity recommendations. The Intervention Group also undergoes a comprehensive lifestyle program that includes high-intensity aerobic and strength exercises, as well as dietary and behavioral counseling. The Intervention Group is gradually introduced to exercise activities organized by Tromsø Municipality and local NGOs. Outcome testing is conducted at baseline, 6, 12, and 24 months, with the primary endpoint (VO2max) assessed at 24 months.

Intervention participants will be divided into 4 groups of 12-15 participants each and perform high-intensity training to target the cardiovascular system and skeletal muscle force-generating capacity. For 12 months, the intervention group performs supervised indoor cycling or outdoor hill interval training twice a week at a relatively high intensity (≥85% of maximal heart rate during 4x4 minutes)

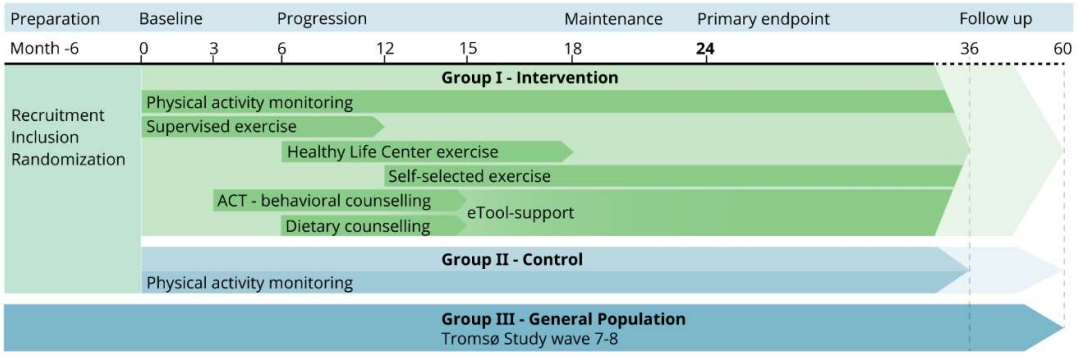
separated by active rest periods at approximately 70% of maximal heart rate. Immediately after the aerobic exercise, participants perform strength training (3 sets of 5 repetitions) involving leg-press, lateral pull-down, and chest press exercises, with an intensity corresponding to ≥80% of their maximal strength. From months 6-12, one of the two weekly exercise sessions will be led by the Healthy Life Center (HLC; "Frisklivssentralen"), enabling a transition to supervised exercise via the Tromsø municipality primary health care. Between month 12-18, the HLC continue to supervise the participants during one weekly exercise sessions, while they are additionally introduced to exercise activities arranged by local NGO:s.

From month 3 to 15, participants will receive behavioral counseling based on the Acceptance and Commitment Therapy (ACT) approach during six 2-hour group sessions. The individual approach aims to enhance participants' capacity to manage challenging cognitive and emotional experiences, foster psychological flexibility and distress tolerance skills, and promote the development of self-efficacy and new behavior patterns that align with their life values.

From month 6 to 15, the intervention group will receive four dietary counseling sessions based on Norwegian nutritional guidelines. Two individual sessions will involve food diaries, while two group sessions with a partner will focus on basic nutritional information and practical food preparation. The objective is to promote a healthy, sustainable, and personalized diet while promoting increased protein intake, reducing the consumption of high-energy-dense foods and drinks with low nutritional value.

From month 3 and onwards, the intervention group will be granted access to the Re-start eTool (https://re-start.no/), which is specifically tailored to older adults. The eTool offers concise and easy-to-understand articles, videos, and self-assessment tools that promote physical activity, healthy dietary habits, and behavioral strategies from the complex intervention. The Re-start eTool aims to provide support and reminders to participants as they gradually transition to independently maintaining the achieved lifestyle habits and physical capacity levels.

Throughout the study period, the intervention instructors and assessors monitor potential adverse events during the exercise and testing phases, and all adverse events are reported to the study coordinator. Measures to mitigate adverse events include: 1) insurance of participants via The Norwegian System of Patient Injury Compensation; 2) involving a MD with sports medicine specialization to ensure treatment of potential injuries; 3) pilot study experiences show that short-term alternative exercises are effective in managing exercise-induced pain and discomfort.



Outcomes

The primary endpoint is change from baseline in mean V̇O2max (ml·kg-1·min-1) at 24 months. Secondary endpoints are change from baseline in mean muscle strength (kg) and mean waist circumference (cm) at 24 months. Tertiary endpoints are change from baseline in mean body composition (appendicular lean mass [g], fat percentage [%], visceral fat [g]), health-related quality of life and cognitive function at 24 months.

	Study period						
	Enrolment	Allocation	Post-allocation				Close-out
TIMEPOINT	-6m	0 (Baseline)	6m	12m	18m	24m[a]	36m[b]
Enrolment:							
Eligibility screen	X	X					
Informed consent		X					
Allocation		X					
Assessments:							
$\dot{V}O_{2max}$ (primary outcome)		X	X	X		X	X
Muscle strength and power		X	X	X		X	X
WC, body weight		X	X	X		X	X
Physical activity (accelerometer)		X	X	X		X	X
Physical activity (wearable)[d]		→	→	→	→	→	→
Body composition (DEXA)		X		X		X	X
Cognitive function (DSST)		X		X		X	
Lung function (spirometry)		X				X	
HGS, 5-CST		X		X		X	X
Blood pressure, HR		X	X	X		X	X
ECG		X				X	
Biological samples:							
Thyroid function		X					
HbA1c, blood lipids, liver enzyme, renal function, cystatin c		X	X	X		X	X
CRP, inflammatory markers		X		X		X	
Gene expression		X		X		X	
Urine		X		X		X	X
Questionnaires[c]		X		X		X	X
Education and income		X				X	
Family and friend network		X		X		X	
Interview data				X		X	
Health economic evaluation						X	
Adverse events[d]		→	→	→	→	→	→

a Time-point for primary outcome assessment

b Planned testing phase that requires separate funding

c Includes health-related quality of life (EQ-5D-5L), life satisfaction (SWLS-5), anxiety and depression (HSCL-5), physical activity (SGPALS), diet (NORKOST), general self-efficacy (GES), physical activity acceptance (PAAQ), physical activity enjoyment (PACES-S) emotional eating (TFEQ), intuitive eating (IES), ideal weight, chronic disease, symptoms and complaints, medication use, smoking status and self-rated health

d Continuously monitored

ACT; acceptance and commitment therapy, WC; waist circumference, DEXA; dual-energy X-ray absorptiometry, DSST; Digit Symbol Substitution Test; HGS; handgrip strength, 5-CST; 5-repetition chair stand test, HR; heart rate, ECG; electrocardiogram = Chair Stand Test, HGS = Hand Grip Strength, WC = Waist circumference ECG = electrocardiogram, CRP; C-reactive protein

Other outcomes include change from baseline in handgrip strength, chair stand performance, perceived self-efficacy, satisfaction with life, mental health status, psychological flexibility, and self-reported diet and smoking at 24 months. We additionally qualitatively assess self-perceived determinants of successful lifestyle change at 24 months and perform a health economic evaluation of the intervention after 24 months, and follow-up on time to event for CVD (myocardial infarction, stroke), diabetes and mortality at 60 months.

Sample size

We need 44 participants in each group to detect a 2.0 ml·kg-1·min-1 mean group difference in $\dot{V}O_2max$ -change (primary endpoint), with an α-level of 0.05, power 80%, and standard deviation (SD) of 3.3. These sample sizes also enable detection of the following between-group differences: lower body strength of 50 kg (SD=40, power>90%) and waist circumference of 4 cm (SD=3.5, power>90%). Expecting an acceptance rate of 30% and an attrition rate of 20%, 353 individuals will be invited and a total number of 110 participants will be block randomized into the intervention and active control groups.

Statistical analysis plan

We will do intention-to-treat analysis and use linear mixed models to assess effects on all outcomes. Linear mixed models let us include all available information for participants who drop out of the trial under the assumption that missing are missing at random. In a sensitivity analysis we will exclude dropouts and use per-protocol analyses.