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CLINICAL RESEARCH
Clinical trials

Effect of 5 years of exercise training on the cardiovascular risk profile of older adults: the Generation 100 randomized trial

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Aims The aim of this study was to compare the effects of 5 years of supervised exercise training (ExComb), and the differential effects of subgroups of high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT), with control on the cardiovascular risk profile in older adults.

Methods and results Older adults aged 70–77 years from Trondheim, Norway (n = 1567, 50% women), able to safely perform exercise training were randomized to 5 years of two weekly sessions of HIIT [~90% of peak heart rate (HR), n = 400] or MICT (~70% of peak HR, n = 387), together forming ExComb (n = 787), or control (instructed to follow physical activity recommendations, n = 780). The main outcome was a continuous cardiovascular risk score (CCR), individual cardiovascular risk factors, and peak oxygen uptake (VO_{2peak}). CCR was not significantly lower [-0.19, 99% confidence interval (CI) -0.46 to 0.07] and VO_{2peak} was not significantly higher (0.39 mL/kg/min, 99% CI -0.22 to 1.00) for ExComb vs. control. HIIT showed higher VO_{2peak} (0.76 mL/kg/min, 99% CI 0.02–1.51), but not lower CCR (-0.32, 99% CI -0.64 to 0.01) vs. control. MICT did not show significant differences compared to control or HIIT. Individual risk factors mostly did not show significant between-group differences, with some exceptions for HIIT being better than control. There was no significant effect modification by sex. The number of cardiovascular events was similar across groups. The healthy and fit study sample, and

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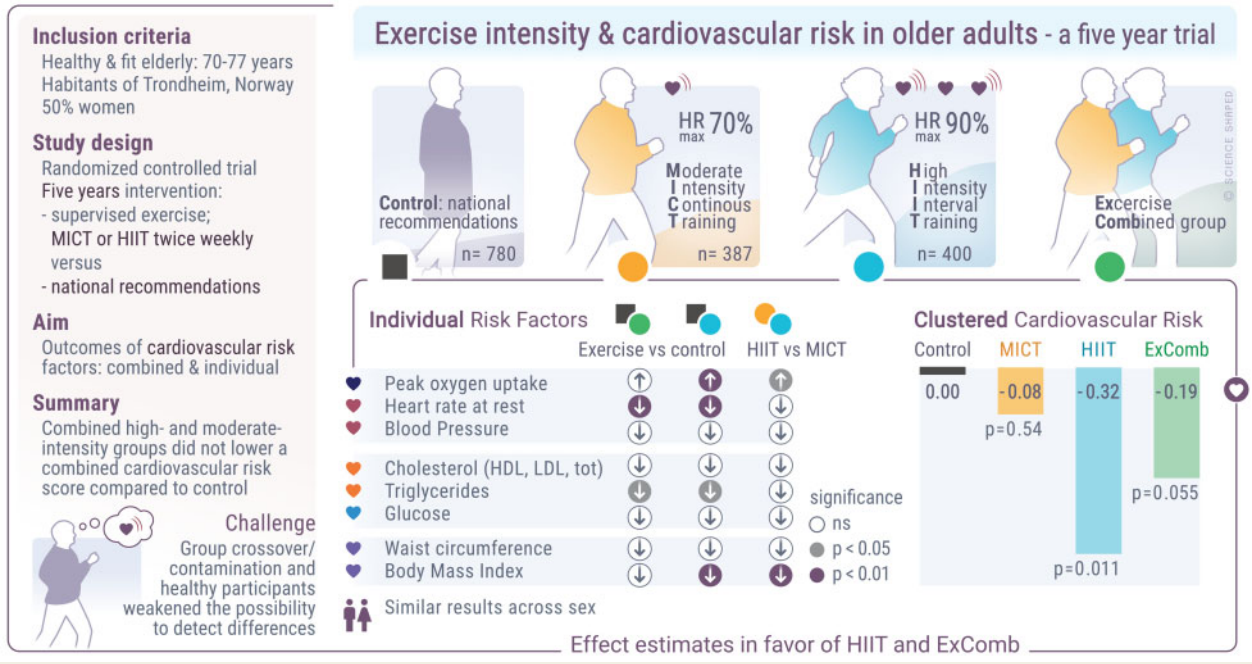
contamination and cross-over between intervention groups, challenged the possibility of detecting between-group differences.

Conclusions Five years of supervised exercise training in older adults had little effect on cardiovascular risk profile and did not reduce cardiovascular events.

Registration ClinicalTrials.gov: NCT01666340.

Graphical Abstract



Five years of supervised exercise did not significantly improve the cardiovascular risk profile of older adults compared to a control group advised to follow national recommendations for physical activity. In comparisons between the different exercise intensities there was a signal towards a favourable effect in the high-intensity interval training group for several of the risk factors, but the present study did not show conclusive evidence.

Keywords Exercise • High-intensity interval training • Ageing • Cardiovascular risk factors • Cardiorespiratory fitness

Introduction

The number of older adults in the world is expected to double between 2015 and 2050.[1] Ageing is associated with unfavourable physiological and functional changes, including changes in cardiorespiratory fitness (CRF) measured as peak oxygen uptake (VO_{2peak}),[2] adiposity,[3] blood pressure (BP),[4] and muscle mass,[5] all of which contribute to increased risk of cardiovascular disease (CVD).

VO_{2peak} is a strong predictor of CVD,[6] and a ~20% decline in VO_{2peak} over 10 years has previously been observed in older adults.[7] Exercise increases VO_{2peak},[8,9] and several studies have indicated that high-intensity interval training (HIIT) gives larger increases when compared to moderate-intensity continuous training (MICT).[10,11] Also, HIIT has shown more pronounced effects on CVD risk factors than MICT in other populations at high CVD risk.[12] Beneficial adaptations in VO_{2peak} and cardiovascular health have been observed even when becoming physically active at older age,[13] and a systematic review of exercise interventions in older adults has indicated positive effects on cardiovascular risk factors.[14] However, effects on several CVD risk factors such as BP and lipids are heterogeneous with variable quality of the available evidence.[14] Also, the impact of different exercise intensities has not been established, and studies lasting >1 year are rare.[10,14] Thus, long-term studies comparing different exercise intensities at similar exercise volumes are needed to be able to give best possible advice regarding physical activity for increasing CRF and reducing CVD risk in older adults. Of note, the current physical activity recommendations do not emphasize performing moderate- or high-intensity exercise over the other, and this needs further investigation.

The aim of this study was to assess the effect of 5 years of supervised exercise training (exercise combined; ExComb) on cardiovascular risk profile compared to Norwegian national physical activity recommendations (control) in older adults. Second, we aimed to

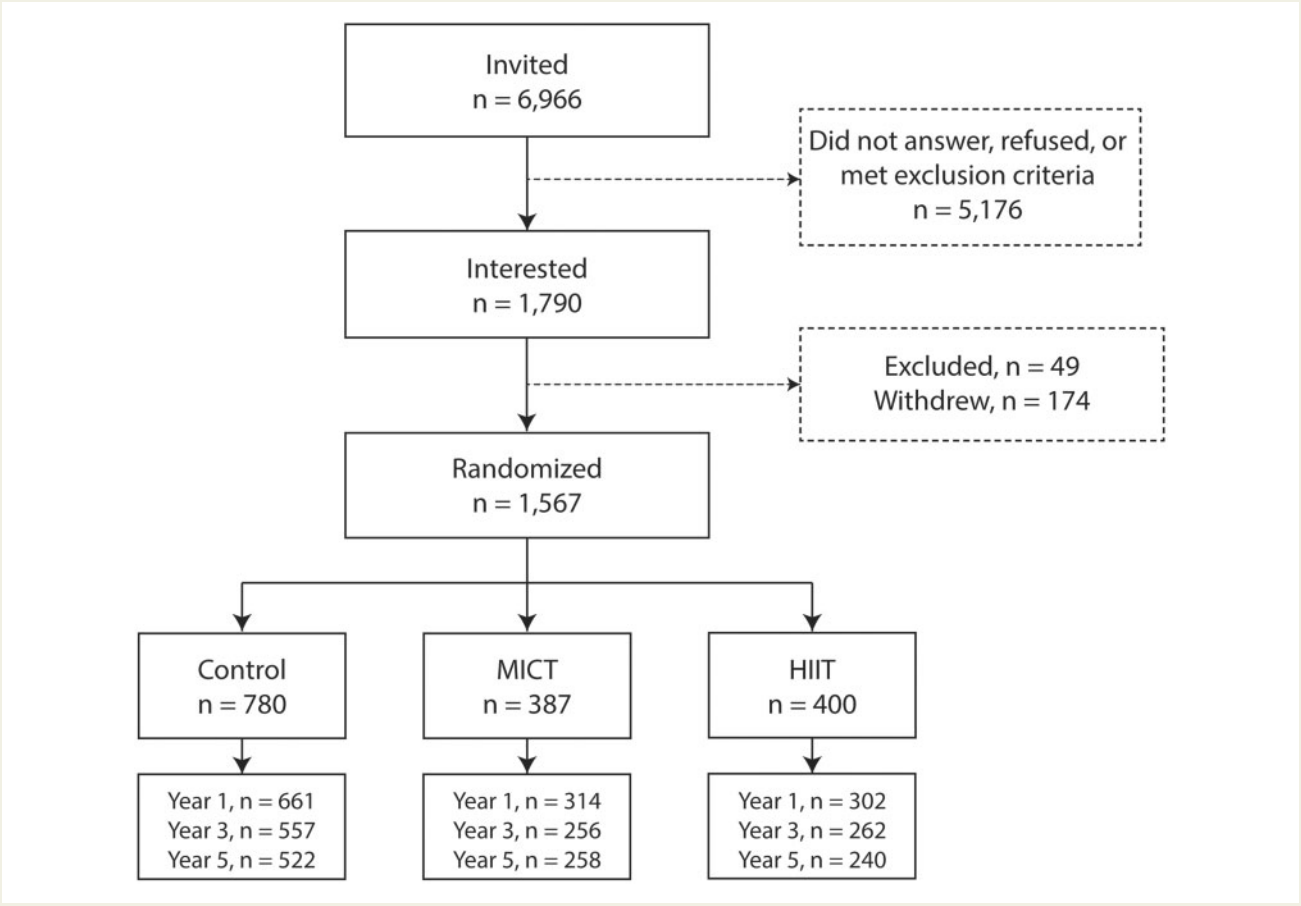


Figure 1 Flowchart of participant inclusion and follow-up. The number of participants showing up for repeated examination and testing at each study year is shown in the box below each intervention group. HIIT, high-intensity interval training; MICT, moderate-intensity continuous training.

assess differential effects of HIIT and MICT compared to each other and control on these outcomes.

Methods

Study population and design

This study includes participants from the Generation 100 study that investigated the effects of exercise training on all-cause mortality (ClinicalTrials.gov: NCT01666340) in older adults aged 70–77 years.[15] Sample size calculations were performed for the main outcome of mortality. In Trondheim (2010), 2% of the population between 70 and 77 years died, and the expected mortality rate after 5 years would be ~10%. With a power of 90%, about 600 participants were needed in each group (ExComb and control) to detect a 50% reduction in mortality (i.e. from 10% to 5%). The study aimed to include 1500 participants to allow for up to 20% of dropouts.[15,16] Here, we address pre-specified secondary outcomes including VO_{2peak} and traditional cardiovascular risk factors. All inhabitants in Trondheim municipality in central Norway born between 1936 and 1942 were invited. Exclusion criteria before and during the study are reported in Supplementary material online, *Methods*. The study was initiated in 2012 and included 1567 participants who were randomized 2:1:1, stratified by sex and cohabitation status, to either a control group (control, $n = 780$), MICT ($n = 387$), or HIIT ($n = 400$). The combination of HIIT and MICT defined the pre-specified ExComb group.

The Unit for Applied Clinical Research at the Norwegian University of Science and Technology (NTNU) performed the randomization to ensure impartial allocation. Participants filled in questionnaires and underwent clinical examinations, blood sampling, and physical tests before randomization (baseline) and after 1, 3, and 5 years (last follow-up in 2018). Overview of study inclusion and design is shown in *Figure 1*, and a detailed study protocol[16] and the primary outcome[15] have been published. The study protocol and statistical analysis plan for the Generation 100 study is available in the Supplementary material online.

The present study was approved by the Regional Committee for Medical Research Ethics (REC South East B; REK2012/381B). All study participants signed an informed consent form prior to inclusion.

Exercise intervention

The control group was asked to follow the recommendations of the Norwegian Health Authorities for physical activity (per 2012),[17] being 30 min of moderate-intensity physical activity most days a week, without receiving further supervision. The HIIT group was asked to complete 40 min of HIIT two times per week, consisting of 4 × 4 min intervals with an intensity ~90% of peak heart rate (HR) during intervals, corresponding to ~16 on the Borg scale.[18] Based upon the testing of VO_{2peak} as described below, we established individual HR-VO_2 relationships to calculate average energy consumption in an HIIT session, which was then used to calculate the volume (minutes) of MICT that was needed to match the 'HIIT-kcal usage'. Based upon these calculations, MICT was

asked to complete 50 min of continuous exercise training two times per week with an intensity of 70% of peak HR/Borg scale ~13. In this way, the only thing that differ between MICT and HIIT was the intensity of the exercise, as we also reported in previous studies.[11,12,19] Every sixth week, both groups met separately for supervised spinning sessions (ergometer cycling) with an exercise physiologist, where they exercised with HR monitors to ensure that recommended relative exercise intensities were being achieved. Supervised training with exercise physiologists present was also offered, meaning that these sessions were not mandatory, twice a week in different outdoor areas, although during winter one session was held indoors. Exercise intensity was evaluated by HR monitors and rating of perceived exertion (Borg scale) during the supervised sessions. Although exercise intensity was given by intervention group, exercise mode was self-selected, and most participants preferred walking.[20] Data from the HR monitoring showed that, for this age group, uphill walking was effective in reaching 90% of peak HR, in line with findings at baseline testing, where 86% of participants were exercising at a treadmill speed ≤6 km/h at peak exercise, which is below the typical walk-run transition.[21] For HIIT and MICT, respectively, the mean HR at the supervised exercises was 93% and 77% at Year 1, 90% and 74% at Year 2, 87% and 74% at Year 3, 91% and 72% at Year 4, and 87% and 69% at Year 5 (all HIIT vs. MICT comparisons $P < 0.001$). In total, the mean HR was 90% in HIIT and 72% in MICT, with rating of perceived exertion of 16.9 and 13.8, respectively.

As pre-defined in the protocol article,[16] adherence to the prescribed exercise program was defined as having performed at least 50% of the prescribed training sessions over the 5 years. After 1, 3, and 5 years, adherence to prescribed exercise was 50%, 49%, and 47% for HIIT and 63%, 55%, and 51% for MICT. Participant in control had a stable physical activity level throughout the study with 78%, 70%, and 69% meeting recommendations after 1, 3, and 5 years, respectively. Furthermore, there was a cross-over between the interventions, particularly in the control group was 23%, 22%, and 18% for HIIT after 1, 3, and 5 years, with corresponding values of 12%, 14%, and 11% for MICT.[15] The mean [standard deviation (SD)] number of weekly exercise sessions at baseline and 5 years was 3.9 (0.9) and 4.0 (0.9) for control, 4.0 (0.8) and 4.1(0.7) for MICT, and 3.9 (0.9) and 4.1 (0.7) for HIIT.

Cardiopulmonary exercise testing

Participants underwent cardiopulmonary exercise testing to voluntary exhaustion on a treadmill (PPS55 Med, Woodway GmbH, Germany), or a bike if physical limitation or balance issues precluded treadmill exercise (Monark cycle ergometer, Monark Exercise AB, Sweden; 3.4% of tests), with continuous gas analysis using the Cortex MetaMax II (Cortex Biophysik Gmbh, Leipzig, Germany) or the Oxycon Pro (Erich Jaeger, Hoechberg, Germany, 3.8% of tests). The same system was used for each participant at all follow-ups, but 43 participants switched between treadmill and cycle ergometer or the other way around during the study due to physical challenges, and for these participants any tests using the cycle ergometer were excluded ($n = 54$) in analyses for VO_{2peak}. Participants' regular medications were continued prior to exercise testing and all other measurements. Test personnel were blinded for participants' intervention arm. The individualized steady-state test protocol started at a speed and inclination set during warm-up guided by the Borg scale. The first stage was held for 3 min, or longer if steady state was not reached. Stage 2 was initiated by increasing the intensity, either by 1 km/h in speed or by 2% inclination (or 10 W if using bike). After completing the second submaximal stage lasting 1.5 min, the intensity increased similarly every minute (or 30 s on bike), or when the values had stabilized, until the participant stopped the test due to exertion, or VO_{2max} was achieved. The protocol lasted 8–12 min as recommended by Froelicher and Myers.[22] The same exercise testing protocol and equipment was used at all study years. Further information on testing and calibration procedures has been described in detail previously.[23] The VO_{2peak} was recorded as the average of the three highest consecutive measures over 30 s. Maximal oxygen uptake (VO_{2max}) was defined as achieved if VO_2 did not increase >2 mL/kg/min the last 30 s before test termination as well achieving a respiratory exchange ratio ≥1.05. Since 40% of tests did not meet objective VO_{2max} criteria, the term VO_{2peak} is used throughout.

Clinical and biochemical measurements

Participants were asked to fast and avoid exercise and alcohol for 12 and 24 h preceding measurements, respectively, although not before exercise testing. Height was measured standing straight against a wall with feet hip-distance apart. Waist circumference was measured above the iliac crest, in a standing position with feet hip-distance apart, arms crossed above the chest, and with relaxed breathing at exhalation. Body mass measurements and calculations of fat-free mass [body mass × (1 - (body fat percentage/100)] were performed on a bioelectrical impedance scale (Inbody 720, BIOSPACE, Seoul, Korea). Body mass index (BMI) was calculated. After resting 5 min in a chair with arms rested, BP was measured twice with a 1-min break from the right upper arm (Philips Medizin Systeme, Boeblingen, Germany). If systolic/diastolic BP differed by ≥10/6 mmHg between measurements, a third measurement was taken, and the average of the last two BP recordings was used. The mean arterial pressure (MAP) was calculated as diastolic BP + 1/3 × pulse pressure. Blood samples were drawn from an arm vein by trained personnel using standardized procedures (St. Olavs University Hospital). Serum high-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC), triglycerides (TG), glucose, and glycosylated haemoglobin were analysed immediately after sampling. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald formula at baseline and Year 1, directly measured by Roche Modular P at Year 3, and by Siemens Advia Chemistry XPT at Year 5. Calculated and directly measured LDL-C have shown good agreement.[24] Information on smoking, alcohol use, previous medical history, and exercise habits was based on self-report. Information on prescription medication use was collected from the Norwegian Prescription Database (Supplementary material online). Data on clinical events were gathered as previously described.[15]

Statistical analyses

Baseline clinical characteristics are presented as mean and SDs or as count and percentages, and for the risk factors graphically as means and 99% Wald confidence intervals (CIs). To assess the combined effect on several cardiovascular risk factors, a continuous cardiovascular risk score (CCR) was constructed by summarizing sex-specific *z*-scores for waist circumference, MAP, the inverse of HDL-C, and the logarithm of TG and fasting glucose, similar to variables used in the definition of the metabolic syndrome.[25] *Z*-scores were calculated by subtracting the mean from the given value and dividing by the SD.[26] The mean and SD from baseline for each variable were used for calculations at all time points, allowing for the detection of difference in change between the groups.[27] Using the same variables as a cluster of metabolic syndrome has been shown to significantly predict CVD in adults and older adults,[28,29] but we chose a continuous score of the same variables instead to reduce information loss and power by dichotomization, in line with other studies assessing cardiovascular risk factors in older adults.[27] To assess the between-group treatment effects for the various outcomes, we specified a linear mixed model adjusting for cohabiting status, sex (variables used in stratified randomization), and age at inclusion. Participants were included as random intercept in the models. Analyses were adjusted for the baseline value based on the rationale and method described by Twisk *et al.*[30] Using this method, the between-group treatment effects are directly interpretable as the estimate for the group × time interaction. For each risk factor two separate

models were performed, one for the ExComb vs. control comparison, and one for the comparison of HIIT and MICT to control. Participants with missing data on at least one of the follow-up time points are also included in the mixed model analysis and contribute to the estimate at these points, though with less weight at these time points than if complete data on that participant were available. Hence, with a mixed model, no imputation of missing data is needed. The estimates from a mixed model analysis are unbiased as under the missing at random (MAR) assumption, while a complete case analysis would be unbiased only under the more restrictive missing completely at random (MCAR) assumption. We analysed for effect modification by sex by including the two-way interaction between time and sex and the three-way interaction between group, time, and sex. All analyses forming basis for main results were performed by the intention-to-treat principle. In addition, selected per-protocol analyses were performed to investigate the impact of exercise adherence (Supplementary material online). Further information including data on the number of participants and observations included in analyses are shown in Supplementary material online, *Table S1*. Due to multiple testing, a two-sided *P*-value of <0.01 was considered statistically significant, and 99% CIs are reported. Statistical analyses were performed using Stata MP 16.0 (StataCorp, College Station, TX, US) and R (www.r-project.org).

Results

Baseline characteristics are shown in *Table 1*. Age (mean, SD) was 72.8 (2.1) years, participation was balanced across sex (50% women), few were current smokers (8.6%), and 12% had a BMI of >30 kg/m^2. The overall drop-out due to death, withdrawal, or exclusion was 25% over the course of the study (further information on dropout in Supplementary material online). From Years 1–5, participation at follow-up measurements declined from 1277 (81%) to 1020 (65%), respectively. Clinical and study characteristics from Years 1, 3, and 5 are available in Supplementary material online, *Tables S2–S4*.

Continuous cardiovascular risk score and individual cardiovascular risk factors

The mean CCR, individual cardiovascular risk factor levels, and VO_{2peak} at baseline and Years 1, 3, and 5 are shown in *Figure 2A* for men and *Figure 2B* for women, and in Supplementary material online, *Table S5* for sexes combined. The main results regarding the effect of ExComb compared to control, and HIIT compared to control and MICT, are shown in *Table 2* as the group × time interaction effects from the linear mixed models. Descriptive data on clinical events during follow-up are shown by intervention groups and sex in *Table 3*.

There were no significant between-group differences at Year 5 for CCR. Also, for ExComb vs. control, there were no significant differences at any study year. However, HIIT had lower CCR compared to control at Year 3 (-0.34, 99% CI -0.66 to -0.02) and borderline at Year 5 (-0.32, 99% CI -0.64 to 0.01), and borderline compared to MICT at Year 3 (-0.35, 99% CI -0.72 to 0.02, *Table 2* and Supplementary material online, *Table S6*).

For the individual traditional cardiovascular risk factors, there were no significant differences between ExComb vs. control at Year 5, except for resting HR (-1.44 b.p.m., 99% CI -2.67 to -0.21). However, HIIT significantly improved MAP at Year 3 (-1.58 mmHg, 99% CI -3.1 to -0.06), resting HR at Year 5 (1.89 b.p.m, 99% CI -3.42 to -0.36), and BMI at Years 3 (-0.26 kg/m^2, 99% CI -0.45 to -0.06) and 5 (-0.24 kg/m^2, 99% CI -0.44 to -0.04) compared to control. MICT showed similar patterns as control without significant differences. There were no significant group differences for lipid measures, systolic and diastolic BP, waist circumference, and glucose measures (*Table 2* and Supplementary material online, *Table S6*).

Peak oxygen uptake

For the total sample, there was practically no change in VO_{2peak} over the 5 years (28.6–28.4 mL/kg/min, 0.7% decline). At Year 5, HIIT had significantly higher VO_{2peak} (mL/kg/min) compared to control (0.76 mL/kg/min, 99% CI 0.02–1.51), but not compared to MICT (0.75 mL/kg/min, 99% CI -0.12 to 1.62). VO_{2peak} scaled to fat-free mass was close to significant at Year 5 for HIIT compared to control (1.0 mL/kg fat-free mass/min, 99% CI -0.02 to 2.02) and MICT (0.96 mL/kg fat-free mass/min, 99% CI -0.23 to 2.15, *Table 2*), but not for ExComb compared to Control. At Years 1 and 3, both ExComb and HIIT alone had significantly higher VO_{2peak} compared to Control, and for HIIT compared to MICT (all $p < 0.01$, *Table 2*). There were no significant between-group differences between MICT and control (Supplementary material online, *Table S6*).

Results by sex

In analyses on effect modification by sex at Year 5, none of the analyses showed significant results. At Year 1, women in HIIT compared to control had a significantly lower effect on waist circumference than men in HIIT (1.8, 99% CI 0.0–3.6, $P = 0.009$).

Discussion

In this large, long-term exercise trial, ExComb did not improve CCR, or individual traditional cardiovascular risk factors, compared to control. Furthermore, although ExComb showed a higher VO_{2peak} at Years 1 and 3 compared to control, the effect estimate was not significant at Year 5. The effect on VO_{2peak} for ExComb was due to a strong and significant effect for HIIT compared to control at all follow-ups, while there was no clear sign of between-group differences on VO_{2peak} for MICT and control. HIIT also showed a significantly lower CCR at Year 3 and near-significant trend at Year 5 compared to control. In general, the results signal an effect on cardiovascular risk reduction of HIIT in older adults mostly mediated through effects on VO_{2peak}, without convincing evidence for other risk factors (*Graphical abstract*). A healthy and for age relatively fit study sample, contamination between intervention groups, and adherence to exercise intervention (cross-over) between intervention groups have likely challenged the possibility to detect between-group differences.

Continuous cardiovascular risk score and individual risk factors

Although none of the group comparisons for CCR were significant at Year 5, the HIIT vs. control comparison was close to significant (-0.32, 99% CI -0.64 to 0.01, $P = 0.011$) and was significant at Year 3. This suggests that, although the individual risk factors mostly did not show significant between-group differences, the combined distribution of important cardiovascular risk factors was improved with HIIT compared to control. However, it should be noted that there were

Table 1 Baseline characteristics by sex and intervention group

Characteristic	Men			Women		
	Control (*N* = 379)	MICT (*N* = 188)	HIIT (*N* = 210)	Control (*N* = 401)	MICT (*N* = 199)	HIIT (*N* = 190)
Age (years)	73 (2.0)	73 (2.1)	73 (2.1)	73 (2.1)	73 (2.0)	73 (2.0)
Weight (kg)	83 (11)	82 (11)	84 (12)	68 (11)	68 (11)	68 (11)
Height (cm)	177 (5.7)	177 (5.9)	177 (6.1)	163 (5.3)	163 (5.0)	163 (5.4)
Fat-free mass (kg)	61 (6.3)	61 (6.6)	61 (6.7)	44 (4.4)	44 (4.1)	44 (4.8)
Body fat (%)	26 (6.2)	25 (6.5)	26 (6.6)	35 (7.1)	34 (7.2)	35 (6.5)
PA adherence[a]	88 (23%)	61 (32%)	64 (30%)	91 (23%)	35 (18%)	50 (26%)
VO_{2peak} (mL/kg/min)	31 (6.8)	32 (6.8)	31 (6.6)	26 (5.0)	26 (5.0)	26 (4.9)
Respiratory exchange ratio	1.1 (0.09)	1.1 (0.09)	1.1 (0.09)	1.1 (0.09)	1.1 (0.09)	1.1 (0.09)
Borg scale peak	17.3 (1.4)	17.2 (1.4)	17.5 (1.3)	17.2 (1.6)	17.1 (1.5)	17.4 (1.4)
Myocardial infarction	30 (8.2%)	19 (11%)	14 (6.9%)	8 (2.1%)	5 (2.6%)	4 (2.2%)
Angina	23 (6.3%)	6 (3.4%)	6 (3.0%)	3 (0.8%)	2 (1.1%)	2 (1.1%)
Heart failure	2 (0.5%)	2 (1.1%)	5 (2.5%)	1 (0.3%)	0 (0%)	0 (0%)
Atrial fibrillation	27 (7.4%)	22 (12%)	20 (10.0%)	9 (2.3%)	8 (4.3%)	4 (2.2%)
Stroke	19 (5.2%)	20 (11%)	8 (4.0%)	12 (3.2%)	8 (4.2%)	9 (5.0%)
COPD	15 (4.1%)	11 (6.1%)	8 (4.0%)	16 (4.2%)	13 (6.9%)	7 (3.9%)
Asthma	23 (6.3%)	13 (7.2%)	20 (9.9%)	34 (8.9%)	22 (12%)	17 (9.4%)
Cancer	51 (14%)	37 (21%)	36 (18%)	62 (16%)	29 (16%)	30 (17%)
Current smoker	30 (8.1%)	20 (11%)	14 (7.0%)	33 (8.6%)	18 (9.5%)	15 (8.2%)
Former smoker	184 (50%)	86 (48%)	99 (50%)	142 (37%)	79 (42%)	59 (32%)
Alcohol, binge[b]	32 (9.1%)	16 (9.6%)	16 (8.2%)	13 (3.6%)	5 (2.8%)	6 (3.6%)
Alcohol (units/week)	4.7 (4.6)	4.5 (4.2)	4.7 (4.8)	3.2 (3.6)	2.5 (3.3)	2.1 (2.7)
Lipid lowering therapy	30 (7.9%)	17 (9.0%)	17 (8.1%)	35 (8.7%)	15 (7.5%)	25 (13%)
Beta blockers[c]	17 (4.5%)	10 (5.3%)	17 (8.1%)	17 (4.2%)	10 (5.0%)	10 (5.3%)
Antihypertensives	147 (39%)	69 (37%)	64 (30%)	124 (31%)	55 (28%)	60 (32%)
Antidiabetic medication	26 (6.9%)	7 (3.7%)	17 (8.1%)	7 (1.7%)	5 (2.5%)	5 (2.6%)
Nitrates	2 (0.5%)	0 (0%)	4 (1.9%)	4 (1.0%)	5 (2.5%)	3 (1.6%)

Values are mean (standard deviation), or *n* (%).
COPD, chronic obstructive pulmonary disease; HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; PA, physical activity; VO_{2peak}, peak oxygen uptake.
[a]Adherence to PA recommendations prior to study inclusion.
[b]Alcohol intake >5 units per sitting frequently (weekly).
[c]Beta-blockers or heart selective calcium channel blockers.

no significant differences in CVD events or deaths between the intervention groups, as previously reported.[15]

The descriptive data (*Figure 2*) showed that the significant effects by HIIT on BMI were mostly mediated through effects in women, with a similar trend for some other risk factors. However, formal testing by including three-way interaction terms did not show significant difference in effect estimates across sex. Still, one might speculate that these trends may stem from men (27%) being more physical activity than women (22%) at baseline.

Although this study did not show a clear effect of HIIT, MICT, or their combination (ExComb) on cardiovascular risk factor reduction beside changes in VO_{2peak} when compared to an active control group, these data should not be interpreted as evidence of lack of an effect of exercise on overall health. We want to emphasize that the study did not have a sedentary control group, and effects of exercise for promotion of health and primary prevention are thoroughly established.[31]

We believe several factors may have affected the possibility of detecting significant between-group differences. First, the participants had better self-reported health and higher education were more physically active and reported less cardiovascular and other disease at study start compared to non-participants,[16] meaning that participants self-selecting to participation had a favourable cardiovascular risk profile compared to the age-matched general population. The mean BP at baseline was indeed ~5 mmHg lower than the average for adults in their 70s in the same area (central Norway),[32] and BMI and lipid profile were similarly favourable. Thus, the potential to improve risk factors beyond baseline levels might have been limited (ceiling effect) due to the self-selection of healthy and fit participants into the study. Furthermore, based on self-reported exercise habits, the proportion of control performing high-intensity exercise was higher than MICT at all follow-ups, whereas HIIT performed considerably more high-intensity exercise than the two other groups.[15] Still, high-intensity exercise was carried out by substantial portions of

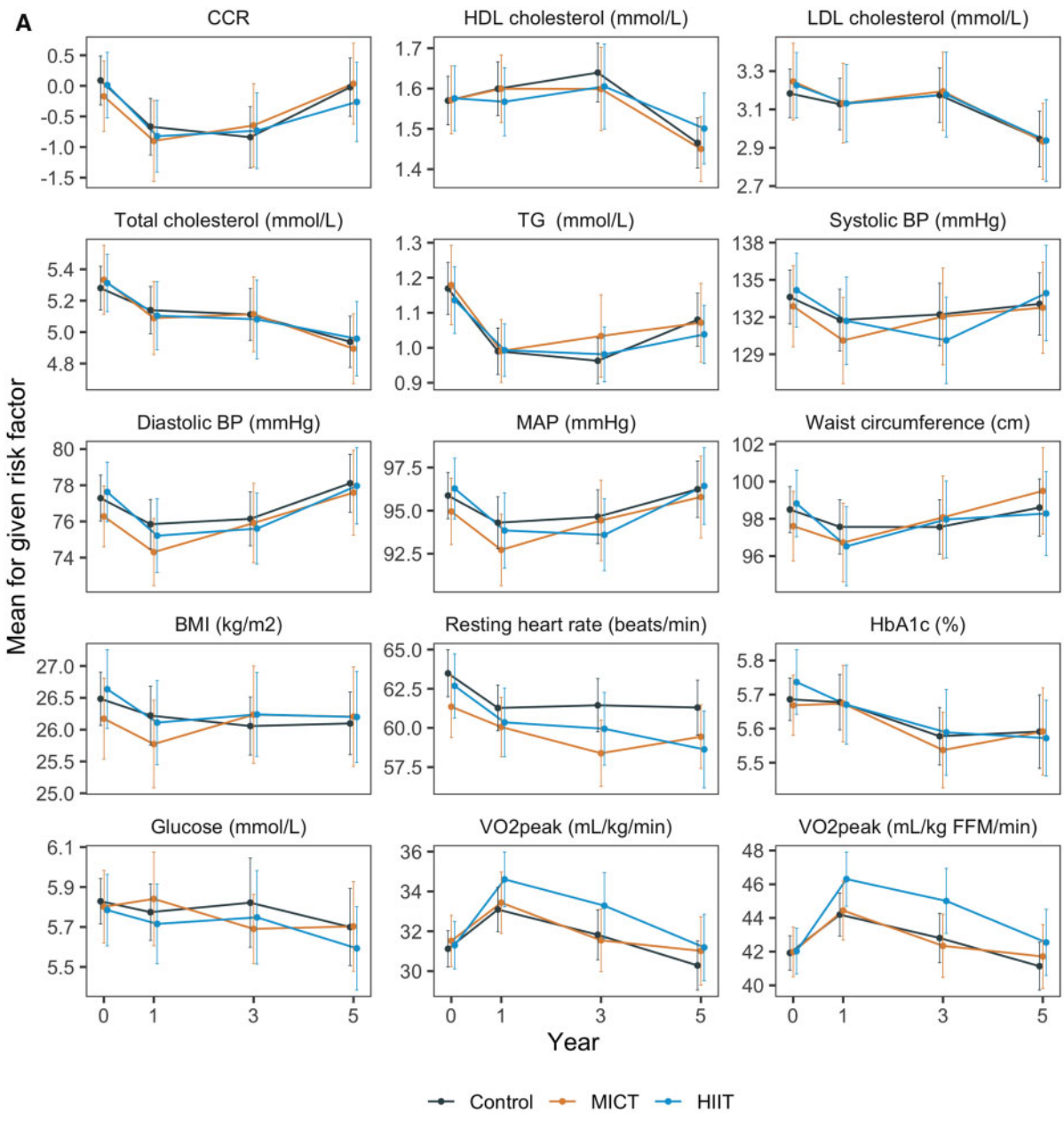


Figure 2 (*A*) Men and (*B*) women. Descriptive data presented as means and 99% confidence intervals for each risk factor at study Years 0 (baseline), 1, 3, and 5 by the three intervention arms. The combination of HIIT and MICT (ExComb) is not shown. BMI, body mass index; BP, blood pressure; CCR, continuous cardiovascular risk score; FFM, fat-free mass; HbA1c, glycosylated haemoglobin; HIIT, high-intensity interval training; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean arterial pressure; MICT, moderate-intensity continuous training group; TG, triglycerides; VO_{2peak}, peak oxygen uptake.

those both in control and MICT,[15] and this contamination between intervention groups likely influenced the ability to detect between-group differences. Especially, due to these factors, the 'exercise vs. control' comparison was blurred.

Several previous short-term studies (<1 year) have investigated the effect of aerobic exercise compared to a control group on cardiovascular risk factors in older adults, showing benefits on BP,[14,33] resting HR,[34] BMI, waist circumference,[35] and glucose homeostasis.[36,37] The effect of exercise on lipids in older adults has shown somewhat conflicting results.[35,38–40] Importantly, evidence on the contribution of different relative exercise intensities in older adults is almost absent. Results from some randomized clinical trials have shown the effect of high-intensity exercise compared to the moderate-intensity exercise on insulin resistance measures,[41,42] somewhat contradictory to our findings of no significant between-group differences for glycosylated haemoglobin and glucose. Self-

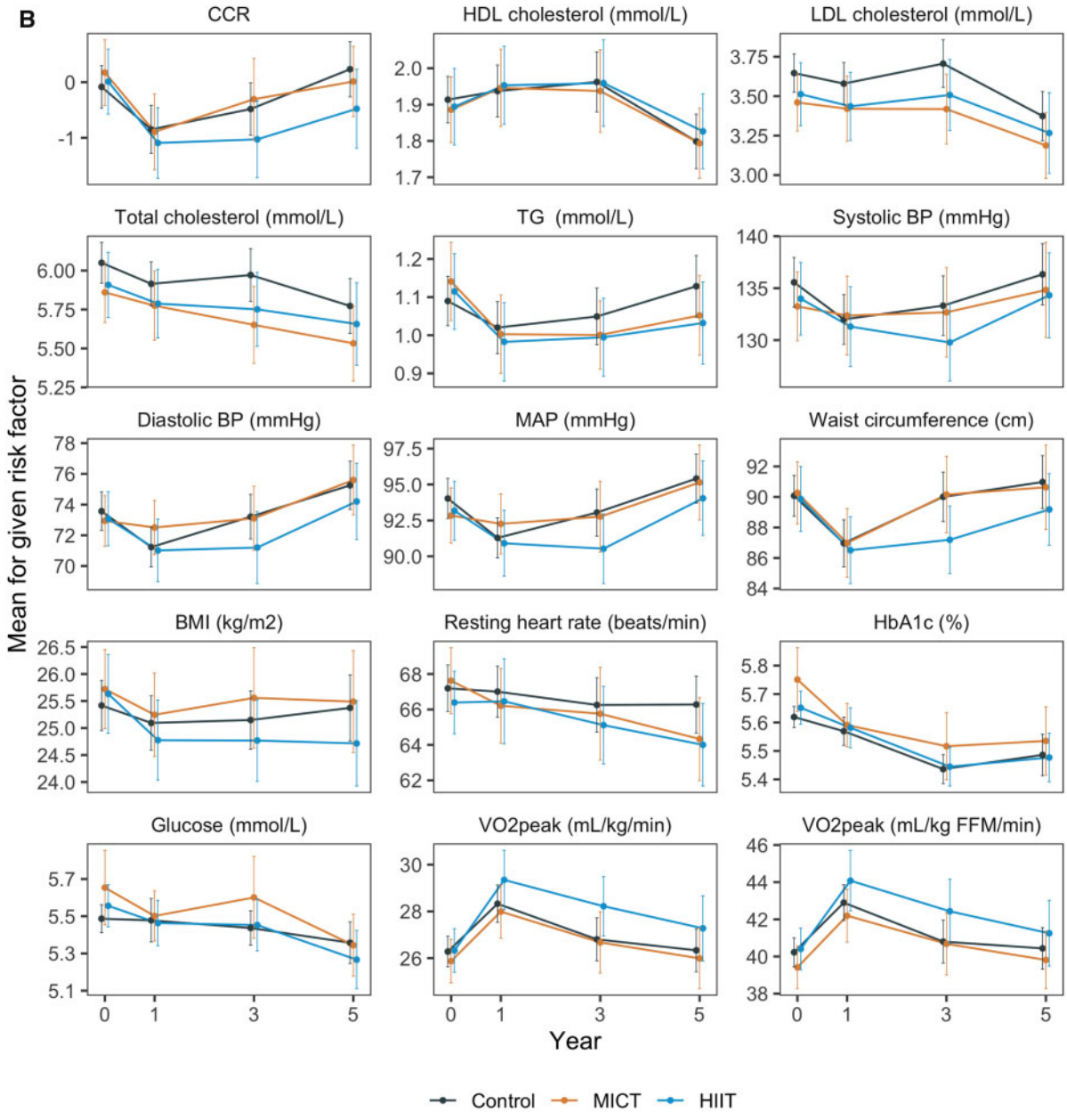


Figure 2 Continued.

reported habitual exercise increased in all groups from baseline to Year 1,[15] and BP measures decreased in all groups with lack of between-group differences after the first year. MAP was significantly lower for HIIT compared to control at Year 3, but also this effect was attenuated at Year 5. The effect of exercise on lipids in older adults has, as mentioned, shown varied results. Similarly, this trial does not show clear between-group effects for different intensities. This is similar to a 1-year trial randomizing 50–65-year-old sedentary adults to high- and low-intensity training or control, without being able to show between-group differences for lipid measures.[43] Large effects of exercise or differential effects of various exercise intensities on lipid levels in older adults is thus not thoroughly established, and factors other than exercise may have a larger relative impact on lipid profiles with higher age. Park *et al.*[44] studied CRF and lipid levels in a cohort of 11 418 men from the Aerobics Center Longitudinal Study and showed how levels of TC, LDL-C, and TG peak around 50 years of age only to decline with higher age, while HDL-C increased steadily. The same study showed that the favourable effect of CRF on lipids weakened with age and was partially gone at high age.[44]

Table 2 Results from linear mixed models showing treatment effect as year × group interaction with 99% confidence interval for ExComb, moderate-intensity continuous training, and high-intensity interval training compared to control as well as descriptive mean (standard deviation) for control

Risk factor	Year	Control,	ExComb vs. control		HIIT vs. control		HIIT vs. MICT	
		Mean (SD)	Estimate (99% CI)	*P*-Value	Estimate (99% CI)	*P*-Value	Estimate (99% CI)	*P*-Value
CCR (sum of *Z*)	0	0 (2.98)						
	1	-0.76 (3.06)	-0.08 (-0.32 to 0.17)	0.42	-0.1 (-0.4 to 0.2)	0.38	-0.06 (-0.41 to 0.29)	0.68
	5	0.1 (2.99)	-0.19 (-0.46 to 0.07)	0.055	-0.32 (-0.64 to 0.01)	0.011	-0.24 (-0.62 to 0.13)	0.095
HDL cholesterol (mmol/L)	0	1.75 (0.51)						
	1	1.78 (0.51)	0.01 (-0.02 to 0.04)	0.51	0.01 (-0.03 to 0.05)	0.53	0 (-0.05 to 0.05)	0.89
	5	1.63 (0.46)	0.01 (-0.03 to 0.05)	0.43	0.03 (-0.02 to 0.07)	0.089	0.04 (-0.02 to 0.09)	0.073
LDL cholesterol (mmol/L)	0	3.42 (0.97)						
	1	3.36 (0.95)	-0.03 (-0.12 to 0.07)	0.48	-0.05 (-0.17 to 0.06)	0.24	-0.05 (-0.19 to 0.08)	0.3
	5	3.16 (0.95)	-0.03 (-0.13 to 0.07)	0.46	-0.04 (-0.16 to 0.09)	0.47	-0.01 (-0.16 to 0.13)	0.81
TC (mmol/L)	0	5.68 (1.1)						
	1	5.54 (1.08)	-0.02 (-0.12 to 0.08)	0.59	-0.03 (-0.16 to 0.09)	0.49	-0.02 (-0.17 to 0.12)	0.67
	5	5.35 (1.13)	-0.05 (-0.16 to 0.07)	0.3	-0.03 (-0.16 to 0.11)	0.64	0.04 (-0.12 to 0.2)	0.54
TG (mmol/L)	0	1.13 (0.53)						
	1	1.01 (0.47)	-0.01 (-0.06 to 0.04)	0.64	-0.01 (-0.07 to 0.06)	0.83	0.01 (-0.07 to 0.08)	0.77
	5	1.1 (0.48)	-0.05 (-0.11 to 0.01)	0.024	-0.06 (-0.13 to 0.01)	0.023	-0.02 (-0.1 to 0.06)	0.45
Diastolic BP (mmHg)	0	75.4 (9.77)						
	1	73.5 (9.48)	-0.09 (-1.13 to 0.95)	0.82	-0.32 (-1.61 to 0.97)	0.52	-0.46 (-1.96 to 1.04)	0.43
	5	76.7 (9.94)	-0.09 (-1.22 to 1.04)	0.84	-0.47 (-1.87 to 0.93)	0.39	-0.75 (-2.36 to 0.87)	0.23
Systolic BP (mmHg)	0	135 (17.5)						
	1	132 (17)	0.07 (-1.89 to 2.02)	0.93	0.25 (-2.18 to 2.68)	0.79	0.35 (-2.48 to 3.18)	0.75
	5	135 (17)	-0.4 (-2.53 to 1.73)	0.63	-0.12 (-2.76 to 2.52)	0.91	0.54 (-2.5 to 3.59)	0.65
MAP (mmHg)	0	94.9 (10.5)						
	1	92.7 (10.2)	-0.04 (-1.21 to 1.13)	0.93	-0.13 (-1.58 to 1.32)	0.82	-0.18 (-1.87 to 1.51)	0.78
	5	95.8 (10.4)	-0.2 (-1.47 to 1.07)	0.69	-0.35 (-1.93 to 1.23)	0.57	-0.31 (-2.13 to 1.51)	0.66
Resting heart rate (b.p.m.)	0	65.4 (10.9)						
	1	64.2 (10.3)	-0.44 (-1.59 to 0.7)	0.32	-0.35 (-1.78 to 1.07)	0.52	0.17 (-1.49 to 1.83)	0.79
	5	63.8 (10.7)	-1.44 (-2.67 to -0.21)	0.003	-1.89 (-3.42 to -0.36)	0.002	-0.86 (-2.62 to 0.9)	0.21
Waist circumference (cm)	0	94.2 (10.7)						
	1	92.1 (11.9)	-0.06 (-0.8 to 0.68)	0.82	-0.3 (-1.21 to 0.62)	0.4	-0.46 (-1.52 to 0.6)	0.26
	5	94.8 (10.9)	-0.09 (-0.9 to 0.72)	0.77	-0.47 (-1.47 to 0.53)	0.23	-0.74 (-1.9 to 0.42)	0.099
BMI (kg/m^2)	0	25.9 (3.42)						
	1	25.6 (3.44)	-0.14 (-0.29 to 0.01)	0.018	-0.18 (-0.37 to 0)	0.011	-0.09 (-0.3 to 0.13)	0.29
	5	25.7 (3.49)	-0.11 (-0.27 to 0.05)	0.072	-0.24 (-0.44 to -0.04)	0.002	-0.25 (-0.48 to -0.02)	0.005
HbA1c (%)	0	5.65 (0.39)						
	1	5.62 (0.47)	-0.03 (-0.07 to 0.02)	0.12	-0.02 (-0.07 to 0.03)	0.34	0.01 (-0.05 to 0.07)	0.62
	5	5.54 (0.58)	-0.01 (-0.05 to 0.04)	0.76	-0.01 (-0.07 to 0.05)	0.59	-0.01 (-0.08 to 0.05)	0.62
Glucose (mmol/L)	0	5.65 (0.75)						
	1	5.62 (0.91)	-0.02 (-0.12 to 0.08)	0.54	-0.04 (-0.16 to 0.09)	0.46	-0.02 (-0.17 to 0.12)	0.67
	5	5.53 (1)	-0.06 (-0.17 to 0.04)	0.13	-0.08 (-0.22 to 0.05)	0.11	-0.04 (-0.19 to 0.12)	0.55
VO_{2peak} (mL/kg/min)	0	28.6 (6.41)						
	1	30.6 (6.87)	0.61 (0.08 to 1.15)	0.003	1.01 (0.36 to 1.67)	<0.001	0.8 (0.04 to 1.57)	0.007
	5	28.4 (6.65)	0.39 (-0.22 to 1)	0.097	0.76 (0.02 to 1.51)	0.008	0.75 (-0.12 to 1.62)	0.027
VO_{2peak} (mL/kg fat-free mass/min)	0	41.1 (6.82)						
	1	43.5 (7.53)	0.76 (0.03 to 1.49)	0.007	1.32 (0.42 to 2.22)	<0.001	1.11 (0.07 to 2.16)	0.006
	5	40.8 (7.38)	0.52 (-0.31 to 1.35)	0.11	1.00 (-0.02 to 2.02)	0.012	0.96 (-0.23 to 2.15)	0.038

BMI, body mass index; BP, blood pressure; CCR, continuous cardiovascular risk score; CI, confidence interval; ExComb, combined exercise groups; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; HIIT, high-intensity interval training; LDL, low-density lipoprotein; MAP, mean arterial pressure; MICT, moderate-intensity continuous training; SD, standard deviation; VO_{2peak}, peak oxygen uptake; TC, total cholesterol; TG, triglycerides.

Table 3 Clinical events during 5 years of follow-up in men and women by intervention groups

Clinical events	Control		ExComb		MICT		HIIT	
	Men	Women	Men	Women	Men	Women	Men	Women
All-cause mortality	5.0 (19)	4.5 (18)	5.5 (22)	3.3 (13)	7.4 (14)	4.5 (9)	3.8 (8)	2.1 (4)
Causes of death								
CVD	0.5 (2)	0.2 (1)	1.3 (5)	0.5 (1)	1.5 (3)	0.5 (1)	1.0 (2)	0
Cancer	2.6 (10)	3.2 (13)	3.2 (13)	2.8 (11)	4.2 (8)	3.5 (7)	2.3 (5)	2.1 (4)
Other	1.8 (7)	1.0 (4)	1.0 (4)	0.5 (1)	1.6 (3)	0.5 (1)	0.5 (1)	0
All CVD	21.1 (80)	11.2 (45)	20.9 (83)	9.3 (36)	19.1 (36)	11.1 (22)	22.4 (47)	7.4 (14)
Myocardial infarction	4.5 (17)	1.7 (7)	4.8 (19)	0.5 (2)	2.1 (4)	0.5 (1)	7.1 (15)	0.5 (1)
Cardiac arrest	0.3 (1)	0	0.5 (2)	0	0	0	1.0 (2)	0
Unstable angina	0.3 (1)	0.2 (1)	0.8 (3)	0.3 (1)	0	0.5 (1)	1.4 (3)	0
Heart failure	1.3 (5)	1.2 (5)	3.3 (13)	1.3 (5)	3.2 (6)	2.0 (4)	3.3 (7)	0.5 (1)
Stroke	5.8 (22)	2.2 (9)	4.0 (16)	2.3 (9)	4.3 (8)	2.5 (5)	3.8 (8)	2.1 (4)
Atrial fibrillation	6.9 (26)	5.5 (22)	10.1 (40)	4.1 (16)	9.6 (18)	6.0 (12)	10.5 (22)	2.1 (4)
Atrial flutter	1.6 (6)	0.7 (3)	2.8 (11)	1.0 (4)	2.7 (5)	2.0 (4)	2.9 (6)	0
Other tachycardia	2.4 (9)	0	1.3 (5)	0.8 (3)	0.5 (1)	1.0 (2)	1.9 (4)	0.5 (1)
PCI	5.5 (21)	1.7 (7)	5.0 (20)	1.2 (5)	3.7 (7)	1.0 (2)	6.2 (13)	1.6 (3)
CABG	2.1 (8)	1.0 (4)	2.5 (10)	0.3 (1)	2.1 (4)	0.5 (1)	2.9 (6)	0
CVD events[a]	21.4 (81)	11.5 (46)	21.3 (85)	9.5 (37)	19.7 (37)	11.6 (23)	22.9 (48)	7.4 (14)
All cancers	14.2 (54)	11.5 (46)	12.1 (48)	11.1 (43)	10.1 (19)	12.1 (24)	13.8 (29)	10.0 (19)
Gastrointestinal	3.2 (12)	1.5 (6)	3.0 (12)	3.3 (13)	2.1 (4)	4.0 (8)	3.8 (8)	2.6 (5)
Respiratory	0.8 (3)	1.2 (5)	1.0 (4)	0.5 (2)	1.1 (2)	0.5 (1)	1.0 (2)	0.5 (1)
Breast	0	2.2 (9)	0	1.3 (5)	0	0.5 (1)	0	2.1 (4)
Prostatic	5.3 (20)		4.3 (17)		2.1 (4)		6.2 (13)	
Cancer events[a]	15.0 (57)	12.1 (50)	13.1 (52)	11.3 (44)	11.7 (22)	12.1 (24)	14.3 (30)	10.5 (20)

Values are % (*n*).
CABG, coronary artery bypass grafting; CVD, cardiovascular disease; ExComb, combined exercise groups; HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; PCI, percutaneous coronary intervention.
[a]Fatal and non-fatal events combined.

Long-term exercise and expected age-related decline of VO_{2peak}

VO_{2peak} increased markedly in all three groups from baseline to Year 1, reflecting changes in exercise habits in all study groups. From Years 1–5 there was a linear decline of ∼2% per year for all three groups combined, similar to the ∼20% 10-year longitudinal decline in VO_{2peak} found in adults >70 years both in the Baltimore Longitudinal Study of Aging,[7] and the Norwegian HUNT study,[45] where the latter is located in the same county as the Generation 100 study. However, due to the significant increase in the first year, VO_{2peak} was higher after 5 years than at baseline in HIIT (+0.5 mL/kg/min), and only slightly below the baseline value for MICT and control (-0.3 and -0.5 mL/kg/min), which is remarkable given the ∼10% expected decline over 5 years. In the mentioned HUNT study,[45] where the mean age was ∼50 years at first survey, those reporting high-intensity exercise at both surveys 10 years apart still had a 1% annual decline in VO_{2peak} on average, similar to the 1.1% annual decline found in those performing moderate-intensity exercise on both occasions, supporting that annual declines are similar across different exercise intensities when they are maintained over time. Given that the decline in VO_{2peak} is more pronounced at higher age,[7,45] the data from our study are well in line with what is expected based on the mentioned observational data also for the HIIT group. In HUNT, changing intensity level of leisure-time exercise from moderate-intensity at the first survey to high-intensity exercise at the second survey was associated with a considerably lower decline of 4.1% over 10 years. Therefore, it is important to note that also in the present study those performing high-intensity exercise had higher absolute values than control and MICT, although the per-year annual decline was similar from Years 1 to 5. This implies that, over time, it seems difficult to overcome age-related declines in VO_{2peak} by exercise, but regular exercise gives higher absolute values to start the decline from. Our observations that VO_{2peak} was higher in ExComb vs. control, and for HIIT compared to MICT and control when scaled to fat-free body mass, are in line with our recent observation when scaling VO_{2peak} directly to body mass,[15] as presented here as well. This demonstrates that changes in VO_{2peak} were due to changes in fitness and not in body composition *per se*.

A larger effect of HIIT compared to MICT and control on VO_{2peak} has previously been shown in small randomized clinical trials with relatively short follow-up,[46] but also short-term studies are scarce in older adults.[10] Thus, these novel long-term results support the use of HIIT for maintaining health, as low VO_{2peak} previously has been established as a strong predictor of dependency,[47] and observational studies suggest ∼15% lower risk of CVD and all-cause mortality per

one metabolic equivalent task (MET, 3.5 mL/kg/min) higher VO_{2peak}.[6] Although an effect estimate of HIIT compared to the control of 0.76 mL/kg/min after 5 years may seem small, moving a population mean implies affecting the distribution of a risk factor such that it may substantially benefit populational health.[48] Importantly, the effects on VO_{2peak} and other cardiovascular risk factors pointed in the same direction as the numerically, but not statistically significant, benefit on survival for HIIT observed in the analysis of the main outcome of the Generation 100 study.[15] Furthermore, of note is that no CVD events occurred during supervised exercise over the study course, indicating safety of HIIT in older adults.[15]

Strengths and limitations

The study is based on data from one of the largest randomized clinical trials performed on exercise in older adults, making the data material unique. However, the study also has notable limitations, in addition to the challenges outlined above. First, adherence to the assigned intervention is challenging for all exercise trials, and in our study, only about half of the participants reported exercise in line with their assigned group for participants in MICT and HIIT. Also, allowing the participants to self-select exercise mode outside organized sessions (walking, cycling e.g.) may have affected exercise intensity and matching of exercise volume. Furthermore, although HIIT was feasible in this healthy and fit sample, this may not be true for all older adults, which in general should be kept in mind when translating our findings to different populations and parts of the world. However, as previously reported, 13% had poor self-reported health at baseline, and CVD and cancer were rather prevalent,[16] suggesting that significant comorbidities are not necessarily an obstacle to perform high-intensity exercise. Loss to follow-up throughout the study introduces the risk of attrition bias, meaning that although analyses were performed by intention-to-treat including all randomized participants, differences in participation rates at follow-up may introduce bias.

Conclusions

Randomization to 5 years of exercise with regular supervision in older adults failed to show lowered individual and clustered cardiovascular risk factors or a higher VO_{2peak} for ExComb compared to control. The significantly higher VO_{2peak} for ExComb at Years 1 and 3 was driven by the effect in HIIT, which had a significantly higher VO_{2peak} at all follow-up years compared to control. Although HIIT showed a mostly non-significant trend of a favourable effect compared to control and MICT for CCR and some individual cardiovascular risk factors, the study did not produce conclusive data regarding favourable health effects of high-intensity exercise compared to moderate-intensity exercise. Despite the large study sample, selection bias favouring participation of healthy participants, incomplete adherence to exercise intervention, contamination between study arms, and an active control group challenged the ability to detect between-group differences.

Supplementary material

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

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Conflict of interest: In the submitted ICMJE form, Dr Wisløff reports being a consultant for PAI Health Norway related to monitoring of physiological variables using wearable technology, not regarded relevant for this study. Thus, the Authors declare that there is no conflict of interest.

Data availability

We are not allowed to share individual data from the current trial, but we open for collaboration with researchers worldwide that will get access to analysed data from our university. We have also established a biobank of blood and genetic material that is planned to be shared with researchers worldwide, but individual data must be analysed within our university and cannot be sent abroad.

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