Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Neuromedicine and Movement Science

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The effects of eight years of aerobic exercise at different intensities on cardiorespiratory fitness and physical function in older adults

A Generation 100 sub study

Master's thesis in Physical Activity and Health
Supervisor: Dorthe Stensvold

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Kunnskap for en bedre verden

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AIM:
INVESTIGATE THE EFFECT OF AEROBIC EXERCISE AT DIFFERENT INTENSITIES ON CARDIORESPIRATORY FITNESS AND PHYSICAL FUNCTION IN OLDER ADULTS

A Generation 100 sub study

49 older adults

70-77 years old

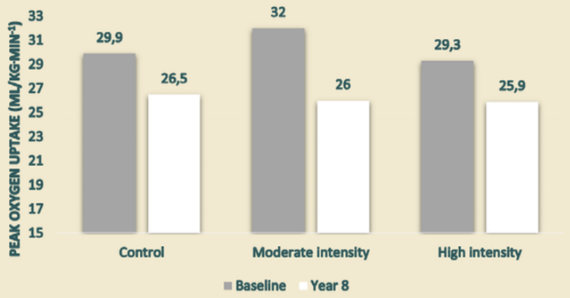
8 years

Randomised into one of three groups

Control group	Moderate intensity	High intensity
National guidelines for physical activity	50 minutes at ~ 70% of maximal heart rate 2x per week	4x4 minutes at 85-95% of maximal heart rate 2x per week

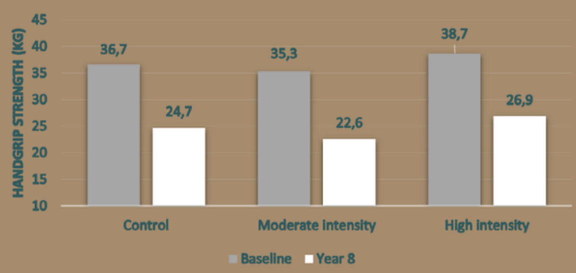
Conclusion:
High intensity aerobic exercise and the control group induced a favourable effect compared to moderate intensity on cardiorespiratory fitness
No group differences were found for physical function

Cardiorespiratory fitness



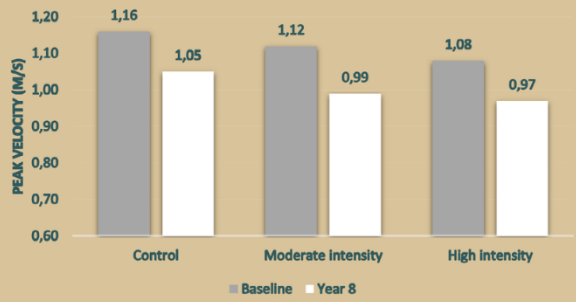
The high-intensity and control group had a lower decline in cardiorespiratory fitness than moderate-intensity

Handgrip strength



No group differences in were found in decline in handgrip strength

Sit-to-stand



No group differences were found in sit-to-stand performance

Abstract

Background: Maintaining cardiorespiratory fitness into old age is important for health, avoiding chronic diseases, and preventing premature mortality. Ageing leads to a decline in cardiorespiratory fitness. However, little is known about long-term effects of different aerobic exercise interventions on cardiorespiratory fitness and on physical function in older adults. The aim of the present study was to examine the effect of eight years of aerobic exercise at different intensities on cardiorespiratory fitness and physical function.

Methods: In total, 49 participants from the Generation 100 study were invited to an eight-year follow-up sub study. Participants had previously been randomised into either a high-intensity interval training group (HIIT) exercising 4x4 intervals at 85-95% of maximal heart rate twice per week, a moderate-intensity continuous training group (MICT) exercising continuously for ~50 minutes at ~70% of maximal heart rate twice per week, or a control group (CON) asked to follow national guidelines for physical activity. Cardiorespiratory fitness was measured by cardiopulmonary exercise test on a treadmill, while physical function was measured by handgrip strength and a sit-to-stand test.

Results: All groups had a significant decline in both cardiorespiratory fitness and physical function after eight years ($p<0.05$). MICT had a higher decrease in cardiorespiratory fitness compared to HIIT and CON after eight years of aerobic exercise compared to MICT ($p<0.05$), with no difference between HIIT and CON. No differences between groups were observed in handgrip strength nor sit-to-stand performance.

Conclusion: After eight years, the group performing aerobic high intensity interval training and the control group had a lower decline in cardiorespiratory fitness compared to the group performing moderate intensity aerobic exercise. There were no group differences in physical function measured by handgrip strength and sit-to-stand after eight years.

Acknowledgements

This master thesis was part of my master's degree in Physical Activity and Health, where I specialised in Movement Science at the Department of Neuromedicine and Movement Science at NTNU.

This final year has consisted of a lot of hard work in gathering and analysing data, and writing the thesis itself. All part of a process which would not be possible without the assistance of several people.

First and foremost, a huge thanks goes out to all participants in this study for taking the time to participate in this project. I am thoroughly impressed by how many were willing to participate, especially given the trying times in which data was collected.

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Trondheim, May 2021

Sveinung Rydland

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Introduction

Ageing

The population of the world is ageing (1). In 2019, there were 703 million people aged 65 or above. By 2050, this number is projected to reach 1.5 billion, with a percentage increase from 9% in 1990, to 16% in 2050. Ageing is associated with a gradual decline in functional ability, increased risk of chronic diseases, and a general decline in capacity (2). However, this decline is not a linear nor a consistent one. Some older adults may enjoy good functioning both physically and mentally, while others may require significant support to meet their basic needs. Although age is often referred to chronologically, physiological changes and levels of functioning are only loosely associated with chronological age, as function and intrinsic capacity can vary widely across older adults (2). Generally, function can be divided into three common periods: 1) a period of relatively high and stable capacity, 2) a period of declining capacity, and 3) a period of significantly declining capacity (2). These are not defined by chronological age and are not necessarily happening at a steady rate. Unexpected events, such as a fall, may cause a disruption in these trajectories (2). Measuring a population based solely on chronological age fails to take into account the burden of an increase in older adults (3). As noted in World Health Organization's (WHO) World report on ageing and health, the primary focus of healthy ageing is the maintenance of functional ability, described as having the capabilities that enable people to be and do what they have reason to value (2). Thus, the focus of future health care should not focus exclusively on curing older adults of disease, but to enable them to maintain their functional ability and prevent onset and/or worsening of disease.

Physical activity (PA) can delay or prevent many of the health challenges associated with ageing, even at a very advanced age (2). To understand how PA can be used to help alleviate the challenges faced by an increasingly older population, it is important to have a fundamental understanding of what PA and exercise is and the difference between PA and exercise. PA is defined as any bodily movement produced by skeletal muscle that requires energy expenditure (4). Exercise refers to planned, structured, repetitive, and purposive PA, where improvement or maintenance of one or several components of physical fitness is the objective (4). Thus, all exercise is PA, but all PA is not necessarily exercise. Utilising exercise to increase PA levels is a way to alleviate healthcare costs, improving functional ability and independence and general health in older people. The recommended strategy by WHO to promote PA, is to address cardiorespiratory fitness, muscle strength and balance, and resistance training (2).

Cardiorespiratory fitness

There is a well-established inverse relationship between cardiorespiratory fitness (CRF) and chronic diseases, and mortality risk (5). A population with a higher cardiorespiratory fitness is therefore more likely to have fewer individuals living with chronic diseases. This in turn can help alleviate the healthcare system, as well as providing a better quality of life for the general population. CRF is the integration of several components which reflects an individual's ability to transport oxygen from the atmosphere to the working mitochondria in the muscles (5). It is a chain of processes that includes lung function, heart function, vascular function, and muscular ability to utilize the oxygen in an appropriate manner, and thus is a means to quantify all these components into one integrated system. By measuring CRF one can therefore quantify an individual's overall cardiorespiratory function. CRF has been shown to be a better predictor of mortality risk than traditional risk factors such as smoking, obesity, hyperlipidaemia and type 2 diabetes (5), underlining the clinical importance of measuring CRF. CRF can be measured directly measured as maximal oxygen consumption (VO_{2max}) from a cardiopulmonary exercise test (6). Although often used interchangeably, VO_{2max} differs from VO_{2peak} (peak oxygen uptake). VO_{2peak} refers to the highest observed value during exercise, while VO_{2max} is levelling-off of oxygen uptake despite an increase in workload, combined with a respiratory exchange ratio (RER) of ≥1.05 (7).

Factors influencing cardiorespiratory fitness

Oxygen uptake is determined by the Fick equation, which can be stated as cardiac output x arteriovenous oxygen difference (a-vO_2 difference) (8). Further, cardiac output is determined by stroke volume (SV) x heart rate (HR). Thus, the peak oxygen uptake is determined primarily by SV, maximal HR (HR_{max}) and a-vO_2-difference. Previous research indicates that VO_{2peak} decreases by ~1% per year until old age, when it accelerates, regardless of PA habits (9). This may be caused by several components, but the main reasons appear to be a lowered HRmax and reduced a-vO_2 difference (10). As a compensatory mechanism, SV can significantly increase with ageing, thus making it possible for older adults to have a peak cardiac output similar to younger people (8). Aerobic exercise may help counteract the age-related changes by increasing SV and a-vO_2 difference (11). Previous studies have found high-intensity interval training (HIIT) to be superior to moderate intensity continuous training (MICT) for improving VO_{2peak} for healthy persons (12), as well as in patient groups (13,14). Further, Stensvold et al. (15) found HIIT to be superior to MICT, and a control group asked to follow national guidelines for PA also in older adults. A recent meta-analysis found HIIT to be superior to MICT in middle-aged and older adults (16). Thus, HIIT seem to be a superior strategy for inducing beneficial cardiovascular adaptations in older adults.

Physical function

Physical function is the ability to perform activities that are essential for functional living, such as walking, feeding, dressing, and bathing, known as basic activities of daily living (ADL) (17). In addition, physical function may also be referred to as activities that allow the individual to live independently in a community, known as instrumental ADL (18). Instrumental ADLs include transportation, shopping, housework and similar. These activities are not necessary for functional living but are highly important for quality of life. A person's capacity to undertake everyday tasks, is denoted by one's functional capacity (19). The time when one needs help to manage daily activities and care, is known as the disability threshold (19). The age at which this threshold is reached varies widely (19), affirming the highly variable functional ability across people of similar age, and illustrates the need for looking beyond chronological age. Functional capabilities at 65-80 years are correlated with functional independence beyond 80 years of age (20).

Handgrip strength is commonly used for predicting physical function (21). It has been found to be a valid and useful biomarker for current and future health status, especially for outcomes such as generalized strength and function, fractures, falls, disease status and comorbidity load, and mortality (22). It has further been found to predict accelerated dependency in ADL and cognitive decline in people >80 years of age (21). High HGS has been found to reduce risk of impaired IADL, and independently associated with functional independence (23), while low HGS is associated with an increased risk of several functional limitations (24).

Measuring HGS may thus provide an indication of an individual's physical function through standardised methods of testing. However, measuring only upper body function may not be sufficient to reflect an individual's overall function (22). A common challenge for older adults is to move into and out of a chair or bed (25). Being able to rise from a seated position to a standing position is important for everyday life, as it is a prerequisite for walking and essential for independent life (26). The sit-to-stand test (STS) is a standard part of assessment of geriatric patients (25), and is a well-established measure of functional lower limb function (27). Although there are several STS protocols, shorter STS-tests are preferred for measuring muscle power (28), with muscle power reported to be a better measure of physical function than strength or endurance (29). Peak velocity during STS has been shown to be an important marker of stair climb time and mobility in older adults with mobility limitations (30), and has been found to be significantly slower in older adults struggling with falls (31).

Physical activity and physical function

There is a bidirectional relationship between PA and physical function. A decline in PA predicts a decline in physical function and vice versa, with physical function more consistently predicting PA levels (32). Thus, one can maintain physical functioning better by maintaining PA levels. This bidirectional relationship provides an opportunity to prevent or stall physical function by being physically active. Furthermore, it affirms the close link between cardiovascular health and physical function and the importance of physical function for cardiovascular health and vice versa. For younger and mid-age people, it is unlikely that PA matters much for physical function as the disability threshold is likely not crossed (19). However, for older adults the difference of the disability threshold between inactive people, and those reporting high PA has been found to be as high as 14 years, with the average age being 70 and 84 years, respectively (19). The burden of an increasingly ageing population may thus be offset by maintaining physical function through PA.

The research on the effect of aerobic exercise intensity on physical function in the general population of older adults is scarce (33) and inconsistent. While one study reported high-intensity exercise to be preferential to moderate-intensity exercise for HGS (34), others did not find any difference between exercise intensities (35,36). Similar inconsistent results are found for STS, where one study found high-intensity to be superior for STS (37), while others found moderate-intensity to be better (34). Others found no difference (35,36).

At the time we initiated this project, the literature lacked high-quality data provided by randomised controlled trials looking at the long-term effect of aerobic exercise at different exercise intensities on cardiorespiratory fitness and physical function. The main aim of the present study is to examine the effect of eight years of aerobic exercise at different intensities on cardiorespiratory fitness in older adults. The secondary aim is to examine the effect of eight years of aerobic exercise at different intensities on physical function in older adults. The hypothesis for the main outcome is that high-intensity-interval training induces a more favourable effect on cardiorespiratory fitness compared to moderate-intensity continuous training and to a control group asked to follow national guidelines for physical activity. For physical function, the hypothesis is that there is no difference between the groups for neither handgrip strength nor sit-to-stand after eight years.

Methods

Study design of Generation 100

The aims were investigated using data and participants from the Generation 100 study, conducted in Trondheim, Norway (38). In 2012, all inhabitants in Trondheim, born between 1 January 1936 and 31 December 1942 were invited to participate in the study. Participants were randomized 1:1:2, stratified by sex and cohabitation (living alone or with someone), into either HIIT (n=400), MICT (n=387), or a control group (CON, n=780). Randomisation was performed by Unit for Applied Clinical Research at the Norwegian University of Science and Technology (NTNU). Participants were tested at baseline, and at one, three, and five years after inclusion. HIIT followed a training protocol consisting of 10 minutes of warm-up, followed by a 4x4 minutes interval session at ∼90% of maximal heart rate. MICT followed a training protocol of ∼50 minutes of moderate-intensity training at ∼70% of maximal heart rate. CON was asked to follow Norwegian guidelines for PA at inception in 2012, i.e., 30 minutes of at least moderate intensity almost every day (39). HIIT and MICT were offered supervised training with exercise physiologists twice per week in different outdoor areas. Every sixth week both exercise groups met separately for supervised spinning sessions (ergometer cycling), where heart rate monitors were used to ensure recommended exercise intensities were achieved. The primary aim of the Generation 100 study was to determine the effects of regular exercise on overall mortality in older adults. Secondary aims were to examine the effect of different aerobic exercise training intensities over a five-year period on morbidity. The study design and aims of the Generation 100 study have been described in further detail previously (38).

The present study is a sub study of the Generation 100 study. In total, 60 participants were randomly recruited from the Generation 100 study. Exclusion criteria were uncontrolled hypertension (systolic blood pressure >220 mmHg, or diastolic blood pressure >110mmHg); symptomatic valvular disease; hypertrophic cardiomyopathy; unstable angina pectoris; primary pulmonary hypertension; heart failure; severe arrhythmia; diagnosed dementia; cancer that made participation impossible; chronic communicable infectious diseases, illness or disabilities that precluded exercise. Furthermore, any heart disease or chronic disease obtained after the five-year testing were excluded. If the participant had experienced an injury or serious illness, a period of three months of no injury/serious illness prior to testing was needed. Due to the COVID-19 situation, airway symptoms were also an exclusion criterion in the present study.

By termination of recruitment in March 2021, we had included 14 participants from HIIT, 18 participants from MICT, and 17 participants from CON (Figure 1).

Flowchart

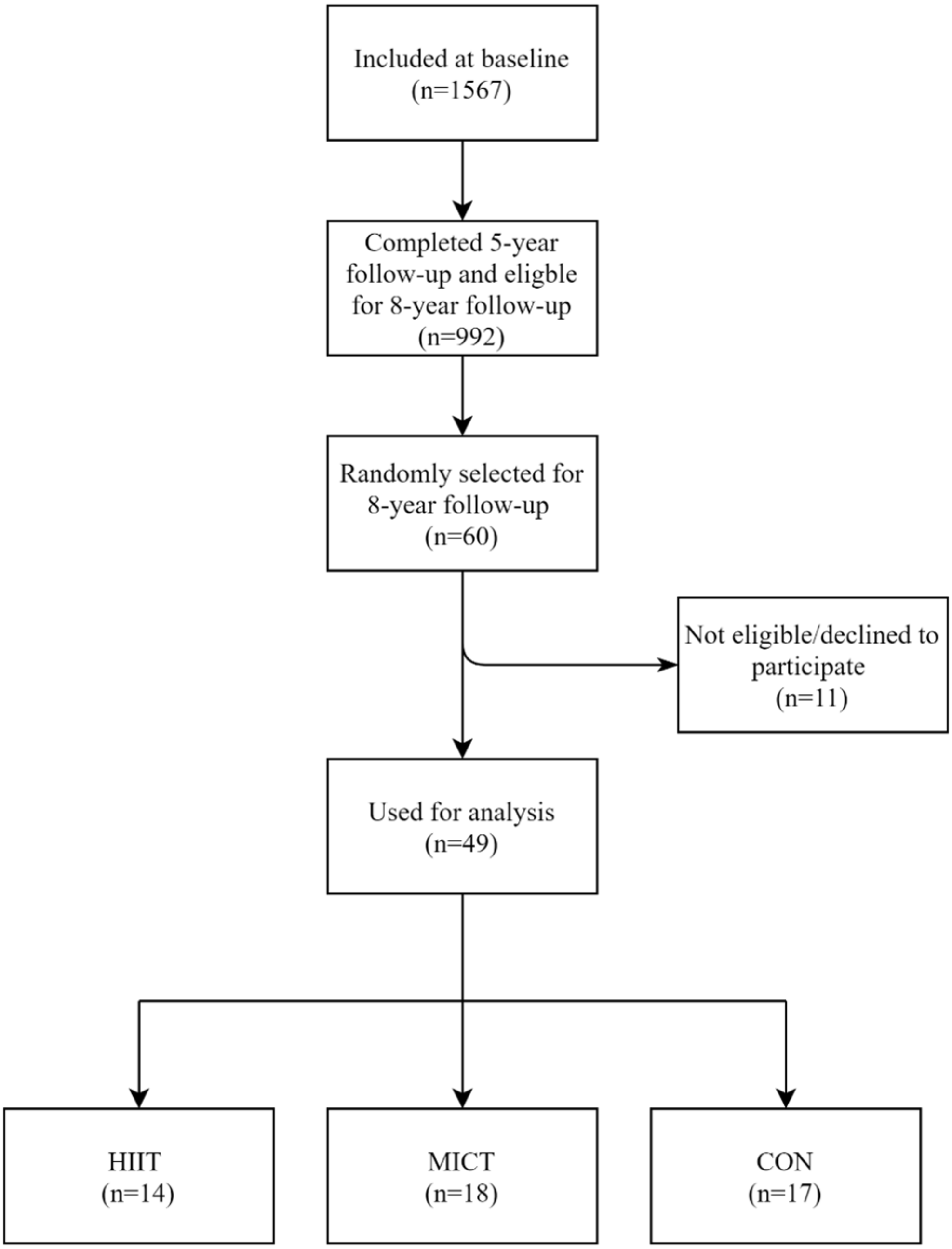

Figure 1:Flowchart of study cohort. HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training; CON: control group

All physical examinations of participants were performed prior to testing. These included, but were not limited to, height, weight, and body mass index (BMI). Height was measured by asking the participant to stand against a wall with feet shoulder-width apart, using a mechanical telescopic measuring stadiometer (Seca 222, Seca, Hamburg, Germany). Weight and BMI were measured by using bioelectrical impedance (Inbody 720, BIOSPACE, Seoul, Korea).

Peak oxygen uptake

Peak oxygen uptake (VO_{2peak}) was measured by a cardiopulmonary exercise test (CPET) on a treadmill (Woodway USA Inc., PPS 55, Waukesha, WI, USA). Participants who were not able to perform the test on the treadmill (n= HIIT:2; MICT: 4; CON:1) performed the test on a stationary bike (Lode B.V. Zernikepark 16, 9747AN, Groningen, The Netherlands). The VO_{2peak} measurements were performed using the Metalyzer II system (Cortex, Germany).

At the start of each test day, volume and gas calibration were performed according to the manufacturer's instruction. If several tests were performed per day, volume calibration was performed between each test, while gas calibration was performed before every fourth test or if ambient air measurements were not approved before any test. An HR monitor (RS100, Polar Electro Oy, Kempele, Finland) was placed on the participant's chest, in proximity to the sternum.

Prior to testing, the participants had a 10-minute warm-up on the treadmill at a self-adjusted moderate intensity, based on 1) self-reported PA level, 2) HR, and 3) feedback from the participant using the Borg scale. The protocol for testing was a three-stage protocol. The first stage consisted of a steady-state 3-minute period with inclination and pace set to the same as end of warm-up). Inclination was usually set at 2% but could vary based on feedback from the participant or evaluation of gait by the testers. The second stage was an increase in workload by increasing the inclination by 2% or speed by 1 km/h and keeping it for 1.5 minutes. In the final stage, speed and/or inclination were increased once per minute until exhaustion or a flattening in the oxygen uptake, indicating a $VO_{2peak}/_{max}$ was reached. The majority (n=32, 65%) did not reach the criteria for VO_{2max} (respiratory exchange ratio (RER) >1.05, or reach a flattening of oxygen consumption), thus, VO_{2peak} is reported in this study. Borg was reported by the participant after each stage, while RER and HR were noted after each stage.

Participants performing the CPET on the stationary bike were asked to keep the rounds per minute (RPM) between 60 and 90, and preferably above 70. The warm-up period was used to find the appropriate resistance for stage 1, i.e., a resistance where the RPM was between 60-90 and Borg between 10-13 The stages of the VO_{2peak} test was the same as the treadmill test, except for increases in workload being increased every 30 seconds instead of one per minute during the maximal stage. From stage 1 to stage 2, the watt was increased by 20 watts. From stage 2 to maximal stage, the resistance was increased by 10 watts. During the maximal stage, the resistance was increased by 10 watts every 30 seconds until failure of the participant to keep the RPM above 60, exhaustion, or the criteria for a maximal test was reached.

Participants with known heart disease (n= HIIT:3; MICT: 3; CON: 2) performed the CPET with a concomitant 10-lead electrocardiogram, using the guidelines for exercise testing for patients with known cardiovascular disease by the American College of Cardiology/American Heart Association (40). If any contraindications of testing were observed, the test was terminated.

Physical Function

Physical function was measured by handgrip strength using the dominant hand, and a sit-to-stand test. The HGS test was performed using a JAMAR Hydraulic Hand Dynamometer (Lafayette Instrument Company, USA), using the average of three tests on the dominant hand. The participants were asked to keep the elbow at 90° and arm adducted. The participants were verbally encouraged throughout the tests to squeeze harder until maximal force was reached. Results of the HGS test are given as maximum force exerted in kg based on the mean of three trials using the dominant hand.

The sit-to-stand test was performed using a 45.5cm chair with a linear encoder connected to a PC running MuscleLab software (Ergotest Innovation, Norway). The chair did not have armrests, but had a backrest, and was placed with the back against a stable surface to prevent the chair from moving during the test. The participants were asked to keep their arms across their chest, and to have their feet planted during the test to prevent any countermovement. The test only measured the concentric phase, so the participants were free to sit down at a self-determined pace. The test was deemed successful if the participant followed these instructions and had 5 trials with no clear outlier trials in terms of distance (cm) and time (s). In the event of outliers, the participants were asked to repeat only the same number of repetitions as there were outliers. Results of STS are given as mean peak velocity in meters per second of five successful trials. Unfortunately, the STS test was not performed at the one-year follow-up.

All CPET, HGS, and STS tests were performed at the NextMove Core Facilities, St. Olav's Hospital, Norway.

Self-reported physical activity

Self-reported physical activity was obtained by a validated questionnaire (41) at one, three, five, and eight-years follow-up. Relevant questions were extracted regarding frequency ("How often do you exercise"; "never or less than once per week" [0], "once a week" [1], "2-3 times a week [2.5], "nearly every day" [5]), duration (For how long do you exercise each time?"; "less than 15 minutes [7.5], "15-30 minutes" [22.5], "30-60 minutes" [45], "more than 60 minutes [60]) ([] denotes assigned value), and intensity using the Borg scale ("on a scale from 6 to 20, how hard do you exercise?"). Minutes per week was calculated by multiplying frequency and duration.

Ethics

The study was approved by the Regional Committee for Medical Research (REC South East B; REK 2012/381 B).

Sample size

The power calculation of the present study was based on an expected 20% difference in VO_{2peak} between the HIIT and control group (42) after eight years. Previous research suggests a VO_{2peak} of approximately 29 ml/kg/min with an SD of 5.9 (7). With a power of 80%, about 15 participants were needed in each group to detect a 20% difference with significance level set at α=0.05.

Statistical analysis

Normality was assessed and confirmed by visual inspection of Q-Q-plots. Continuous variables are presented as mean (SD) and categorical variables as n, unless stated otherwise. Linear mixed models (LMM) were used to examine the estimated change over time for the primary outcome (VO_{2peak}) and for the secondary outcomes (handgrip strength and peak velocity). The primary and secondary outcomes were used as dependent variables for statistical analyses, while the groups were used as independent variables. Time (baseline, one, three, five, and eight years) and intervention group (HIIT vs CON, HIIT vs MICT, and MICT vs CON) were used in three-way interaction analyses as categorical covariates. The main analysis compared HIIT, MICT, and CON in an intention-to-treat analysis. A two-sided p-value of ≤0.05 was considered statistically significant. P-values and 95% confidence intervals were used to demonstrate association between groups and outcome measures. Statistical analyses were performed using the IBM SPSS statistics 26.0 program.

Results

Descriptive characteristics

Descriptive characteristics of participants at baseline are presented in Table 1. There were no significant differences between groups at baseline.

Table 1: Descriptive characteristics of participants pre-and postintervention.

	HIIT (n=14)	MICT (n=18)	CON (n=17)
Age (years)	73.3 (2.2)	72.3 (1.7)	72.4 (1.8)
Male (%)	50%	50%	59%
Height (cm)	173.4 (9.5)	171.9 (8.3)	173.1 (8.5)
Weight (kg)	79.9 (13.1)	74.5 (10.9)	78.4 (11.5)
BMI (kg/m^2)	26.6 (3.5)	25.2 (3.1)	26.1 (2.8)

Data is presented as mean (SD). HIIT: High-intensity interval training; MICT: moderate-intensity continuous training; CON: control group, BMI: Body mass index; PA: physical activity

Cardiorespiratory fitness

The mean values obtained during the CPET at baseline and eight-year-follow-up are presented in Table 2 and change in VO_{2peak} is presented in figure 2. The mean estimated changes and group differences in VO_{2peak} are presented in Table 3. At baseline there were no statistically significant differences in VO_{2peak} between groups, and all three groups had a significant decline in VO_{2peak} after eight years. However, HIIT and CON had a significantly lower decrease in VO_{2peak} compared to MICT ($p=0.046$ and $p=0.041$ for HIIT and CON, respectively) after eight years. There were no differences between HIIT and CON after eight years. There were no significant differences in VO_{2peak} changes between the groups from baseline to one, three, or five years. The measured decline in HIIT and CON after eight years was 3.4 ml/kg·min^{-1}, while the decline in MICT was 6.0 ml/kg·min^{-1} (Table 2).

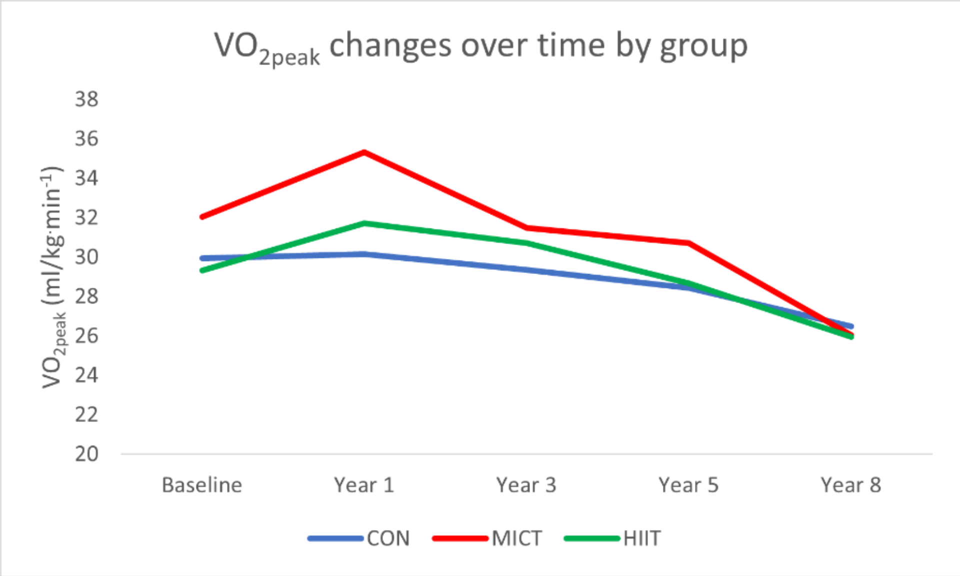

Figure 2:Mean change in VO_{2peak} over time by group. HIIT: high-intensity interval training; MICT: moderate-intensity continuous training; CON; control group, VO_{2peak}: peak oxygen uptake.

Physical function

The mean values obtained during HGS and STS at baseline and eight-year-follow-up are presented in Table 2 and Figure 2 and 3, respectively. The mean estimated changes and group differences in HGS, and STS are presented in Table 3. There were no significant differences between groups in HGS or STS at any timepoint. All groups had a significant decline from baseline to year eight. The measured decline in HIIT was 11.8 kg, MICT 12.7 kg, and CON 12.0 kg (Table 2). The measured decline in STS for HIIT and CON after eight years was 0.11 m/s, while the decline in MICT was 0.13 m/s (Table 2).

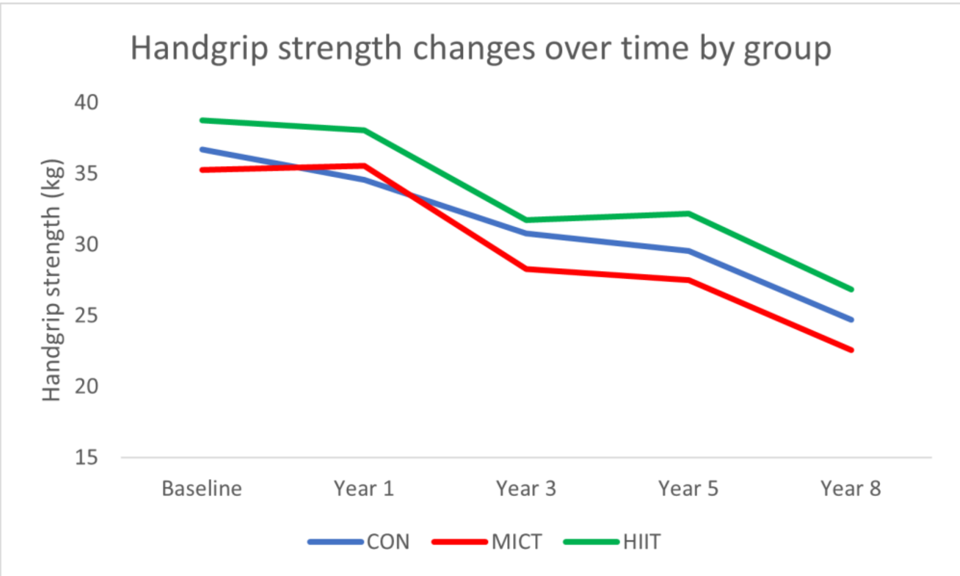

Figure 3: Mean change in Handgrip strength over time by group. HIIT: high-intensity interval training; MICT: moderate-intensity continuous training; CON; control group.

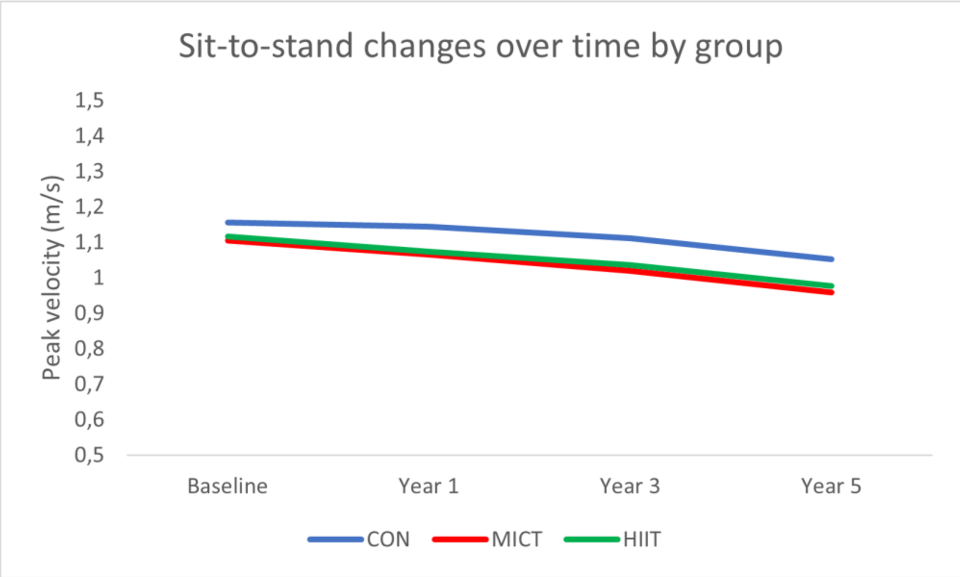

Figure 4: Mean change in peak velocity changes over time by group. HIIT: high-intensity interval training; MICT: moderate-intensity continuous training; CON; control group.

Table 2: Cardiorespiratory variables and physical function from baseline and after eight years

Time	HIIT (n=14)	MICT (n=18)	CON (n=17)
Baseline			
Peak oxygen uptake ($L{\cdot}min^{-1}$)	2.32 (0.56)	2.37 (0.52)	2.34 (0.52)
Peak oxygen uptake ($ml/kg{\cdot}min^{-1}$)	29.3 (5.9)	32.0 (6.4)	29.9 (4.9)
HR_{max}	156 (12)	159 (16)	154 (16)
$Borg_{max}$	16.9 (2.2)	17.8 (1.2)	17.5 (1.4)
Max RER	1.15 (0.07)	1.14 (0.08)	1.13 (0.12)
Handgrip strength (kg)	38.7 (12.8)	35.3 (11.5)	36.7 (10.5)
Sit-to-stand (peak velocity (m/s))	1.08 (0.29)	1.12 (0.22)	1.16 (0.21)
Year 8			
Peak oxygen uptake ($L{\cdot}min^{-1}$)	2.00 (0.52)	1.84 (0.39)	2.00 (0.56)
Peak oxygen uptake ($ml/kg{\cdot}min^{-1}$)	25.9 (6.5)	26.0 (6.8)	26.5 (6.2)
HR_{max}	142 (15)	143 (19)	141 (17)
$Borg_{max}$	17.6 (1.1)	17.0 (1.6)	17.1 (1.9)
Max RER	1.05 (0.06)	1.06 (0.05)	1.02 (0.09)
Handgrip strength (kg)	26.9 (12.4)	22.6 (9.7)	24.7 (9.5)
Sit-to-stand (peak velocity (m/s))	0.97 (0.23)	0.99 (0.25)	1.05 (0.22)

Data is presented as mean (SD), HIIT: High-intensity interval training; MICT: moderate-intensity continuous training; CON: control group. HR_{max} in beats per minute; Borg on a scale from 6-20; $Borg_{max}$: rate of perceived exertion on Borg scale at termination of test; RER: respiratory exchange ratio.

Table 3: Estimated change in cardiorespiratory fitness and physical function at one-, three-, five-, and eight-year follow-up.

		Differences (interaction between group and time)					
		HIIT vs MICT		**HIIT vs CON**		**MICT vs CON**	
Outcome	Time	Estimate (95%CI)	p	Estimate (95%CI)	p	Estimate (95%CI)	p
	Baseline						
VO_{2peak}		-2.7 (-7.2, 1.8)	.229	-0.6 (-5.1, 3.9)	.788	2.1 (-2.1, 6.4)	.325
Handgrip strength		3.5 (-4.9, 11.9)	.409	2.1 (-6.4, 10.6)	.630	-1.4 (-9.4, 6.5)	.721
Peak velocity		-0.04 (-0.20, 0.12)	.632	-0.08 (-0.24, 0.09)	.362	-0.04 (-0.19, 0.12)	.641
	Year 1						
VO_{2peak}		-0.5 (-3.1, 2.1)	.723	1.8 (-0.8, 4.5)	.174	2.3 (-0.2, 4.8)	.074
Handgrip strength		-0.2 (-3.5, 3.1)	.911	0.9 (-2.4, 4.2)	.589	1.1 (-2.1, 4.3)	.499
	Year 3						
VO_{2peak}		1.2 (-1.4, 3.9)	.354	1.8 (-0.8, 4.5)	.173	0.6 (-1.9, 3.1)	.635
Handgrip strength		0.3 (-3.0, 3.6)	.851	-0.1 (-3.4, 3.2)	.953	-0.4 (-3.5, 2.7)	.792
Peak velocity		0.02 (-0.09, 0.13)	.714	-0.03 (-0.14, 0.08)	.595	-0.05 (-0.15, 0.05)	.326
	Year 5						
VO_{2peak}		0.6 (-2.0, 3.2)	.629	0.9 (-1.7, 3.5)	.512	0.2 (-2.2, 2.7)	.853
Handgrip strength		1.2 (-2.0, 4.4)	.451	0.6 (-2.7, 3.8)	.721	-0.6 (-3.7, 2.4)	.679
Peak velocity		0.01 (-0.10, 0.11)	.868	-0.03 (-0.14, 0.07)	.519	-0.04 (-0.14, 0.06)	.386
	Year 8						
VO_{2peak}		2.6 (0.1, 5.2)	.046*	0.1 (-2.5, 2.7)	.954	-2.6 (-5.0, -0.1)	.041*
Handgrip strength		0.8 (-2.4, 4.0)	.614	1.1 (-2.2, 4.4)	.506	0.3 (-2.8, 3.4)	.854
Peak velocity		0.01 (-0.09, 0.12)	.794	-0.01 (-0.12, 0.09)	.839	-0.02 (-0.12, 0.07)	.625

Data is presented as estimated differences and 95% confidence intervals (CI). HIIT: High-intensity interval training; MICT: moderate-intensity continuous training; CON: control group. 95%CI: 95% confidence intervals. VO_{2peak} estimates from ml/kg·min^{-1}; handgrip strength estimates in kg; peak velocity estimates in m/s.
STS data from year one was not obtained.
*=significant changes between groups (p≤0.05)

Self-reported physical activity

Exercise duration, frequency, and intensity after one year, three years, five years, and eight years follow-up are presented in Table 4.

Table 4: Overview of exercise duration, frequency, and intensity in the three groups.

	HIIT Mean (SD)	MICT Mean (SD)	CON Mean (SD)
Year 1			
Exercise duration (minutes per session)	49.6 (13.9)	45.5 (11.8)	45.0 (14.7)
Exercise frequency (sessions per week)	3.4 (1.2)	2.8 (1.2)	3.1 (1.6)
Exercise intensity (6-20 Borg scale)	13.9 (1.8)	13.0 (2.2)	13.2 (2.3)
Minutes per week	160.1 (72.9)	132.2 (69.6)	151.6 (82.9)
Year 3			
Exercise duration (minutes per session)	45.0 (11.9)	45.4 (7.5)	49.2 (10.2)
Exercise frequency (sessions per week)	3.3 (1.6)	3.3 (1.3)	3.8 (1.4)
Exercise intensity (6-20 Borg scale)	14.7 (2.6)	13.3 (2.1)	13.6 (1.5)
Minutes per week	139.9 (70.4)	144.2 (55.6)	181.9 (71.3)
Year 5			
Exercise duration (minutes per session)	50.4 (13.6)	45.8 (13.3)	48.1 (12.7)
Exercise frequency (sessions per week)	3.2 (1.5)	3.2 (1.4)	3.3 (1.6)
Exercise intensity (6-20 Borg scale)	14.1 (1.9)	13.0 (2.2)	13.4 (1.9)
Minutes per week	165.3 (92.6)	153.1 (76.5)	168.1 (88.4)
Year 8			
Exercise duration (minutes per session)	45.0 (13.0)	48.4 (11.3)	47.0 (12.2)
Exercise frequency (sessions per week)	3.0 (1.0)	2.0 (1.0)	3.2 (1.3)
Exercise intensity (6-20 Borg scale	12.6 (2.3)	13.1 (1.9)	13.0 (2.3)
Minutes per week	139.8 (97.6)	95.5 (51.4)	154.3 (85.6)

HIIT: High-intensity interval training; MICT: moderate-intensity continuous training; CON: control group**,** SD: Standard deviation

Discussion

Cardiorespiratory fitness

The main finding was that after eight years of aerobic exercise, the high-intensity interval training group and the control group had a lower decline in cardiorespiratory fitness compared to the moderate-intensity training group. There was no difference between the high-intensity interval training group and the control group asked to follow national guidelines for physical activity. The hypothesis of HIIT inducing favourable effects to MICT for cardiorespiratory fitness in older adults was thus confirmed.

Due to the correlation between CRF, mortality, and health (5), maintaining CRF with advancing age is of importance when prescribing aerobic exercise programs to older adults. The findings of HIIT having a superior effect to MICT on cardiorespiratory fitness is well-documented in the literature (12–16). Nevertheless, this study is the first to evaluate the effect of HIIT versus MICT after an eight-year intervention. The present study adds knowledge to the literature by demonstrating that significant differences in cardiorespiratory fitness can be found between HIIT and MICT over a long time period. It has previously been shown that even a small difference of 1 $ml/kg{\cdot}min^{-1}$ in VO_{2peak} can reduce the risk of premature mortality (15), thus the observed 2.6 $ml/kg{\cdot}min^{-1}$ difference between both HIIT and CON compared to MICT, could potentially have a significant impact on health and survival. Further, this study demonstrates that HIIT and CON is superior to MICT in a less controlled setting than previously used in most studies. The participants meet for mandatory training every sixth week and were offered to attend voluntary training twice per week. This indicates that prescribing high-intensity exercise may be given even without highly controlled supervision and elicit significant health benefits for older adults. From a public health perspective, this may be important even though the estimated difference was smaller than what has been previously found in some more tightly controlled studies (12). Furthermore, due to the more real-life setting of the present study, the results are arguably more generalisable to the general population. Interestingly, there were no differences in CRF between HIIT and CON after eight years. The control group tended to exercise more and with a higher intensity than MICT, thus the role of CON as representatives of the general population of older adults can be questioned. Similar findings were shown in the main Generation 100 study (15), demonstrating the challenges of including an appropriate control group in randomised controlled trials. It is important to note that HIIT reported to exercise at a higher intensity than MICT and CON at one-, three-, and five-years follow-up. However, at year eight, HIIT reported to exercise almost at the same intensity as MICT and CON. Conversely, MICT and CON reported the same exercise intensity throughout the study period. Importantly, data on physical activity was collected during the lockdown due to COVID-19. Thus, our data indicate that older adults might find it more challenging to perform HIIT during a lockdown compared to moderate-intensity aerobic exercise.

Nevertheless, the findings are promising for high intensity aerobic exercise without strict supervision being effective for CRF compared to moderate intensity. Furthermore, the efficacy of prescribing high intensity without strict supervision for maintaining CRF to older adults compared to moderate intensity without strict supervision is in line with the findings from the main Generation 100 study (15). Despite this, our data indicate that prescribing exercise without supervision can be done and give significant health benefit. Some caution might be due as MICT had more participants testing on an ergometer bicycle after eight years which may have caused a lower VO_{2peak} at eight years. However, excluding those who tested on the ergometer bike at eight years from the analysis found HIIT to elicit a greater favourable effect on CRF compared to MICT. The significant difference in change in VO_{2peak} between MICT and CON, were no longer present. Thus, the difference between MICT and CON is partly explained by ergometer test differences.

The decline in VO_{2peak} seen in all three intervention with advancing age is in line with previous research of age-related decline (9). Although all three groups had an increase in VO_{2peak} after one year, showing that also older adults can improve VO_{2peak}, , the subsequent decline in VO_{2peak} in all other follow-ups may indicate that there may be an attenuated response to exercise with age, which has been found in previous research (43). Thus, the prescribed exercise may have been enough to increase the VO_{2peak} at initiation but may not have consisted of sufficient volume/intensity to give a further increase in nor maintain VO_{2peak} past year one follow-. Importantly, all participants were above the threshold for independent living (18 $ml/kg\cdot min^{-1}$ for men and 15 $ml/kg\cdot min^{-1}$ for women (44) at the eight-year follow-up.

HR_{max} was reduced in all groups, which may partly explain the decline. All three groups also experienced a lower maximal RER, despite reporting a higher rating of perceived exertion on the Borg scale at termination of the CPET. Fuller et al. (8) found similar results when comparing persons of different age, indicating a reduced maximal RER may be associated with age. No measurement of SV or a-vO_2 difference were taken in the present study, and thus no conclusions regarding mechanisms can be drawn.

Physical function

There were no group differences in the estimated change for handgrip strength or for sit-to-stand after eight years. Thus, aerobic exercise, regardless of intensity, did not seem to counteract age-related decline in neither HGS nor STS.

The literature regarding the effects of different aerobic exercise intensities on HGS and STS is conflicting, with the most consistent finding being no difference between aerobic exercise intensities (35,36). This is the first study to investigate the effect of aerobic exercise at different intensities over an eight-year period and adds novel knowledge regarding the long-term effects of aerobic exercise intervention on physical function in older adults. Our finding supports previous research that aerobic exercise at different intensities do not elicit different effects on HGS and STS. The majority of studies on the effect of aerobic exercise on HGS and STS employ moderate-intensity interventions (45), and none have used the same HIIT protocol as used in the present study. Thus, directly comparing the present study to other studies is challenging. In addition to the lack of similar protocols for aerobic exercise, there is a lack of standardisation of what constitutes high intensity and moderate intensity. One study reporting high-intensity aerobic exercise to be preferential to moderate-intensity set the limit for high intensity and moderate intensity lower than in the present study (34). Similarly, in a systematic review vigorous activity was classified as "walking for exercise", while moderate activity was classified as normal walking or gardening (45), further illustrating the need for similar protocols and definitions of different intensities. It may be that one reason for conflicting findings is the different classification of intensity zones.

Importantly, it has been reported that combining aerobic exercise with resistance exercise elicits greater favourable effects in physical function(45). The likely reason for no difference between HIIT, MICT, and CON in this study is that aerobic exercise intensity itself is not a clear determinant of physical function measured by HGS and STS, and that aerobic exercise might need to be supplemented with resistance exercise to induce significant outcomes. The major benefit of aerobic exercise has been reported to be between light intensity/sedentary and moderate intensity with no great benefit coming from increasing aerobic exercise intensity (45,46). It may therefore seem probable that at least moderate intensity is needed for a noticeable effect from aerobic exercise on physical function. Therefore, it seems likely that to induce favourable effects on physical function a minimum of moderate intensity is needed, but any further increase in intensity is unlikely to give further noticeable benefits.

Nevertheless, there was a significantly greater effect of higher intensity aerobic exercise on CRF. Due to the proposed limit of 18 $ml/kg \cdot min^{-1}$ and 15 $ml/kg \cdot min^{-1}$ of VO_{2peak} for functional independence for men and women, respectively (44), and the notion that CRF may be used as a predictor of physical function (47), it might be advisable that at least some of the aerobic exercise is performed at higher intensities to ensure one stays above this threshold.

It might be that tight supervision is needed to ensure exercise protocols are followed sufficiently to induce improvements in HGS and STS, as shown in previous studies. The present study included older adults than what was present in the shorter studies. It is plausible that the higher age limited the response to exercise compared to their relatively younger counterparts. Furthermore, the participants in the present study are likely more active than the general population of older adults, thus the lack of improvement could be due to a ceiling effect. Following the exercise principle of diminishing returns (48), the participants of the present study may have needed a higher volume or intensity to induce these improvements. To the best of our knowledge the present study is the only randomised controlled trial investigating long-term effects of aerobic exercise at different intensities on HGS and STS in older adults, and thus there are no other studies to directly compare results with. The lack of high-quality research into the effect of aerobic exercise on physical function has been previously noted (33). The present study thus adds knowledge to a topic which needs more high-quality research, especially considering the potential for alleviating the burden of an ageing population.

In the present study, we aimed to get a comprehensive overview of the participants' physical function by including measurements of both upper-body function and lower-body function, as using only measurements of one of these may not be sufficient for overall physical function (22). To the best of the author's knowledge, there are no other studies than those connected to the Generation 100 study that uses the same protocol for sit-to-stand, thus making any direct comparison impossible. This does not mean that any comparison is pointless, but rather that the results cannot be directly compared to other studies to the same degree as HGS can be, where similar protocols are followed. Lastly, the intervention consisted solely of aerobic exercise, as did the self-reported PA by participants. Any additional exercise directly targeting HGS directly, or indirectly through resistance exercise was not recorded in this study. Thus, any external factors related to other exercise modes were not accounted for, and the results should therefore be interpreted with some caution.

All three groups declined in HGS after eight years. At baseline, all males were below 26 kg, which may be considered clinically weak for males (24). After eight years, six males (23%) were below this limit. For females, one (4%) was below 16 kg, which may be considered clinically weak (24). After eight years, eleven females (48%) were below this limit. Because aerobic exercise does not seem to be an effective method to prevent the age-related decline in physical function, regardless of intensity, additional exercise modes may be advisable to maintain physical function with advancing age.

Self-reported physical activity

On a group level, all three groups met the recommended amount of physical activity per week. HIIT did not exercise at the prescribed ≥15 Borg scale intensity at any timepoint but exercised with a higher intensity than both MICT and CON at all points except at year eight. It could be speculated that the higher exercise volume in HIIT and CON at eight years was the primary driver of differences in change in cardiorespiratory fitness. However, these differences were not seen at other timepoints where exercise volume differed between groups and is therefore unlikely. Importantly, the eight-year follow-up took place during the COVID-19 pandemic, which may have caused alterations in exercise intensity, frequency, and duration. Thus, our data indicate that during a lockdown where gyms are closed and social distancing is required, it may be more challenging to perform high-intensity interval training. Lastly, the intensity was self-reported using a subjective measure, and the reported intensities at eight years may be due to HIIT reporting lower intensities than what would be objectively measured.

Strengths and limitations

There are several limitations to this study. First and foremost, the real-life settings probably resulted in a cross-over between interventions. The exercise patterns were assessed subjectively by questionnaire, which may not be fully accurate. However, due to the large scope of the Generation 100 study, objective measures of all participants were not feasible, and subjective measures are thus a viable option. Importantly, the questions regarding physical activity used in the questionnaire have previously shown sensitivity to predict current and future cardiovascular health (49,50). Furthermore, selection bias may have influenced the results and weakened generalisability. The healthy volunteer bias may have meant the participants who volunteered for this study were fitter than those who did not want to participate. Thus, both baseline values and eight-year values might be higher than the general population for this age group. Although baseline values were not statistically significant, the higher MICT values at baseline may have affected results. Specifically, the four highest recorded values at baseline were all in the MICT group. Based on additional analyses, excluding these participants resulted in a steeper decline for MICT, and clearer differences between the groups, as well as making baseline values more similar. Lastly, the COVID-19 pandemic may have caused a lower PA level and exercise intensities among participants, which may have influenced results. Of particular note is the notion that performing HIIT seem to be more challenging during COVID-19. Regarding STS, there is a scarcity of standardization of protocols for using STS focussing on muscle power (29), as well as a lack of other studies using a similar protocol with peak velocity as outcome measure. Comparisons with other studies are therefore not feasible.

The main strength of this study is that it is a randomized controlled trial with a long follow-up time. All three outcomes were measured using common, reliable, and validated test instruments, except from STS. CPET tests were standardised, meaning the impact of having several test personnel over the intervention should have minimal impact. The equipment used in HGS and STS was the same for all timepoints. The physical function tests consisted of both upper-body and lower-body functional tests. The study’s real-life setting makes generalising results to a larger population more accurate than if it were more tightly controlled.

Conclusion

Aerobic high-intensity interval training and controls asked to follow the national recommendations of physical activity had a lower decline in cardiorespiratory fitness compared to moderate-intensity continuous training in older adults after eight years. For physical function, there were differences between groups in neither handgrip strength nor sit-to-stand after eight years, indicating that aerobic exercise intensity is not determinant for physical function when measured by handgrip strength and sit-to-stand in older adults.

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