Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Circulation and Medical Imaging

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The Role of Prescribed Exercise Intensity in the Change in Cardiovascular Risk Factors in a Sedentary Elderly Population

Master's thesis in M.Sc. Exercise Physiology
Supervisor: Dorthe Stensvold and Thomas Fremo
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Abstract

Background: Cardiovascular disease (CVD) is the leading cause of death worldwide. Low cardiorespiratory fitness (CRF) as well as sedentary behaviour are both strong predictors for CVD, CVD mortality and all-cause mortality. Additionally, high CRF has been shown to alter or eliminate some of the adverse health effects of sedentary behaviour. However, data on the sedentary elderly population is limited, and more research on how different exercise intensities can induce a change in CRF and CVD risk factors is needed. **Objective:** The present study aimed to investigate the effect of high intensity interval training versus moderate intensity training on cardiovascular risk factors and CRF in initially sedentary elderly men and women. **Methods:** In total, 490 elderly and sedentary men and women (aged 72,9±2,2) were randomized into one of the following three groups: control (CON; n=253), following current physical activity recommendations by the Norwegian directorate of Health; moderate-intensity training (MIT; n=117), doing 50 mins of continuous moderate-intensity exercise twice a week, corresponding to 70% peak heart rate; high intensity training (HIT; n=120), doing two bouts of 40 min exercise per week performing 4x4 intervals at 85-95% of peak heart rate, with active rests between intervals at ~ 60-70% of peak heart rate. Direct ergospirometry was used to assess peak oxygen uptake (VO_{2peak}). In addition, measures of CVD risk factors included waist circumference, triglycerides, high density lipoprotein cholesterol, glycated hemoglobin A1c and blood pressure. Groups were analysed as entire groups and per protocol using an ANCOVA test measuring differences in changes between groups after three years of intervention. **Results:** Whole group change in VO_{2peak} did not differ significantly between groups. However, waist circumference in HIT differed from MIT (p=0.01) due to a trend to decrease in HIT and increase in MIT. Within group change of CVD risk factors showed a significant decrease in triglycerides for CON and MIT. HDL significantly increased for CON and HIT and glycated hemoglobin A1c significantly decreased for all groups. In the per protocol analysis HIT differed significantly in change of VO_{2peak} compared to MIT (p=0.03) and showed a strong trend to differ from CON (P=0.057), this is due to the significant decrease in CON and MIT VO_{2peak}. Noteworthy is the adherence to training specific protocol with 73% in MIT and 47% in HIT. **Conclusion:** All three intervention groups seem to have received some beneficial effect on CVD-risk factors, with no difference in the between-group change. On the contrary per protocol data shows that HIT significantly differed in VO_{2peak} change against MIT and a strong trend towards CON, due to a stagnation in HIT and a significant decrease in CON and MIT. Low adherence in the HIT group must be taken into account when assessing the results.

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Abbreviations

BP	-	Blood pressure
CON	-	Control group
CRF	-	Cardiorespiratory fitness
CVD	-	Cardiovascular disease
HbA1c	-	Glycated hemoglobin A1c
HDL	-	High-density lipoprotein
HIT	-	High intensity training
HR	-	Heart rate
MIT	-	Moderate intensity training
PA	-	Physical activity
SB	-	Sedentary behaviour
TG	-	Triglycerides
VO_{2max}	-	Maximal oxygen uptake
VO_{2peak}	-	Peak oxygen uptake
WC	-	Waist circumference

Introduction

Cardiovascular disease (CVD) is the number one cause of death worldwide.[1] Globally 31% of all deaths are accounted by CVD,[1] and even worse is the situation in the European region where it amounts up to 50% of all deaths.[1] Both The European Heart Network and The World Health Organization state that physical activity (PA) plays a key role in attenuating the risk of CVD,[2] and according to The World Health Organization 60% of the world's population is not sufficiently physically active.[1] According to Kohl et al.[3] inactivity is a pandemic and he argues that over 5 million deaths are related to inactivity world-wide.[3] For the European economy alone, this is estimated to cost between €80-196 billion annualy.[3] The sedentary elderly population is at high risk of developing CVD,[4] and avoiding heart disease could potentially save society resources and increase the individual's quality of life.[2] As the elderly population increases, the cost of disease will simultaneously follow. Today this age group constitutes 8.5% of the total global population, according to the United states census bureau[6] , and is expected to reach 17% in 2050, an increase from 617 million to 1.6 billion world-wide.[6] In 2040 the number of elderly Norwegians aged 67+ is estimated to double compared to 2010.[5] Both moderate- and high-intensity training has shown a positive effect on reducing the risk of CVD and mortality.[7] Numerous cohort studies found increased exercise intensity to be associated with a greater risk reduction for CVD and all-cause mortality.[8-10] Lee et al.[11] found that, when assessing long term risk of CVD, high intensity training (HIT) elicited a greater protecting effect than moderate intensity training (MIT).[11] In a review by Swain and Franklin[12] studying the difference between MIT and HIT on CVD risk, they concluded that with an equal energy expenditure between the training modalities, exercise at high intensity elicits better CVD risk decreases, than MIT.[12]

Sedentary aging and cardiorespiratory fitness: a health perspective

Sedentary behaviour (SB) is described as one of the major risk factors for CVD.[13-16] WHO categorises inactivity as the fourth leading risk factor for global mortality, and estimates that 30% of all ischemic heart diseases can be attributed to physical inactivity.[15, 17] Humans are not built for SB and the phenomenon has been described as "the sedentary death syndrome".[18]

Age specific cardiorespiratory fitness (CRF), most accurately measured as maximal or peak oxygen uptake ($VO_{2max/peak}$),[19] has been closely linked to CVD.[20, 21] With age, SB increases[22] and CRF declines by approximately 6% per decade[23, 24] It is crucial to find ways to prevent both negative associations and implement strategies to healthy aging.[5] CRF declines with age,[23] primarily due to reduced and maldistributed cardiac output, and secondarily to the muscles' oxidative capacity declining with age. This is partly caused by a mitochondrial dysfunction, which has been documented in the elderly.[25] In this population segment, the peripheral oxygen consumption in the muscle has been observed to decline by 50% which cannot be explained by changes in the capillary bed.[26] In relation to this is a study by Rogers et al.[27] studying the aging of master athletes who continue their vigorous endurance training throughout life. Their data suggest that the decline in VO_{2max} is only half of the CON group, and that the decline in maximal HR is happening as fast as their less active counterparts.[27] This is supported by Hagberg[28] who also suggest that training can slow the rate of decline, thus it amount to 10% per decade in sedentary individuals and only by approximately 5% in active individuals.[28] The physiological aging mechanism related to a decline in PA,[29] is mainly due to a reduction in the amount of muscle fibres, as well as an atrophy of type 2 fibres making exercise more troublesome.[30] This decline is mainly from the age of 50 where the approximate rate is 12-14% loss per decade.[31] Furthermore, a rapid decline of 30% in the cardiorespiratory system is shown in the age span between 40 and 60 years of age.[32]

Interestingly, Fitzgerald et al.[33] found this age-dependant decline to be greater for people who were endurance-trained compared to sedentary, although this could be associated with a baseline effect, where endurance training has greater values at start. Exercise was not a strong enough factor to attenuate the age-related decline for this group.[33]

The importance of cardiorespiratory fitness versus physical activity

Physically active elderly have reported better overall health, and studies show that the overall health care expenditures are lower and that the elderly suffer less from mobility limitations than their sedentary counterparts.[34-36] Although CRF and PA are related, due to the fact that an increased activity level with sufficiently high intensity, duration

and frequency, will subsequently increase the CRF, they are not the same.[37] PA is related to activity behaviour, while CRF is a measurable physiological characteristic.[38] In scientific papers, either PA or CRF are often being used as a measurement of the individuals' aerobic function somewhat interchangeably. In a Meta-analysis of 23 papers, Williams[39] compared the difference between the effect of PA and CRF on CVD risk and found a strong correlation between the two.[39] While the highest percentile of physically active individuals only receives a 30% reduction in risk of CVD in comparison to the lowest percentile, the highest percentile of CRF participants receive a 65% reduction compared to their lowest belonging group.[39] When comparing PA and CVD risk there is an almost linear relationship, while with CRF there is a very large drop in risk between the lowest and second lowest quartile. Although both factors have strong correlations with CVD risk, this proves that PA and CRF are vastly different in their effect on CVD risk especially for the least active/fit.[39] This is in line with Sandbakk et al.[4] who found that even after a prolonged time of SB, individuals with high age-specific CRF fully attenuate the adverse effects of CVD risk factors clustering related to SB.[4] This was demonstrated even when not meeting the recommendations for PA. Furthermore, they found that just a single hour of sedentary time was associated with a 22% to 27% increase in the likelihood of having a CVD risk factor clustering in women and men respectively.[4]

Studies have found that HIT with 4x4 min intervals at 85-95% of the maximal heart rate is superior to moderate continuous training with 70% of maximal HR at improving $VO2_{max}$.[14] Wisløff et al.[40] who studied the effect of this training modality on the population enrolled in the Norwegian HUNT study found that a single high-intensity exercise session per week was associated with a 39% and 51% reduced mortality rate among 27.143 healthy men and 28.929 women, respectively.[40] However, no studies have examined the effect of long term high-intensity exercise in a sedentary elderly population. Therefore, to better understand the impact of exercise intensity on CVD risk factors in this population, further research is needed on the effect and feasibility of long term exercise in the sedentary elderly population, including studying a larger group, using direct measurements of SB such as accelerometer data and using $VO_{2max/peak}$ as CRF testing.

Risk factors for cardiovascular disease and their relation to exercise

According to the World Health Organization's 10th revision of the International Statistical Classification of Diseases[17] , all diseases involving the circulatory system are classified as CVD.[17] Although longevity has increased and the CVD-mortality rate has decreased since 1975, likely due to increased medical treatment and not a decrease in the prevalence of the disease itself.[41] However, patients with CVD still suffer from complications and require costly medications that constitute a heavy expense for society.[42-44] The behavioural factors used for assessing CVD risk described by Alberti et al. include tobacco smoking, alcohol consumption and physical inactivity.[45] Clinical risk factors include obesity, diabetes, high cholesterol, high triglycerides (TG), high blood glucose, elevated waist circumference (WC) and high blood pressure (BP).[45] The non-modifiable factors include age, gender, genetics, hereditary diabetes, ethnicity and socio-economic status.[1] All together, high cholesterol, diabetes, high BP, obesity and smoking accounts for more than half of all CVD deaths.[46]

Most CVDs are caused by an underlying mechanism in the blood vessels.[47] Atherosclerosis, a build-up of fatty substances in the blood vessels, is one of the main risk factors for CVD.[48] These fatty streaks in the blood vessels have the potential to build up into plaques and culminate in thrombotic occlusions, which in turn can block the arteries, causing ischemia in nearby tissues.[47] Additionally, the blood vessels lose their pliable nature, making them less elastic.[47] Lastly, the plaque formation can rupture and trigger a blood clot formation. If this formation is close to the heart, such as in a coronary artery, it can cause heart attack and if it's in relation to the brain, it will cause a stroke, both due to ischemia of the tissue.[49]

On the interior wall of the blood vessels, there is a one-cell-thick layer of endothelial cells which acts as an interactive membrane between the vessel and tissue. This specialized layer has several functions, both in forming a barrier from thrombogenic tissues, acting as a thromboresistant layer, and protecting the blood from clotting, as well as being involved in the vasoconstriction and -dilation, due to a production of nitric oxide.[50] Dysfunction in this system has been suggested to be the first step in atherosclerosis, and it's argued that it's a loss in the endothelium-derived nitric oxide that is accountable.[51] Shear stress to the artery wall induced by exercise

has been shown to improve the endothelial function, and can pose a plausible reason for the protective factor of exercise in CVD, as exercise increases nitric oxide and it inhibits several steps in the formation of atherosclerosis.[52] This is in line with research done by Bode-Böger et al.[53] who found that after a bout of submaximal exercise the bioavailability of nitric oxide increased.[53]

Lipid profile

When TG and cholesterol are being transported in blood, they are dependent on lipoproteins for transport, due to their inability to be dissolved in the blood itself.[54] An abnormal lipid profile includes high levels of low-density lipoprotein, high levels of TG and low levels of high-density lipoprotein (HDL).[54] Low-density lipoproteins being the proteins that carry the highest amount of lipids and have the least amount of protein, have been found to be atherogenic.[55] Lipoproteins have the ability to transport both cholesterol and TG from the liver to the cells, but in a case of excess amount of these, the lipoproteins deposit them in the arterial walls.[55] HDL on the other hand acts as an anti-atherogenic, and is to a higher degree being used to assess the effect of exercise, as it is responsible for the transportation of the deposited cholesterol and TG back to the liver, and prevents plaques in the arteries.[56] Exercise can reduce TG in the blood serum and increase the high density lipoprotein-cholesterol, furthermore there has been found effects on total cholesterol, low-density and very low-density lipoprotein-cholesterol. [57, 58] In a study by Kraus et al. [57] where he studied the amount and intensity of training needed for reducing blood lipoproteins, he randomized sedentary overweight individuals with dyslipidaemia into three different groups of high-amount-high-intensity, low-amount-high-intensity and low-amount-moderate-intensity training. They found that the group with the highest amount of weekly training had the greatest result in reducing the lipoprotein profile. Noteworthy is that they found the improvements in $VO2_{max}$ did not correlate to intensity, but solely to the amount of weekly exercise.[57]

Blood pressure

High BP, or hypertension is known to harm the blood vessels and increase the risk of CVD.[59] Endothelial dysfunction, inflammatory responses, oxidative stress as well

as insulin resistance have shown to increase BP.[60] Oxidative stress has been linked to endothelial dysfunction, through inhibiting the function of nitric oxide, and these two factors have been described as the main pathophysiological mechanisms behind hypertension, dyslipidaemia and atherosclerosis.[50, 61] Both in normotensive and hypertensive individuals regular exercise has been shown to lower BP, in the latter by as much as 5-15 mmHg.[60, 62] Evidence shows that moderate to vigorous PA, and in particular aerobic exercise that will result in improved CRF, are associated with a reduction of BP levels and a lowering in the incidence of hypertension.[60, 63] In addition, a reduction in sedentary time or replacing it with PA has also proven to lower hypertension. [63]

Blood glucose

Hyperglycaemia is the state of having elevated levels of fasting blood glucose.[64] Insulin as a hormone is responsible for regulating blood glucose levels through cell glucose uptake.[65] Insulin resistance is where the tissue becomes less efficient in reacting with insulin and becomes impaired in its uptake of glucose into the cell, resulting in hyperglycaemia.[65] Fluctuations in blood glucose and hyperglycaemia are both risk factors for CVD i.e. triggering inflammatory responses caused by increased mitochondrial superoxide production, resulting in oxidative stress[66] and endoplasmic reticulum stress. [67] Exercise has been shown to increase the activity of the enzymes in the mitochondria, effecting the insulin resistance, and has been shown to aid in the glycemic control.[68] In recent years glycated hemoglobin A1c (HbA1c) has been shown to be a reliable risk factor for CVD in both diabetic and non-diabetic patients due to a lowered sensitivity to fasting.[69] By measuring how much glucose is bound to haemoglobin, it is possible to achieve a more long term blood glucose level test, in addition to avoiding the need for a fasting period before testing.[69]

Obesity and overweight

There are several possibilities for measuring weight and the impact of weight loss on health outcomes.[70] Measures include: body fat percentage, body mass index, waist-to-hip-ratio and WC.[70] Overweight, defined as having a body mass index >25, is associated with hypertension, hypercholesterolemia, increased plasma glucose and

inflammation all increasing the risk of CVD.[71] A decrease in body fat percent and weight in obese people is, on the other hand, seen to lower the risk of developing CVD and all-cause mortality.[21, 72] Fat cells act as an endocrine organ and have an important role in the morbidities associated with being overweight, including CVD.[73] Long term exercise has shown promising effects on atherogenic activity in the blood mononuclear cells, such as a decrease in atherogenic cytokines and increase in atheroprotective cytokines.[74] Studies have found both body mass index and in particular waist-circumference to correlate with CVD risk. [75] Earlier studies advocate BMI as an indicator of overall adiposity,[76] whereas the measure of WC has been suggested for indicating abdominal obesity and therefore is a good predictor of abdominal fat.[77] This is to a higher extent related to the development of CVD. [78]

Measurement of physical activity, intensity and sedentary behaviour

Although exercise is widely accepted as an intervention tool, as described in the sections above, research is still challenged by the assessment method. Whether the researcher use self-reported questionnaire, exercise diaries, accelerometers, HR or pedometer, all of these methods have their benefits and pitfalls.[79] The golden standard when measuring PA, and subsequently total energy expenditure, is the double-labelled water test.[80] Although being the most accurate test, it is very troublesome, expensive and labour-intensive for all parties involved.[80] The most widely used method for assessing PA is self-reported measurements, either by filling out a questionnaire or being interviewed.[81] The advantages are that it's easy and cheap, but as it relies on the subject to remember intensity, duration, frequency and time the data reported can suffer a recall bias.[79] Several studies have compared the validity of different questionnaires to the double-labelled water test and have shown inconclusive results, being both over- and underestimating the actual PA-level.[82-84] A study by Duncan et al.[85] studied the ability of sedentary patients to recall PA accurately and found a tendency for the subjects to overestimate their activity level especially in MIT. Although not accurate on an individual level, self-reported questionnaires are known to be significantly more reliable at a population level.[82, 86]

HR can be used to estimate the energy expenditure on the basis of a linear relationship to oxygen uptake.[87] It provides real-time data of the rate, time and

intensity, and can therefore be more accurate than questionnaires.[87, 88] HR monitors are well suited for categorization of groups, instead of telling the exact amount of PA, due to the fact that HR and energy expenditure is not in a linear relationship at low intensities where it can be confounded by stress, caffeine and body position.[89]
Accelerometers can detect movement in three planes and are able to convert acceleration into metrics of interest using them to estimate intensity or energy expenditure.[80, 90] Accelerometers have shown to be feasible for large scale longitudinal studies, that investigate SB and clinical outcomes.[4, 91] As the accelerometer measures locomotor activity when worn on the hip, is it not able to detect either upper body movement or any strength training or carrying additional weight.[90] Accelerometers have therefore mainly been used in population where the main PA consists of walking, running or other locomotive activities. [92, 93]

Risk related to exercise

In relation to exercise intensity and risk of adverse events, Albert et al.[94] found that there is a short-term risk of sudden death among otherwise healthy subjects when engaging in vigorous exercise, however the absolute risk hereof is 1 per 1.51 million exercise bouts.[94] Although exercise is mainly a protective factor for disease, a number of potential risks are still at play. Most reported is musculoskeletal injuries and muscle soreness.[95] More serious adverse risks include arrhythmias, myocardial infarction and rhabdomyolysis.[95] Rognmo et al.[96] studied the risk of exercise in a cardiac rehabilitation setting, and found no difference between moderate- and high-intensity training, and that there generally was a low risk of mortality in both groups.[96] Contrary to Rognmo et al,[96] high-intensity workouts have been shown to increase the likelihood of acute myocardial infarction and sudden death, in sedentary people with CHD.[97] HIT training has, prior to this study, shown to be superior to MIT in inducing favourable changes in CVD risk factors.[12] However there is limited data comparing the long-term effect on HIT to MIT in sedentary elderly adults. If proven superior, an HIT regime will constitute an accessible, cheap and readily available treatment with few negative, yet many positive side effects.

Aim

The aim of this study was to examine whether prescribed high-intensity and/or moderate intensity training, compared to a control group, over a 3-year period can increase CRF and attenuate the adverse health effect of SB in the elderly population. The CVD risk factors being: WC, TG, HDL cholesterol, BP, HbA1c.

Hypothesis

It was hypothesized that HIT would yield greater decreases in the risk factors for CVD, compared to both MIT and a control group following the national PA recommendations, in an elderly sedentary population over a 3-year period.

Secondarily that HIT over a 3-year period would increase VO_{2peak} in an elderly sedentary population.

Methods

Design

Data from the Generation 100 Study was used as a basis for the present study. Generation 100 is a randomized controlled clinical trial, with the main purpose of examining the effect of a 5-year exercise regime on mortality in the elderly population.[92] It is designed as a type IIb clinical trial, which has the intent of finding the optimum amount/intensity of exercise. Inclusion of participants began August 2012 and stopped in June 2013. The study ran until June 2018. Baseline testing was performed before randomization, then further follow-up testing was performed after 1, 3 and 5 years. Data from the baseline testing and the three years follow-up was used in the present study, and only participants with clinical data after three years were included (Figure 1). The Unit for Applied Clinical Research at the Norwegian University of Science and Technology developed a randomisations protocol to ensure a non-biased allocation of participants. Hereafter the participants received information about their specific intervention in both verbal and written form. Participants were stratified by sex and marital status before they were randomized 1:1 into an exercise group or into a CON group. Generation 100 was registered as a clinical trial in the registry, August 2012 ClinicalTrials.gov, Identifier: NCT01666340). The study was conducted according to the SPIRIT statement and followed the

principles of the Helsinki Declaration. The study is approved by The Regional Committee for Medical Research Ethics, Norway (REK 2012/381). Prior to the start of the study all participants signed a written consent form.

Population

All inhabitants of Trondheim, Norway born between the years 1936-1942 (n=6966), were contacted for participation. After agreeing to participate and meeting the criteria set by the Generation 100 project,[92] 1567 individuals (790 women), were included for baseline testing. In the current study, only sedentary participants were included by measure of accelerometer data. The participants wore an ActiGraph GT3x+ accelerometer (ActiGraph, LLC). The instrument was only allowed to be removed in case of exposure to water, such as showering or water sports. For analysing the data, the ActiLife software version 6.11.5 (ActiGraph, LLC) was used. Data recorded during the night (from midnight till 6AM) was excluded from analysis. This set the daily recording to 18 hours. A period of more than 60 minutes with zero counts was defined as non-wear time. The timespan of recording was set to 7 continuous days. Only participants who had sufficient data (defined as at least 4 days of 10 h/d or more of valid data recorded) were included in the study. Hereafter sedentary time was calculated as less than 100 counts per minute measured on the uniaxial measurement. Moderate and vigorous activity was set to a measure of 1952 counts per minute or more, by adding time spent in coherent bouts of 10 minutes; a maximum of 2 times 2 minutes interruptions was allowed. Data was then converted into hours. Finally, for assessing whether PA recommendations were reached, the American college of sports medicine/American heart association guidelines for the elderly was used.[98] The guidelines define that an accumulated time of 21,43 min/day or more (ie, ≥150 min/week) spent in moderate to vigorous intensity activity is meeting recommendations.[98,99] After exclusion there was a remainder of 230 men (47%) and 260 (53%) women.

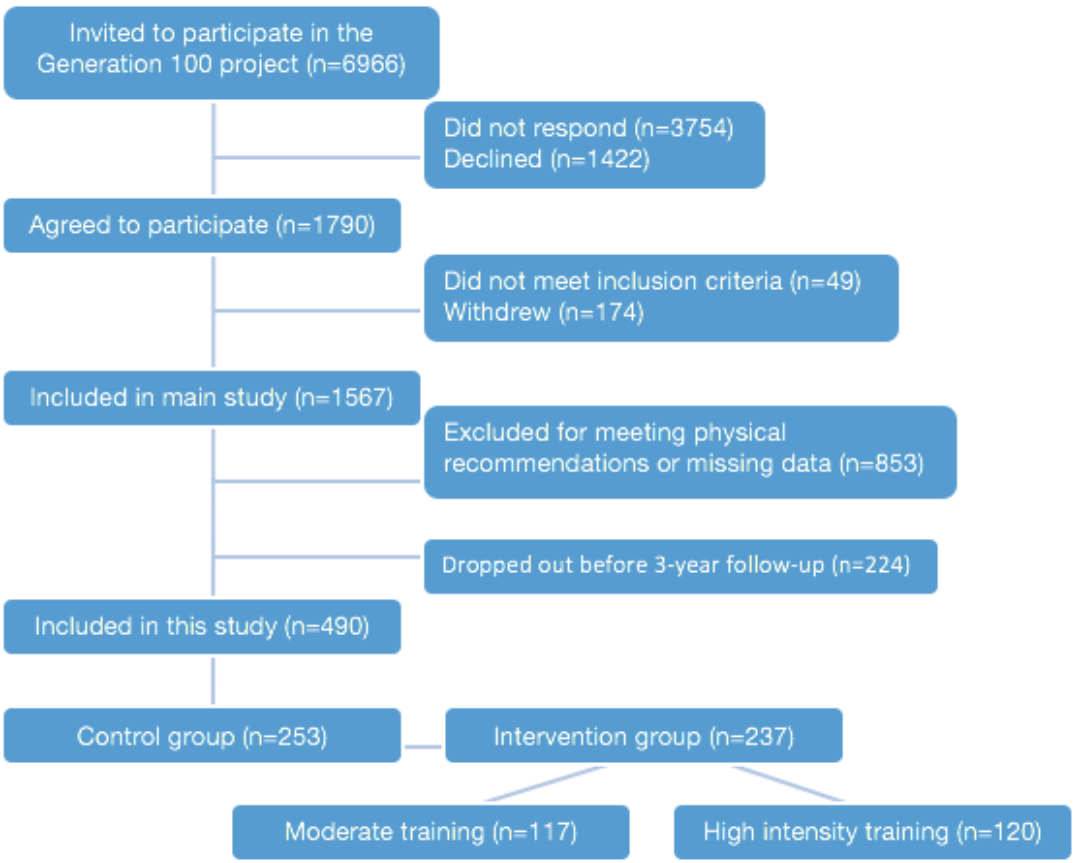

Figure 1. Flow chart

Intervention

Control group

Participants allocated to the CON group were instructed to follow current PA recommendations by the Norwegian directorate of Health.[100] The recommendations consist of 30 minutes of moderate-level PA per day, in 2012 and changed in 2014 to include 75 minutes or more a week at high-intensity level.[101] The CON group, in opposition to the exercise groups, did not have access to supervised training. This is to reflect the current 'treatment' of this population.

High-intensity training

Participants allocated to the high-intensity training group were instructed to perform two bouts of 40 min exercise per week.[102] Participants were offered organised training twice per week at different locations in Trondheim. Here, under supervision, they underwent a light 10-minute warm-up followed by 4x4 interval periods, with 3 minutes

of active breaks in between intervals. During the interval, the intensity was set to correspond to 85-95% of peak HR, translating to ~16 on the Borg Scale.[102] During the active breaks participants were asked to work at ~12 on the Borg scale, which translates to 60-70% of peak HR.[102] For every sixth week the participants had to come in for a supervised spinning session on ergometer bicycles. Here they exercised with HR monitors, to check that they were able to exercise at the prescribed intensity.

Moderate-intensity training

Participants allocated to the moderate-intensity training group were prescribed 50 min of continuous moderate-intensity exercise twice a week. They were prescribed to train at approximately 13 on the Borg scale, corresponding to 70% peak HR.[102] In terms of frequency, supervised training and exercise types, the same rules applied as for the HIT group.

Adherence

The per protocol analysis included participants who followed the prescribed training protocol. In the 3-year questionnaire three questions were used to assess training adherence. Question 18 (frequency), 20 (duration) and 24 (Borg scale) were used to transform data into mins/week. Hereafter the following protocol was used to assess training adherence: CON was not adjusted for analysis, MIT was defined as exercising ≥2 times a week with a duration of ≥30 mins at a Borg level of ≥11, HIT was defined as exercising ≥2 times a week with a duration of ≥15-29 mins at a Borg level of ≥15.

Clinical measurements

Anthropometric measurements

Height was measured by positioning the participants against a wall with their feet at shoulder width apart. Measurements were taken to the closest millimetre. Weight, body composition and BMI were measured on a bioelectrical impedance scale (inBody 720, Biospace CO, Ltd). WC was measured from the upper line of the iliac crest around the torso, meanwhile the participants held their arms crossed over their chest, with normal breathing. Measurement was to the closest millimetre after the third exhale.

Blood pressure

After sitting at rest for 5 minutes, BP and resting HR was measured using a Philips IntelliVue MP50 (Philips medizin systeme, Boeblingen, Germany). BP measurement was performed twice on both arms with a minute break in between. If a big difference occurred, being more than 10mmHg difference in systolic or 6 mmHg diastolic between first and second measurement, a third measurement was taken. The average of the last two measurements on the right arm was used in this present paper.

Blood sampling

Participants were encouraged to fast overnight before blood sampling. The blood samples were taken from an arm vein. Serum TG, HbA1c, HDL and total cholesterol were measured immediately by using standard protocol at St. Olavs Hospital, Trondheim, Norway.

Cardiorespiratory fitness test

Gas exchange ergospirometry (MetaMax II, Cortex Biophysik, Leipzig, Germany) or Oxycon Pro (Erich Jaeger, Hoechberg, Germany) were used to obtain adequate VO_{2max} or VO_{2peak} measurements. A mask (Hans Rudolph Inc) fitting appropriately without leaking air was connected to the gas analyser. HR was monitored using the Accurex RS300X SD device (Polar Electro). Daily calibration of the gas analyser along with calibration after every 5 tests was done with ambient air and a reference gas mixture containing 5% CO_2 and 15% O_2 or with an alternate mixture of 4% CO_2 and 16% O_2 (Scott Medical Products). Before each test, calibration of barometric pressure and volume with a 3-litre syringe (5530 series, Hans Rudolph Inc) was performed. In addition, the MetaMax 2 performed an automatic calibration with a standardized motorized mechanical lung (motorized syringe with Metabolic Calibration Kit, Vacumed, Timik, AS, Oslo). Using a treadmill, (Woodway USA Inc., Waukesha, WI, USA) initial warm up speed and incline were adjusted individually in relation to reported Borg level, recorded HR and breathing frequency. The warm up lasted approximately 10-minutes, after which the mask and HR monitor was fitted. The CRF test was initiated using same intensity as the end of the warm up, a ramp protocol as

previously described in a published Gen100 method study,[92] was used hereafter. The protocol was split into 3, with the first two steps focusing on work economy measurements. The first step lasted for three minutes hereafter the inclination increased by 2% and the second step lasted 2 minutes. From that point on, the focus was to attain the highest oxygen uptake possible. The workload was increased by adjusting the inclination and speed when O_2 uptake stabilized or approximately every minute. Increments were done either by increasing 1km/h or by increasing the incline with 2%. A mix of the two was allowed (0,5km/t, 1% incline). Participants not able to walk due to pain or immobility were allowed to conduct the test on a cycle ergometer where the workload increased by 10 Watt every 30 seconds. In total, 10 participants in this study performed the bike test. CRF-tests continued until exhaustion (VO_{2peak}) or until the test was deemed adequate by the VO_{2max} criteria. These included a levelling off of O_2 despite a further increase in workload (oxygen uptake didn't increase more than 2 $mL \cdot kg^{-1} \cdot min^{-1}$ in two 30 second periods) indicating a plateau as well as a respiratory exchange ratio of >1.05. Due to the gas analyser reported measurements every tenth second the average of the highest 3 consecutive measurements were used as $VO_{2peak/max}$. In this study, the body weight ratio ($mL \cdot kg^{-1} \cdot min^{-1}$) and absolute litre ($L \cdot min^{-1}$) values were used. Participants known for pre-existing heart disease were tested under ECG monitoring with a doctor's presence. The American College of Cardiology/American Heart Association guidelines for exercise testing of patients with known CVD were followed.[103]

Statistical analysis

All variables were examined for the assumption of normal distribution by Shapiro-Wilk normality test and standard visual inspection (histograms and Q-Q plots).[104] Baseline differences between genders were determined by an independent sample t-test. As the primary analysis for comparison between groups an ANCOVA model comparing the change scores between each group was used. To calculate significant changes within groups a paired sample t-test was used. IBM SPSS 25 statistics software (SPSS Inc, Chicago, USA) was used for all statistical analyses and two-sided p-value < 0.05 was accepted as statistically significant.

Results

Descriptive statistics

Participants' baseline characteristics are presented in Table 1. The participants were between 70 and 77 years of age, and there was a representation of 50,8% women. At baseline, men had significantly higher WC (8,6%), diastolic BP (5%), VO_{2peak} (mL/kg/min) (25,2%) and sedentary time (h/d) (3%) compared to women. Women showed significantly higher HDL cholesterol (20,1%). On average participants were found to spend 77,9% and 75,8% of their time in SB for men and women respectively.

Table 1. Baseline characteristics of study participants

Variable	Men (n=241)	Women (n=249)
Age (years)	72.9 (2.2)	72.9 (2.1)
Waist circumference (cm)	98.4 (10.0)	90.6 (10.9) *
Triglycerides (mmol/L)	1.19 (0.59)	1.11 (0.58)
HDL cholesterol (mmol/L)	1.54 (0.41)	1.85 (0.49) *
Glycated hemoglobin A1c (%)	5.71 (0.49)	5.68 (0.44)
Blood pressure (mm Hg)		
Systolic	132.6 (16.6)	132.6 (17.4)
Diastolic	76.7 (9.4)	73.0 (9.7) *
Physical fitness		
VO_{2peak} (L/min)	2.64 (0.47)	1.73 (0.28) *
VO_{2peak} (mL/kg/min	32.32 (6.15)	25.82 (4.64) *
Sedentary time (h/d)	14.03 (1.11)	13.66 (1.15) *

Values are presented as mean (±standard deviation) HDL = high-density lipoprotein cholesterol, VO_{2peak} = peak oxygen uptake, h/d = hours daily *significant different from men ($p<0.01$)

Changes in cardiovascular risk factors in association with training modality

Dropout rates from baseline to three years were equal in HIT, MIT and CON (33%). Gender proportions, did not differ significantly between groups at baseline nor change significantly over the 3-year period. Table 2 shows the changes in risk factors for CVD after the 3-year intervention. Between group differences showed WC to significantly differ between the HIT and MIT group due to a slight increase in MIT and decrease in HIT. Within group changes showed CON and HIT significantly decreased TG by 10%. HDL cholesterol significantly increased by 3% and 4% for CON and HIT, respectively. All groups significantly decreased HbA1c by 3%. CON and MIT significantly decreased VO_{2peak} (mL/kg/min) by 2,4% and 4,8%, respectively.

Table 2. Changes in cardiovascular risk factors

Variable	CON (n=253)		MIT (n=117)		HIT (n=120)	
	Baseline	3-year	Baseline	3-year	Baseline	3-year
Waist circumference (cm)	93.7 (10.5)	94.0 (11.1)	95.6 (12.0)	96.3 (11.5)	95.0 (11.4)	94.3 (11.4) ☩
Triglycerides (mmol/L)	1.12 (0.56)	1.02 (0.44) *	1.22 (0.63)	1.11 (0.45) *	1.14 (0.58)	1.07 (0.41)
HDL cholesterol (mmol/L)	1.75 (0.49)	1.79 (0.52) *	1.67 (0.46)	1.69 (0.49)	1.63 (0.48)	1.70 (0.49) *
Glycated hemoglobin A1c (%)	5.65 (0.37)	5.51 (0.44) *	5.78 (0.61)	5.61 (0.61) *	5.72 (0.46)	5.56 (0.46) *
Blood pressure (mmHg)						
Systolic	132.1 (16.4)	130.7 (16.4)	132.6 (18.9)	131.4 (17.6)	133.7 (16.3)	131.7 (14.9)
Diastolic	75.1 (10.0)	74.9 (9.3)	74.4 (8.6)	75.0 (9.3)	74.6 (10.1)	74.1 (10.0)
Physical fitness						
VO_{2peak} (L/min)	2.17 (0.61)	2.11 (0.64) *	2.16 (0.57)	2.12 (0.57) *	2.25 (0.61)	2.21 (0.62)
VO_{2peak} (mL/kg/min)	29.3 (6.5)	28.8 (6.9) *	28.1 (6.3)	27.4 (6.3) *	29.4 (6.0)	29.3 (6.4)

Values are presented as mean ±standard deviation CON = Control group; MIT = Moderate intensity training; HIT = High intensity training; HDL = High-density lipoprotein; VO_{2peak} = Peak oxygen uptake; h/d = Hours daily *****significant difference from baseline value within the group ($p<0.05$) ☩ Significantly different in change from moderate intensity training ($p<0.05$)

Training adherence and per protocol analysis

Data showed significantly higher self-reported training intensity (Borg) in the HIT group with a mean of 14±2 compared to both CON (13±2) and MIT (13±2). No differences were found in frequency or duration of exercise. Adherence to training specific protocol was found to be 75% in CON, 73% in MIT and 47% in HIT. In the CON group 49% exercised at MIT level and 26% at HIT level. In the MIT group 6% exercised at HIT level and 20% below the physical activity recommendations. In the HIT group 47% exercised at MIT level and 6% below the physical activity recommendations.

Per protocol analysis of between group changes showed that increase in HDL significantly differed between HIT (7%) and MIT (1%). In addition, VO_{2peak} (mL/kg/min) in HIT differed significantly from MIT and show a strong trend to differ from CON ($p=0.06$), due to a stagnation in HIT and a decrease in CON (2%) and MIT (2%) as illustrated in figure 2. Within group changes showed MIT significantly decreased TG by 10% and HIT significantly decreased HDL by 7%. MIT and HIT both significantly decreased HbA1c by 3%.

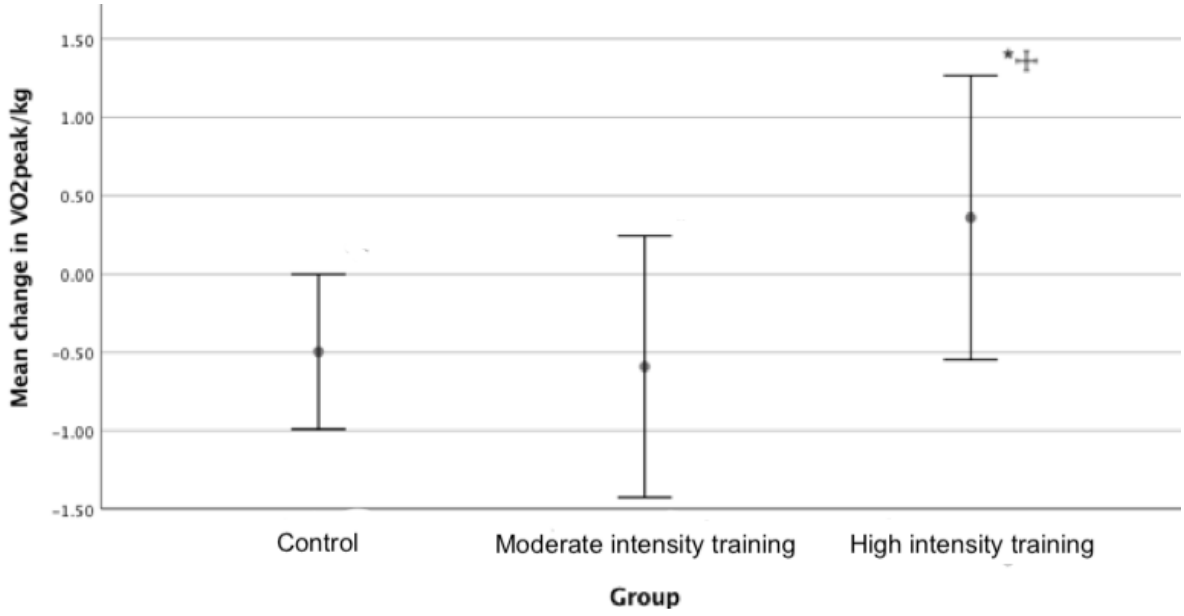

Figure 2. Mean change in VO_{2peak} (mL/kg/min)
Note: Values are presented as mean change in VO_{2peak} (mL/kg/min) and error bars as 95% confidence intervals.
***** Significantly different from moderate intensity training ($p<0.05$) ✢ Trend to differ from control ($p=0.057$)

Discussion

The main purpose of this study was to compare the effect of long term HIT vs MIT and CON on CRF and CVD risk factors in a cohort of sedentary, elderly individuals. The main finding of this thesis is that change in CRF and risk factors did not differ between the intervention groups, and thus prescribed exercise intensity is not crucial for a change in the risk factor profile. Thereby the main hypothesis, that HIT would yield a greater decrease in the risk factors for CVD than that of both MIT and the national PA recommendations in an elderly sedentary population over a 3-year period, is rejected. The secondary hypothesis is also rejected as neither HIT nor any of the groups were able to increase VO_{2peak} over the 3-year period. It is worth noting that the per protocol analysis showed the HIT group significantly differed in VO_{2peak} (mL/kg/min) change from both MIT ($p=0.03$) and a strong trend in CON, ($p=0.057$) due to a significant decrease in the CON and MIT groups and a stagnation in the HIT group. Our data shows that exercise as a general intervention seems to lower HbA1c and TG in addition to increasing HDL, as all three intervention groups had favourable changes in these risk factors. The similar results in each group might be explained by the fact that there was a low adherence to training-specific protocol in each of the intervention groups, combined with a high proportion of overlap.

Cardiovascular risk factors and changes between groups

Studies have shown that exercise has a positive effect on WC[12,57] TG, HDL,[57, 58] glycemic control,[68] BP[60, 62] and CRF.[105-110] Despite a varying definition of intensity, previous clinical trials have generally reported superior improvements for glycemic control,[111] diastolic BP[112] and CRF after HIT (minimum >60% of aerobic capacity) in comparison to MIT with equal workload.[113, 114] On the other hand, studies indicate intensity doesn't seem to influence change in WC,[12, 57] lipid profile[41] or systolic BP[115,63] between HIT and MIT.

Waist circumference

A significant difference between HIT and MIT groups was shown in WC. This is due to a trend for the MIT group to increase WC (p=0.08) and a trend in the HIT group to decrease WC (p=0.07). These finding are somewhat in line with prior studies showing that HIT has the ability to lower body fat but not necessarily yield a change in BMI nor weight.[116] Furthermore, a systematic review and meta-analysis have found that long term HIT >12 weeks can decrease WC in overweight to obese populations, and that the effect does not apply for healthy individuals.[117]

Lipid profile

The CON and MIT groups showed a significant decrease in TG. Noteworthy is that every group in this study, including the HIT group, lowered TG although not significantly (p=0.1) These results indicate that training may alternate TG in elderly sedentary adults. These results, indicating intensity doesn't play a role in TG change, have also been demonstrated in earlier studies in 50-65 year olds.[117, 118]

Significant increases in HDL were shown in both CON and HIT. No significant change was seen in MIT (p=0.2). Despite these significant differences within groups, there were no differences between groups in both protocols of analysis. Our data, that change in HDL, is intensity independent and is supported by Kraus et al.[57] who studied sedentary overweight individuals having dyslipidaemia. They demonstrated that high amount of exercise had the best effect on the lipid profile, independent of intensity.[57] The long intervention period of this study seems to affect HDL levels in accordance to an article by King et al.[118] who found that change in HDL wasn't observable in the

elderly in a short-term period, whereas a longer exercise period of >1 year seem sufficient enough to alter the HDL level.[118] Other studies seem to support this by showing no change in HDL over a short period of training <16weeks.[117]

Glycated hemoglobin A1c

Studies have found that light to moderate intensity exercise and especially HIT attenuates HbA1c in diabetics.[119, 120] In a study by Segerström et al.[121] they found that the amount of exercise is related to the decrease of HbA1c[121] Støa et al.[122] found that HIT was more effective than MIT, even with the MIT group having a different baseline level than HIT.[122] A study by Fisher et al.[123] showed that low-volume HIT and MIT both provided similar results in lowering glucose tolerance for up to 48-hours following last exercise bout.[123] This is in line with the present study showing all groups and all genders exhibited a significant decrease in HbA1c. This constitutes an important risk reduction of CVD as studies report a 15-20% reduction in CVD events when HbA1c is reduced by 1%.[124, 125]

Blood pressure

No significant changes or differences between groups were observed in neither systolic nor diastolic BP. Earlier studies have shown some decreases in diastolic BP in short time HIT (<12 weeks) for overweight individuals and both systolic and diastolic decreases in long term HIT (>12 weeks).[117] In the current study, 35% of the participants used hypertensive drug treatment at baseline and at the 3-year testing, there was less than a 1% change. Therefore, the use of hypertensive drugs cannot account for the lack of decrease in BP. The results presented seem to be in contrast with the majority of earlier studies which found MIT and HIT equal in lowering BP.[117,126,127] Tjønna et al.[126] found a significant decrease of 10mm Hg systolic and 6 mm Hg diastolic in individuals with the metabolic syndrome.[126] and Molmen-Hansen et al.[127] found a 12 mm Hg decrease in systolic BP for people with hypertension doing HIT.[127] The present study failed to show similar results, which may be due to normal baseline values, low exercise adherence or the relatively large medicated proportion. Other studies have shown that in order to decrease blood pressure in normotensive patients, a higher degree of adherence and volume is needed.[115]

Peak oxygen uptake

Although the VO_{2peak} (mL/kg/min) did not increase significantly for HIT, the per protocol analysis showed a significant difference between the HIT and MIT group and a trend to differ from CON (p=0.057). The latter being an interesting find as 26% of the CON group trained at HIT levels while only 6% in MIT training at HIT level. This suggests that intensity is a determinant for altering VO_{2peak}. It is noteworthy that the HIT group was the only group to not significantly decrease VO_{2peak}. A majority of studies seem to support HIT being superior in increasing VO_{2peak} in obese patients[105], heart patients[106, 107], postmenopausal women[108] and diabetics[109]. This is further supported by Westen et al[110], who showed similar results in participants with coronary artery disease, heart failure, hypertension, metabolic syndrome and obesity.[110] The stagnation in VO_{2peak} in the HIT group may be seen as beneficial when compared to a study by Fitzgerald et al.[33] showing that age-related decline in VO_{2max} is roughly 10% per decade,[33] and Sandbakk et al.[4] , who showed that even relatively small changes in CRF have potentially major effects on the CVD risk factor profile, especially in the elderly.[4]

Dropout and training intensity adherence

It is documented that around half of the participants enrolled in an exercise program will drop out within the first 6 months.[128] In relation to a clinical trial setting Henderson et al[129] found a 13% dropout at the 1 year follow-up exercise intervention on the sedentary elderly population.[129] In the present study, there was a dropout rate of 33%. The relatively high proportion of dropouts in our study may be due to the long intervention period. This study is one of the largest randomized controlled trials, and thus the first to report the dropout rate after such a long intervention in the elderly. In addition, our group was sedentary at baseline. Dropout in the elderly sedentary population has been suggested more likely due to change of interests, alternative training programs or the fact that the incidence of chronic diseases preventing participation increases with age.[130] In fact, a study has shown that 21% of dropouts from training studies do not fall back in sedentary behaviour, but instead change to alternative training programs that may fit their individual needs better.[131] The current study highlights the difficulty of changing lifestyle behaviour. Previous studies have shown that following correct protocol, whether it's above or below the target intensity

level, has proven difficult. In a study by Ellingsen et al.[132] studying heart patients, 51% of HIT participants trained below target intensity and 80% of participants in the MIT group trained at higher intensities than prescribed.[132] In the current study, 48% of participants allocated to HIT trained at MIT level and 6% of MIT participants trained at HIT level, thus making significant changes in CVD risk factors difficult to prove between groups due to a very similar intervention.

In a paper by Dishman and Buckworth[133], they found that sustained involvement in an exercise routine is more likely if there is provided a social aspect, such as a group or social environment setting.[133] Community-based, group exercise programs have shown promising results of increasing adherence to sustained exercise programs with rates of 75% in a long-term program (≥1 year). [134] The high adherence in the MIT group might be due to the social aspect around the training in our study (73%). However, the adherence in the HIT group was low, with only 47%, despite an equal social environment, proving other factors must be at play. A good preliminary physical ability along with a high self-perceived enjoyment of training have been linked to increased adherence.[135,136] Interestingly, in a paper by Hardcastle et al.[137], they contend that HIT may be unlikely to be taken up by the sedentary population, based on the arduous state of intensity, and that it may evoke perceived incompetence, lower self-esteem and potential failure.[137] Another study showed that HIT was rated as the least enjoyable training modality and they concluded that long-term adherence to this intensity protocol was less likely for the least trained individuals.[114] In fact, in a study by Perri et al.[138] they showed that increasing frequency from 3-4 days a week to 5-7 days a week increased the accumulation of exercise without a decline in adherence, whereas if they increased intensity, a significant decreased in adherence and a concurrent decrease in completion of exercise was found in a 6 month period.[138] The focus in this study has mainly been on exercise and the physiological adaptations. Future studies should give more emphasis on whether a sedentary population will feel capable and sufficiently motivated to take up and maintain a high intensity regime that is far from their prior experience and level. This may give a clue to why the adherence in the HIT group lacked behind the other intervention groups with an adherence of only 47%.[114]

The Hawthorn effect, being the change of behaviour in participants as a

reaction to being observed, must be taken into consideration.[139] In the present study, the CON group has an exercise adherence rate of 75% eliminating exercise intensity differences between groups. This may be the reason why the CON group decreased risk variables in line with what is seen in the other two intervention groups.

Sedentary behaviour as an independent risk factor for cardiovascular disease

Katzmarzyk et al.[140] proved that increasing CRF can attenuate the adverse effects of the metabolic syndrome to a level similar to what is seen in healthy individuals.[140] On that rationale, the HIT group should present greater CVD risk reductions based on its expected superiority in increasing CRF.[105-110] This is based on the assumption that the association between SB and CVD risk is due to the lack of PA and not the presence of SB. This assumption is contrast with a cross-sectional study done by Healy et al.[141], who examined the relationship between television time and CVD risk in men and women that reported at least 150 minutes of moderate to vigorous intensity exercise per week.[141] They found that there was a significant deleterious dose-response of television viewing time and WC, systolic BP and blood glucose in both men and women in addition to TG, HDL and cholesterol in women.[141] These findings suggest that the adverse health consequences of SB may be unaffected by reaching the current physical exercise guidelines.[141] It has been proven that low-intensity activity has a strong inverse relationship with sedentary time[142] and, furthermore, epidemiologic evidence suggests that spending more time in low-intensity behaviour in contrast to SB decreases CVD risk factors due to a linear relationship with a number of CVD risk markers. [142, 143] In line with this is a meta-analysis by Chau et al. who found that the risk of mortality when sitting 10 hours a day can be altered by reducing sitting time, as the mortality rate in the sedentary population was 52% higher than those who were sitting only 1 hour a day.[144] Strengthening these results further is a systematic review and meta-analysis studying all forms of SB on CVD risk, where they found that SB was associated with increased risk of CVD incidence and mortality independently of exercise.[145] The findings discussed above may suggest that the amount of time spent in SB is positively related to CVD risk and that promoting low-intensity activity as an additional approach could have shown greater results in mediating CVD risk among the sedentary population.

Strengths and limitations

The primary strength of this study is a large population size acquired through the enrolment in the Generation 100 study, inviting all men and women aged 70-77 living in Trondheim (a total of 6966 invited and a representation of 22.5%) were included in the main study.[92] In addition, the long intervention period is unique. The participants who enrolled reported better health as well as higher education than the ones who chose not to participate.[92] On the other hand, the study included a diverse range of both healthy people as well as ones with many comorbidities. In addition, the participants reported a wide range of baseline activity levels.[92] The study population appear to be more fit as seen in baseline CRF of their US counterparts[146] while seemingly corresponding to similar samples as seen in the Nord-Trøndelag Health Study (HUNT).[24] The participants were very ethnically homogenous with a predominantly white population, which demands caution when transferring this data to other populations.

The data presented could potentially have been affected by lifestyle factors not included in this study. Diet has been strongly linked to CVD risk factors, but was unfortunately not available in the 3-year follow up data. In addition, drug treatment data is not presented due to a prolonged acquisition time, but could potentially have altered the results, particularly for TG and HDL.

Due to the long intervention time, there was a change in the testing staff from baseline to the 3-year testing. Strict protocol and thorough lab training was set in place to increase inter-testing reliability. The testing facility was located at a teaching hospital cooperating with an international university, which posed a communication challenge for some of the testing staff and the participants.

In terms of reliability and validity, the use of directly measured CRF testing, a test protocol followed until exhaustion and the metric of sitting time, objectively measured by accelerometer in order to assess baseline SB were strengths. But using the 1952 count per minute cut-off to assess moderate to vigorous PA in the inclusion criteria may have underestimated the PA, thus derived from counts used for healthy younger populations. 3-year accelerometer data was not available, but could have aided greatly in the understanding of change in SB.

Supervision and adherence to training-specific protocol are the main

limitations in the current study. Voluntary weekly classes were held to instruct in correct technique and to induce higher adherence, which was also supported by several strategies set in place. Exercise logs sent in by post or registered electronically were used as a motivational booster. Furthermore, during the randomisation process, spouses were allocated to the same intervention group, so as to make it easier logistically and to hinder cross-over training. One year into the study an attendance committee was launched to implement strategies that would increase attendance, such as different social events and activities. Noteworthy is that this study is very close to a real life setting and that recommendations and protocols followed in this study are close to what is being used in rehabilitation and offered by public institutions. Self-reported frequency, intensity and time were used to assess training adherence and to determine the per protocol group. This data is subject to recall bias and a demand bias: "The Good-Subject Effect".[147]

Lastly in 2014 the current PA recommendations set by the Norwegian directorate of Health got updated to include HIT[101.] This may have influenced the results of the CON group in which they may have started a new training modality as shown by 26% training at HIT levels.

Conclusion

Several significant risk factor reductions were found in all intervention groups, with few differences between HIT, MIT and CON. Our data indicates that exercise intensity does not play a crucial role in changing the risk factors for CVD over a 3-year period in the sedentary elderly population. It is worth noting that the per protocol data shows HIT might be crucial to counteract the decrease in VO_{2peak}, as when seen in contrast to the decline in the MIT and CON group. High intensity training may therefore be essential for altering CRF in the sedentary elderly. Our data has shown that adherence to training-specific protocols seems challenging in the initially sedentary elderly.

Perspectives

Future studies including data on change in drug treatment as well as confounding factors, such as diet, should be initiated in the pursuit of understanding the effect of exercise intensity on the sedentary elderly population. In addition, more focus should

be given to a controlled setting to improve adherence. Lastly, qualitative studies may aid in discovering new modalities or settings that increase participation rates and adherence.

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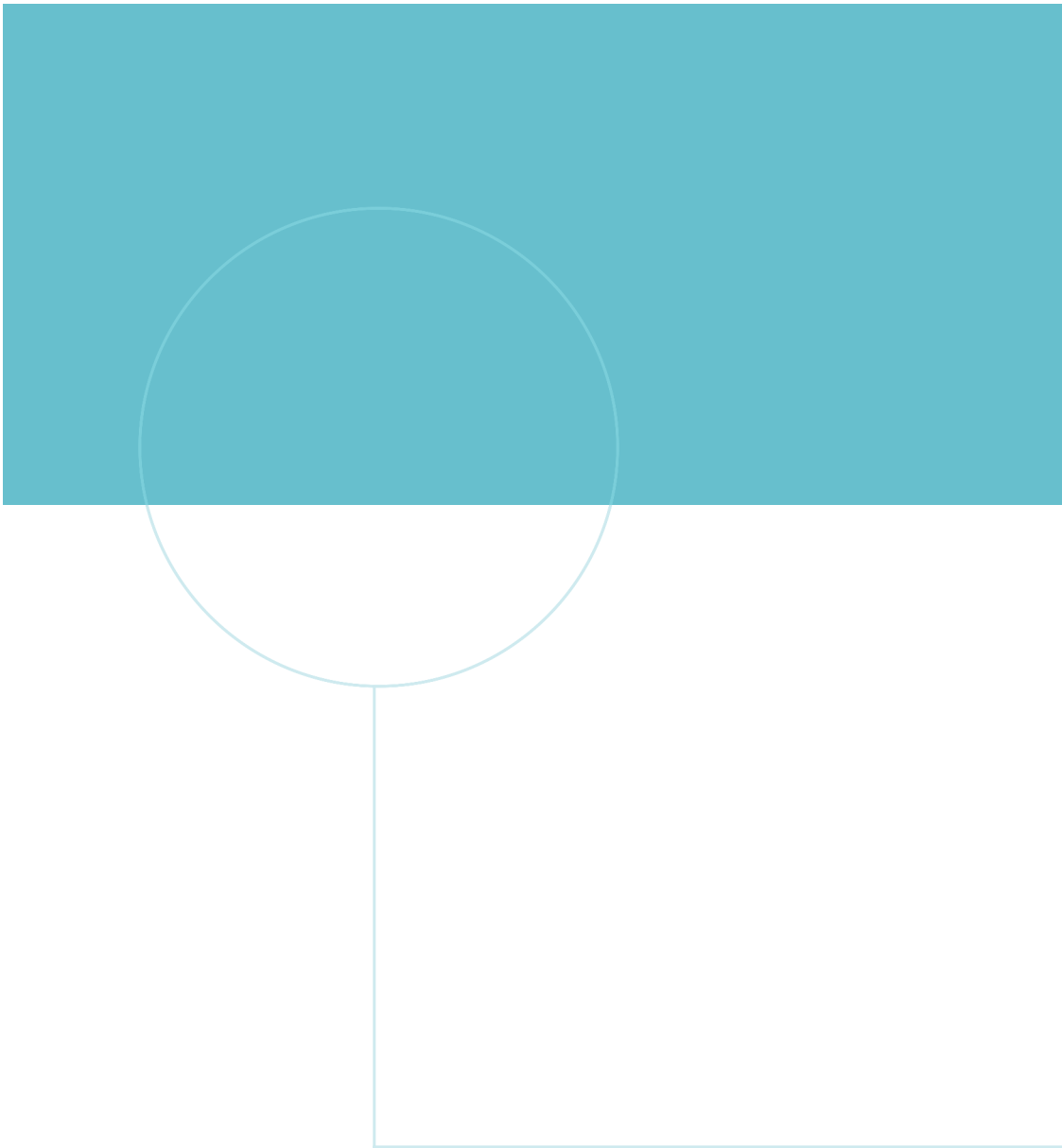

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