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Effects of long-term aerobic exercise on metabolic syndrome in older adults

– a substudy of the randomized controlled trial
Generation 100

Master's thesis in Exercise Physiology

Supervisor: Dorte Stensvold

June 2019

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Abstract

Background: Metabolic Syndrome (MetS) increases the risk for developing a cardiovascular disease, which is the leading cause of death worldwide. Due to an increase in the prevalence of MetS, it is of paramount importance to address proper MetS prevention and treatment strategies. Since studies examining exercise effects on MetS in older populations are scarce and inconsistent, the aim of this thesis is to examine the effects of long-term aerobic exercise on the prevalence and risk factors of MetS in older adults.

Methods: This thesis includes a sub-population of the randomized controlled trial Generation 100 (mean age 73 years). Subjects were included if they were defined with MetS according to the last-updated definition (AHA/NHLBI and IDF, n=345). Waist circumference (WC), triglycerides (TGs), high density lipoprotein-cholesterol (HDL-C), systolic and diastolic blood pressure (SBP, DBP), glycated hemoglobin (HbA1c) and peak oxygen uptake ($\dot{V}O_{2peak}$) were measured at baseline and after five years. The participants were randomized into one of the three following groups: control, moderate intensity training (MIT) or high intensity interval training (HIIT). The HIIT group was instructed to perform two training sessions per week with four by four-minute intervals at an intensity of 85-95% of the maximal heart rate. The MIT group was asked to exercise two times a week continuously for 50 minutes at an intensity of 70% of the maximal heart rate. The control group was advised to follow national physical activity guidelines, which correspond to daily 30 minutes of physical activity at a moderate intensity. Outcome measures were changes in prevalence and individual risk factors of MetS.

Results: 38% of the total sample was not defined as having MetS anymore after five years of intervention (37% of the control, 37% of the MIT, and 42% of the HIIT group). The control group displayed significant ($p<0.05$) reductions in TGs (-6.8%), HDL-C (men: -5.3%; women: -8.7%), and $\dot{V}O_{2peak}$ (men: -10%; women: -6.6%). The MIT group displayed a significant ($p<0.05$) increase in WC (only men: +1.6%), and significant ($p<0.05$) reductions in HDL-C (men: -7.7%; women: -5.5%), HbA1c (-1.7%) and $\dot{V}O_{2peak}$ (only men: -10.4%). The HIIT group increased WC (only men: +1.4%) and decreased TGs (-13%), HbA1c (-3.5%), and $\dot{V}O_{2peak}$ (only men: -4.6%) significantly ($p<0.05$). No significant differences between the groups were found after five years of intervention (except in women in the HIIT group who displayed a significant lower reduction in $\dot{V}O_{2peak}$ compared to the control group).

Conclusion: Exercise positively affected the prevalence and risk factors of MetS in older adults. Although the HIIT group showed more favorable changes within the group, the lack of significant differences between the groups indicate that the three interventions had overall similar effects on the prevalence of MetS and its individual risk factors. Due to a possible cross-over in the exercise groups and a highly active control group, more controlled studies are needed to further examine the effect of different intensities. Nevertheless, these results encourage the use of exercise as treatment strategy in older adults with MetS.

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Definitions

Physical activity

any bodily movement that results in energy expenditure

Exercise

subcategory of physical activity that includes structured, planned, repetitive and regularly performed body movement aiming to improve physical fitness

Physical fitness

ability of an individual to perform physical activity; relates to attributes that an individual has or achieves, as cardiorespiratory and muscular endurance; often referred to as cardiorespiratory fitness

Maximal oxygen uptake

highest possible oxygen uptake and utilization during exercise, implying the physiological limit of an individual to take up oxygen; determined by the Fick equation: maximal cardiac output (stroke volume · heart rate) · maximal arteriovenous oxygen-difference (measure for oxygen utilization in the tissues)

Peak oxygen uptake

highest attained oxygen uptake in an incremental test, when maximal oxygen uptake cannot be achieved due to bodily limitations or not fulfilled criteria

Cardiovascular disease

collection of diseases related to the heart and the blood vessels (e. g. coronary heart, cerebrovascular, peripheral heart disease)

Type 2 Diabetes

chronic disease, where the body becomes resistant to insulin

Metabolic Syndrome

multiplex risk factor for the development of cardiovascular disease and Type 2 Diabetes; includes the five risk factors abdominal obesity, high blood pressure, high levels of triglycerides, low levels of high density lipoprotein-cholesterol, and high levels of fasting glucose

Abbreviations

BP	Blood pressure
CPET	Cardiopulmonary exercise testing
CRF	Cardiorespiratory fitness
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
FG	Fasting glucose
HbA1c	Glycated hemoglobin
HDL-C	High density lipoprotein-cholesterol
HIIT	High intensity interval training
MetS	Metabolic Syndrome
MIT	Moderate intensity training
PA	Physical activity
SBP	Systolic blood pressure
TG	Triglyceride
$\dot{V}O_{2max}$	Maximal oxygen uptake
$\dot{V}O_{2peak}$	Peak oxygen uptake
WC	Waist circumference

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Introduction

Today's western society displays a lifestyle that is characterized by malnutrition and physical inactivity, influencing both physical and mental health.¹ Such an unhealthy living can evoke different disabilities and illnesses such as skeletal and joint problems, overweight, and cardiovascular and metabolic diseases that can ultimately lead to death.¹ The lack of physical activity (PA) has been shown to be one of the leading risk factors for mortality worldwide, accounting for about 3.2 million deaths per year.² A population that is very prone to being physical inactive is older adults.³⁻⁵ The process of aging generally involves a progressive loss of physiological function, resulting in a decline in muscle function, a loss of muscle mass,⁶ alterations in hormonal and metabolic functions,⁷ and changes in body composition.⁸ Furthermore, exercise capacity, a measure for physical fitness, is shown to decrease about 10% per decade.⁹ The physiological changes seen with aging threaten the health condition and constitute risk factors for developing disorders such as cancer, Type 2 Diabetes (T2D), and Metabolic Syndrome (MetS).¹⁰ The latter increases the risk for developing a cardiovascular disease (CVD) which is the leading cause of death, responsible for about 17.8 million deaths worldwide in 2017.^{11,12} Importantly, survival rates in the older population have increased,¹³ and the world's amount of older adults above 60 years of age is estimated to increase from 14% (year 2020) to 23% over the next four decades.¹⁴ In Norway, the amount of individuals over 70 years is predicted to double from 2018 to 2060.¹⁵ Furthermore, many of the diseases that previously led to premature death, now belong to the category of chronic diseases,¹⁶ leading to the aging population having more people living with chronic diseases and co-morbidities in many years. Thus, a serious challenge is not only a worsened quality of life at an individual level, but also the expected burden on our health care system and the economic cost related to that.¹⁷ Given the fact that the amount of older people rises and both the individual risk factors¹⁸⁻²⁶ and the prevalence of MetS²⁷⁻²⁹ is increasing with age, it is of paramount importance to address proper lifestyle interventions such as a change in diet and an increase in PA. Since studies examining the effect of exercise in older people with MetS are sparse, the main aim of this thesis is to examine the effects of long-term aerobic exercise on prevalence of MetS and its individual cardiometabolic risk factors in older individuals.

Metabolic Syndrome

Definition and prevalence

The MetS, also known as cardiometabolic syndrome, (metabolic) syndrome X and insulin resistance syndrome,³⁰ is constituted by the clustering of five different risk factors including abdominal obesity, increased levels of fasting glucose (FG), decreased levels of high density lipoprotein-cholesterol (HDL-C), high levels of triglycerides (TGs), and high blood pressure.¹² The syndrome increases the risk for the

development of CVDs (two-fold risk) and T2D (five-fold risk).¹² Additionally, MetS increases the risk for developing cancer, particularly pancreatic, breast, liver and colon cancer.^{17, 31, 32} Furthermore, MetS has been linked to inflammatory processes,³³ endothelial dysfunction,³⁴ low levels of maximal oxygen consumption ($\dot{V}O_{2max}$),^{35, 36} depression, physical dependence and decreased quality of life.³⁷

The use of different cut-off points for the individual components of MetS makes the assessment of prevalence difficult. Definitions come from the World Health Organization (WHO), the National Cholesterol Education Program – Third Adult Treatment Panel (NCEP:ATPIII), and the International Diabetes Federation (IDF) (see cut-off points in Appendix 1, Supplemental Table 1). Representatives of the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) and of the IDF came together in 2005 in order to discuss and reconcile the definitions with different cut-off points.¹² Consequently, Alberti et al.¹² published a paper in 2009 with a new common definition based on the statement of AHA/NHLBI and the IDF. Abdominal obesity is not an obligatory component anymore (as it was in the IDF definition), but it has to be one of the five components, such that the presence of any three of five abnormalities build the definition for MetS.¹² Notably, this definition is incorporated by ethnic specific measures regarding the assessment of waist circumference (WC) for abdominal obesity (see Appendix 1, Supplemental Table 2), and it is currently the last-updated definition of MetS (cut-off points see Table 2).^{12, 38} In general, the use of the IDF definition often results in higher prevalence numbers.²⁸ The NHANES (National Health and Nutrition Examination Survey)²⁷ data from 2003 to 2012 revealed that the overall prevalence of MetS was 33%, with the prevalence among older people (≥ 60 years of age) being greater with 46.7% (NCEP:ATPIII definition). This is in line with Hildrum et al.²⁸ who found a marked increase in the age-specific prevalence of MetS. The prevalence in the age group 70–79 years was four- and seven-fold higher in comparison to the age group 20–29 years in men and women, respectively (IDF definition).²⁸ Sandbakk et al.³⁹ found in an older population of 70–77 year old individuals 32.9% of women and 36.9% of men being defined as having MetS (last-updated definition¹²). These results clearly show that it is very difficult to assess uniform prevalence measures. Thus, it is important to agree on the use of one single definition to be able to provide consistent prevalence numbers that make comparisons easier.

Abdominal obesity

People with obesity are often also diagnosed with MetS (59.6% of obese men and 50% of obese women),⁴⁰ and the worldwide prevalence of obesity is at an epidemic level (about 300 million people), which puts a substantial concern on the development of MetS.^{17, 41} Especially people with abdominal obesity are likely to have MetS.^{38, 42} Abdominal obesity is more strongly linked to CVD and overall mortality risk compared to the measure of body mass index (BMI), both in adult and older populations.^{43, 44} Importantly, BMI is a

measure of overall obesity, not taking into consideration the percent body fat and distribution of fat throughout the body.⁴⁵ Waist circumference on the contrary reflects a measure of central fat mass and is thus, more applicable in defining MetS and establishing its risk for CVD.⁴⁶

Body composition and fat distribution differ with gender, where men tend to have a more abdominal fat distribution.⁴⁷ In regard to this, several examinations in different ethnic populations revealed mean WC being larger in adult males than in females.⁴⁸⁻⁵¹ It has been suggested to consider individuals to be abdominally overweight with WC cut-off points of ≥ 94 cm and of ≥ 80 cm, and to be abdominally obese with measures of ≥ 102 cm and ≥ 88 cm for men and women, respectively.⁵² The MetS definition also includes different cut-off points for different ethnicities since WC both in US men and women has been found to be averagely higher than in Caucasian and Asian men and women,⁴⁸⁻⁵¹ and the risk that is associated with a certain WC differs depending on the population.¹² Thus, higher thresholds are used for ethnic groups from the US compared to populations in Europe.¹²

Prevalence of abdominal obesity increases with age with a range between 44.3% and 53.7% in older men (65–75 years of age) and 74.5% and 80% in older women compared to 13.8% to 29.7% and 20.5% to 61.2% in younger men and women (20–44 years of age), respectively.^{18, 19} Aging displays total body fat changes, effects on fat distribution and composition, and an increase in fat mass.^{53, 54} The aging body distributes its fat from subcutaneous depots to visceral depots,⁵⁴ possibly explaining the increasing prevalence of abdominal obesity with age. Additionally, the age-induced increase and redistribution in fat mass could be one of the main reasons for the increasing MetS prevalence among older populations.⁵⁵ Abdominal obesity is characterized by an atherogenic (promoting build-up of fatty plaques in the blood vessels) lipoprotein profile and a dysfunction of the adipose tissue that is related to the production of inflammatory cytokines.⁵⁶ This leads to a low-grade, chronic inflammation and contributes to metabolic alterations,⁵⁶ increasing the risk for CVD and overall-mortality.

Abnormal levels of blood lipids

Abnormal amounts of TGs and HDL-C levels have been attributed to be the leading cause for arteriosclerotic cardiovascular disease,⁵⁷ and have been found to be significantly and independently linked to myocardial stroke and infarction in individuals with MetS.^{58, 59} Furthermore, low HDL-C levels are highly associated with coronary heart disease risk.⁵⁷ Since men were found to generally display lower HDL-C levels than women, different cut-off points for male and female individuals are suggested (see Table 2).^{60, 61}

Aging seems to be associated with a decrease in HDL-C.²⁰⁻²² Wilson et al.⁶² claim the aging process itself and increasing obesity to be determinants of the HDL-C decline. Triglyceride levels clearly increase with age,^{63, 64} which is probably attributable to an increased body weight, decreased PA,⁶⁴ abdominal obesity

and/or glucose intolerance in older adults.⁶⁵ Eberly et al.⁶⁶ examined the risk factor distribution among US men (mean age 53 years) diagnosed with MetS and found high blood pressure, high levels of TGs and low levels of HDL-C the most often occurring and clustered components. Looking into an older population (55–75 years of age) results in the finding that Stewart et al.⁶⁷ observed high levels of TGs the third common component and low HDL-C levels the least common. However, prevalence numbers are high – according to NHANES⁶⁸ (2003–2006) 53% of US adults (≥ 20 years of age) exhibit lipid abnormalities, whereas the prevalence for low HDL-C levels is around 23% and for high TG levels about 30%.

From a pathophysiological point of view, low amounts of HDL-C and high levels of TGs lead to a build-up of lipids, followed by plaque formation in the arterial walls, which can rupture, break loose or clog in small arteries in the heart or brain, causing serious adverse events as myocardial infarction or stroke.^{38, 69, 70}

High blood pressure

A systolic blood pressure (SBP) above 130 mmHg and a diastolic blood pressure (DBP) above 80 mmHg are usually considered as high blood pressure (hypertension).⁷¹ Stewart et al.⁶⁷ reported that high blood pressure is the leading component among the MetS factors in older adults. The NHANES study⁷² (1999–2000) revealed that hypertension was the most common risk factor of MetS in men (41%) and the third common risk factor in women (37%) ≥ 20 years of age. Hypertension prevalence increases with age with 59.8% in older US men (≥ 65 years of age) compared to 13.3% in younger US men (20–44 years of age). The corresponding numbers for US women are 71.7% and 8.7%, respectively.²³ Possible pathophysiological mechanisms for an increased prevalence of hypertension with advanced age include arterial stiffness, hormonal changes, a decreased arterial distensibility (elasticity), and a decreased baroreceptor sensitivity.^{73–75} Hypertension can damage arteries which might consequently get blocked and limit the blood flow to the heart, brain or kidneys – this constitutes one of the major risk factors for developing a CVD, stroke or kidney disease.^{76, 77} In addition, having high blood pressure increases the risk for peripheral artery disease by damaging blood vessels in especially arms and legs, causing fatigue and pain.⁷⁶ Other risks are angina, and vision loss through damaged arteries in the eyes.⁷⁶

High blood glucose levels

Fasting glucose levels ≥ 100 mg·dL⁻¹ (≥ 5.6 mmol·L⁻¹) are set as the cut-off point for MetS,¹² whereas prediabetes is defined with FG levels between 100–125 mg·dL⁻¹ (5.6–7.0 mmol·L⁻¹) and T2D with levels ≥ 126 mg·dL⁻¹ (≥ 7 mmol·L⁻¹).^{25, 78} Glycated hemoglobin (HbA1c) is often used in assessing T2D with levels $\geq 6.5\%$ (for prediabetes between 5.7–6.4%).^{25, 78} Importantly, HbA1c has been suggested to be used instead of FG for diagnosing diabetes and diabetes risk since it is a chronic marker of hyperglycemia (high blood sugar levels), it does not require fasting samples and is less dependent on day-to-day perturbations.⁷⁸

The National Diabetes Statistics Report (2017)²⁵ revealed that about 34% of US adults older than 18 years were diagnosed with prediabetes. In addition, the prevalence was increasing with age, where 48.3% in the age group ≥ 65 years had high FG levels.²⁵ Age-induced pathophysiological mechanisms point towards a direct effect on β -cells in the pancreas, resulting in an impaired function and consequently in insulin secretion decline.⁷⁹ Indirect effects of aging on high blood sugar levels deal with genetic risk, increased obesity, decreased PA and increased inflammation, all leading in a second step to insulin resistance.⁷⁹ Possible consequences of hyperglycemia are atherosclerosis, diabetic retinopathy, coronary artery disease, peripheral artery disease and stroke.⁸⁰

Clinical usefulness

There have been discussions about the clinical usefulness of the MetS. Critics refer to the lack of one precise definition, making prevalence comparisons difficult, and state that individuals with a different cluster-pattern might not convey the same CVD risk, and might therefore need different treatment options.⁸¹ Other points of criticism are that the treatment of the syndrome as such is not different than the treatment for its individual components,⁸² and that the diagnosis of MetS does not portend absolute risk since its assessment does not consider absolute risk factors as age, sex (even though some cut-off points are gender specific), family history and smoking.^{12, 83} However, whilst absolute risk models as the Diabetes Prediction Model or the Framingham Risk Score predict either diabetes or CVD risk, respectively, the MetS predicts both outcomes.⁸⁴ Furthermore, the components of MetS clearly define a particular combination of risk factors for an adverse outcome, and it has been shown that the clustering of risk factors in MetS constitutes a greater risk for CVD and T2D than the risk of the factors individually.^{32, 85, 86} According to Huang et al.⁸³ defining individuals with MetS can be seen as shorthand for physicians and clinicians in determining possible underlying mechanisms. They argue with the main use of defining people with MetS not being necessarily just the general risk assessment of CVD and T2D, but identifying a certain subgroup of individuals that share pathophysiological processes.⁸³ The concept of MetS also facilitates researching on a genetic basis and thus, might eventually lead to a better understanding of possible treatment options.⁸³ Lastly, the last-updated definition¹² is based on a simple clinical examination, and individuals with MetS will likely benefit from interventions that reduce the risk factors.⁸⁴ Notwithstanding the critique of the clinical usefulness of MetS, it constitutes a simple health concept with a clear need to manage and treat the risk factors to diminish the development of comorbidities and to prevent premature death – regardless of MetS being considered as syndrome or not.^{81, 84}

Physical activity and MetS

Whereas PA is defined as 'any bodily movement produced by skeletal muscles that results in energy expenditure', exercise is a subcategory of PA and includes a structured, planned, repetitive and regularly performed bodily movement aiming to improve physical fitness.⁸⁷ Physical fitness in turn – often referred to as cardiorespiratory fitness (CRF) – is related to the capacity of both the cardiovascular and the respiratory system to deliver oxygen and remove carbon dioxide from the tissues.⁸⁸ Cardiorespiratory fitness is mostly assessed with cardiopulmonary exercise testing (CPET) that measures oxygen uptake ($\dot{V}O_2$), where the highest possible $\dot{V}O_2$ and oxygen utilization during exercise is defined as $\dot{V}O_{2max}$, implying the physiological limit of an individual to take up oxygen.⁸⁸⁻⁹⁰ The occurrence of a plateau in $\dot{V}O_2$, even though work rate is still increasing, determines the achievement of the true/physiological $\dot{V}O_{2max}$.⁸⁸ However, some individuals have difficulties to reach $\dot{V}O_{2max}$ due to functional limitations or lung diseases and the term $\dot{V}O_{2peak}$ (peak oxygen uptake) is used to determine the highest attained $\dot{V}O_2$ in an incremental test.⁸⁸ It is shown that $\dot{V}O_{2max}$ decreases about 10% per decade,⁹ and that the aging process is accompanied by cardiovascular impairments such as a decreased cardiac output, decreased maximal heart rate, and an increased blood pressure.⁹¹ Nevertheless, studies have shown that exercise can improve $\dot{V}O_{2max}$ similarly throughout different age groups, and that older individuals can have similar training responses as their younger counterparts.^{91, 92} High intensity interval training (HIIT) has been shown to be superior to moderate intensity training (MIT) in improving $\dot{V}O_{2max}$ in healthy adults,⁹³ in diseased populations,^{94, 95} and in older individuals.^{96, 97} Additionally, studies have shown an association between the prevalence of MetS and low $\dot{V}O_{2max}$, which led to the suggestion to use low $\dot{V}O_{2max}$ as an additional risk factor of MetS.^{35, 36} Physical activity plays a key role in the primary intervention strategies for preventing and treating MetS.^{38, 98} Observational studies as a meta-analysis by He et al.⁹⁸ found a weak association of moderate levels of leisure time PA and a statistically significant association of high levels of leisure time PA with a reduced risk of MetS. This is in line with Lin et al.⁹⁹ who observed middle-aged women reporting high or moderate PA levels to be at a significant lower risk of developing MetS than women reporting low levels of PA. The authors found a significant dose-response of PA level on reducing the risk of MetS and all its components.⁹⁹ Further, it has been shown in intervention studies that exercise can reduce MetS prevalence both in adult^{100, 101} and in older populations.^{102, 103} High intensity interval training has been observed to reduce MetS prevalence statistically significant more than MIT in adults,¹⁰¹ but there are no studies comparing the effectiveness of HIIT and MIT in older adults with MetS, and thus, this remains a topic to examine. Exercise has also been shown to be beneficial for improving MetS risk factors by reducing abdominal obesity,^{96, 101, 104-107} improving blood lipids,^{96, 108} reducing hypertension,^{96, 109-111} and improving glycemic control.^{96, 112-116} Especially HIIT has been observed to have superior effects compared to MIT. Coker et al.¹⁰⁴

found visceral fat only decreased after HIIT in overweight older adults, and Maillard et al.¹¹⁷ observed significantly reduced abdominal fat mass after HIIT, but not after MIT in older women with T2D. Izadi et al.¹¹¹ showed HIIT being beneficial in reducing hypertension in older individuals, and Støa et al.⁹⁶ found HbA1c only significantly reduced after HIIT with a significant difference to MIT in older subjects with T2D. However, studies looking into the training effects of different intensities on the individual MetS risk factors in older adults are scarce. Especially the effect of HIIT compared to MIT on abnormal levels of blood lipids in older adults needs to be determined. Since Tjønnå et al.¹⁰¹ could show that HIIT was superior to MIT in reversing MetS risk factors in an adult population, this should also be addressed in older populations. The use of different exercise protocols and relatively short intervention periods in the aforementioned studies (6–52 weeks) further elucidate the need for more research. Gray et al.¹¹⁸ claim studies examining the promising HIIT and also MIT programs with a follow-up period of several years in order to provide less conflicting results. Importantly, studies with a focus on real-world settings outside the strictly controlled laboratory setting with easy-accessible and low-cost interventions are much needed.¹¹⁸

Call for data

The increasing number of older adults in addition to the increase in prevalence of MetS place a substantial burden not only on the individual, but also on the society and health care system with increased economic cost. This development clearly demonstrates the need for strategies aiming to prevent and treat MetS. Improving the MetS risk factors with proper treatment options and reducing medication could not only enhance quality of life but also potentially decrease the health care costs and thus, minimize the health care burden. Even though exercise has the potential to be used in a preventive and treatment strategy for MetS, studies examining the effects in older adults with MetS are scarce and inconsistent and there is a clear need for providing more and coherent information.

Aim and hypothesis

The aim of this thesis is to examine the effects of long-term aerobic exercise on the prevalence and individual risk factors of MetS in older adults. The hypothesis is that a 5-year exercise intervention induces positive changes in the individual risk factors and prevalence of MetS in older adults. Additionally, HIIT is hypothesized to be more effective in improving individual risk factors and thus, in reducing the prevalence of MetS compared to the MIT and the control group.

Methods

Study population and design

This thesis includes a sub-population of the Generation 100 study, a large randomized controlled trial evaluating the effects of long-term exercise (five years) on morbidity and mortality in older adults (detailed study protocol¹¹⁹ has been published previously). Briefly, all inhabitants of Trondheim born between the 1st of January 1936 and 31st of December 1942 were invited for participation (n=6966), whereof 1790 agreed to participate. After exclusions (criteria see Table 1¹¹⁹) and withdrawals, a total of 1567 subjects (790 women) were, stratified by marital status and sex, randomized 1:1 to a control and an exercise group. The exercise group was further randomized into a MIT and a HIIT group (randomization procedure was conducted at the Norwegian University of Science and Technology by the Unit for Applied Clinical Research). The present study includes all subjects defined as having MetS (AHA/NHLBI and IDF¹²) at baseline, whereas participants with incomplete data on individual MetS components (n=252) were excluded. After exclusion, 179 men and 166 women (total study sample n=345) were included for analysis (see Participant flow chart in Figure 1). All subjects gave written consent before participation in the main study, which was approved by the Regional Committee for Medical Research Ethics (REK 2012/381B), Norway, and fulfills the principles of the Declaration of Helsinki. The study is registered in the clinical trials registry (ClinicalTrials.gov, Identifier: NCT01666340).

Table 1: Exclusion criteria for the Generation 100 study

Exclusion criteria
Illness or disabilities that preclude exercise or hinder completion of the study
Uncontrolled hypertension
Symptomatic valvular, hypertrophic cardiomyopathy, unstable angina, primary pulmonary hypertension, heart failure or severe arrhythmia
Diagnosed dementia
Cancer that makes participation impossible or exercise contraindicated (considered individually, in consultation with physician)
Chronic communicable infectious diseases
Test results indicating that study participation is unsafe
Participation in other studies conflicting with participation in Generation 100

Outcomes

The primary outcome measure was the change in MetS prevalence throughout five years within and between three different groups (i.e. control, MIT and HIIT). Secondary outcome measures were changes in the individual risk factors WC, TGs, HDL-C, SBP, DBP, and HbA1c within and between all three groups.

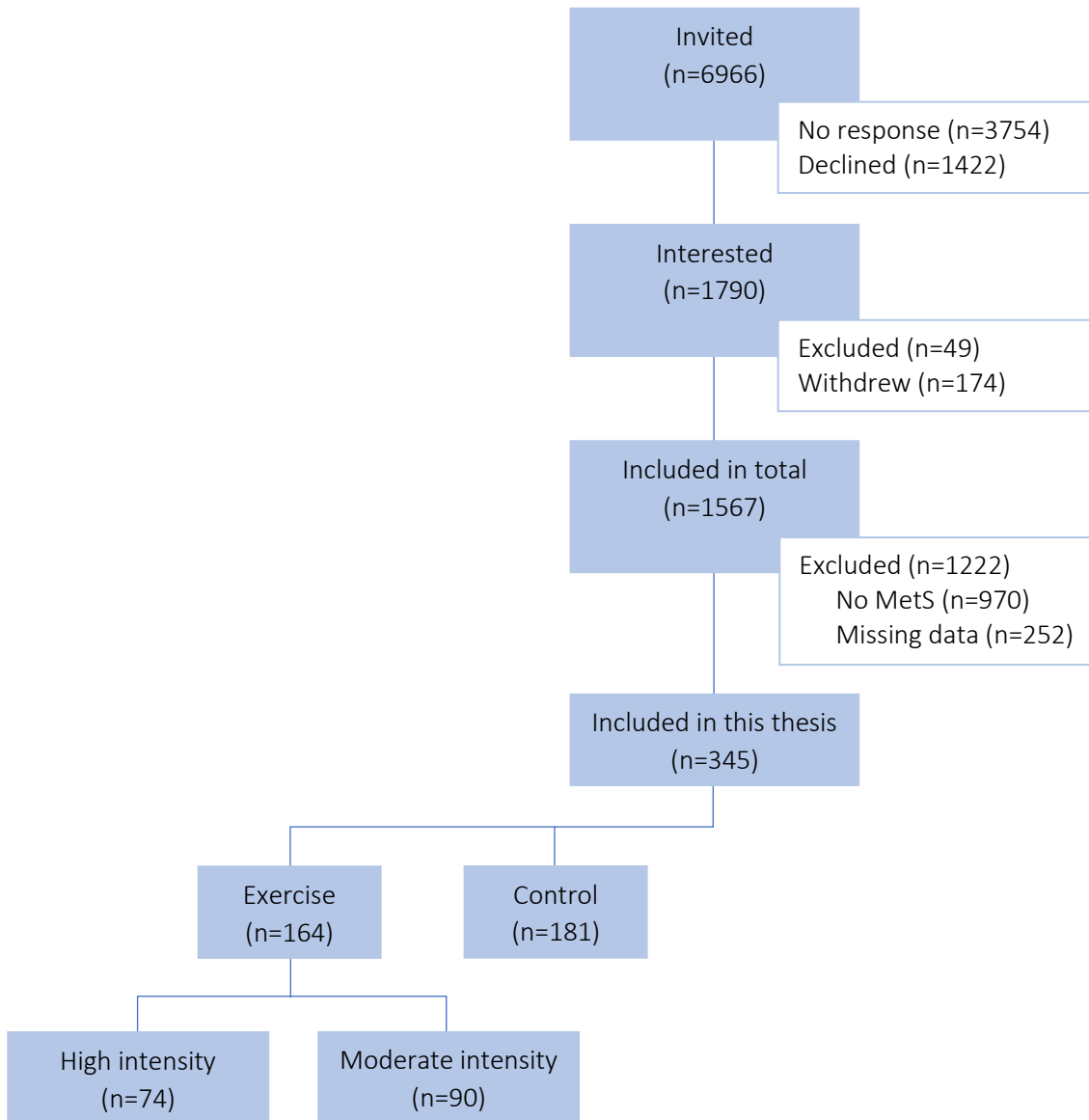


Figure 1: Participant flow chart. MetS = Metabolic Syndrome

Examinations

All data collection took place at AHL-Centre (Akutten og Hjerter-lunge-senteret) at St. Olavs Hospital in Trondheim, Norway. Professional personnel performed the clinical examinations for the baseline measurements between August 2012 and June 2013. Five-year measurements were carried out from

August 2017 until June 2018 (blinded personnel). All examinations were conducted on two different days, whereas day one consisted of blood pressure (BP) and heart rate (HR) measurements, measuring of anthropometric features (i.e. body composition, weight), and taking blood samples. Cardiopulmonary exercise testing with a conclusive conversation was performed on day two. All subjects were asked to come in a fasting state for test day one (at least twelve hours), and not to exercise, not to ingest caffeine, alcohol or nicotine prior to the tests. Questionnaires were given to the participants on test day one with the request of bringing them completed back on day two.

Blood pressure

Blood pressure measurements were taken after resting in a sitting position for five minutes using a Philips IntelliVue MP50 (Philips medicine system, Böblingen, Germany) with a customized cuff. This device is controlled frequently since it is under the St. Olavs University Hospitals (Trondheim) quality control system. The BP was measured two times in the right arm with a one-minute break in between. In case the two measurements differed more than ten mmHg in systolic and/or more than six mmHg in diastolic BP, a third measurement was taken. The average of the right arm BP measurements served as assessment values for the MetS cut-off points in this thesis.

Anthropometric features

Weight and body composition were measured with bioelectrical impedance (Inbody 720, BIOSPACE, Seoul, Korea). The participants were tested standing barefoot on a pair of electrodes in the floor scale and holding a pair of handles with two additional electrodes (subjects with a pacemaker were not tested). Height was assessed with a stadiometer (Seca 222, Hamburg, Germany) to the nearest millimeter with the participant standing shoulder-width and heels to the wall.

Waist circumference was measured with an inelastical measuring tape at the iliac crest (upper border) horizontally around the waist (to the nearest millimeter). Clothing and accessories (e. g. belt) had to be removed and the participants were asked to stand still in a shoulder-width position and the arms crossed over the chest. The participants were then requested to relax and breath normally, and at the end of the third expiration the measurement was taken without compressing the skin. Additionally, to avoid a possible underestimation of the WC measurement, the personnel ensured that the participants did not expire exaggeratedly during the measurement.

Blood sampling

Glycated hemoglobin, TGs and HDL-C levels were measured after obtaining blood samples from an arm vein using standardized procedures at St. Olavs Hospital in Trondheim.

Qualitative Data

Medication use ('Medication and type'), activity level of the control group ('Have you averagely been active 30 minutes daily in the last five years?'), and adherence of the MIT and HIIT group ('Did you averagely train once a week with the prescribed intensity in the last five years?') were assessed via interview on test day one and two. Adherence to the training sessions was defined as having performed at least 50% of the training¹¹⁹. The BORG scale¹²⁰ of perceived exertion was used to assess intensity (see *Spørreskjema 2 IV – 5 års undersøkelse* in Appendix 3), where a perceived exertion from 11 to 14 was considered as moderate intensity, and a perceived exertion of ≥ 15 was considered as high intensity. Portion sizes of daily meals were used to analyze diet behavior (see diet questionnaire *Hva spiser du?* in Appendix 3).

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed at the Core Facility NeXt Move at the Norwegian University of Science and Technology, Trondheim, on a treadmill (Woodway USA Inc., Waukesha, WI, USA) or bicycle (Monark Ergonomic 839 E, Sweden) according to the Generation100 protocol.¹¹⁹ Subjects with a history of or present heart disease were tested under electrocardiogram (ECG) monitoring (n=54), where the American College of Cardiology/American Heart Association guidelines were followed.¹²¹

Cardiopulmonary exercise tests were performed with the gas analyzers Cortex MetaMax I and II, (Cortex Biophysik GmbH, Leipzig, Germany) and Oxygen Pro (Erich Jaeger, Höchberg, Germany). Heart rate was monitored via an Accurex RS300X SD device (Polar Electro Oy, Kempele, Finland). Before starting CPET, the ergospirometry equipment was calibrated against a motorized standardized mechanical lung (Motorized Syringe with Metabolic Calibration Kit, VacuMed, Canada). The Calibration of the gas analyzer was performed in the beginning of the test day and after every fourth test with both ambient air and a reference gas mixture that contained 15% oxygen and 5% carbon dioxide (Scott Medical Products, Breda, Netherlands). The gas analyzer was calibrated against barometric pressure daily prior to the tests and against volume before each CPET.

Heart rate, $\dot{V}O_2$, respiratory exchange ratio (RER), and perceived exertion (BORG scale) were assessed with an individualized ramp protocol at three different levels. The first two levels (Step 1 and Step 2) were submaximal steady state measurements to assess work economy, and the third level corresponded to a maximal exercise test. After informing the participants about the test, CPET started with a warm-up for about ten minutes on a treadmill or a bicycle (participants that were not able to walk on a treadmill due to disability or leg pain (n=8)). The participants were wearing an appropriately fitting face mask (Hans-Rudolph, Germany) that was attached to the gas analyzer. The workload was individualized and selected on the self-reported PA level, the HR and the perceived exertion. The testing personnel encouraged the participants not to hold on to the treadmill's railing during CPET to facilitate the achievement of a $\dot{V}O_{2max}$

test. In case of balance problems, the subjects were allowed to hold on gently. After the first submaximal level (Step 1) which lasted for three minutes at the same speed and inclination as the warm-up, the inclination was increased by 2% (bicycle: 25 Watt) for one and a half minutes (Step 2). After the first two steps, the workload was increased as follows: either 2% inclination or 1 km·h⁻¹ (bicycle: 10 Watt every 30 seconds) until voluntary exhaustion or the criteria for a maximal exercise test were reached. These include an RER ≥1.05 in addition to a plateau in $\dot{V}O_2$ despite increasing workload (no increase higher than 2 mL·kg⁻¹·min⁻¹ in two 30 second periods, increments were given every ten seconds). Not all participants reached $\dot{V}O_{2max}$, and thus $\dot{V}O_{2peak}$ will be used as term in this thesis. Peak oxygen uptake was calculated as the average of the highest three consecutively measured $\dot{V}O_2$ -values. The highest HR attained and measured in the CPET plus five beats was used as maximum HR.

Interventions

The control group was advised to follow national PA guidelines,¹²² which correspond to daily 30 minute PA at a moderate intensity (in 2012). The HIIT intervention consisted of two weekly workouts including a ten-minute warm-up, four four-minute high intensity periods (85-95% of HR_{peak}, BORG scale 16) with three-minute lasting active recovery periods (60-70% HR_{peak}, BORG scale 12) in between (about 40 minutes in total). The MIT sessions also consisted of two weekly workouts. In order to ensure isocaloric exercise, subjects trained continuously for 50 minutes at 70% of HR_{peak} (BORG scale 13).

The training sessions varied between outdoor and indoor training as walking/running, spinning and cross-country skiing. Supervised training was offered two times a week for the two exercise groups, and to ensure that the subjects train at the target intensity, they met every six weeks for an obligatory supervised spinning session with HR monitors.

Metabolic Syndrome definition

The MetS risk factor cut-off points of the last-updated joint definition of AHA/NHLBI and IDF were used for defining MetS (see Table 2).¹² Since the most recent recommendation of the American Diabetes Association⁷⁸ (2010) points towards the use of HbA1c instead of FG levels for the diagnosis of pre(diabetes), and several studies support the use of HbA1c in defining individuals with MetS,¹²³⁻¹²⁶ the cut-off point for FG is replaced by the cut-off point for HbA1c for prediabetes and diabetes (i.e. ≥5.7%).

Statistics

All descriptive data are presented as mean ± standard deviation. Visual evaluation (i.e. QQ-plots and histograms with normal curve) and tests for normality were used for the assessment of normally distributed data. If normal distribution was in doubt, non-parametric tests were run. Paired sample t-tests were performed to assess within-group changes from baseline to 5-year follow-up. General linear models

(univariate ANCOVA) were executed for analyzing between-group differences. Categorical variables were analyzed with non-parametric tests. For statistical analyzes the software IBM SPSS Statistics Version 25 (SPSS, Inc, Chicago, USA) was used, and graphs were created with Microsoft Excel Version 1812 for Office 365. Two-sided p-values of <0.05 were accepted for statistical significance.

Table 2: Cut-off points for MetS according to the joint definition of AHA/NHLBI and IDF¹²

Variable	Cut-off point
Waist circumference	country- and population specific EU: ≥94 cm for men, ≥80 cm for women
Triglycerides*	≥150 mg·dL ⁻¹ (1.7 mmol·L ⁻¹)
HDL-C*	<40 mg·dL ⁻¹ (1.0 mmol·L ⁻¹) for men <50 mg·dL ⁻¹ (1.3 mmol·L ⁻¹) for women
Blood pressure*	≥130 mmHg (systolic) and/or ≥85 mmHg (diastolic)
Fasting glucose*	≥100 mg·dL ⁻¹ (5.6 mmol·L ⁻¹)
HbA1c*	≥5.7%

MetS = Metabolic Syndrome; AHA/NHLBI = American Heart Association/National Heart Lung, and Blood Institute; IDF = International Diabetes Federation; HDL-C = High density lipoprotein-cholesterol; EU = Euroid; HbA1c = Glycated hemoglobin; * = or drug treatment

Results

Baseline characteristics

Baseline characteristics of the study participants are shown in Table 3, where both data from the total sample, and men and women separately are described. The participants of the study sample were between 70 and 76 years old, and with 48.1% represented by women. At baseline, men had a statistically significant higher weight (22.1%), height (8.6%), BMI (3.7%), WC (8.7%), lower HDL-C levels (23.4%), higher DBP (5.4%), and $\dot{V}O_{2peak}$ in $mL \cdot kg^{-1} \cdot min^{-1}$ (16.6%) than women (all $p < 0.01$).

The majority of participants had three risk factors at baseline (64.6%) followed by four risk factors (22.9%) and five risk factors (12.5%). The most prevalent MetS risk factors were high WC (96.2%), high BP (91.6%), and high HbA1c levels (81.7%), followed by high TG (45.2%) and low HDL-C levels (33.3%).

Table 3: Characteristics of study participants at baseline

Variable	Total (n=345)	Men (n=179)	Women (n=166)
Age (years)	73 ± 2	73 ± 2	73 ± 2
Weight (kg)	80.7 ± 13.3	88.4 ± 11.0*	72.4 ± 10.3
Height (cm)	170.6 ± 8.8	177.3 ± 5.9*	163.3 ± 4.8
BMI ($kg \cdot m^{-2}$)	27.6 ± 3.3	28.1 ± 3.0*	27.1 ± 3.5
WC (cm)	99.6 ± 10	103.6 ± 8.6*	95.3 ± 9.6
TGs ($mmol \cdot L^{-1}$)	1.41 ± 0.86	1.43 ± 0.67	1.39 ± 0.69
HDL-C ($mmol \cdot L^{-1}$)	1.57 ± 0.48	1.41 ± 0.37*	1.74 ± 0.52
SBP (mmHg)	138 ± 16	137 ± 15	139 ± 17
DBP (mmHg)	77 ± 9	78 ± 9*	74 ± 9
HbA1c (%)	5.9 ± 0.5	5.9 ± 0.5	5.9 ± 0.5
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	2.21 ± 0.57	2.59 ± 0.49*	1.80 ± 0.28
($mL \cdot kg^{-1} \cdot min^{-1}$)	27.5 ± 5.4	29.5 ± 5.4*	25.3 ± 4.4
($mL \cdot kg^{-0.75} \cdot min^{-1}$)	82.2 ± 16.5	90.3 ± 16.2*	73.5 ± 11.6

The data are presented as mean ± standard deviation. BMI = Body Mass Index; WC = Waist circumference; TGs = Triglycerides; HDL-C = High density lipoprotein-cholesterol; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HbA1c = Glycated hemoglobin; $\dot{V}O_{2peak}$ = Peak oxygen uptake
*significant different from women ($p < 0.01$)

Within- and between-group changes

Metabolic Syndrome prevalence decreased from 100% at baseline to 62% after five years of follow-up ($p < 0.05$). Separating into the different intervention groups, 37% of the control, 37% of the MIT and 42% of the HIIT group were not defined as having MetS anymore after five years, without a statistically significant difference between the three groups (see also Figure 2). Among the participants who were not defined as having MetS anymore after the 5-year follow-up, the highest changes were found in TG and

HbA1c levels with 87.9% and 79.2% of the individuals having reduced their TG and HbA1c levels below the cut-offs for defining MetS, respectively.

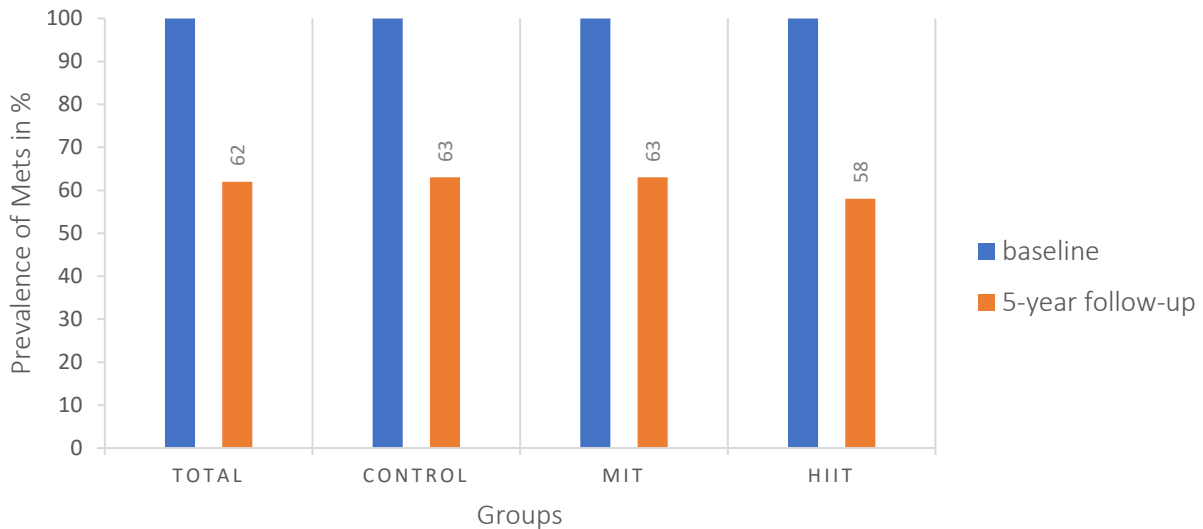


Figure 2: Prevalence of MetS at baseline and after five years of intervention. MetS = Metabolic Syndrome; MIT = Moderate intensity training; HIIT = High intensity interval training

Table 4 shows the changes in risk-factors comprising the MetS after the 5-year intervention in each group. Data for men and women are presented separately for the gender-specific cut-off points WC and HDL-C, and additionally for $\dot{V}O_{2peak}$. Sample sizes for men were n=42 (control), n=48 (MIT), and n=39 (HIIT). Corresponding numbers for women were n=89 (control), n=42 (MIT), and n=35 (HIIT).

Men in MIT had a 1.6% increase ($p<0.05$), and men in HIIT a 1.4% increase ($p<0.05$) in WC. The control group decreased TGs by 6.8%, and the HIIT group decreased TG levels significantly by 13.0%. Men decreased HDL-C significantly by 5.3% (control group), and 7.7% (MIT group). Corresponding decreases for women were 8.7% and 5.5% in the control and MIT group, respectively ($p<0.05$). Both the MIT and HIIT group decreased their HbA1c levels significantly by 1.7% and 3.5%, respectively. Men decreased $\dot{V}O_{2peak}$ in $mL \cdot kg^{-1} \cdot min^{-1}$ by 10% (control), 10.4% (MIT) and 4.6% (HIIT). Only women in the control group decreased $\dot{V}O_{2peak}$ in $mL \cdot kg^{-1} \cdot min^{-1}$ significantly by 6.6%.

Regarding between-group differences, solely $\dot{V}O_{2peak}$ was found to be significantly different between the HIIT and the control group in women. No other between-group differences were found.

Table 4: Baseline and 5-year characteristics for risk factors related to MetS

Variable	Control (n=181)		MIT (n=90)		HIIT (n=74)	
	Baseline	5-year	Baseline	5-year	Baseline	5-year
MetS (n/%)	181/100	114/63*	90/100	57/63*	74/100	43/58*
WC (cm)						
Men	103.2 ± 7.8	103.8 ± 8.5	104.4 ± 10.5	106.1 ± 11.3*	103.7 ± 7.8	105.2 ± 9.1*
Women	95.1 ± 9.7	95.7 ± 9.9	94.7 ± 9.3	95.7 ± 10.7	96.4 ± 9.9	96.3 ± 8.1
TGs (mmol·L⁻¹)	1.42 ± 0.67	1.33 ± 0.56*	1.41 ± 0.71	1.31 ± 0.59	1.39 ± 0.67	1.23 ± 0.45*
HDL-C (mmol·L⁻¹)						
Men	1.39 ± 0.35	1.32 ± 0.36*	1.40 ± 0.42	1.30 ± 0.30*	1.46 ± 0.37	1.42 ± 0.33
Women	1.75 ± 0.53	1.61 ± 0.47*	1.74 ± 0.56	1.65 ± 0.4*	1.74 ± 0.48	1.62 ± 0.33
SBP (mmHg)	139 ± 16	137 ± 17	137 ± 17	136 ± 17	138 ± 15	137 ± 16
DBP (mmHg)	77 ± 10	77 ± 10	74 ± 8	76 ± 10	78 ± 9	78 ± 10
HbA1c (%)	5.9 ± 0.4	5.8 ± 0.7	6.0 ± 0.7	5.9 ± 0.7*	5.9 ± 0.4	5.7 ± 0.5*
$\dot{V}O_{2peak}$						
Men						
(L·min ⁻¹)	2.59 ± 0.47	2.34 ± 0.57*	2.66 ± 0.42	2.38 ± 0.47*	2.66 ± 0.52	2.52 ± 0.49*
(mL·kg ⁻¹ ·min ⁻¹)	29.8 ± 5.0	27.1 ± 6.2*	30.9 ± 5.2	28.0 ± 5.5*	29.8 ± 5.6	28.5 ± 5.5*
(mL·kg ^{-0.75} ·min ⁻¹)	90.9 ± 15	82.5 ± 18.8*	94 ± 15.2	84.8 ± 16.3*	91.5 ± 16.6	87.2 ± 16.1*
Women						
(L·min ⁻¹)	1.81 ± 0.26	1.68 ± 0.25*	1.85 ± 0.22	1.75 ± 0.31*	1.89 ± 0.31	1.81 ± 0.32‡
(mL·kg ⁻¹ ·min ⁻¹)	25.8 ± 4.0	24.2 ± 4.6*	26.2 ± 4.2	25.2 ± 5.0	25.6 ± 4.6	25.4 ± 5.0‡
(mL·kg ^{-0.75} ·min ⁻¹)	74.5 ± 10.5	69.7 ± 11.8*	75.8 ± 11.0	72.6 ± 13.5*	74.8 ± 12.7	73.7 ± 13.8‡

The data are presented as mean ± standard deviation. MIT = Moderate intensity training; HIIT = High intensity interval training; MetS = Metabolic Syndrome; WC = Waist circumference; TGs = Triglycerides; HDL-C = High density lipoprotein-cholesterol; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HbA1c = Glycated hemoglobin; $\dot{V}O_{2peak}$ = Peak oxygen uptake

*significant different from baseline (p<0.05)

‡significant different from change in control (p<0.05)

Sub-analyses

Peak oxygen uptake and MetS

Comparing the change in $\dot{V}O_{2peak}$ between participants who were not defined as having MetS anymore after five years and participants who still were defined as having MetS showed that the subjects without MetS displayed a statistically significant (p<0.01) less decrease in $\dot{V}O_{2peak}$ than participants with MetS (–0.99 mL·kg⁻¹·min⁻¹ versus –2.42 mL·kg⁻¹·min⁻¹, see also Supplemental Figure 1 in Appendix 2).

Adherence and exercise intensity

In total, 90% of the MIT and 60.8% of the HIIT group stated to have trained once a week as prescribed in the last five years (p<0.001 for between-group difference). In the MIT group 13.6% claimed to have trained with a high intensity, and in the HIIT group 44.4% stated to have trained with a moderate intensity.

In the control group, 89% stated to have been physically active for averagely 30 minutes every day in the last five years. Of those, 57.1% claimed to have been active with a moderate intensity, and 27.3% stated to have been active with a high intensity.

Diet behavior

Analyzing the portion sizes of daily meals (i.e. breakfast, lunch, dinner, supper, night meal) revealed no significant differences between the groups after five years of intervention. No statistically significant within-group changes were found for portion sizes of breakfast, dinner, supper, and night meal in any of the intervention groups. Lunch size decreased in the MIT group from 0.8 portions at baseline to 0.7 portions after five years of intervention ($p < 0.05$).

Discussion

The main finding in this thesis is that 38% of the total study population was not defined as having MetS anymore after five years of intervention. Thirty-seven percent of the control, 37% of the MIT and 42% of the HIIT group was not defined as having MetS anymore after the follow-up. Major positive changes for the secondary outcome measures were a decrease in TG levels in the control group, a decrease in HbA1c levels in the MIT group, and decreased levels in both TGs and HbA1c in the HIIT group. Additionally, in contrast to the control and MIT group, HDL-C did not decrease significantly in the HIIT group. Even though HIIT seemed to have induced slightly more favorable changes, the lack of significant differences between the groups indicate that all three interventions in the present study had the same effect on the prevalence of MetS and its individual risk factors.

Change in prevalence and risk factors of MetS

The observed overall decrease in MetS prevalence from 100% at baseline to 62% after five years is in line with Chang et al.¹⁰² who found a decrease in MetS prevalence from 100% to 66.7% after a 6-months exercise intervention in older adults. The endurance program consisted of three 40-min sessions per week and a 40-min walking plan at five days a week.¹⁰² Unfortunately, no detailed information is given about the intensity. However, MIT and HIIT in this thesis showed a 11% and 26% larger decrease in MetS prevalence with a lower training volume (two sessions per week), indicating that the longer exercise intervention might have been more favorable and effective in reducing MetS prevalence. Kemmler et al.¹⁰³ observed that a multipurpose exercise program (aerobic dance, coordination, isometric strength training, and others) decreased the prevalence of MetS by 30.3% in older women. The endurance component of the intervention consisted of high intensity exercises for 20 minutes between 70–85% of HR_{max} .¹⁰³ This intensity was lower than in the HIIT modality in this thesis (85–95% of HR_{peak}) which could explain the lower decrease in prevalence of MetS (30% versus 42%). Another possible explanation for the difference could be that in Kemmler et al.¹⁰³ only women were included. However, additionally, multipurpose interventions preclude the assessment of independent effects of the incorporated modalities and thus, limit the comparability to single-modality interventions as in this thesis.

The prevalence of MetS after five years was not significantly different between the groups in the present study. Contrary to this findings, Tjønnå et al.¹⁰¹ found that HIIT decreased MetS prevalence by 45.5% and MIT by 37.5%, with a significant difference between the groups. The higher percentages and the significant between-group difference in Tjønnå et al.¹⁰¹ could be ascribed to more strictly supervised and monitored training sessions and the considerably younger age of the participants (mean age 52 years).

Even though the control group just got the advice to be physically active, this seems to have been enough to induce a change in activity level. In addition, repeated testing throughout the 5-year follow-up possibly

increased the motivation of the control group to be active. Indeed, individuals in the control group were observed to be more active than they were supposed to be. More than half of the control group (57.1%) claimed to have been active with a moderate intensity and almost a third (27.3%) stated to have been active with a high intensity. Hence, most of the individuals in the control group exercised comparable to the actual protocol of the MIT or HIIT group.

Interestingly, the control and the MIT group decreased the prevalence of MetS over the 5-year follow-up to the exact same extent. In addition to the similar exercise patterns in these two groups, this finding could be attributable to the fact that more individuals in the MIT group than in the control group (18% versus 12%) had all five risk factors present, and more people in the control than in the MIT group had just three risk factors (65% versus 58%). Thus, it is likely that the control group could decrease their risk factors more easily and additionally, that they were closer to the cut-offs than the MIT group.

In addition, there might have been a possible cross-over in exercise modalities between the exercise groups, such that individuals in HIIT trained with a too low and subjects in MIT with a too high intensity. In total, 13.6% of the MIT group state to have trained with a high intensity and almost half of the subjects in the HIIT group (44.4%) state to have trained with a moderate intensity.

These factors could explain why firstly, the MIT and control group displayed the same results, and secondly, that no statistically significant difference between all three groups was found. Potentially, a larger difference between the groups could have been observed, if the individuals only performed the prescribed exercise, if the training sessions were more strictly monitored, and if adherence in the HIIT group was higher (60.8%). However, the intervention was only partly controlled, and it is therefore likely that the findings reflect the PA in a real life setting of free-living older adults.

This thesis is the first study that examined and adds information about the effects of a 5-year aerobic exercise intervention on the prevalence and cardiometabolic risk factors of MetS in older adults. Comparing three different groups, it did not seem to matter to which exercise group the individuals were randomized – advising people to stick to national guidelines with regular follow-up tests seemed to have been enough to significantly reduce the prevalence of MetS. Hence, the results of this thesis show that exercise seemed to be beneficial for reducing the prevalence of MetS in a population of older adults. It has also been shown that PA is inversely related to the development of MetS,^{98, 99, 127} and that the prevalence of MetS is associated with a low $\dot{V}O_{2max}$,^{35, 36} indicating that having a higher CRF is positively related to a reduced risk of developing MetS. This is in line with the findings of this thesis, showing that CRF is low among individuals with MetS. Compared to reference values from HUNT (The Nord-Trøndelag Health Study),¹²⁸ which were measured in a healthy older population, men and women in this thesis were

observed to have a 19.7% and 11.9% lower $\dot{V}O_{2peak}$ in $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, respectively. Additionally, the data of this thesis revealed that the participants who were not defined as having MetS anymore after five years of intervention had a significantly lower decrease in $\dot{V}O_{2peak}$ during the 5-year follow-up compared to the participants who were still defined as having MetS. Hence, the smaller the decrease in, and thus, the higher $\dot{V}O_{2peak}$, the more beneficial it seemed for the classification of MetS in this population of older adults.

Individual risk factors

Of 131 participants who were not defined as having MetS anymore after the 5-year follow-up, 87.9% reduced their TGs, and 79.2% reduced their HbA1c levels below the cut-offs for defining MetS. Thus, reduced TG and HbA1c levels seem to have been primarily affected by the intervention and were likely most responsible for the reduction of MetS prevalence.

For both the control and the HIIT group a significant decrease in TG levels was observed, but since the MIT and control group decreased their TG levels to the same extent, the non-significant finding in the MIT group is most likely due to the smaller sample size compared to the control group. Seals et al.¹²⁹ has previously shown that TG levels decreased after high intensity training, but not after low intensity training. However, no statistically significant difference between the groups were found in the present thesis, indicating that MIT seemed to have been as effective as HIIT in inducing a reduction in TG levels. Since Seals et al.¹²⁹ included only healthy participants, this could indicate that a higher intensity is needed to lower TG levels in healthy people. In contrast, Kelley et al.¹⁰⁸ and Motoyama et al.¹³⁰ observed TG levels not to be decreased after about nine months of moderate intensity exercise. Hence, the fact that the participants in the control and the HIIT group in the present study decreased their TG levels indicates that the intervention in the two abovementioned studies might have been too short to induce any changes.

Glycated hemoglobin decreased significantly in both the MIT and HIIT group, but without a significant difference between the groups. This is in line with two meta-analyses^{112, 113} who found the effects of HIIT not being different from MIT in a population of 21–68 year old individuals. Thus, intensity does not seem to play a major role in reducing HbA1c levels, and moderate intensity seems to be enough to induce significant changes. Noteworthy, Støa et al.⁹⁶ found only HIIT being effective in reducing HbA1c levels with a significant difference between the HIIT and the MIT group. Possibly, the positive effect of MIT in the present study is attributable to the considerably longer intervention period compared to Støa et al.⁹⁶ (twelve weeks). However, studies examining the effect of different intensities on HbA1c levels (especially prediabetes) in older adults are scarce and should be emphasized in the future.

High density lipoprotein-cholesterol was found to be significantly decreased for the control and the MIT groups, but not for the HIIT groups, indicating that HIIT had a more beneficial effect on HDL-C than the

two other groups. However, the lack of a significant between-group difference precludes any definite superior effect of HIIT. Additionally, the MIT and HIIT group in women reduced HDL-C to the same extent, but only the change in the MIT group was observed to be statistically significant, likely due to the bigger sample size. Hence, all three groups in women decreased their HDL-C levels to a similar extent. Findings of other studies are inconsistent with some reporting increased HDL-C levels after aerobic exercise^{108, 130} and others showing HDL-C levels not being affected by exercise.^{131, 132} However, in this thesis, HDL-C levels were averagely quite high with the levels being above the cut-off for MetS. Thus, the participants displayed HDL-C levels in a normal range, indicating that there might not have been much room for improvement. However, since the levels decreased from baseline to the 5-year follow up, five years of aging might have been superior to any possible exercise-induced changes and instead, affected the HDL-C levels negatively.

No significant within-group or between-group changes could be observed in SBP and DBP. A meta-analysis by Kelley & Kelley¹¹⁰ found aerobic exercise being efficient in reducing SBP significantly, but not DBP. The authors state that the small decrease in SBP and the lack of a decrease in DBP could be attributable to low baseline values, limiting the potential gain in terms of BP reductions.¹¹⁰ This could also be a reason in this thesis – both SBP and DBP among the different groups were averagely not very high (average DBP below the cut-off points for defining MetS). Additionally, BP lowering medication (48% took hypertension medication) might have attenuated or overridden possible exercise-induced improvements in BP in the present study. However, the non-significant, but small decrease in SBP in this thesis is likely to be clinically important since a 2 mmHg reduction was estimated to decrease the risk of coronary heart disease mortality by 4%, of stroke mortality by 6%, and of all-cause mortality by 3% in middle-aged adults.¹³³ This might also possibly be applicable to this and other populations of older individuals.

Waist circumference was not reduced by exercise in women. This is in line with Maillard et al.¹¹⁷ who did not find a reduction in WC after high and moderate intensity training in a population of older women. However, abdominal obesity is increasing with age,^{18, 19} and the intervention in this thesis might have counteracted a further increase of WC in women. It has previously been shown that a 6-months exercise intervention significantly decreased WC compared to a control group in men.¹⁰⁶ This is in discordance to the findings of this thesis, where both exercise groups in men showed a significant increase in WC. However, the training frequency in the abovementioned study was higher than in this thesis (5-6x/week), possibly explaining the inconsistency. Additionally, it is likely that the interventions in the present study could not counteract the age-induced increase in abdominal obesity in men. The difference in body composition and fat distribution between males and females, with men tending to have a more abdominal fat distribution,⁴⁷ could possibly explain why some male subjects worsened their WC despite of exercise.

Since studies examining the effects of exercise on prevalence and individual risk factors of MetS in older people are scarce and inconsistent due to differently used training modalities, follow-ups and the use of different MetS definitions, more studies are needed to confirm the results of this thesis in larger populations with older adults having MetS. Additionally, studies should emphasize the comparison of different groups to examine if intensity yet might play a larger role in decreasing MetS prevalence among older adults since it already has been demonstrated in adults.¹⁰¹ Nevertheless, the data of this thesis support the use of exercise as treatment strategy for MetS in older populations.

Study strengths and limitations

The longitudinal study design, the very long intervention period of five years and the relatively large sample size in this thesis (345 older individuals) are strengths of the present study. However, the sample includes only Norwegians and mostly white individuals, which limits the generalizability to other populations. Nevertheless, the study sample represents the Norwegian older population pretty well since all older adults in Trondheim born between 1936 and 1942 were invited.

A limitation is the mostly uncontrolled setting without objectively monitored training sessions, comprising a low internal validity. A better strategy to assess adherence would have been objectively measured exercise via strictly supervised and monitored (i.e. heart rate monitoring to check the target intensity) training sessions, but this is rather hard to accomplish and expensive in such a big study population (1567 individuals in the original Generation 100 study) over such a long period of time due to the need of a lot of equipment and staff. However, the unmonitored setting is at the same time a very big strength of the study, since this is much closer to a real-life setting than any other strictly supervised, monitored and controlled study. Hence, the low internal validity translates into a high external validity, and the generalizability to every-day situations in the real world of older adults is great in similar populations.

The use of questionnaires for the assessment of medication use and adherence to training is a limitation as they constitute subjective measures and recall bias. Notably, information from the Norwegian Prescription Database was not available and self-reported medication intake was used for analyzes.

The inclusion of diet behavior is a strength of this thesis. Since no significant within- or between-group differences were observed (the small decrease in lunch size in MIT is considered irrelevant), it is very likely that the risk factor changes seen in the present study were caused by exercise.

Another strength of the study is the implementation of and randomization to three different groups, and that randomizing spouses to the same group probably increased the participants' motivation to exercise and adhere to training. However, since it is very unethical to advise a control group not to do any training and to be sedentary, this control group was advised to be moderately active for 30 minutes almost every

day (Norwegian Guidelines). Thus, the control group was technically a third exercise group with a different activity protocol. Additionally, the guidelines are not very different from the training approach of the MIT protocol, which could have made it difficult to find any significant differences between the two groups. The original measure for abnormal glucose levels in MetS is FG.¹² Also for the diagnosis of (pre)diabetes assessing of FG was the standard measurement since decades.⁷⁸ However, the American Diabetes Association⁷⁸ suggests the use of HbA1c instead of FG for diagnosing (pre)diabetes and diabetes risk since it is highly standardized by now and has several advantages over the use of FG. It does not require fasting samples which makes the measurement more convenient, it is less dependent on day-to-day perturbations, ruling out biased FG measures during illness and stress periods, and HbA1c it is a chronic marker of blood glucose levels and not an acute 'snapshot' as FG is.⁷⁸ However, since HbA1c is not (yet) incorporated in the definition of MetS, the comparability to other MetS studies that use FG can be limited. Notably, when using FG, the exclusion of a lot of individuals due to insufficient fasting time would have comprised power issues in this thesis.

Future perspectives and implications

The burden that the combined and individual risk factors of MetS place on the individual and society, clearly demonstrates the needs for strategies aiming to prevent and treat MetS. Based on the findings of the present study, more emphasis should be put into the examination of the effect of different training intensities with objectively monitored exercise sessions to find the most effective treatment option. Additionally, low CRF has been shown to be present in older adults with MetS^{35, 36} and is an independent risk factor for all-cause and CVD-mortality both in adult¹³⁴⁻¹³⁶ and in older populations.¹³⁷ This thesis supports the finding of low CRF being present in older individuals with MetS, but more studies are needed that examine the effect of exercise with different intensities on improving CRF in older populations with MetS. Furthermore, since the individual risk factors tend to change with aging,¹⁸⁻²⁶ the current cut-off points might fit better for younger adults, and introducing separate cut-offs for older adults (in addition to gender and ethnicity) could be considered. Lastly, more emphasis could be put into the examination of physiological mechanisms behind exercise-induced risk factor changes to extend the understanding of how exercise might influence the different risk factors of MetS, and consequently how to most effectively use exercise as treatment strategy. Overall, most important future implications are to establish and realize large health initiatives and to come closer to finding a 'gold-standard' – a most effective treatment option. Exercise has several advantages as it is immediately available and a safe and low-cost treatment option.¹³⁸ Furthermore, it can possibly decrease the use of pharmacological therapy that requires multiple agents, increases the health care costs and also the risk of any adverse events/side effects.¹³⁹

Conclusion

This thesis demonstrates that exercise positively affected the prevalence and risk factors of MetS in older adults. It could be shown that more than one third of the participants were not defined as having MetS anymore after the 5-year intervention. Further, all three groups induced favorable changes in the individual risk factors. However, against the hypothesis, no statistically significant difference was found between the groups, indicating that exercise intensity does not seem to play a crucial role in reducing MetS prevalence in older adults. However, due to a possible cross-over in the MIT and HIIT group and a highly active control group, it is likely that the actual intensities in the groups did not differ a lot, which could account for the lack of a difference. Hence, more controlled studies are needed to further examine the effect of different intensities on MetS prevalence in older adults. Nevertheless, data from the present study encourage the use of exercise as treatment strategy in older adults with MetS.

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Appendix

Appendix 1 – Different definitions for MetS

Supplemental Table 1: Cut-off points for MetS, defined by WHO, NCEP:ATPIII and IDF¹⁷

Variable	WHO	NCEP:ATPIII	IDF
	high insulin level + one of the following	any three of the following:	
Waist circumference	>37"	>40" for men >35" for women	prerequisite (gender & ethnicity specific see Supplemental Table 2) + 2 of the following:
Body mass index	>30 kg·m ⁻²	-	
Triglycerides	≥150 mg·dL ⁻¹	≥150 mg·dL ⁻¹	≥150 mg·dL ⁻¹
HDL-C	<35 mg·dL ⁻¹ for men <39 mg·dL ⁻¹ for women	<40 mg·dL ⁻¹ for men <50 mg·dL ⁻¹ for women	<40 mg·dL ⁻¹ for men <50 mg·dL ⁻¹ for women
Blood pressure	-	≥130 mmHg (systolic) ≥85 mmHg (diastolic)	≥130 mmHg (systolic) ≥85 mmHg (diastolic)
Fasting glucose	-	≥110 mg·dL ⁻¹	≥5.6 mmol·L ⁻¹ or T2D
Microalbuminuria	>30 mg·g ⁻¹	-	-

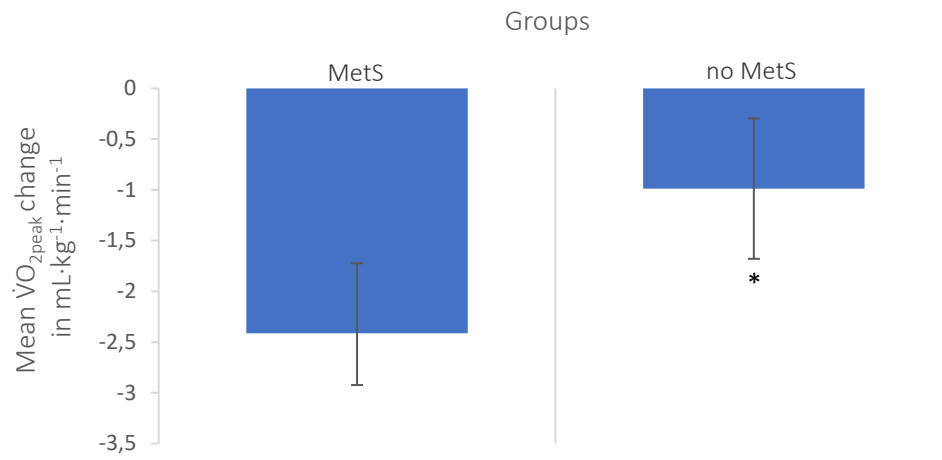
MetS = Metabolic Syndrome; WHO = World Health Organization; NCEP:ATPIII = National Cholesterol Education Program - Third Adult Treatment Panel; IDF = International Diabetes Federation; HDL-C = High Density Lipoprotein-Cholesterol; T2D = Type 2 Diabetes

Supplemental Table 2: Gender & ethnicity specific cut-off points for WC according to IDF¹⁷

Ethnicity	Male	Female
USA	>102 cm	>88 cm
European	>94 cm	>80 cm
South Asian	>90 cm	>80 cm
Central and south American	>90 cm	>80 cm
Middle Eastern/Mediterranean	>94 cm	>80 cm
Sub-Saharan/African	>94 cm	>80 cm
Chinese	>90 cm	>80 cm
Japanese	>90 cm	>80 cm

WC = Waist circumference; IDF = International Diabetes Federation

Appendix 2 – Mean $\dot{V}O_{2peak}$ change in individuals with and without MetS after five years



Supplemental Figure 1: Mean change of $\dot{V}O_{2peak}$ in participants with and without MetS after five years of intervention. Error bars represent 95% confidence interval. MetS = Metabolic syndrome; $\dot{V}O_{2peak}$ = peak oxygen consumption; *statistically significant different from change in *MetS* ($p < 0.01$)

Mosjon og fysisk aktivitet

Med mosjon mener vi at du f.eks. går tur, går på ski, svømmer eller driver trening/idrett. Fysisk aktivitet omfatter både fysisk aktivitet i hverdagen, planlagte aktiviteter og trening.

27. På en skala fra 6-20, hvor hard er aktivitetene du vanligvis utfører når du mosjonerer / trener? (Ta et gjennomsnitt av den siste uka) (sett ett kryss)

- 6
- 7 - Meget, meget lett
- 8
- 9 - Meget lett
- 10
- 11 - Ganske lett
- 12
- 13 - Litt anstrengende
- 14
- 15 - Anstrengende
- 16
- 17 - Meget anstrengende
- 18
- 19 - Svært anstrengende
- 20





Prosjektnr:

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Hva spiser du?

Dato: . . dag.mnd.år

MÅLTIDER

Hvilke måltider spiser du? Frokost Lunsj Middag Kvelds Natt

Hvor mange mellommåltider spiser du per dag? 0 1 2 >= 3

Hvor stor porsjon spiser du til: (porsjonsstørrelser er definert i vedlegget bak)

Frokost ½ 1 1½ 2 >2

Lunsj ½ 1 1½ 2 >2

Middag ½ 1 1½ 2 >2

Kvelds ½ 1 1½ 2 >2

Mellommåltid ½ 1 1½ 2 >2

