Linn Marita Hagen

High intensity interval training in reduction of anxiety symptoms in adults with the metabolic syndrome: Secondary analyses from the multicenter study EX-MET

Master's thesis in Exercise Physiology
Supervisor: Linda Ernstsen
June 2020

Master's thesis

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Linn Marita Hagen

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Abstract

Background. Anxiety disorders are associated with the onset and progression of cardiac disease. Increased prevalence of anxiety symptoms has recently been reported amongst people with the metabolic syndrome. Individuals with the metabolic syndrome are already at high risk for developing cardiovascular disease (CVD) and having comorbid anxiety symptoms could increase risk of CVD, demonstrating the need for proper treatment for this comorbid state. Aerobic interval training has been established to be more effective than moderate continuous runs on several outcomes, however, this has not been investigated on anxiety symptoms in individuals with MetS.

Objective. The primary aim of the current study was to describe the prevalence of caseness anxiety in a sample of adults with MetS and to investigate the efficacy of different volumes of high intensity interval training (HIIT) compared to current exercise guidelines of moderate-intensity continuous training (MICT) in reduction of anxiety symptoms in adults with MetS. The secondary aim is to assess if change in aerobic capacity may explain the result.

Methodology. This study used data from a randomized multicentre trial with a between subject design, and the primary outcome was different cardiovascular parameters. 135 patients from medical centres in Norway and Germany are included and were randomly assigned to either 1x4 min- high intensity interval training (1-HIIT, n=39), 4x4 min- high intensity interval training (4-HIIT, n=51) or moderate intensity continuous training (MICT, n=45). Participants were assessed for anxiety symptoms and $\mathrm{VO}_{2\mathrm{peak}}$ at baseline, after a 16 weeks training intervention and at 1-year follow-up. Anxiety symptoms data were measured by the validated Hospital, Anxiety and Depression Scale (HADS-A). In the HADS analysis the Kruskal Wallis test was used to determine changes between the groups, and Wilcoxon Signed Ranks tests for changes within each group and across all observations. The one-way ANOVA was used to determine changes in $\mathrm{VO}_{2\mathrm{peak}}$ between the groups, while one-sample t-tests were performed to determine changes within each group and across all observations.

Results. In the total sample, 25% had elevated levels of anxiety symptoms indicating caseness anxiety. From baseline to 16 weeks and baseline to 1-year, only the 4-HIIT group showed a significant reduction in anxiety symptoms (p=0.02, p=0.05), however, there was no difference in the reduction between the groups (p=0.23, 0.76). In the pooled analysis there was a significant reduction from baseline to 16 weeks (p=0.01) and baseline to 1-year (p=0.04). All groups showed a significant increase in $\mathrm{VO}_{2\mathrm{peak}}$ from baseline to 16 weeks (p=0.00), with only a tendency towards a significant difference between the groups (p=0.07). There was a significant increase in $\mathrm{VO}_{2\mathrm{peak}}$ from baseline to 16 weeks (p=0.00) in the pooled analysis.

Conclusion. The prevalence of anxiety symptoms in this sample of adults with metabolic syndrome was considerably higher compared to the general population. HIIT and MICT were equally effective in reducing anxiety symptoms, thus, increasing weekly physical activity levels through aerobic exercise may be an effective strategy to reduce anxiety symptoms in this population. Supervised training improving aerobic capacity is an additional benefit for the reduction of CVD-risk in adults with metabolic syndrome.

Key words: Metabolic Syndrome; Anxiety; Anxiety Symptoms; Aerobic Exercise; HIIT; MICT

Sammendrag

Bakgrunn. Angstlidelser er assosiert med utviklingen- og progresjon av kardiovaskulære sykdommer. Økt prevalens av angstsymptomer hos individer med metabolsk syndrom har nylig blitt rapportert. Individer med metabolsk syndrom har en allerede forhøyet risiko for å utvikle kardiovaskulære sykdommer og å ha angst i tillegg kan øke denne risikoen ytterligere. Det er derfor viktig å finne en behandling for denne tilstanden. Aerob intervalltrening har blitt anerkjent for å være mer effektivt enn kontinuerlig trening med moderat intensitet på flere utfall, noe som ikke blitt undersøk på angstsymptomer hos individer med metabolsk syndrom enda.

Hensikt. Hensikten med denne studien var i hovedsak å beskrive prevalensen av angst i et utvalg av voksne med metabolsk syndrom og undersøke effekten av ulike volum av høyintensitetsintervaller sammenlignet med dagens treningsanbefalinger om kontinuerlig trening på moderat intensitet i å redusere angstsymptomer hos voksne med metabolsk syndrom. Det var også ønskelig å undersøke om en økning i oksygenopptak kan forklare resultatene.

Metode. Denne studien brukte data fra en randomisert multisenterstudie, hvor hovedutfallet var forskjellige kardiovaskulære parametere. 135 personer fra Norge og Tyskland er inkludert i studien, og randomisert til enten 1x4 min høyintensitetsintervaller (1- HIIT), 4x4 min høyintensitetsintervaller (4-HIIT) eller kontinuerlig trening på moderat intensitet (MICT). Deltakerne ble undersøkt for angstsymptomer og oksygenopptak ved baseline, etter en 16-ukers treningsintervensjon og ved 1-års oppfølging. Angstsymptomer ble målt ved den validerte Hospital Anxiety and Depression Scale (HADS), og analyser av forskjeller på endringer mellom gruppene ble analysert med Kruskal-Wallis. Wilcoxon Signed Ranks test ble brukt til å undersøke endringer i angstsymptomer innad i gruppene og på hele utvalget. En-veis ANOVA ble brukt for å analysere forskjeller i endringen mellom gruppene i VO_{2peak}, mens one-sample t-test ble brukt på endringer innad i gruppene og på hele utvalget.

Resultat. 25% av hele utvalget i denne studien viste høye angstnivåer. Det var en statistisk signifikant reduksjon i angstsymptomer innad i 4-HIIT-gruppa både fra baseline til 16 uker (p= 0.02), og fra baseline til 1-års (p=0.05), men det var ingen signifikant forskjell mellom gruppene. I analyser på hele utvalget, var det en statistisk signifikant reduksjon i angstsymptomer både fra baseline til 16-uker (p= 0.01) og baseline til 1-års (p=0.04). VO_{2peak}-analyser viste en signifikant økning i oksygenopptak på alle gruppene (p=0.00), men det var ingen forskjell mellom gruppene etter 16 uker (p=0.07). I hele utvalget ble det funnet en statistisk signifikant økning fra baseline til 16 uker (p= 0.00).

Konklusjon. Forekomsten av angst blant voksne med metabolsk syndrom var betydelig høyere enn i den generelle befolkningen. HIIT og MICT var like effektivt i å redusere angstsymptomer, så å øke det fysiske aktivitetsnivået gjennom aerob trening kan derfor være en effektiv måte å redusere angstsymptomer hos voksne med metabolsk syndrom på. Veiledet trening for å øke oksygenopptak er et viktig tiltak for å redusere kardiovaskulær risiko hos voksne med metabolsk syndrom.

Nøkkelord: Metabolsk Syndrom; Angst; Angstsymptomer; Aerob trening; HIIT; MICT

Abbreviations

MetS	Metabolic syndrome
CVD	Cardiovascular disease
T2D	Type 2 diabetes
IDF	International Diabetes Federation
WC	Waist circumference
HDL-C	High density lipoprotein
NCEP	National Cholesterol Education Program
ATP-III	Adult Treatment Panel III
HIIT	High intensity interval training
HR_{max}	Maximal heart rate
BbA1c	Glycated hemoglobin
NOx	Nitric oxide
LT	Lactate Threshold
VO_{2peak}	Peak oxygen uptake
MICT	Moderate intensity continuous training
VO_{2max}	Maximal oxygen uptake
BP	Blood pressure
GAD	Generalized anxiety disorder
PTSD	Post traumatic stress disorder
HR	Heart rate
CO	Cardiac output
SV	Stroke volume
$a - vO_{2diff}$	Arterio-venous difference
NTNU	Norwegian University of Science and Technology
REK	Regional Committee for Medical Research Ethics
HADS	Hospital Anxiety and Depression Scale
TGL	Triglycerides
FGP	Fasting glucose
SPSS	Statistical Package for the Social Sciences

RPE	Rate of perceived exertion
EDTA	Ethylenediaminetetraacetic acid
1x4- HIIT	1x4 min high intensity interval training
4x4- HIIT	4x4 min high intensity interval training
SD	Standard deviation
95% CI	95% confidence interval
ANOVA	Analysis of variance
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
Q	Quartile
ST	Strength training
RM	Repetition maximum
SA	Somatic arousal
NA	Negative affect
PA	Positive affect
HPA-axis	Hypothalamic-pituitary-adrenal axis

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1.0 Introduction

1.1 Metabolic Syndrome

Metabolic syndrome (MetS) is a health disorder characterized by metabolic abnormalities that predict an increased risk to develop cardiovascular disease (CVD) (1, 2), type 2 diabetes (T2D) and has an increased risk of all-cause mortality (3, 4). It is estimated that 20-25% of the world's adult population have MetS, and the prevalence has been increasing over the years (5-7). It is expected that the prevalence will increase in parallel to the pandemic of obesity and overweight, which affects about 312 million and 1.1 billion people worldwide, respectively (8, 9).

The International Diabetes Federation (IDF) has defined MetS as abdominal obesity measured in an elevated waist circumference (WC) as the main criteria, in addition to any of the two following four factors; dyslipidaemia mirrored in a reduced HDL-C; high levels of triglycerides; hypertension; and high fasting glucose (10). However, noteworthy, other expert groups (World Health Organization, National Cholesterol Education Program, European Group for the Study of Insulin Resistance) use different definitions. The definition by NCEP and IDF are the ones most commonly used (11), and the Adult Treatment Panel III (ATP-III) guidelines from the NCEP are now in line with the IDF definition, except from using elevated waist circumference as the central and essential component.

1.1.1 Metabolic Syndrome and Exercise

Levels of physical activity is associated with the development of MetS (12), the risk of occurrence (13) and the components of MetS (14). It is also reported that people with MetS have a reduced aerobic capacity compared to their healthy counterparts (15). For this reason, aerobic exercise has been investigated in MetS.

Exercise training may reverse most of the risk factors of MetS and also protect against premature cardiovascular death (16-18). A recent meta-analysis (19) investigated different aerobic training regiments on clinical outcomes in patients with MetS, and improvements in all clinical outcomes (cardiovascular and metabolic) was found in all regiments. A12 weeks high intensity interval training (HIIT) program (treadmill, 3 days/wk, 70-90% of maximal heart rate (HR_{max})) was found to positively affect inflammatory profile (reduced pro-inflammatory interleukins) and an increase in other parameters (glucose, HbA1c and NOx) on postmenopausal women with MetS (20). Further, high-intensity exercise training (midway between their lactate threshold (LT) and peak oxygen uptake (VO_{2peak})) was superior to low-intensity exercise training (intensity at or below their LT) for reducing total abdominal fat and subcutaneous abdominal fat, and thereby reducing waist circumference in obese women with MetS after 16 weeks (21). In a rat model comparing the effects of HIIT (4 min bouts of 80-90% of maximal oxygen uptake (VO_{2max}), 1 hr/day, 8 weeks) and moderate intensity continuous training (MICT) (continuous run at 70% VO_{2max}, 1.5 hr), HIIT was superior to MICT in reducing cardiovascular risk, and it was linked to more superior effects on VO_{2max}, endothelial function, blood pressure (BP), and metabolic parameters in several tissues (22). MICT has been shown to reduce arterial stiffness after an 8 weeks aerobic exercise training program's (cycling, 3 days/wk for 60 min/day, moderate intensity) (23), and in ameliorating MetS severity, low-volume HIIT (51 min/week) was as effective as high-volume HIIT (114 min/week) and MICT (150 min/week) after a 16 weeks intervention period (24). The most optimal training regimen is still under investigation.

1.2 Anxiety

In 2017, it was estimated that 792 million people were living with a mental disorder, which is 10% of the population worldwide (25). Amongst these disorders are anxiety disorders, which are neuropsychiatric and stress-related disorders. The global prevalence of anxiety has been estimated to be 7.3%, ranging from 5.3% in African cultures to 10.4% in Euro/Anglian cultures (26). An estimate from 2017, states that 284 million people worldwide are affected by an anxiety disorder, making it the most prevalent mental health and neurodevelopmental disorder (25). The same estimates showed that the prevalence is higher in females than males in all countries. Numbers from the second Norwegian Nord-Trøndelag Health Study (1995-97) found that 11.3% of those who participated had anxiety symptoms above the validated cut-off for caseness anxiety, and that 64.3% of them were women (27).

Anxiety involves anticipation of future threat, which overlap with the feeling of fear. Fear is the emotional response to real or perceived imminent threat, and it is often associated with surges of autonomic arousal necessary for fight or flight, thoughts of immediate danger, and escape behaviours. Anxiety has been divided into several disorders, collectively called anxiety-disorders. These include general anxiety disorder (GAD), panic anxiety, selective mutism, social anxiety, phobias and post-traumatic stress disorder (PTSD). These anxiety disorders share features of excessive fear and anxiety, related behavioural disturbances, and differ from each other in the matter of to which objects and/or situations they occur. (28)

The symptoms of anxiety include nervousness, restlessness, increased heart rate (HR), rapid breathing, feeling weak or tired, trembling, trouble sleeping, trouble concentrating, difficulty controlling worry, gastrointestinal problems and having the urge to avoid things that trigger anxiety (29). An emerging literature supports that anxiety disorders increase the risk for incident CVD but a causal relationship has not been demonstrated (30).

1.2.1 Anxiety and Exercise

Low physical activity levels have been reported among people with anxiety (31), and physical inactivity has been shown to be significantly associated with anxiety symptoms (32). This is mirrored in findings that lower aerobic capacity is associated with a higher risk of anxiety symptoms (33, 34). For this reason, aerobic exercise has been investigated on anxiety.

Light leisure activity has been reported to be associated with lower reporting of anxiety symptoms (35). The effect of tai chi and yoga on anxiety levels has also been investigated (36), however, equivocal findings have been reported and further research on the effects of these exercise modes on anxiety is warranted (37). In a meta-analysis of the anxiolytic effects of aerobic exercise on anxiety symptoms in people with anxiety disorders (38), studies with different intensities were included. These studies compared aerobic exercise groups exercising on different intensities with an inactive control group, and all the exercise groups showed reductions. This demonstrates a positive effect of aerobic exercise on anxiety regardless of exercise intensity. A study that investigated different aerobic exercise intensities (60% VO_{2max} or 80% VO_{2max} and a control group, for 20 min) on anxiety in women of different ages (39), found that high intensity exercise was superior to moderate intensity in reducing anxiety symptoms. However, this study only investigated acute bouts and the long-term effect is therefore not known.

Exercise may be a useful treatment for anxiety, but it has been suggested that lack of data from rigorous, methodologically sound RCTs precludes any definitive conclusions about its effectiveness (40). Studies investigating exercise on anxiety are scarce, they show different results and studies have not aimed to see the effect of different aerobic intensities in a long-term effect.

1.3 Metabolic Syndrome and Anxiety

There are no direct numbers on the prevalence of comorbid MetS and anxiety, but due to the established relationship between physical- and mental health (41), increased attention has been given to the mental health of different patient groups, such as in patients with MetS. An increased prevalence of anxiety symptoms is reported amongst MetS patients (16%) (42, 43), and although research on the association between MetS and anxiety has been equivocal, a systematic review and meta-analysis from 2016 investigated 18 studies and established an association between MetS and anxiety (44). This is in line with more recent research (45, 46). An increased prevalence of MetS in patients with medically diagnosed anxiety (16.7%) has also been reported (47), suggesting a bidirectional relationship between MetS and anxiety (48). Interestingly, rats on a 24-weeks sucrose-diet has been indicated to develop MetS associated with anxiety-like behaviour (49), demonstrating a possible close link between MetS and anxiety.

Having additionally anxiety- and/or depressive symptoms to MetS adds to the risk of developing CVD, making the risk even higher (43).

1.3.1 Metabolic Syndrome and Anxiety, and Exercise

Several studies also confirm the increased prevalence of MetS in people with several mental disorders, such as schizophrenia (50), but the literature on the effect of exercise interventions on mental health outcome in adults with MetS is scarce. To my knowledge, only one study to date has investigated the effects of exercise on comorbid MetS and anxiety. This was examined in patients with anxiety disorders (51), and they reported improvements in metabolic function together with a reduction in anxiety levels after 3 months of 30-min of moderate exercise (walking, aerobic dance, tai-chi, yoga) per day for 5 days a week. This demonstrates a positive effect of aerobic exercise in treating comorbid MetS and anxiety in patients with anxiety disorders, suggesting that these diseases might be simultaneously reversed.

1.4 Physical Activity and Aerobic Capacity

Physical Activity. Physical activity is any body movement produced by muscle that results in energy expenditure (52), and the current exercise guidelines for adults are to do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week, 75 min of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity (53). Higher levels of physical activity has been shown to decrease the risk of all-cause mortality in healthy individuals, patients with hypertension, T2D, and CVD, regardless of body weight (54). Higher levels of physical activity has also been shown to improve health-related quality of life in the general population (55). When assessing the association between sitting time and physical activity, higher levels of moderate intensity physical activity (ie, about 60–75 min per day) seem to even eliminate the increased risk of death (56).

Aerobic capacity. Aerobic capacity is measured as VO_{2max}, which has been defined as the maximum amount of oxygen that can be taken up and utilized by active muscles during heavy exercise (57). VO_{2max} is primarily determined by the hearts cardiac output (CO), which expresses the amount of blood pumped by the heart during a 1-min period, a result of the hearts stroke volume (SV) and HR. However, the muscles ability to extract oxygen from the blood is also a determining factor for a persons VO_{2max}, which can be measured as the arterio-venous oxygen difference ($a - vO_{2diff}$). Therefore, VO_{2max} can be expressed according to the Fick equation: VO_{2max} = (SV · HR) · ($a - vO_{2diff}$).

Improvements in VO_{2max} is only possible through aerobic exercise. Exercise is physical activity that is planned, structured and repetitive for the purpose of conditioning any part of the body (58). Aerobic exercise targets improvements in VO_{2max}, which relates to adaptations in respiratory-, metabolic- and vascular functions. Aerobic exercise follows the three exercise principles for exercise-induced physiologic adaptations; frequency, intensity and duration of the exercise, where the adaptations primarily depends on the intensity of overload (59). Depending on a persons' initial training status (60) there seems to be a threshold intensity for improvements in VO_{2max} at approximately 55-65% of HR_{max} (61), where higher intensities (90-95% HR_{max}) in terms of intervals have been shown to be more effective than slow- and moderate intensities (70%-85% HR_{max}) in continuous runs (62).

1.5 Objective

Both MetS and anxiety are two highly prevalent diseases across the world. The established relationship between mental- and physical health has resulted in an increased interest in the mental health of MetS patients. Individuals with MetS are showing an increased prevalence of anxiety symptoms, which together with an increased risk for developing CVDs when having MetS and additionally anxiety, gives reason to investigate effective treatment for this comorbid state. People with MetS and anxiety are demonstrating a sedentary lifestyle, and one of the consequences of low physical activity levels amongst people with MetS and anxiety has been reflected in their reporting of low aerobic capacity. Together with the already increased risks of developing CVD when having MetS and additionally anxiety, low levels of physical activity and low aerobic capacity in these patient groups will also add to this risk. The fact that the top two causes of deaths worldwide in 2016 were caused by CVD's (ischemic heart disease and stroke) (63), preventing the development of CVD in patients with MetS and anxiety is warranted. However, it remains to be investigated if today's guidelines for moderate intensity physical activity is enough to reduce anxiety symptoms in patients with MetS or if higher intensities can be more effective, and if any decrease in anxiety symptoms is followed by increase in aerobic capacity.

The primary aim of the current study is to describe the prevalence of caseness anxiety in a sample of adults with the metabolic syndrome, and investigate the efficacy of different volumes of high intensity interval training (HIIT) compared to current exercise guidelines of moderate-intensity continuous training (MICT) in reduction of anxiety symptoms in adults with the metabolic syndrome. The secondary aim is to assess if improvement in aerobic capacity may explain the results.

2.0 Methodology

2.1 Study Design

This was a randomized multicentre trial, a part of the EX-MET (exercise in prevention of metabolic syndrome) study conducted by a research group at the Norwegian University of Science and Technology (NTNU). A between-subject design was used, where each participant has tested only one condition and was only exposed to a single interface. Analysis of the data was according to the way we intended to treat the subjects, not in the way they were actually treated, thus, an intention to treat approach was used.

Data was collected from 1.01.13 – 31.12.16, and further details about the methods of the EX-MET study can be found here; Tjønna et al. (2018) (64).

2.2 Subjects

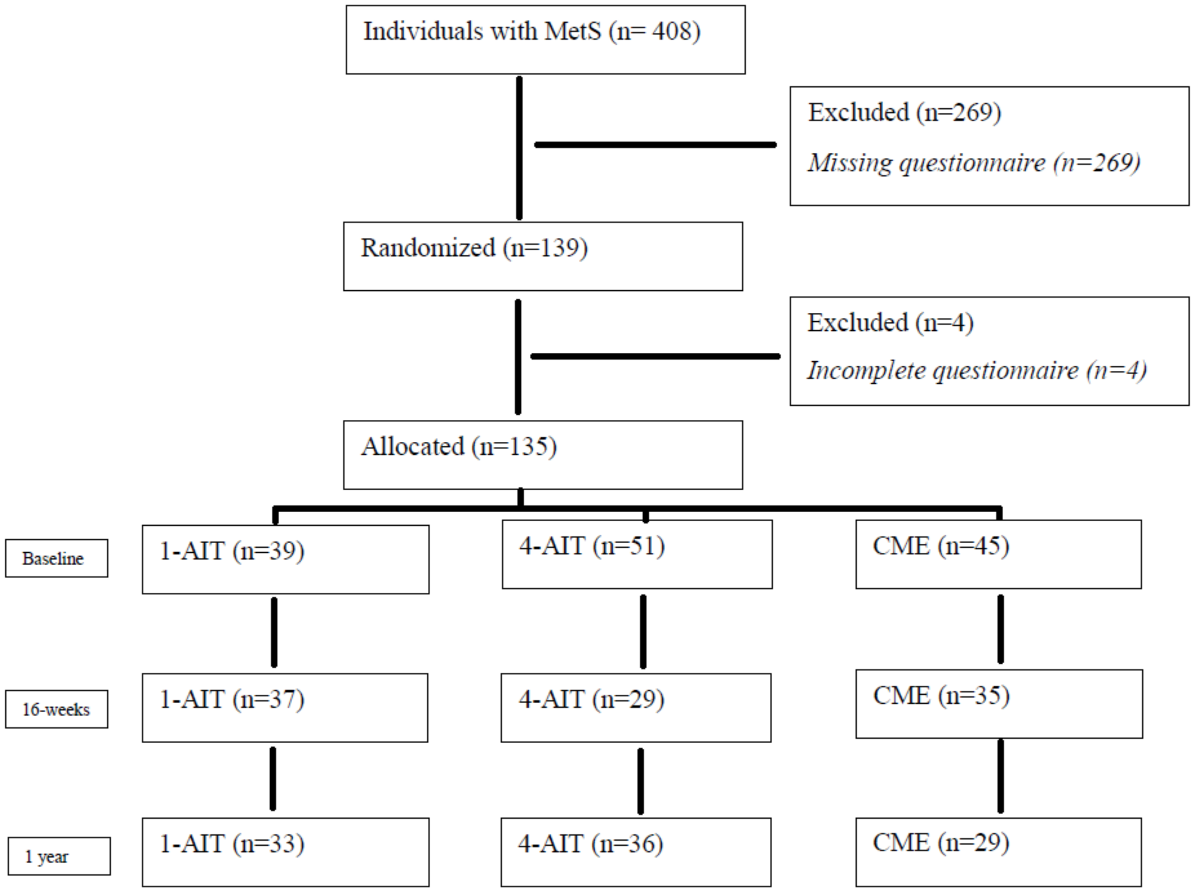

Figure 1. Flow chart.

Subjects were recruited by public advertisement in the paper and posters posted in different locations. The recruitment advertisement warranted adults showing light overweight in addition to any of the following criteria: reduced glucose tolerance, type 2 diabetes (T2D) or blood pressure (BP) above 135/90. Screening was done before inclusion. 408 patients (men and women, aged < 30), from 5 different centres (Norway, Germany, Australia, Brazil and Equador), met the definition of metabolic syndrome (MetS) according to the International Diabetes Federation (IDF) criteria (10), and were recruited to participate in the EX-MET study. However, only 139 individuals from Norway (Trondheim, n=81 and Stavanger, n=14) and Germany (München, n=40) had answered the Hospital Anxiety and Depression Scale (HADS) questionnaire. Of the 139 questionnaires, 4 questionnaires were incomplete and to limit study biases; these were excluded. Therefore, 135 individuals are included in the current study.

2.3 Ethical Issues

The study/EX-MET has been approved by the Regional Committee for Medical Research Ethics (REK 2011/2150), and was registered in the clinical trials registry in august 2012 (ClinicalTrials.gov, Identifier: NCT01676870).

Oral and written informed consent was obtained from all participants before inclusion.

2.3.1 Storage of Data and Preservation of the Participants Anonymity

All HADS questionnaires were treated with carefulness. Questionnaires from Trondheim and Stavanger were kept in folders in a locked locker at St. Olav's Hospital in Trondheim and were not allowed to be taken out of the building, while questionnaires from München were scanned, sent per e-mail and stored in a safe database. The database was only accessible when connected to the hospitals/campus' internet, and access to the digital folders had to be given by an IT-consultant at NTNU. To preserve the participants anonymity, their randomization number was the only identity marker used, and the collected- and analysed data was also stored in a safe database.

2.4 Physical and Clinical Examination

The participants were tested at baseline, after the 16 weeks training intervention and after 1-year at their respective centres (St. Olavs, NTNU, Trondheim; Universitetssykehuset, Stavanger; Universitätskrankenhaus, München). All equipment used at the respective centres were validated up against the equipment in Trondheim, and the equipment listed below is the equipment used in Trondheim.

2.4.1 Metabolic syndrome

Definition of MetS was determined in accordance to the IDF definition (10) by central obesity and additionally two of the other factors; elevated triglycerides (TGL), reduced high density lipoprotein cholesterol (HDL-C), hypertension and/or elevated fasting glucose (FGP). The MetS components according to the IDF definition are presented in table 1.

Table 1. MetS components according to the IDF definition.

Components	Male	Female
WC (cm)	>94	>80
TGL (mmol/L)	>1.7	
HDL-C (mmol/L)	<1.0	<1.3
BP (mm Hg), SBP/DBP	>130/85	
FGP (mmol/L)	>5.6	

WC: waist circumference; TGL: triglycerides; HDL-C: high density lipoprotein cholesterol; BP: blood pressure; FGP: fasting glucose.

2.4.2 Hospital Anxiety and Depression Scale (HADS) Questionnaire

HADS (Appendix 1) is a self-report questionnaire comprising 14 4-point Likert-scale items covering anxiety and depression symptoms for the previous 2 weeks. 7 questions are there to detect anxiety symptoms, and measures generalized autonomic anxiety and indicates physiological and emotional states characterized by high muscle tension and strong feelings of subconscious and uncontrollable fear or anger (64). At the end of the questionnaire the total sum of all answers is being calculated, and the clinical cut-off point is set to ≥8 for caseness anxiety. The questionnaire has been found to be valid in both somatic, psychiatric and primary care patients and in the general population (65).

The questionnaires were plotted into an excel-file, and to avoid study bias, the plotted data was controlled by another individual. After controlling for correct plotting, the excel-file was transferred into statistical package for the social sciences (SPSS) for analysis.

2.4.3 Peak Oxygen Uptake (VO_{2peak})

Peak oxygen uptake (VO_{2peak}) (mL·kg^{-1}·min^{-1}) was directly measured either on a treadmill (WOODWAY PPS55, Woodway GmbH, Weil am Rhein, Germany) (or a cycle ergometer, dependent on the preferred type of exercise during the intervention) using a direct ergospirometry system (Jaeger Oxycon Pro, CareFusion Germany 234 GmbH, Höchberg, Germany).

Protocol. The subjects started with a 10 min warm-up, where speed was adjusted individually. After the warm-up, the participants performed an individualized treadmill ramp protocol with individualized constant band speed and increased inclination by 2% when oxygen uptake stabilized at each workload until VO_{2max} was reached. A levelling off of oxygen uptake despite increased workload, a respiratory exchange ratio >1.05 and the rate of perceived exertion (RPE) on the Borg scale at >18 was used as criteria for maximal oxygen uptake. This was not accomplished in all patients and the results are therefore by definition VO_{2peak}.

2.4.4 Blood Samples and Blood Pressure Measurements

Blood samples were obtained from an arm vein after a 12-h overnight fast. TGL, glucose and HDL-C were measured using standard procedures at respective hospitals or centres. Serum ethylenediaminetetraacetic acid (EDTA) plasma was centrifuged at 2500 rpm for 10 min at 20°C.

BP was measured after a 12-h overnight fast and following 15 min of seated quite rest with a Suntech Tango (Suntech Medical, Ltd. Oakfield Industrial Estate Eynsham, Oxfordshire, England).

Waist circumference (WC) was measured with a measuring tape at the central point between the lowest rib and the highest point at the iliac crest, on light clothing.

2.5 Training Intervention

The training intervention had a duration of 16 weeks and consisted of supervised- and unsupervised training sessions. The supervised training sessions were conducted on a treadmill or a cycle ergometer in the hosting research institution, whereas the unsupervised training sessions were performed outdoor/indoor involving different activities such as running, walking, cycling, rowing, swimming and skiing.

Heart rate (HR) was monitored (Polar electro, Kempele, Finland) during all supervised exercise sessions to ensure that the participants were reaching the prescribed target HR. Participants were encouraged to purchase their own HR monitor to keep track of their own training during the unsupervised sessions. Otherwise, they were instructed to use the Borg 6-20 scale (rating of perceived exertion) to serve as a guide towards the exercise intensity achieved (66). HR and RPE during all training (unsupervised and supervised) sessions were monitored and recorded. Participants were provided with a training log to record all unsupervised training sessions.

The participants were randomized into three groups: 1x4 min- high intensity interval training (1-HIIT), 4x4 min- high intensity interval training (4-HIIT), and moderate intensity continuous training (MICT). The 1-HIIT and 4-HIIT group performed three training sessions per week with a duration of 17 min and 38 min per session, respectively. Two of these sessions were supervised. Both the 1-HIIT and 4-HIIT groups started with a 10 min warm-up at 60-70% of peak heart rate (HR_{peak}), and then performed 1x4 min and 4x4 min intervals at 85-95% of HR_{peak} (RPE on 15-17 on Borg scale), respectively. The 4-HIIT group had 3 min of active recovery at 60-70% of HR_{peak} between each interval. Both groups ended their session with a 3 min cool-down at 60-70% of HR_{peak}. The MICT group performed 5-7 training sessions per week, where each session contained continuously trains for >30 min at a target intensity of 60-70% of HR_{peak} (RPE of 11-13 on Borg scale). Two of these sessions were supervised.

After the 16 weeks training intervention the participants were asked to continue their training sessions as prescribed. Supervised follow-up training was given only once a month up until 1-year, with the rest of the sessions performed unsupervised in an unsupervised environment. The participants continued to log and record their training sessions and monitored their intensity with either HR or RPE during the unsupervised phase.

2.6 Analysis of the Data

All statistical analysis was conducted using the IBM SPSS (Version 25) for windows.

Subject characteristics were summarized and expressed as mean ± standard deviation (SD).

In anxiety symptom score analysis, data was not normally distributed as tested with Shapiro-Wilk test for normality. Non-parametric tests were therefore used to analyse this data. All anxiety symptom score values were expressed as median and 95% confidence interval (95% CI), and the statistical significance level was set to $p < 0.05$.

Baseline scores of anxiety symptoms were compared with the 16-weeks scores and the 1-year scores. The Kruskal-Wallis test was used for comparison in changes between the groups, and the Wilcoxon Signed Ranks Test was used to confirm differences in change within each group and across all observations.

VO_{2peak} data was normally distributed as tested with Shapiro-Wilk test for normality. Parametric tests were therefore used to analyse all VO_{2peak} data. VO_{2peak} values were expressed as mean ± SD, and the statistical significance level was set to $p < 0.05$.

Baseline VO_{2peak} measurements were compared to the 16 weeks and 1-year measurements. The one-way analysis of variance (ANOVA) was used for comparison in changes between the groups, while the One-Sample T-Test was performed to determine the changes within the groups and across all observations.

3.0 Results

3.1 Subject Characteristics

Table 2. Baseline characteristics of the study participants (n=135) stratified by intervention group.

Characteristics	1-HIIT (n=39)	4-AHIIT (n=51)	MICT (n=45)
Age in years, mean ± SD	51 ± 10	53 ± 8	52 ± 10
Women/men, n	19/20	21/30	17/28
Marital status			
Living alone, n (%)	8 (20.5)	8 (15.7)	7 (15.6)
Living together, n (%)	31 (79.5)	43 (84.3)	38 (84.4)
Level of education			
Primary school, n (%)		2 (3.9)	2 (4.4)
High school, n (%)	13 (33.3)	13 (25.5)	8 (17.8)
University, n (%)	21 (53.8)	28 (54.9)	28 (62.2)
Other, n (%)	5 (12.8)	8 (15.7)	7 (15.6)
BMI (kg·m^2), mean ± SD	32.3 ± 5.4	31.2 ± 4.7	31.5 ± 4.6
MetS components			
WC (cm), mean ± SD	108.9 ± 12.7	106.1 ± 12.9	108 ± 11.2
SBP (mmHg), mean ± SD	136.4 ± 19.4	137 ± 14.3	134.8 ± 14.7
DBP (mmHg), mean ± SD	85.7 ± 13	88.7 ± 11.2	84.9 ± 10
TGL (mmol/L), mean ± SD	1.9 ± 1	1.8 ± 0.9	1.8 ± 0.8
HDL-C (mmol/L), mean ± SD	1.3 ± 0.4	1.3 ± 0.4	1.1 ± 0.3
FPG (mmol/L), mean ± SD	6.3 ± 1.3	6.2 ± 1.9	6.3 ± 2.5
VO_{2peak} (mL·kg^{-1}·min^{-1}) mean ± SD	28.4 ± 7.8	27.9 ±6.7	28.9 ± 7.8
HADS-A score, median (Q1,Q3)	7.0 (3.0,9.0)	5.0 (3.0,7.0)	4.0 (2.5,6.5)
HADS-A score, mean ± SD	6.4 ± 3.8	5.4 ± 3.7	4.8 ± 4.0
HADS-A score ≥8, n (%)	15 (38.5)	11 (21.6)	8 (17.8)

Data are presented as mean ± standard deviation (SD) and median (Q1: quartile 1, Q3: quartile 3).1-HIIT: 1x4 min high intensity interval training; 4-HIIT: 4x4 min high intensity interval training; MICT: moderate intensity continuous training; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TGL: triglycerides; HDL-C: high-density lipoprotein cholesterol; FPG: fasting glucose; CRP: C-reactive protein; VO_{2peak}: peak oxygen uptake; HADS-A: hospital anxiety and depression scale- anxiety.

Subject characteristics are presented in table 2. The overall prevalence of caseness anxiety was 25% of the total sample (data not shown).

3.2 Hospital Anxiety and Depression Scale – Anxiety (HADS-A)

Table 3. The median of the absolute values in anxiety symptom score at baseline, 16 weeks and 1-year in each intervention group.

	Baseline			16 weeks			1-year		
Group	n	Median	CI	n	Median	CI	n	Median	CI
1-HIIT	39	7	(4,8)	36	4.5	(3,8)	32	4	(1,6)
4- HIIT	51	5	(4,6)	29	4	(3,5)	36	4	(3,5)
MICT	45	4	(3,5)	34	2.5	(2,4)	28	4	(2,6)

Data are presented as median. CI: 95% confidence interval; 1- HIIT: 1x4 min high intensity interval training; 4- HIIT: 4x4 min high intensity interval training; MICT: moderate intensity continuous training.

Table 4. Within- and between group median changes from baseline to 16 weeks and baseline to 1-year in anxiety symptom score in each intervention group.

	Baseline to 16 weeks					Baseline to 1-year				
Group	n	Median change	CI	p-value (w)	p-value (b)	n	Median change	CI	p-value (w)	p-value (b)
1- HIIT	31	0	(-2,1)	0.51	0.23	27	0	(-2,1)	0.68	0.76
4- HIIT	24	-1	(-3,0)	0.02*		33	-1	(-2,0)	0.05*	
MICT	29	0	(-2,0)	0.09		26	-1	(-2,1)	0.18	

Data are presented as median. CI: 95% confidence interval; p-value (w): within group median changes; p-value (b): between group median changes; 1- HIIT: 1x4 min high intensity interval training; 4- HIIT: 4x4 min high intensity interval training; MICT: moderate intensity continuous training.
*: $p < 0.05$

Table 5. The median change from baseline to 16 weeks and baseline to 1-year in anxiety symptom score across all observations.

Baseline to 16 weeks				Baseline to 1-year			
n	Median change	CI	p-value	n	Median change	CI	p-value
84	-1	(-1,0)	0.01**	86	-1	(-1,0)	0.04*

Data are presented as median. CI: 95% confidence interval.
*: $p < 0.05$
**: $p < 0.01$

The median of the absolute values in anxiety symptoms score in each intervention group is presented in table 3. The 1-HIIT group had the highest median both at baseline and 16 weeks and is the only group with a reduction in anxiety symptoms on all observations. There was a 35.7% reduction from baseline to 16 weeks, and a 12% reduction from baseline to 1-year. The 4-HIIT group showed a 20% reduction both from baseline to 16 weeks and baseline to 1-year. The MICT group had a 37.5% reduction from baseline to 16 weeks, however, no change in the absolute median is present from baseline to 1-year. In fact, the absolute median increased from 16 weeks to 1-year, increasing anxiety symptoms back to baseline level at 1-year.

Within- and between group median changes in anxiety symptom score from baseline to 16 weeks and baseline to 1-year in each intervention group are presented in table 4. There was no statistically significant reduction in anxiety symptoms within the 1-HIIT group, whether from baseline to 16 weeks (p=0.51) nor from baseline to 1-year (p=0.68). There was a statistically significant reduction in anxiety symptoms within the 4-HIIT group both from baseline to 16 weeks (p=0.02) and from baseline to 1-year (p=0.05). There was no statistically significant reduction in anxiety symptoms whether from baseline to 16 weeks (p=0.09) nor from baseline to 1-year (p=0.18) within the MICT group.

Although there is little difference within the groups, there was a statistically significant difference within the 4-HIIT group both at 16 weeks and 1-year, however; when all groups are compared, there is no statistically significant difference in the reduction of anxiety symptoms between the groups, whether from baseline to 16 weeks (p=0.23) nor from baseline to 1-year (p=0.76).

The median change in anxiety symptom score from baseline to 16 weeks and baseline to 1-year across all observations are presented in table 5. There is a strong statistically significant reduction in anxiety symptoms from baseline to 16 weeks (p=0.01) and a statistically significant reduction from baseline to 1-year (p=0.04) across all observations.

3.3 Peak Oxygen Uptake (VO_{2peak})

Table 6. The mean of the relative values of VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) at baseline, 16 weeks and 1-year in each intervention group.

	Baseline			16 weeks			1-year		
Group	n	Mean	SD	n	Mean	SD	n	Mean	SD
1- HIIT	46	28.71	7.52	41	30.37	8.52	34	29.30	7.94
4- HIIT	55	28.75	7.33	46	32.81	8.08	39	30.44	7.42
MICT	50	28.86	8.04	43	31.08	9.31	34	30.07	9.83

Data are presented as mean. SD: standard deviation; 1- HIIT: 1x4 min high intensity interval training; 4- HIIT: 4x4 min high intensity interval training; MICT: moderate intensity continuous training.

Table 7. Within- and between group mean changes in VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) from baseline to 16 weeks and baseline to 1-year in each intervention group.

	Baseline to 16 weeks					Baseline to 1-year				
Group	n	Mean change	SD	p-value (w)	p-value (b)	n	Mean change	SD	p-value (w)	p-value (b)
1- HIIT	41	1.74	2.90	0.00**	0.07	34	0.59	3.72	0.36	0.98
4- HIIT	46	3.16	3.79	0.00**		39	0.59	4.83	0.45	
MICT	43	1.78	2.98	0.00**		34	0.43	3.53	0.48	

Data are presented as mean. SD: standard deviation; p-value (w): within group median changes; p-value (b): between group median changes; 1- HIIT: 1x4 min high intensity interval training; 4-HIIT: 4x4 min high intensity interval training; MICT: moderate intensity continuous training.
*: $p < 0.05$
**: $p < 0.01$

Table 8. The mean change in VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) from baseline to 16 weeks and baseline to 1-year across all observations.

Baseline to 16 weeks				Baseline to 1-year			
n	Mean change	SD	p-value	n	Mean change	SD	p-value
130	2.26	3.31	0.00**	107	0.54	4.07	0.17

Data are presented as mean. SD: standard deviation.
*: $p < 0.05$
**: $p < 0.01$

The mean of the relative VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) measurements at baseline, 16 weeks and 1-year in each intervention group are presented in table 6. All groups showed an improvement in VO_{2peak} from baseline to 16 weeks and a reduction from 16 weeks to 1-year, however, the 1-year values were still higher than the baseline values. The 1-HIIT group showed the least increases in VO_{2peak} with a 5.5% increase from baseline to 16 weeks, and only a 2% increase from baseline to 1-year. The 4-HIIT group showed a 14.1% increase in VO_{2peak} from baseline to 16 weeks, presenting the highest increase of all groups, however, only a 5.5% increase from baseline to 1-year. The MICT group had a 7.1% increase in VO_{2peak} from baseline to 16 weeks, and a 4.0% increase from baseline to 1-year.

Within- and between group mean changes in VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) from baseline to 16 weeks and baseline to 1 year in each intervention group are presented in table 7. All groups showed a strong statistically significant increase in VO_{2peak} ($p=0.00$) from baseline to 16 weeks, however, none of the groups showed a statistically significant increase from baseline to 1 year ($p=0.36$, $p=0.45$, $p=0.48$, for 1- HIIT, 4- HIIT and MICT, respectively). There was a trend towards a statistically significant difference in the increase of VO_{2peak} between the groups from baseline to 16 weeks ($p=0.07$), however, not from baseline to 1 year ($p=0.98$).

The mean changes in VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) from baseline to 16 weeks and baseline to 1 year across all observations are presented in table 8. There was a statistically significant increase in VO_{2peak} from baseline to 16 weeks ($p=0.00$), but no statistically significant increase from baseline to 1 year ($p=0.17$).

4.0 Discussion

The aim of the current study was to describe the prevalence of caseness anxiety in a sample of adults with the metabolic syndrome and to investigate the efficacy of different volumes of high intensity interval training (HIIT) compared to current exercise guidelines of moderate-intensity continuous training (MICT) in reduction of anxiety symptoms in adults with the metabolic syndrome (MetS). The second aim was to assess VO_{2peak} to explain the results. The main findings were; the prevalence of caseness anxiety in this sample of adults with MetS was 25%; and the different volumes of HIIT and the current exercise guidelines of MICT did not show any difference in reducing anxiety symptoms. However, a reduction regardless of the intervention group was found. This effect seemed to be both short-term and long-term. An improvement in VO_{2peak} was found in somehow similar patterns as to the reductions in anxiety symptoms, however, did not show the same effect within each group nor the same long-term improvements.

4.1 Hospital Anxiety and Depression Scale-Anxiety (HADS-A)

The prevalence of caseness anxiety in this sample of adults with MetS was substantially higher (25%) compared to the general population (27, 67, 68). The 4-HIIT group was the only group showing statistically significant reduction within the group, which is contradictory, because there was no difference in the reduction between the groups. This demonstrates no difference in the effectiveness of different volumes of HIIT compared to MICT in reducing anxiety symptoms whether after a 16 weeks intervention period or at 1-year follow-up. However, in the pooled sample, a statistically significant reduction was found, demonstrating that aerobic exercise, regardless of intensity, is effective in reducing anxiety symptoms in adults with MetS. This effect was shown both after 16 weeks and at 1-year follow-up, thus, aerobic exercise seems to have both a short-term and long-term effect on the reduction of anxiety symptoms in adults with MetS.

Higher intensities have been shown to have beneficial effects on mental health compared to MICT in other patient groups (69, 70), however this seems not to be the case in patients with stress-related disorders (71), including anxiety disorders. The study participants in the current study were not included based on a diagnosis of an anxiety disorder, however, it has previously also been shown that exercise effectively reduces anxiety symptoms regardless of severity of anxiety (72), suggesting that higher intensities compared to moderate intensities give no advanced effects in reducing anxiety symptoms.

The results of the current study showing that exercise regardless of intensity is effective in reducing anxiety symptoms is supported by a meta-analysis that investigated low and moderate intensity exercise (aerobic exercise, yoga, walking, strength, coordination, balance) on mild and moderate anxiety symptoms in midlife and older women (73). Compared to control groups, only the exercise groups showed a reduction in anxiety symptoms and there were no significant differences between the low- and moderate intensities. In contrast to the current study, this meta-analysis found a greater improvement related to the duration of the study intervention (12 weeks – 4 months versus 6 – 14 months), rather than the exercise intensity. They found a significant difference between the short-term effects and the long-term effects, whereas the current study found both a short-term effect and long-term effect. This meta-analysis also demonstrated that both low and moderate intensities are effective in reducing anxiety symptoms, which is in line with other studies (74, 75).

When not compared either to a control group nor another exercise group, HIIT has been shown to be effective in reducing anxiety symptoms in advance-stage lung cancer patients (76). This was shown in a prospective, 1-group design study, with supervised group training for 1.5 h, 2 times a week with strength training (ST) (3 sets of 5-8 repetitions at 70%-90% of 1 repetition maximum (RM)) and HIIT (85-95% HR_{max}, 10-15 min) on a bicycle ergometer for 6 weeks. This demonstrates that high intensity training (HIT) both as ST and HIIT is effective in reducing anxiety symptoms. Together with the above-mentioned studies and the ones mentioned in the introduction, there is a tendency toward common results of intensity-independent reductions in anxiety symptoms of different patient groups. However, as also mentioned in the introduction, the effects of tai chi, yoga and other meditation regiments of exercise, which are of low intensity, warrants further investigation (37). Noteworthy; the different diagnoses of anxiety, the different ways to measure anxiety and the different outcome measurements of anxiety, makes it difficult to compare studies. In addition, anxiety is often used as a collective term, which makes it diffusive to know which aspects of anxiety some studies revolve around.

4.1.1 Possible Physiologic Mechanisms

It seems that the somatic arousal (SA) dimension of anxiety is stronger associated with MetS than the negative affect (NA) and positive affect (PA) dimensions, and also more with some of the MetS components than others (77). Since MetS is not a direct diagnosis, but a description of a physiologic state comprising different metabolic abnormalities, the participants will not all show the same composite state of MetS. It can therefore not be ruled out that some of the participants in the current study were less affected by anxiety symptoms, due to having those MetS components less associated with the SA dimension, such as HDL-C and FGP (77). Hence, exercise could also affect the participants differently. This can be demonstrated through the investigation of HIIT to improve insulin quality of participants with MetS with and without T2D (78). The insulin quality was only improved in those without diabetes.

Ongoing metabolic dysregulation could be causing symptoms of anxiety, and common pathophysiologic pathways between MetS and anxiety has been suggested. A chronic low-grade inflammation and oxidative physiologic state has been linked to both MetS (79, 80) and anxiety (81, 82), which further are hallmarks of CVDs. Exercise has been shown to have an effect on both inflammation (83) and oxidative stress (84). After regular exercise, reduced inflammatory markers and simultaneously increased anti-inflammatory substances are reported (83, 85). This is related to regular exercise and intensity is not reported, however, investigations into inflammatory biomarkers showed greater improvements after exercise with high intensity compared to moderate intensity (86), which demonstrates that higher intensities might be more effective in reducing inflammation. This has also been reported in the effect of aerobic exercise on oxidative stress, due to exercises effects on brachial artery vascular function, which has a tendency to positively influence oxidative stress (87), however, moderate intensity has also been shown to be effective in reducing oxidative stress (88).

In addition to inflammation and oxidative stress, anxiety has also been linked to dysfunction of some important metabolic pathways (82) and dysfunction of the hypothalamic-pituitary-adrenal axis (HPA-axis) (89). The chronic inflammation apparent in anxiety leads to dysfunction of some metabolic pathways, such as the kynurenine-pathway. An imbalance between the anxiolytic and neuroprotective effects, and the anxiogenic and neurodegenerative effects of the metabolites of this pathway, give higher levels of anxiogenic and neurodegenerative effects, which further causes an anxious physiologic state. It can be speculated if the effect of aerobic exercise reported on inflammation will also benefit this imbalance and may even retrieve it. Dysfunction of the HPA-axis occur from stress exposure. With exposure to traumatic and stressful events, such as exposure to fear- and anxiety-provoking stimuli, the HPA-axis is reactivated, the immune system activates, and pro-inflammatory cytokines are released. This lead to negative consequences on brain neurogenesis and neuroplasticity (90-92). Aerobic exercise has been proven to be effective in improving HPA-axis function (93).

Endocannabinoids have anti-anxiety effects through the regulation of dopaminergic and glutamatergic signals (94-96), and it is argued that physical activity and exercise may activate the endocannabinoid system to increase endocannabinoids and modulate adenosine receptors. Activation of the endocannabinoid system may produce analgesia, reduce anxiety and induce euphoria (94).

Aerobic exercise involves exposure to physiological cues similar to those experienced during anxiety reactions, like increased HR, respiration and perspiration. It might be suggested that regular exposure to such physiological cues decreases the sensitivity for anxiety in the participants everyday life, leading to reductions in anxiety symptoms. Higher intensities have been shown to reduce anxiety sensitivity to a greater extent than low intensity (97), which might explain the equivocal findings on studies investigating the effect of low intensities (tai chi, yoga, meditation etc.) on anxiety symptoms.

The main study of EX-MET has yet not been published, thus, no analysis on inflammation or oxidative stress were performed. For future studies, analysis on inflammation and oxidative stress should be performed to closer investigate the possible physiological mechanisms that might be behind the positive effects of aerobic exercise in reducing anxiety symptoms in adults with MetS.

4.1.2 Possible Mechanisms Related to the Exercise Program

The current study involved both supervised and unsupervised exercise sessions, where the first phase of 16 weeks was mainly supervised training and the second phase until 1-year follow-up was mainly unsupervised. Supervised versus unsupervised exercise has been compared in a longitudinal study that aimed to improve different physiological parameters (98). After the unsupervised phase of the study, the majority of the participants reported that they stopped or hardly did any exercise at all in the unsupervised phase of the intervention, which was reflected in their decrease of improvements in the physiological outcomes. Since the reduction in anxiety symptoms remained statistically significant also at 1-year follow-up after the unsupervised part in the current study, this probably means that the participants did not totally stop exercising. Still, we do not know if they continued to exercise in line with the original protocol in the unsupervised phase of the study.

The unsupervised training phase in the current study did involve the participants to record their own training sessions in a provided training log, and it has been reported that self-reported levels of recreational physical activity is correlated with better mental health, including fewer symptoms of anxiety (99). It has also been reported that participants low in trait anxiety has shown to report fewer stressful events on the days on which they exercised, together with higher ratings of positive moods (100). This means that even though the participants of the current study possibly and assumingly reduced their training sessions in the unsupervised phase of the study, the exercise they did do, might have led to less stressful events post-exercise and more positive moods. This might have been enough to maintain their reduced anxiety symptoms from the 16 weeks supervised phase also during the unsupervised phase. However, the participants log of their training sessions was not a part of the current study. It is therefore not known how much each participant did exercise in the unsupervised phase.

Importantly, little can be stated about compliance in the current study, since compliance data on the participants were scarce.

The recruitment process should also be addressed. The participants were not recruited from primary care, and it can therefore be assumed that the participants were not the ones with the most severe state of MetS nor those with the highest anxiety symptoms. It is therefore also unlikely that any of the participants had an anxiety diagnosis that could have affected the results. The use of anxiolytic medicine was not reported amongst any of the participants from Norway, however, this was not the medication of interests at screening and it can therefore not be ruled out that there have been some underreporting of anxiolytics amongst these participants. Anxiolytic medication use of the German participants is not known. People recruited from the general population based on a set of criteria for inclusion to participate in research, are assumingly also the most motivated. Motivational factors can therefore also not be ruled out to explain the results of the current study.

Another important issue is that all three groups did some kind of aerobic exercise, meaning that there were no physical inactive control group to compare with. It is well-known that the largest effect from physical activity interventions can be measured among those being sedentary starting to do regular exercise (101), which could be the case for the MICT group in the current study. In fact, a systematic review supports that sedentary behaviour is associated with MetS (102) suggesting that the effect from aerobic exercise on anxiety symptoms may have been more pronounced with a sedentary control group in the current study. Nevertheless, inviting patients to participate in a clinical study only for comparison (not offering any kind of intervention) is considered unethical (103).

4.2 Peak Oxygen Uptake (VO_{2peak})

4-HIIT was the most effective training intervention in the relative VO_{2peak} measurements, however, the increase was not statistically significant different from the other groups. Thus, 1-HIIT, 4-HIIT and MICT are equally effective at improving VO_{2peak} in patients with the metabolic syndrome after a 16 weeks aerobic exercise intervention period. The 1-year follow-up measurements showed no statistically significant improvement in VO_{2peak}, as also shown in the pooled analysis at 1-year follow-up. This shows that the improvements in VO_{2peak} are only temporary.

The fact that all intervention groups showed a statistically significant increase in their aerobic capacity might be explained by the fact that the participants initial fitness status was low, reducing their sensitivity to improvements. 55-65% of HR_{max} has been stated to be a threshold intensity for improvements in aerobic capacity (61) and all groups performed aerobic exercise above this intensity threshold. This is in line with other studies investigating aerobic capacity in individuals with MetS. A recent study has compared different volumes of HIIT (4- HIIT: 4x4min at 90% HR_{max}, 1- HIIT: 10x1min at 100% HR_{max}) and MICT (50 min at 70% HR_{max},) to each other with a non-exercise control group (104). Their results also suggested that any aerobic training program of 16 weeks with a frequency of three times per week is sufficient stimulus to raise aerobic capacity in patients with MetS. The more effective improvements from HIIT on aerobic capacity in healthy subjects might be due to them having an initially greater aerobic capacity. Considering a person’s initial training status is important when exercising for physiological adaptations (59), demonstrating that greater intensities are needed for those with an initially greater aerobic capacity, such as in healthy individuals (59).

It has also been reported that an 8 weeks training intervention of HIIT and MICT on VO_{2peak} in obese adults and middle-aged (105) and older adults with T2D (106) were showing similar patterns as the study mentioned above (104), with an equal effectiveness of HIIT and MICT. Like the participants in the current study, the participants of these studies (104-106) were also exhibiting an initially low aerobic capacity, which supports low initial fitness status as an explanation to the equal effectiveness of HIIT and MICT.

The short-term effect of the improvements in VO_{2peak} might be due to the suggested different effects of supervised versus unsupervised training. A longitudinal study (98), mentioned previously in the discussion, investigated the effectiveness of supervised and unsupervised exercise on physical activity, muscular endurance, and cardiovascular parameters. They found that the outcome variables improved after 5 months of supervised exercise but were then reduced after 5 weeks of unsupervised exercise. These results are in line with the results on VO_{2peak} in the current study. Further (98), upon the end of the two phases of exercise, they distributed questionnaires on how the participants experienced supervised and unsupervised exercise. 100% of the study participants reported that they had higher self-efficacy for exercise at the end of the supervised training. However, after the unsupervised training program, 76% stated that they did not exercise at all or only exercised a few times and wished they had been able to do more, demonstrating a lack of motivation to do exercise without being supervised.

The insignificant increase in VO_{2peak} from baseline to 1-year follow-up might also be due to the participants not exercising at the correct intensity in the unsupervised phase of the study. During the supervised training, all participants were wearing a HR monitor, assuring that they were exercising at the correct intensity. Participants were recommended to buy a HR monitor to wear in the unsupervised phase, however, we do not know how many of the participants that actually did this. It is therefore possible that the participants were exercising at a lower intensity than prescribed, because they had to depend on their subjective feeling of intensity related to the Borg Scale. Subjective measurements of intensity with the Borg Scale has been shown to lead to overestimation of the intensity in people with a panic disorder (107). It has also been shown that participants with less self-efficacy show a slower rate of change in RPE as a function of exercise intensity, with an initial gradual curve at lower intensity and a more dramatic trajectory at higher intensity (108). Less self-efficacy with unsupervised training and/or overestimation of intensity using RPE might also be an explanation to the lower

VO_{2peak} measurements after the unsupervised phase compared to measurements after the 16 weeks of supervised training in the current study.

It has been found that aerobic fitness does not protect against anxiety symptoms (109). However, according to the results in the current study, aerobic capacity did seem to follow the same patterns as the reduction in anxiety symptoms after the 16 weeks intervention period in the pooled analysis. In contrast to the previous mentioned study (109), the current study therefore suggests that aerobic fitness might have a protective role against anxiety symptoms after a 16 weeks supervised exercise intervention and can partly explain the results of the reduction in anxiety symptoms in these adults with MetS. This does not seem to be the case at 1-year follow-up after the unsupervised phase.

Although the reduction in anxiety symptoms in adults with MetS might only partly be explained by aerobic capacity, improvements in VO_{2peak} is still important in adults with MetS and anxiety symptoms, due to their established heightened CVD-risk. It has been reported that both in healthy subjects and subjects with CVD, the peak exercise capacity was a stronger predictor of an increased risk of death than clinical variables or established risk factors such as hypertension, smoking, and diabetes, as well as other exercise-test variables, including ST-segment depression, the HR_{peak}, or the development of arrythmias during exercise (110). This study (110) confirmed the protective role of a higher exercise capacity even in the presence of other risk factors, suggesting that exercise capacity might be the single most important factor in reducing the risk of death. The peak exercise capacity is reflecting aerobic capacity, and it is therefore of great importance to increase physical activity levels and aim to improve aerobic capacity to lower the risk of death even in the presence of other risk factors, such as in people with MetS showing anxiety symptoms. This demonstrates that increasing VO_{2peak} also in a long-term perspective would be beneficial. However, if motivational factors are the determining factor to why participants did not manage to maintain their improved aerobic capacity in the unsupervised phase, an optimal training regimen addressing this issue has to be further investigated.

The main EX-MET study has not yet been published, and other cardiometabolic markers of MetS have therefore not been analysed and reported in the current study. It cannot be ruled out that other factors linked to MetS could better explain the reductions in anxiety symptoms.

4.3 Strengths and Limitations of the Study

The strengths of the current study were; 1) it was the first study to investigate the effect of aerobic exercise on anxiety symptoms in adults with MetS; 2) a validated questionnaire for the assessments of anxiety symptoms was used; 3) the equipment used has been validated across the centres.

The current study has several limitations. First, participants were not included based on high levels of anxiety symptoms, and it is therefore not known if this exercise regime would have the same effects on caseness anxiety. Second, there was no control group included. Third, this was a multicentre trial, which has been shown to be hard to manage. There is no guarantee that the different centres have given equal effort into the quality of the process. Fourth, data on anxiolytic medicine was scarce and we can therefore not rule out that some of the participants changed or started on an anxiolytic medical treatment during the intervention. Fifth, data on compliance was hard to gather from all centres, and the total compliance is therefore not known. Sixth, the main EX-MET study is a much bigger study than what there are participants in the current study, and it was therefore many missing questionnaires. Seventh, there was an unequal number of participants in the groups at baseline, meaning that the group with the greatest number of participants also had a greater variance.

5.0 Conclusion

The current study showed that there is an elevated prevalence of anxiety symptoms in adults with MetS compared to the general population, which demonstrates the importance of addressing the mental health of adults with MetS. Aerobic exercise proved to be effective in reducing anxiety symptoms in this population, however, intensity does not seem to be an important factor for this reduction. According to the research literature low physical activity levels are reported amongst people with MetS, thus, increasing physical activity levels might therefore be the most important factor in reducing anxiety symptoms in adults with MetS. Aerobic exercise seems to be a good strategy for this purpose, and a supervised phase followed by an unsupervised phase does seem to provide both short-term and long-term effects in the reduction of anxiety symptoms in adults with MetS.

VO_{2peak} might partly be an explanation to the reduced anxiety symptoms after the 16 weeks supervised phase, however, at 1-year follow-up after the unsupervised phase, VO_{2peak} does not seem to follow the reduction of anxiety symptoms. Nevertheless, improvements in aerobic capacity after supervised training is an additional benefit of the aerobic exercise to reduce the already established heightened cardiovascular risk in people meeting the definition of MetS.

Proposed mechanisms related to the reduction in anxiety symptoms might be physiologic mechanisms involved in risk factors related to MetS and anxiety that have been shown to be positively affected by aerobic exercise. Further, motivational- and psychological factors are important and need further investigation.

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Appendix 1

HAD

Hospital Anxiety & Depression Scale (januar 1999)

Navn: ______________________ Fødselsdato: ______________

Dato for utfylling: ______________ Pasient nr.: ______________

Behandler: ______________________________

Rettledning

Legen er klar over at følelser spiller en stor rolle ved de fleste sykdommer. Hvis legen vet mer om følelser, vil han/hun bli bedre i stand til å hjelpe deg.

Her kommer noen spørsmål om hvorledes du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser den siste uken. Ikke tenk for lenge på svaret – de spontane svarene er best.

1. Jeg føler meg nervøs og urolig

- ❑ 3 Mesteparten av tiden
- ❑ 2 Mye av tiden
- ❑ 1 Fra tid til annen
- ❑ 0 Ikke i det hele tatt

2. Jeg gleder meg fortsatt over tingene slik jeg pleide før

- ❑ 0 Avgjort like mye
- ❑ 1 Ikke fullt så mye
- ❑ 2 Bare lite grann
- ❑ 3 Ikke i det hele tatt

3. Jeg har en urofølelse som om noe forferdelig vil skje

- ❑ 3 Ja, og noe svært ille
- ❑ 2 Ja, ikke så veldig ille
- ❑ 1 Litt, bekymrer meg lite
- ❑ 0 Ikke i det hele tatt

4. Jeg kan le og se det morsomme i situasjoner

- ❑ 0 Like mye nå som før
- ❑ 1 Ikke like mye nå som før
- ❑ 2 Avgjort ikke som før
- ❑ 3 Ikke i det hele tatt

5. Jeg har hodet fullt av bekymringer

- ❑ 3 Veldig ofte
- ❑ 2 Ganske ofte
- ❑ 1 Av og til
- ❑ 0 En gang i blant

6. Jeg er i godt humør

- ❑ 3 Aldri
- ❑ 2 Noen ganger
- ❑ 1 Ganske ofte
- ❑ 0 For det meste

7. Jeg kan sitte i fred og ro og kjenne meg avslappet

- ❑ 0 Ja, helt klart
- ❑ 1 Vanligvis
- ❑ 2 Ikke så ofte
- ❑ 3 Ikke i det hele tatt

8. Jeg føler meg som om alt går langsommere

- ❑ 3 Nesten hele tiden
- ❑ 2 Svært ofte
- ❑ 1 Fra tid til annen
- ❑ 0 Ikke i det hele tatt

9. Jeg føler meg urolig som om jeg har sommerfugler i magen

- ❑ 0 Ikke i det hele tatt
- ❑ 1 Fra tid til annen
- ❑ 2 Ganske ofte
- ❑ 3 Svært ofte

10. Jeg bryr meg ikke lenger om hvordan jeg ser ut

- ❑ 3 Ja, jeg har sluttet å bry meg
- ❑ 2 Ikke som jeg burde
- ❑ 1 Kan hende ikke nok
- ❑ 0 Bryr meg som før

11. Jeg er rastløs som om jeg stadig må være aktiv

- ❑ 3 Uten tvil svært mye
- ❑ 2 Ganske mye
- ❑ 1 Ikke så veldig mye
- ❑ 0 Ikke i det hele tatt

12. Jeg ser med glede frem til hendelser og ting

- ❑ 0 Like mye som før
- ❑ 1 Heller mindre enn før
- ❑ 2 Avgjort mindre enn før
- ❑ 3 Nesten ikke i det hele tatt

13. Jeg kan plutselig få en følelse av panikk

- ❑ 3 Uten tvil svært ofte
- ❑ 2 Ganske ofte
- ❑ 1 Ikke så veldig ofte
- ❑ 0 Ikke i det hele tatt

14. Jeg kan glede meg over gode bøker, radio og TV

- ❑ 0 Ofte
- ❑ 1 Fra tid til annen
- ❑ 2 Ikke så ofte
- ❑ 3 Svært sjelden

Takk for utfyllingen!

Sum A:

1+3+5+7+9+11+13= ____________

Sum D:

2+4+6+8+10+12+14= ____________

Sum A + D: ____________

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