Ida Almenning

The effect of high-intensity interval training versus strength training to improve body composition in women with polycystic ovary syndrome.

A randomized controlled trial.

Master Thesis in Clinical Health Science,

Obesity and Health.

Trondheim, March 2014

Norwegian University of Science and Technology,

The Faculty of Medicine,

Department of Public Health and General Practice.

NTNU – Trondheim
Norwegian University of
Science and Technology

ACKNOWLEDGEMENTS

This thesis is part of my master's degree in Clinical Health Sciences, Obesity and Health, The Faculty of Medicine, Department of Public Health and General Practice, Norwegian University of Science and Technology (NTNU), Trondheim. The study was conducted at the Department of Circulation and Medical Imaging (ISB).

Several people have been very helpful and supportive. Without help from each and every one of them, this master thesis would have been impossible. Therefore, I would like to express my gratitude and thanks:

My supervisor Post-Doc. Trine Moholdt for her kind help, support and guidance throughout the project. For always being available and positive, and for the great commitment and interest in the project. Your knowledge has proven decisive for both the writing process and the final result.

Kirsti Krohn Garnæs for her great help in the project.

Ingerid Arbo, Guri Molden and the other biochemical laboratory scientists in the Cardiac Exercise Research Group (CERG) for helping us with the biochemical part.

The physiotherapy students from Sør-Trøndelag university college (HIST), Emma Woldseth Brørs and Silje Nyborg for helping us with training sessions and body composition measurements.

3T fitness center for good cooperation and contribution through the intervention.

Thanks to all the participants for volunteering to participate in the study.

Finally, thanks to my good friend and fellow student Astrid Rieber-Mohn for good collaboration and support, and for all the good discussions and the time we spent together throughout the study period.

Ida Almenning

Trondheim, March 2014

BACKGROUND FOR THIS MASTER`S THESIS

This master`s thesis is a part of a larger study that was conducted in the Women's clinic, St. Olav's hospital in Norway, in cooperation with the Norwegian University of Science and Technology (NTNU), The Faculty of medicine. This randomized controlled trial investigated the effect of high-intensity interval training versus strength training in women with polycystic ovary syndrome (PCOS) on several outcome measures. The following measurements were performed at baseline (week 0) and after the intervention period (week 11):

Biochemical: Insulin sensitivity measured with the homeostatic model assessment for insulin resistance (HOMA-IR) method (1). HOMA-IR was calculated as (FPI*FPG)/22.5, where FPI and FPG are fasting insulin and fasting glucose, respectively. Blood values of testosterone, sex-hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), estradiol, progesterone, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, insulin c-peptide, glucose, follicle-stimulating hormone (FSH), luteinizing-hormone (LH), thyroid-stimulating hormone (TSH), prolactin, anti-mullerian hormone (AMH), albumin, high-sensitivity c-reactive protein (hs-CRP). Blood samples were obtained in the morning after an overnight fast. Blood samples were analyzed according to standard local procedures at the Department of medical biochemistry, St.Olav's University Hospital, Trondheim, Norway.

Physiological: Aerobic capacity measured as maximum oxygen uptake [in ml/min/kg] using a direct ergospirometry system with a mixing chamber (Oxycon Pro, Erich Jaeger GmbH, Hoechberg, Germany). All tests were performed on a treadmill (Woodway USA Inc., Waukesha, WI, USA).

Anthropometrical: Height [cm] was measured using a standard stadiometer. Body weight [kg], BMI [kg/m^2] and body composition (body fat [kg and percentage], muscle mass [kg] and visceral fat [VFA, cm^2]) was measured using a bioelectrical impedance scale (BIA) (InBody720, Biospace CO, Ltd, Seoul, Korea). Fat distribution was measured as waist circumference (WC) in cm at the level of the umbilicus using a measuring tape. Blood pressure [diastolic and systolic, in mmHg] was measured using an automatic blood pressure device (Welch Allyn, Germany).

Endothelial function: Measured as flow-mediated dilatation (FMD) of the brachial artery (in percentage change compared to baseline) using high-resolution vascular ultrasound (14MHz Doppler probe, GE Vingmed Ultrasound AS, Horten, Norway).

Biochemical hyperandrogenism (total testosterone [nmol/L], SHBG [nmol/L], free androgen index (FAI)) and *clinical hyperandrogenism* defined as the presence of hirsutism (Ferriman-Gallwey score greater than or equal to eight) (2) was measured.

Menstruation, psychological well-being and *physical activity* was registered with a questionnaire.

Ovulation frequency was recorded during the intervention period of 10 weeks and in the following 16 weeks (26-29 weeks from baseline) by using menstruation diaries.

In this thesis, the primary outcome measurements are body composition and visceral fat, and secondary outcome measurements are body weight and waist circumference. Other outcome measures are not further elaborated.

ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 6-20% of reproductive-age women. Women with PCOS tend to accumulate more upper body fat, and the syndrome is often present with abdominal obesity and visceral adiposity which is further associated with metabolic – and cardiovascular complications. Despite well-established benefits of exercise and its recommendation in PCOS management, few randomized controlled trials have evaluated the benefits of exercise as the only intervention on body composition in women with PCOS. **Objective:** The aim of the present study was to investigate the effect of high-intensity interval training (HIT) and strength training (ST) versus control, on body composition in women with PCOS. **Methods**: We did a randomized controlled trial, including 31 previously sedentary women randomly assigned to one of three groups; High intensity interval training (HIT; *n* = 10), strength training (ST; *n* = 11) and control (CG; *n* = 10). At baseline and 10 weeks follow-up, body composition and anthropometrics was evaluated and compared between groups. **Outcome measures:** Body composition and visceral fat (VF), body weight, and waist circumference (WC). **Results:** Twenty-five women completed the study intervention and post-training testing (ST; *n*=8, HIT; *n*=8 and CG; *n*=9). Weight did not change in any group. There was a significant decrease in percentage fat mass (FM) after ST [EMM: -1.6, 95% CI: -2.5 to -0.7] and HIT [EMM: -0.9, 95% CI: -2.2 to -0.0], respectively. Fat-free mass (FFM) increased significantly after ST [EMM: 1.2, 95% CI: 0.4 – 2.1], but not after HIT [EMM: 0.4, 95% CI: -0.2 to 1.1]. There was no significant between-group differences in the change in percentage FM (p=0.54) and FFM (p=0.18). There was no changes in WC or VF within or between groups. **Conclusion:** These data indicates that in the absence of body weight changes, both ST and HIT have beneficial effect on body composition in women with PCOS. Percentage FM decreased significantly after both ST and HIT, and FFM increased significantly after ST.

Key words: Polycystic ovary syndrome/ exercise training/ body composition / fat distribution/ visceral fat/ strength training/ high-intensity interval training

RELEVANCE

Lifestyle intervention is recommended as first-line therapy in PCOS management. Despite this, a limited number of studies have examined exercise as an independent intervention in PCOS. The few studies that exist have used moderate-intensity endurance training, or exercise in combination with diet. Previous studies have been conflicting in regard to the effect of exercise training on body composition in PCOS women, and the effect of different types of exercise is still unknown. Most previous studies report change in body weight, without changes in body composition – a valuable measure of the fat distribution and health risk in these women. This study is one of few randomized, controlled trials on the isolated effects of different modes of exercise training on body composition in women with PCOS, but further research is needed to establish guidelines for exercise in treatment and management of this syndrome.

TABLE OF CONTENTS

ABBREVIATIONS

BMI	Body mass index
CVD	Cardiovascular disease
DM2	Diabetes mellitus 2
FM	Fat mass
FFM	Fat-free mass
HIT	High-intensity interval training
HR_{max}	Maximum heart rate
IGT	Impaired glucose tolerance
IR	Insulin resistance
PCOS	Polycystic ovary syndrome
RMR	Resting metabolic rate
ST	Strength training
VF	Visceral fat
WC	Waist circumference
1RM	One repetition maximum

1 THEORETIC BACKGROUND

Polycystic ovary syndrome (PCOS) is a chronic condition and the most common endocrine disorder of women in reproductive age (3, 4), affecting 6-20% (5) depending on the population studied and the diagnostic criteria used (5, 6). PCOS, first known as Stein-Leventhal Syndrome, was described in 1935 as amenorrhea associated with bilateral polycystic ovaries (7). In recent times, PCOS proved to be significantly more complex than first thought (8). The syndrome presents multiple associated pathologic conditions rather than a single disorder, and the clinical implications vary across the lifespan (8, 9). PCOS has become a major public health concern with reproductive, cardiovascular, metabolic, and psychological dysfunctions, which seems to be increasing in parallel to the obesity epidemic exacerbating both the prevalence and severity of PCOS (10, 11).

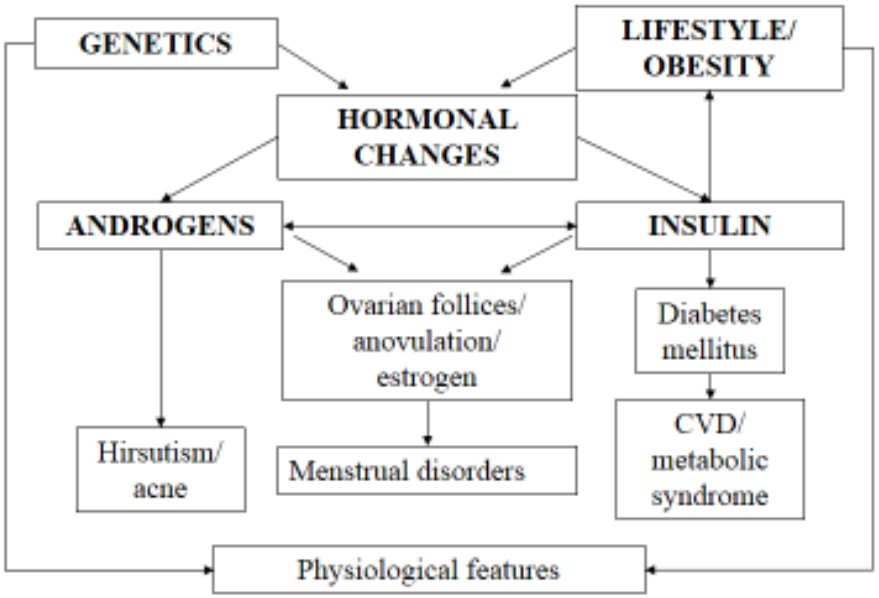


Figure 1: Factors affecting the development of PCOS

1.1 Causes and pathophysiology of PCOS

PCOS is a complex, heterogeneous and poorly understood syndrome with reproductive, metabolic and psychological features (9, 11). Reproductive features include anovulation, irregular menstrual cycle, pregnancy complications, infertility, clinical hyperandrogenism (elevated androgens) and biochemical hyperandrogenism (hirsutism and androgens affecting body tissue) (11). Metabolic features includes increased prevalence of metabolic syndrome (12), impaired glucose tolerance, insulin resistance (IR), type 2 diabetes mellitus (DM2) and cardiovascular disease (CVD) risk factors (3, 11, 13). As many as one-third of women with PCOS develop DM2 through the lifespan (10). Psychological features related to PCOS includes depression, anxiety, poor self-esteem and body image, reduced quality of life, social phobia, eating disorders and higher rates of suicidal attempts than in the general population (14-16). The impact on psychological features in women with PCOS is more extensive than previously thought (8, 11, 15, 16).

The pathophysiology of PCOS is probably multifactorial, and remains largely unclear, although a hormonal imbalance created by a combination of increased androgens and/or insulin are implicated (3, 8). Hyperandrogenism and IR is a central feature to the etiology of PCOS, which further contributes to metabolic and reproductive complications (8). Insulin increases the luteinizing hormone (LH) production, and can indirectly raise the serum concentration of free testosterone by inhibiting the hepatic production of sex-hormone-binding globulin (SHBG) (17). In addition, insulin stimulates glucose transport in adipose tissue and skeletal muscle. Further, androgens bind to the androgen receptors, present in adipose tissue (higher in visceral fat than in subcutaneous fat), and regulates several aspects of adipose cell function (17).

Genetics, environmental factors (diet, physical inactivity and weight gain), ovarian dysfunction and hypothalamic pituitary abnormalities are also associated with the hormonal disturbance in PCOS (4, 9, 11). Genetic factors seems to influence the development of PCOS, as women with a family history of PCOS are more likely to develop the syndrome (18). The role of genetic factors in the etiology of PCOS development is possibly different in lean and obese women (19). However, several genes has been studied, but not yet proven to be different in lean and obese women with PCOS (18).

1.2 Symptoms of PCOS

Women usually present clinically with concerns regarding menstrual irregularities, hirsutism and infertility (20). In reproductive aged women, PCOS is associated with reproductive morbidity, abnormal uterine bleeding, miscarriage and other pregnancy complications (20, 21), and as many as 75% of women with PCOS suffer from a form of menstrual disorders (22). The characteristic multiple ovarian cysts that can occur, often fail to discharge their ova, which can lead to infertility (18). Further, the corpus luteum does not form, and levels of progesterone does not rise normally in the luteal phase of the menstrual cycle. This further prevents the normal progesterone-driven hyperplasia, leading to long or irregular cycles or amenorrhea (18).

PCOS is also associated with hyperandrogenism (23, 24). Increased levels of testosterone and luteinizing hormone (LH), and reduced amount of the transport molecule sex hormone binding globulin (SHBG) and progesterone is often observed (18). In addition, Anti-Mullerian hormone (AMH) concentration is measured to be two times higher in women with PCOS compared with normal controls (25). The most common signs of clinical hyperandrogenism are acne, hirsutism and acanthosis nigricans (dark, velvety thickening of the skin) (18, 23, 26).

IR and impaired glucose intolerance (IGT) are common features in PCOS, and the prevalence of DM2 and IGT are 10% and 35% among PCOS women (18). IR, DM2, IGT, increased insulin levels, dyslipidemia and hyperandrogenism are all metabolic symptoms that are seen in PCOS (24). Furthermore, dyslipidemia and acanthosis nigricans may also increase the risk of hyperestrogen-related cancer (endometrial and breast cancer) and CVD (27).

Obesity is a risk factor for the development of PCOS, with the distribution of fat localized in the upper body sites, as an important factor (18, 28). Excess body weight, increased WC, and weight gain, especially abdominal and VF accumulation are common features of PCOS (23, 26). This leads to an increased risk of CVD and DM2 in these women (9), and the prevalence of these diseases seems to be higher in overweight PCOS women compared to normal weight women with PCOS (29). This may be due to the increased circulating levels of free testosterone and insulin in overweight compared to normal weight PCOS women (18). Further, obstructive sleep apnea (OSA) and nonalcoholic fatty liver disease (NAFLD) are other symptoms in PCOS, and associated with obesity (9).

In addition, psychological disorders, such as anxiety and depression are often seen in women with PCOS (26). Such problems are probably associated with IR and the physical symptoms of the syndrome (hirsutism, obesity, acne) (26).

Women with PCOS do not typically experience all of the symptoms, and the presentation is highly variable in symptoms and clinical and biological manifestations of this condition (10).

1.3 Diagnosis of PCOS

In 1990 The National Institute of Health (NIH) published the first diagnostic criteria for PCOS comprising hyperandrogenism (biochemical or clinical) and anovulation (30). Later, it has become clear that the syndrome encompasses a broader spectrum of symptoms than those defined in the NIH-criteria. In 2003, the European Society for Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM) international consensus workshop group therefore expanded the diagnostic criteria for PCOS by also including ovarian morphology (31). The 2003 Rotterdam criteria are a result of this, and includes two of the following three criteria: hyperandrogenism (clinical and/or biochemical), irregular ovulatory periods [>35 days menstrual cycle or <10 menstruations/year] or ultrasound polycystic ovary (PCO) morphology [≥ 10 peripheral cysts 3-8 mm in diameter and/or volume ≥ 10 ml] (31). The Rotterdam criteria takes greater account of the wide range of features PCOS is characterized by, as compared with NIH criterion. The Rotterdam criteria are currently the recommended and most commonly used definition of PCOS in countries outside the U.S. (9). In recent times, the Androgen Excess and PCOS Society (AE-PCOS Society) criteria (22) defined PCOS as clinical or biochemical hyperandrogenism associated with oligo-anovulation or PCOs. This criterion, together with the NIH-criteria, differs from The Rotterdam criteria by hyperandrogenism being a requirement to get the diagnosis (22). Known disorders (such as androgen-secreting neoplasm, late-onset congenital adrenal hyperplasia, Cushing syndrome, hyperprolactinemia, hypo- and hyperthyroidism), which mimic the PCOS phenotype are exclusion criteria in all of the definitions (5, 9, 22, 31).

In addition, it has been suggested that AMH concentration may be useful in the diagnosis of PCOS (25). AMH levels are shown to be significantly increased in women with PCOS compared to

normal controls, and are strongly correlated to hyperandrogenism and anovulation (25). However, increased AMH concentration is not jet a criterion for diagnosing PCOS.

Although PCOS is a common endocrine disorder, the clinical practice for diagnosis is inconsistent and needs to be improved as many women are undiagnosed with the syndrome (8, 32, 33). The patients history (menarche, oral contraceptive pill use, weight gain), physical examination (vital signs, hair and skin, pelvic exam, BMI, WC), laboratory testing (free androgen levels, lipid profile, insulin, glucose) and transvaginal sonography are important components in diagnosing PCOS (10, 11).

1.4 Management/treatment of PCOS

There is no known curative treatments for PCOS. Treatment of women with PCOS depends on what the symptoms are. There is considerable variability in symptoms and their severity, thus the need for treatment and the type of treatment required will vary among women with PCOS. Because of the increased incidence of CVD and DM2 among women with PCOS, strategies to prevent these two morbidities should be highly emphasized (34). The therapy of PCOS often focuses on treatment of symptoms and prevention of further complications, especially addressing reproductive dysfunction and IR (35). Life-style intervention is regarded as first-line therapy, and includes diet, exercise and weight loss (3, 4, 8, 10, 11). Weight reduction is recommended for overweight women with PCOS (9), especially reduction in abdominal and visceral fat (34). Weight loss of 2-5% combined with exercise, can decrease androgen levels, improve hirsutism and regularize the menstrual cycle (18). Treatment strategies with both diet and exercise are often advocated (9). Exercise *per se* (both with and without weight loss) (34) can have positive effects on IR and VF in women with PCOS (23, 36).

In addition, the psychological factors often present in association with PCOS need to be screened for (8, 15, 16). Further, pharmacologic therapy can be relevant and involve the targeting of hyperandrogenism, reproductive and metabolic features, and includes starting on oral contraceptive pill (OCP), cyclic progestin, insulin sensitizing agents, anti-androgens and Metformin (3, 8, 35). Metformin is the most common medication for treating IR in women with PCOS (9). OCP is used to treat menstrual irregularities, hirsutism and acne (9). Orlistat can promote weight loss, and can

be recommended it lifestyle change is not sufficient (26). However, there is no pharmacological therapy that fully reverses the hormonal distribution and treats all clinical features in PCOS (4, 37), and such agents should therefore be used in combination with lifestyle changes or if lifestyle changes are not sufficient (26).

1.5 PCOS, obesity and body composition

The prevalence of overweight and obesity is increasing worldwide, and has become one of the most important health problems in the world (38). From the mid-1980s, the prevalence of obesity has increased in both Western and non-western countries, and public health experts are calling it an epidemic. Obesity, defined as "*abnormal or excessive fat accumulation that presents a risk to health*" (39), worsens the hormonal disturbance and clinical features of PCOS by increasing androgens and insulin (3, 40). However, increased androgens itself may contributes to increased abdominal fat tissue in women with hyperandrogenism (41). Overweight, obesity or central obesity is common features of PCOS, but the exact prevalence is unknown (40). A systematic review and meta-analysis by Lim et al. (40) investigated 30 eligible studies on the effect of overweight and obesity in PCOS. They reported that being overweight or obese was significantly associated with worse metabolic and reproductive outcomes measured, when compared to normal-weight PCOS women. Obesity significantly changes the reproductive and endocrine environment in PCOS (40). Excess body weight, especially abdominal and visceral adiposity appears to exacerbate IR (42), reproductive and metabolic futures, increase risk for DM2, CVD, hyperandrogenism, infertility and pregnancy complications both independently and by exacerbating PCOS (9, 43). Further, the major endocrine symptoms of PCOS are most likely associated with the amount of fat accumulation in the upper body sites (28).

Both obese and lean women with PCOS tend to have a different body composition and fat distribution when compared to weight-matched controls (28, 40, 44-47), with a tendency to centralized fat in the upper body region – so called android fat accumulation (19, 28, 44, 47, 48). Several studies on obesity, body composition and metabolic disturbance in PCOS have found PCOS women to have significantly higher amount of central adiposity independent of obesity (19, 28, 44, 45, 47, 49, 50). Further, central adiposity (visceral and subcutaneous fat) seems to be higher in lean women with PCOS than lean controls (19), despite same age and BMI (44).

Svendsen and colleagues (19) conducted a study on obesity, body composition and PCOS. Thirty-five women with PCOS and 25 control women were included, and body composition was measured by dual X-ray absorptiometry scan. They reported significantly higher trunk/peripheral ratio in lean women with PCOS than lean controls. Battaglia et al. (45) also investigated whether lean women with PCOS had a more android fat distribution compared to women with polycystic ovaries and healthy controls. They found that 86% of women with PCOS had android fat accumulation, compared to 26% of women with polycystic ovaries (but not fulfilled the PCOS diagnosis), and 7% of control women (45). The mechanism underlying the abnormal fat accumulation remains unknown, but is potentially associated with the hormonal imbalance (hyperandrogenism) present in the syndrome (49). Central fat accumulation, especially VF, is known to be more metabolic active in the production of molecules with inflammatory and pro-atherogenic activity than fat accumulated in the lower body sites, leading to a hormonal imbalance and a greater health risk (41, 45, 46, 51). In addition, visceral adiposity expresses several enzymes in the metabolism of steroid hormones (41). Androgens affect body fat distribution and muscle mass in both men and women (49). Women with PCOS often present increased testosterone levels and decreased estrogen levels, thereby similar to hormone levels in men (49, 52). This may lead to a masculine body fat distribution favoring the deposition of fat, especially in visceral adipose tissue depots (49). Therefore, the distribution of fat seems to be, at least in part, result of the imbalance between androgens and estrogens in these women (49).

Obesity and overweight may be both a triggering factor and a result of the pathophysiology of PCOS (44). However, several studies have suggested that fat distribution might be more important than the total amount of body fat, in terms of health risk associated with the syndrome (45, 52). Therefore, obesity cannot alone explain the health risks associated with PCOS as many non-obese PCOS women have excessive VF. Further, favorable changes in body composition, with reduced fat percentages and amount of VF seem to have positive effect on metabolic and reproductive outcomes in these women (40).

1.6 Exercise - impact on body composition in PCOS

It is well documented that exercise training improves several health-related outcomes, including reduced risk of CVD, DM2, all-cause morbidity and mortality, and improvement in psychological variables in healthy adults (53, 54). Further, moderate-intensity aerobic exercise and/or strength training (ST) has consistently been shown to improve health-related outcomes (DM2 and CVD risk factors) in other high-risk groups (55-58). In overweight or obese individuals, both aerobic training, ST and the combination of these have shown to improve body composition, especially reducing VF, maintaining FFM and reducing FM (36, 59-61). Aerobic exercise training improves body composition and CVD risk markers such as adverse lipid profile, blood pressure and DM2 risk, independently of weight loss (62). In addition, exercise training has been shown to maintain resting metabolic rate (RMR) and increase FFM during weight loss, in contrast to diet-induced weight loss that is associated with a decreased FFM, leading to decreased RMR (29).

Irving and colleagues (55) investigated the effects of endurance exercise training intensity on abdominal VF and body composition in obese women with metabolic syndrome. Twenty-seven middle-aged obese women were randomized to 16 weeks of either no exercise, maintaining their physical activity level, low-intensity aerobic exercise (at or below their lactate threshold level) or high-intensity exercise (between their lactate threshold level and VO_{2peak}). The duration of each exercise session was adjusted so that each participant expended the same amount of calories per training session. The high-intensity exercise group significantly reduced total abdominal fat, subcutaneous fat and VF compared to the moderate-intensity exercise group, under isocaloric training conditions. This study therefore suggest that body composition changes were affected more effectively with high-intensity exercise for reducing abdominal, subcutaneous and VF in obese women with metabolic syndrome (55). In contrast, Slentz et al. (57) reported that both low amount (19.2 km/week) of moderate-intensity (40-55% VO_{2peak}) and low amount (19.2 km/week) of high-intensity (65-80% VO_{2peak}) endurance training were equally effective in reducing FM and WC in previous sedentary overweight adults. However, they also found that high amount (32 km/week) of high-intensity endurance training (65-80% VO_{2peak}) was more effective in reducing FM than the two low amount protocols. It has been debated whether HIT (63) or moderate-intensity training (64) is more advantageous in other high-risk groups (65). With regard to decrease in FM and body weight, total energy expenditure seems to be the key factor (55). However, some studies

have found the intensity of exercise to induce greater increase in FFM (66) and decrease in FM (57), total abdominal and subcutaneous fat, and VF under equivalent energy expenditure (55). A clear dose-response effect between amount and intensity of exercise, and decrease in central obesity and FM has been found, leading to improvements in total body fat, VF and risk of CVD, DM2 and hypertension (56, 57). Suggesting that an interaction between training volume and training intensity exists, especially considering VF loss. It has been shown that HIT induces secretion of lipolysis hormones, including growth hormone and epinephrine, which leads to greater energy release and fat-oxidation after exercise (67). Further, it is reported that under isocaloric conditions HIT can induce a greater negative energy balance compared to low-intensity exercise training (68). In relation to the type of intervals, the 4x4 minutes interval has been found to positively affect fasting glucose levels, insulin sensitivity, fitness and fat metabolism in subjects with metabolic syndrome (63). Further, 10x1 minute intervals has been found to improve glucose control and induce adaptions in skeletal muscle in DM2 patients, which is further linked to improved metabolic health (69). A review on exercise training by Chicco et al. (65) have suggested that HIT and ST may provide benefits that exceed or supplement those elicited by continuous aerobic exercise training.

The American Heart Association recommendation has included strength training (ST) in their exercise guidelines for individuals with and without CVD (60). ST, which involves the use of muscular strength to work against a resistive force or move a weight, have beneficial effects on several health parameters in adults, such as increased FFM, muscular strength, insulin sensitivity, bone mineral density, modestly decreased FM and VF, and reduced CVD risk (70). Favourable changes in body composition such as increased FFM and decreased FM are seen even when weight remains constant (60, 71). An increase in FFM can have beneficial health effects, both in short – and long term. Skeletal muscle is an important component in the energy metabolism, because these cells have the greatest ability to regulate the energy metabolism in relation to activity level and regulate the energy balance (72). Botero and colleagues (73) investigated the effects of ST two times weekly on body composition in 23 post-menopausal women. They found a significant increase in FFM and a decrease in FM after 12 months of periodized ST. ST can increase FFM, but studies are conflicting in evidence regarding reduction in FM and VF (61, 73, 74).

Despite well-established benefits of exercise training and its recommendation in PCOS management, a limited number of studies have examined the impact of aerobic exercise intensity

and ST on body composition and VF in women with PCOS. Vigorito and colleagues (75) is one of the few studies that have examined the beneficial effects of moderate exercise training (40 min cycling at 60-70% $VO_{2max,}$ three times per week) as the sole treatment in women with PCOS. Ninety overweight PCOS women were randomly subdivided to either three months of structured aerobic exercise or no exercise. BMI and WC were significantly reduced ($p < 0.001$) in the exercise group compared to the non-exercise group. Also Palomba et al. (51) ran a pilot study on structured exercise training (three times per week at 60-70% VO_{2max}) versus high-protein diet in 40 obese women with PCOS. They reported significant reductions in body weight, BMI and WC after both interventions, with no difference between the groups. Another study by Hutchinson et al. (50) investigated the effects of exercise on body composition. Twenty overweight PCOS women and 14 overweight non-PCOS women underwent 12 weeks (three times weekly) intensified exercise programme (sequentially altered between moderate-intensity at 75-85% HR_{max} and HIT 6x5 minutes intervals at 95-100% HR_{max}). VF was significantly reduced in both groups, in the absence of change in body weight. This study suggests that weight loss should not be the sole focus of exercise programs in these women as exercise can improve body composition without significantly altering body weight (65). One study by Roessler et al. (76) examined the effects of HIT (three times weekly of cycling and walking/running at 80-100% HR_{max} in the intervals) in overweight women with PCOS. Seventeen sedentary, overweight women were randomized in a 16 weeks crossover trial (eight weeks of HIT and eight weeks of group counselling). They found that HIT (three to five minutes intervals at 80-90% HR_{max} and 20s to three minutes intervals at 80-100% HR_{max}) in combination with counselling had beneficial effects on body weight and WC. Only one study (59) have examined the effect of ST on body composition in women with PCOS. Ninety-four obese women with PCOS were randomized to either diet only (5000-6000 kJ/d), diet plus aerobic exercise (five times weekly at 60-80% HR_{max}) or diet plus ST and aerobic exercise (two times weekly at 65-75% 1RM and aerobic exercise three times weekly at 75-80% HR_{max}) for 20 weeks. All groups reduced body weight and WC with no difference between treatments ($p>0.05$). However, only the exercise groups reduced FM ($p<0.01$) and FFM ($p=<0.03$) after the exercise interventions.

Based on the available literature, there is no reason to believe that having PCOS will negatively affect the ability to respond exercise, and that exercise programmes in PCOS women are well tolerated and safe (36).

2 INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of women in reproductive-age and a leading cause of infertility, affecting 6-20% (5) depending on the diagnostic criteria used. PCOS is associated with multiple reproductive disorders, and featured by polycystic ovaries, menstrual dysfunction, infertility, and biochemical (elevated androgens) and clinical (hirsutism and/or acne) hyperandrogenism (31, 59, 76). PCOS is also a major unrecognized cardiovascular disease factor because of the increased prevalence of subclinical atherosclerosis, DM2, hypertension, metabolic syndrome, and dyslipidemia and glucose intolerance (77, 78). Although not included in the diagnostic criteria, weight-independent insulin resistance (IR) is strongly implicated in the etiology of the syndrome, as more women with PCOS have IR and DM2 compared to weight matched controls (35, 50, 79-81). The mechanisms underlying this intrinsic IR in PCOS remain unclear, but potentially these are associated with increased abdominal VF (28, 46, 50, 82). Women with PCOS are more commonly overweight or obese (38-66%) with increased central adiposity (45, 47, 48, 83), although this does not form part of the diagnostic criteria for the syndrome (35, 36). Further, it appears that physical inactivity, weight gain and genetic predisposition play important roles in the clinical expression of PCOS (76).

Lifestyle intervention is regarded as first-line therapy in women with PCOS (84), and has been proposed to improve both metabolic and reproductive manifestations of the syndrome (3, 85). Lifestyle modification strategies in PCOS include dietary intervention, weight loss and increased physical activity (84). Despite this, following modest weight loss, weight maintenance is challenging in long term and if weight is regained it may worsen clinical features in PCOS (35). Exercise training improves several health related outcomes (9, 51, 86), and it is a key predictor of long-term weight maintenance (36, 87), possible because of greater preservation of FFM and maintenance of resting metabolic rate (RMR), compared to diet-induced weight loss (59, 88). Further, regular aerobic exercise has been found to alter body composition and provide weight loss in overweight women with PCOS (35, 51). Therefore, exercise as a part of the treatment in PCOS may be favorable (35, 86). However, there is a lack of well-designed studies on the effect of exercise as an independent intervention on clinical outcomes and body composition in these women (9, 35). Especially, knowledge on the effect of different types, intensities, frequency and duration of exercise is needed. Most of the prior studies on exercise in PCOS have used moderate exercise

intensity. There exists a gap in the literature on the effect of other exercise intensities (low – or very high-intensity exercise) on health parameters in PCOS women (35). To date there are no studies that have examined the effect of HIT on body composition in women with PCOS, without combining it with other types of exercise or diet. However, HIT has been found to have high impact on body composition (especially VF), and anthropometrical outcomes in subjects with other metabolic conditions (55, 58). The effects of intensity and amount of aerobic exercise training on body composition and anthropometric outcomes have been somewhat conflicting across studies (35, 36, 55, 57). In addition, the majority of many studies have reported changes in body weight, without changes in body composition (35, 36, 51, 75). Measuring changes in body composition provides valuable information on changes in FFM, and fat distribution (especially VF) associated with IR, CVD and health risk in PCOS (35). No prior study has examined the effect of ST alone on body composition and fat distribution in PCOS women. To date, most studies focus on dietary treatment or a combination of both diet and exercise (aerobic exercise or the combination of aerobic exercise and ST), which makes it difficult to assess the effect of exercise (and different types of exercise) as an independent intervention on body composition. To evaluate exercise as an independent therapy in PCOS, exercise needs to be assessed in a broad range of women, both lean and obese, with varying degrees of symptoms.

2.1 Main objective and hypothesis

We hypothesized that both ST and HIT would improve body composition in women with PCOS. In addition, we assumed based on the previous literature that such improvements would lead to improvement in clinical features and risk factors associated with the syndrome. Therefore, the main objective of this study was to examine the effect of structured exercise training for 10 weeks in women with PCOS, and to compare the effects of HIT and ST on body composition. Primary outcome measurements were body composition and VF. Secondary outcome measurements were body weight and WC.

3 MATERIALS AND METHODS

3.1 Participants

Thirty-one previously sedentary premenopausal women with PCOS (age 18-45 years) were recruited via public advertisement at local stores and public places, and announced at the hospital, university and college webpages, between June 2013 and October 2013.

Inclusion criteria were defined according to the Rotterdam criteria for diagnosing PCOS (31), based on the presence of two of the following three criteria; hyperandrogenism, irregular anovulatory periods (>35 days menstrual cycle or <10 menstruations/year) or ultrasound polycystic ovary (PCO) morphology (≥10 peripheral cysts 3-8 mm in diameter and/or volume ≥10 ml). Hyperandrogenism was defined as biochemical (total testosterone >1,4 nmol/L) and/or clinical (Ferriman-Gallwey scoring system with a total score above or equal to eight, defined as hirsutism) (2). Both women diagnosed with PCOS and women with symptoms of PCOS were recruited. Patients who had a PCOS diagnosis from a gynecologist did not have to go through additional screening. Other subjects had to go through screening at a gynecologist after baseline testing to confirm that they had PCOS according to the Rotterdam criteria as described above.

Exclusion criteria include regular high-intensity endurance or strength training (defined as >2 hours of vigorous exercise per week), physical ailments/injuries that limited exercise performance, on-going pregnancy, concurrent treatments (insulin sensitizers as metformin and pioglitazone) or drugs known to affect gonadotropin or ovulation, with a wash out period of one month prior to inclusion (with the exception of regular use of oral contraceptives before, during and after the intervention period).

Diet was not controlled, but women were encouraged not to change their diet during the study period. The study was approved by The Regional Committee for Medical and Health Research Ethics (REK), and participants provided written informed consent before entering the study.

3.2 Study design

This study was a randomized, controlled trial with three parallel arms. The allocation to this superiority trial was 1:1:1 to a high-intensity interval training (HIT) group, a strength training (ST) group and a control group (CG). Subjects were stratified according to BMI $<$ or $\geq$ 27 based on a previous study (89), and randomized to one of the three groups after baseline testing. A computer random number generator developed and administered at The Faculty of medicine, Department of Public Health and General Practice, NTNU, Trondheim, Norway, was used to randomize. Data were collected from August to December 2013. Data from all subjects who came back for testing after the intervention period were used in the analyses; hence, it was an intention-to-treat design.

3.3 Interventions

Participants were asked to attend three weekly exercise sessions for 10 weeks with a trained exercise physiologist. This gave a total of 30 exercise sessions. Participants completed exercise diaries to monitor their training progress and calculate the compliance. Compliance was calculated as the number of sessions completed divided by the number of scheduled sessions in the study.

3.3.1 High-intensity interval training (HIT)

The HIT sessions included two 4x4 minutes interval sessions (Figure 2) and one 10x1 minute interval session (Figure 3). The HIT consisted of treadmill or outdoor running/walking and/or cycling on spinning bike (self-selected). Exercise intensity for the HIT 4x4 program was 90-95% individual maximum heart rate (HR_{max}) as measured in the baseline exercise test (week 0). At the 4x4 minutes intervals, the training started with a 10 minutes warm-up period at 60-70% of HR_{max}, followed by four intervals of 4 minutes trying to reach 90-95% of individual HR_{max}. There was a 3 minutes active recovery period with the intention to reach 60-70% of HR_{max} between each interval. The training session was terminated by a 10 minutes cool-down period at 50-70% of HR_{max}. Total exercise time per session was 45 minutes.

At the 10x1 minute intervals (Figure 3), the participants did a 10 minutes warm-up at 60-70% HR_{max} followed by 10x1 minute intervals trying to reach the maximal intensity (that can be performed for one minute). Each interval was separated by 1 minute active recovery period of very light intensity exercise, walking/cycling at low pace. The training session was terminated by a 5 minutes cool-down at 50-70% of HR_{max}. Total exercise time per session was 36 minutes.

To ensure that the participants completed sessions and trained at the right intensity, each participant was given a heart rate monitor (Polar RCX3, POLAR, Oulu, Finland) to lend throughout the intervention. Speed and incline was adjusted continuously to ensure that each session was performed at the assigned intensity. Interval intensity averaged across all intervals for all participants in the HIT group was estimated as minutes of the total exercise session (including warm-up and cool-down) where they reached >90% of $HR_{max.}$ During the training period, all training files were recorded and stored at the www.polarpersonaltrainer.com (online training diary) to ensure quality and performance in sessions.

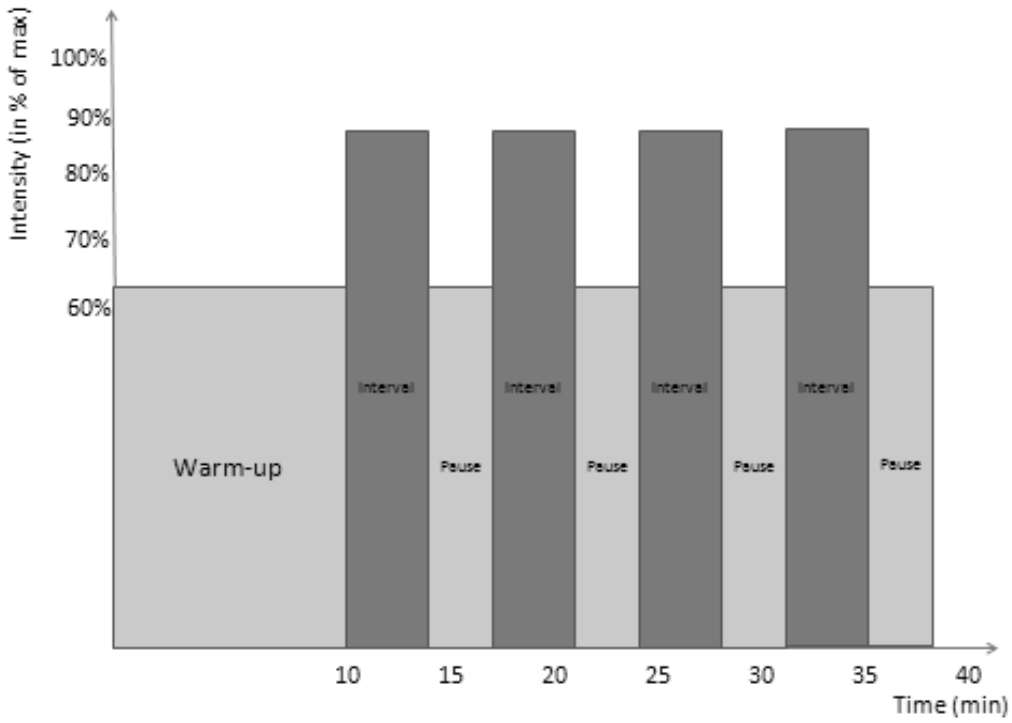


Figure 2. High-intensity interval training, 4x4 min model.

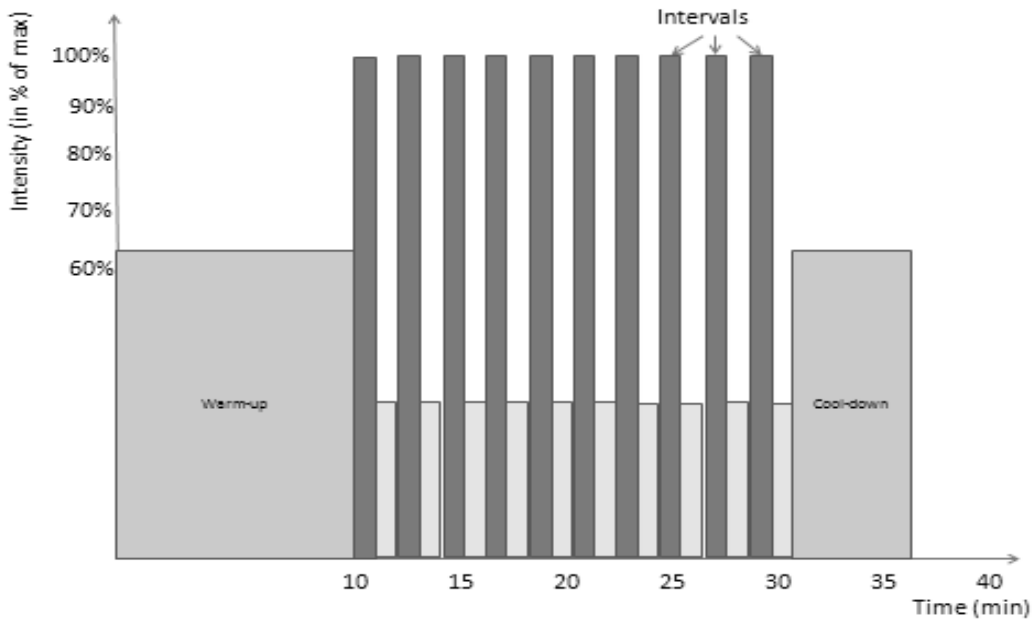


Figure 3. High-intensity interval training, 10x1 min model with 100% effort trying to reach 100% of HR_{max}.

3.3.2 Strength training (ST)

The ST started with a 10 minutes warm-up on a treadmill/rower/cycle, and was followed by dynamic strength drills at 75% of the subject's 1RM (one repetition maximum). The 75% of 1RM was based on the weight [kg] each participants lifted 10 repetition maximum. 1RM refers to the maximal amount of weight lifted once with proper technic for a specific exercise. Each drill consisted of 10 repetitions and three sets separated by 1 minute rest between sets. The training program contained eight exercises on the major muscle groups: Leg press, lunge, standing bent rowing, lat-pull-down, shoulder press, chest press, push-ups and core (plank exercise, held as long as possible, times three) (Appendix G). In order to progress in strength, there was a gradual increase in resistance (number of kg, time held in plank and difficulty or numbers of push-ups) to maintain the number of repetitions recommended (75% of 1RM). The training load was increased progressively once the subjects could successfully perform three sets of 10 repetitions at that load. We suggested one "rest-day" between sessions to ensure full recovery of the muscles. To obtain good technique, progress and to provide motivation, a trained exercise physiologist supervised all participants once weekly. All sessions were conducted at a local fitness center with good accesses to equipment. Total exercise time per session was 45 minutes.

3.3.3 Control group (CG)

Women in the control group were advised to continue with their everyday physical activity, and adhere to the recommended 150 minutes of weekly moderate-intensity exercise (53, 90), without any follow-up, during the 10 weeks intervention period. The study investigators had no contact with the control group between baseline testing and post-testing. After post-testing, the control group received one month free training at a local fitness centers, and they were offered the HIT and ST training programs.

3.4 Measurements

The order of the testing and protocols were identical for each participant at baseline and post-tests. Baseline measurements were carried out before randomization. Later assessments were done non-blinded (as we had not enough research staff to allow for blinded assessments). The women underwent testing at baseline (week 0), and post-intervention (week 11). All measurements were performed during one day at each time point, and total time spent in the laboratory this day was about 4 hours. To avoid the influence of circadian variation participants were tested in the morning. Participants were asked to fast for 12 hours, avoid alcohol and tobacco, and refrain from exercise for 48 hours prior to testing sessions. Identical and calibrated equipment were used in all tests to avoid errors. It was not feasible to control for menstrual cycle phase in most of the women with PCOS, because of the erratic nature of their cycles. However, nine of the women had normal menstrual cycle, and post-testing was scheduled at the same time in the menstrual cycle as baseline tests.

The study was carried out at the Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), in collaboration with the Women's Clinic, St. Olav's hospital, both Trondheim, Norway.

3.5 Body composition and anthropometric outcomes

3.5.1 Primary outcome measurements

Body composition and VF was measured with the participants wearing light clothing and without shoes or socks, by using InBody720 bioelectrical impedance analysis (BIA) (InBody720, Biospace CO, Ltd, Seoul, Korea). This analysis provides data regarding body water, FFM and FM. The following body composition measurements were analyzed: percentage FM, FM [kg], FFM [kg], and VF [VFA, cm^2].

This method estimates body composition by measuring the impedance (or resistance) to a small electrical current (50 kHz) which passes across body tissues. Resistance to an applied alternating current is a function of tissue composition: the greater the FFM of an individual, the faster the current will travel (because of its water and electronic content). Population specific equations are used to estimate percentage FM and FFM. An estimate of VF is graphed and a value > 100 cm^2 is considered significant abdominal obesity (Figure 4). To improve statistical predictability, the measurement require age, sex, body weight and height. Estimates can be affected by numerous variables: body position, hydration status, consumption of food and beverages, ambient air, skin temperature, recent physical activity and conductance of the examining table (91). We therefore standardized procedures to minimize error, including fasting prior to measurement, wearing light clothes only and measuring at the same day of menstruation cycle in regularly cycling women. Percentage body fat over 33% (women 20-39 years) is considered overweight, and over 39% obese (92).

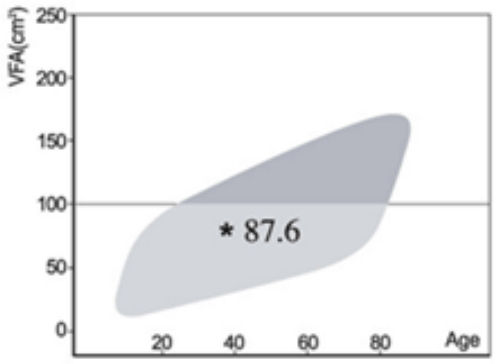


Figure 4: Visceral fat area (VFA) in cm^2 according to age. Shaded area shows the average VF by age. The apteryx illustrates a measurement on InBody720 bioelectrical impedance scale (BIA) of a 39 years old person.

3.5.2 Secondary outcome measurements

Body weight (to the nearest 0.1 kg) and BMI (body weight [kg]/ height [m^2]) were calculated by InBody720 bioelectrical impedance scale (BIA).

BMI was defined according to WHO guidelines (61); BMI greater to or equal 25.0 was considered overweight, and BMI greater to or equal 30.0 was considered obesity.

WC was measured to the nearest 0.5 cm horizontally at the level of the umbilicus by using a metric tape with the women in standing position and at normal expiration (93).

Height was measured to the nearest 0.5 cm, standing with heels against the wall and without shoes using a standard stadiometer.

3.6 Sample size

The study sample size was calculated based on the primary outcome measure of the whole study: inulin sensitivity. We selected the sample size to provide a statistical power of 80%, and with a 0.05 alpha level (two-tailed), to detect a difference in HOMA-IR of 18%, based on a previous study (94). This gives a minimum sample size of seven subjects in each group. To allow for 20% drop out, and due to some uncertainty in the calculation, we included minimum 10 subjects in each group, giving a total of 31 subjects.

3.7 Statistical analysis

Baseline characteristics were compared between groups, using one-way analysis of variance (ANOVA). The analyses were done on an intention-to-treat basis, with outcome measures analyzed according to the treatment to which patient were randomized to. Results are reported as mean ± standard deviation (SD). The mean changes in each group are reported as the estimated margin of the mean (EMM), as assessed by 95% confidence interval (CI). Within-group differences were considered significant when the 95% CI did not include zero (95). Covariance analysis, with the Bonferroni adjustment, were used to test differences between groups, with the difference (Δ-value) as the dependent factor, group variable as the fixed factor, and baseline values as covariates (96). P-values of <0.05 were considered significant.

Statistical analyses were processed using a Statistical Package for Windows, IBM SPSS Statistics software program version 20 (SPSS Inc., Chicago, IL., USA). Figures and tables were made using Microsoft Excel (version 2010), Microsoft Corporation and Microsoft PowerPoint (version 2010), Microsoft Corporation.

3.8 Ethics

The study protocol was approved by the Regional Committee for Medical Research Ethics in Norway (REK), June 2013, reference number 2013/886/REK midt (appendix A). The Department of Public Health and General Practice at the Norwegian University of Science and Technology (NTNU) approved the study.

All participants signed consents for participation before entering the study. Participants could at any time withdraw from our study, without further justification. All data was treated confidentially to protect the participant privacy. Blood samples were stored in a research biobank. All data were stored in a de-identified form in SPSS files. They will be deleted no later than 2024.

3.9 Time schedule and financing

REK approved the study in June 2013, and recruitment was carried out between June 2013 and October 2013. Baseline testing was done between August and October 2013, and the intervention was conducted between August and December 2013. Post-testing started in October 2013 and until the end of December 2013. Analyses were performed in January 2014 (Appendix C).

The authors have no economic interest in this study. The project received a small grant from Norwegian University of Science and Technology, Department of Public Health and General Practice to cover expenses (Appendix C). We also received a grant from the Norwegian Sports Medicine Research Fund.

4 RESULTS

Baseline characteristics of the participants are shown in Table 1, and a flow-chart of the study is outlined in Figure 5. At baseline, women (*n*=25) were overweight (BMI 26 ± 5.5) with a mean WC of 92cm ± 15.2, percentage FM of 32 ± 8.1 and VF of 101 ± 43.9. There were no significant differences in baseline characteristics between groups (Table 1). None of the participants began any treatment (insulin sensitizers as metformin and pioglitazone) or started on drugs known to affect gonadotropin or ovulation during the study. The exercise compliance were 27 ± 1.9 (90%) and 26 ± 6.5 (87%) of the prescribed exercise sessions in the HIT and ST group. In the 4x4 minutes intervals 8.9 minutes (19.8%) of the total exercise session (including warm-up and cool down) was >90% of HR_{max}. In the 10x1 minute intervals 5.15 minutes (14.3%) of the total exercise session (including warm-up and cool down) was >90% of HR_{max}, respectively. 6 participants dropped out (loss-to-follow-up) during the intervention period due to illness not related to exercise or due to time concern (Figure 5). We experienced no adverse effects during the study period. No major complications occurred during the study period.

Table 1. *Baseline Characteristics of Total Group and After Randomization Into Groups (HIT, ST and CG group).*

Variable	**Total group (*n*=25)**	**HIT (*n*=8)**	**ST (*n*=8)**	**CG (*n*=9)**
Age [y]	27.2 ± 5.5	26.4 ± 4.9	27 ± 4.0	25.7 ± 5.1
Body weight [kg]	74 ± 17.2	68 ± 14.1	77 ± 20.9	75 ± 17.0
Height [cm]	168.8 ± 6.0	170 ± 6.1	168 ± 5.1	169 ± 7.3
Body mass index [kg/m^2]	26 ± 5.5	24 ± 4.8	27 ± 6.6	26 ± 5.2
Waist circumference [cm]	92 ± 15.2	89.4 ± 14.1	93.8 ± 17.7	92.6 ± 15.5
Fat mass [%]	32 ± 8.1	30 ± 8.1	33 ± 9.7	34 ± 7.0
Fat mass [kg]	25 ± 12	22 ± 9.4	27 ± 15.4	26 ± 11.3
Visceral fat [VFA,cm^2]	101 ± 43.9	86 ± 39.3	107 ± 52.4	110 ± 40.8
Fat free mass [kg]	27 ± 3.6	26 ± 3.4	28 ± 4.0	27 ± 3.6

Data presented is means ± standard deviation (SD) if not otherwise stated. There were no baseline differences between groups in age, body weight, height, body mass index, waist circumference, fat mass [%], fat mass [kg], visceral fat [VFA,cm^2] or fat-free mass [kg].

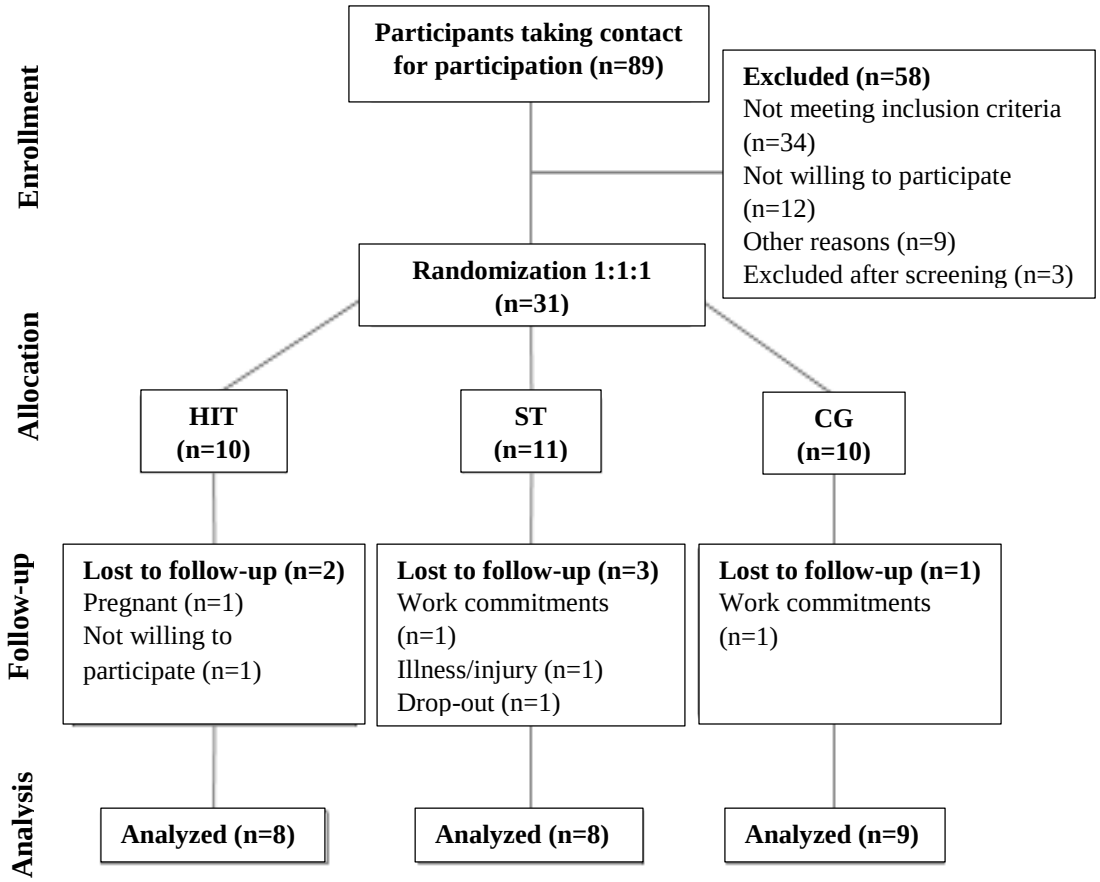


Figure 5. Flow-chart of participants in the study.

As can be seen from Table 2 and Figure 6 and 8, percentage FM was significantly reduced after ST and HIT with 4.8% and 3%, respectively. There was non-significant between-group difference in fat percentage change (p=0.54). FM [kg] was significantly reduced in the HIT group with 2.8%, but not in the ST group (Table 2, Figure 8). There was no significant between-group difference in FM [kg] change. FFM increased significantly after ST with 4.4% (Table 2, Figure 7-8), but there was no significant between-group difference in change (p=0.18). We saw no significant changes in weight, BMI, WC or VF between baseline and post-testing in neither group (all 95% CIs included zero, Table 2, Figure 8). There was a trend towards reduced VF after HIT (Table 2, Figure 8), but no significant changes between groups in VF changes.

Table 2. *Outcome variables at baseline and after 10 weeks of HIT, ST and CG for participants completed post-testing.*

	ST		HIT		CG	
	Pre	Post	Pre	Post	Pre	Post
Weight [kg]	77.0±20.9	78.1±20.0	68.3±14	68.5±14.2	75.3±17	75.5±17.5
EMM	1,1		0.2		0.4	
95 % CI	-1.2 to 3.5		-1.0 to 1.3		-1.8 to 2.6	
BMI	27.1±6.6	27.5±6.1	23.8±4.8	23.9±4.8	26.3±5.2	26.4±5.3
EMM	0,4		0.1		0.1	
95 % CI	-0.3 to 1.1		-0.3 to 0.4		-0.7 to 0.8	
WC [cm]	93.8±17.6	92.8±16.4	89.4±14.1	87.2±16.6	92.6±15.5	92.3±16.4
EMM	-1.0		0.4		-0.2	
95 % CI	-2.5 to 0.5		-4.4 to 5.3		-3.9 to 3.5	
FM [kg]	27.1±15.4	26.1±14.7	21.6±9.4	21.0±9.4*	26.2±11.3	25.9±11.4
EMM	-1.0		-0.6		-0.3	
95 % CI	-2.1 to 0.1		-1-1 to -0.0		-2.2 to 1.6	
FM [%]	33.1±9.7	31.6±9.4*	30.2±8.1	29.3±7.9*	33.6±6.9	32.9±7.3
EMM	-1.6		-0.9		-0.7	
95 % CI	-2.5 to -0.7		-2.2 to -0.0		-2.2 to 0.9	
VF [VFA, cm^2]	106.6±52.4	105.5±48.4	85.7±39.3	82.4±38.7	109.9±40.8	109.7±41.0
EMM	-1.0		-3.3		-0.3	
95 % CI	-4.6 to 2.5		-6.9 to 0.3		-7.7 to 7.1	
FFM [kg]	27.7±4	28.9±4.1*	25.8±3.4	26.3±3.2	27.0±3.6	27.4±3.8
EMM	1.2		0.4		0.4	
95 % CI	0.4 - 2.1		-0.2 to 1.1		-0.3to 1.0	

Variables are expressed as means ± standard deviation (SD). Changes from pre-test to post-test are expressed as estimated marginal means (EMM) and 95% confidence interval (CI).

*Significant changes from baseline to post-test (zero not within the 95% CI).

BMI = Body Mass Index, WC = Waist Circumference, FM = Fat Mass, VF = Visceral fat, FFM = Fat Free Mass.

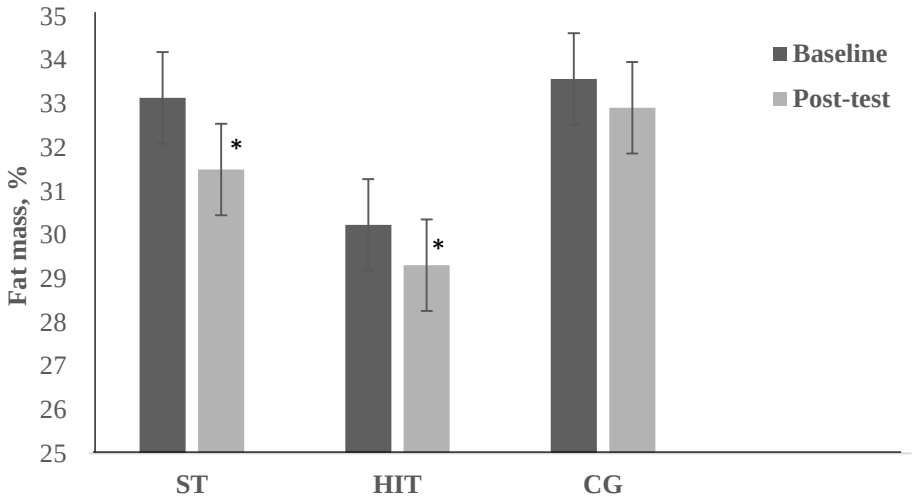


Figure 6: Fat mass [%] at baseline (dark grey bars) and post-testing (light grey bars). Data are means ± standard error of the mean (SEM). *= significant changes (within group). ST = Strength Training, HIT = High-Intensity Interval training, CG = Control Group.

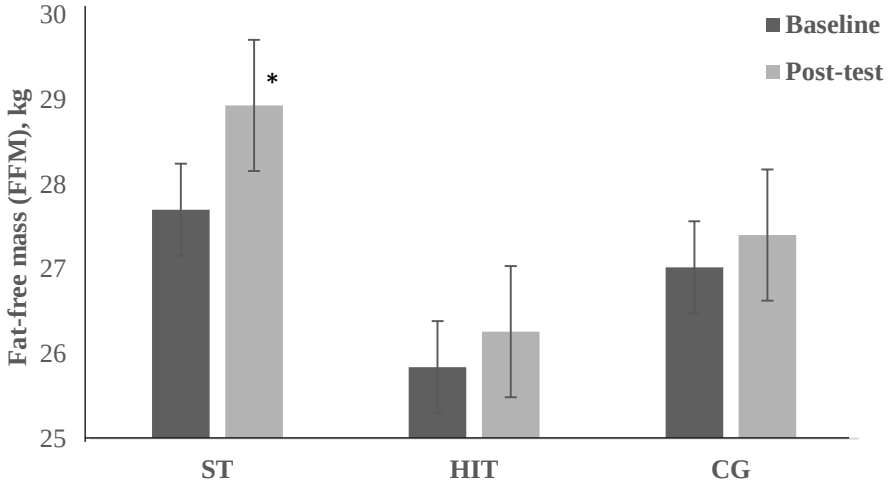


Figure 7: Fat-free mass (FFM) at baseline (dark grey bars) and post-testing (light grey bars). Data are means ± standard error of the mean (SEM). * = significant changes (within group). ST = Strength Training, HIT = High-Intensity Interval training, CG = Control Group.

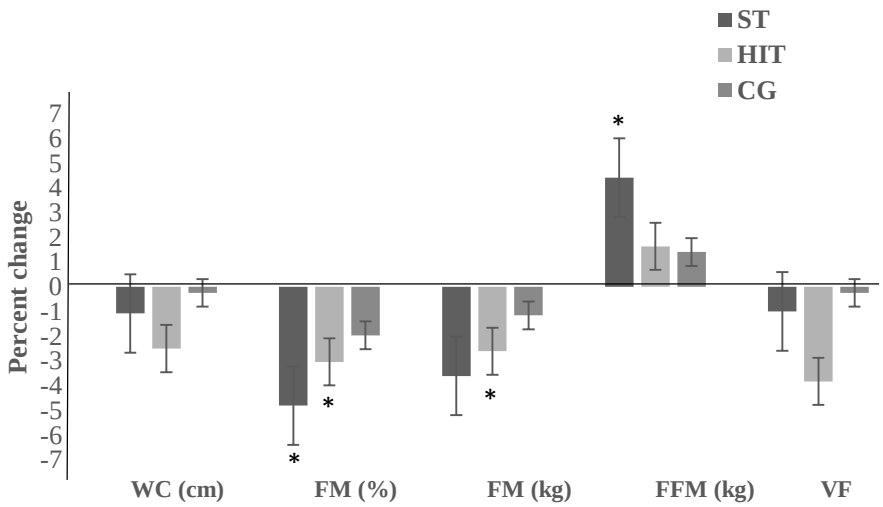


Figure 8: Mean percentage change ± standard error of the mean (SEM) of the body composition values from baseline to post-testing. * = significant changes (within group). ST = Strength Training, HIT = High-Intensity Interval training, CG = Control Group, WC = Waist Circumference, FM = Fat Mass, FFM = Fat-Free Mass, VF = Visceral fat.

5 DISCUSSION

5.1 Main findings

We evaluated the effect of 10 weeks HIT and ST on body composition in women with PCOS. To our knowledge, this is the first randomized clinical trial to compare HIT and ST as independent interventions in these women. This thesis is concentrated on the effect of exercise on body composition and other important issues such as cardiometabolic and endocrine outcomes are acknowledged, but are not mentioned in this thesis.

The main findings of our study was significant decrease in percentage FM after both ST and HIT with 4.8% and 3%, respectively. Further, we found a significant increase in FFM after ST of 4.4%. There was no difference in FM or FFM in the control group. We found no significant difference in body weight, WC or VF within any group. Although not significant, the HIT group had an estimated reduction in VF of -3.3 (95% CI: -6.9 to 0.3; Table 2), which may indicate a tendency toward an effect. We found no significant between-group differences and therefore no evidence for a different effect between the exercise interventions, or above the control group.

5.2 Comparison to existing literature

A previous randomized controlled trial by Thomson et al. (59) found a significant decrease in FM and increased FFM in obese PCOS women after both moderate-intensity exercise and ST in combination with a low-calorie diet. Women (*n*=94) in their study were randomized to 20 weeks of either diet only, diet plus aerobic exercise (five times weekly at 75-80% HR_{max}) or diet plus ST and aerobic exercise (two times weekly at 65-75% 1RM and three times weekly at 75-80% HR_{max}). All groups reduced body weight and WC, with no difference between treatments ($p>0.05$). However, the exercise groups had 45% greater reduction in FM and 60% better preservation of FFM after the intervention. Hence, compared with diet alone, exercise in combination with diet provided more favorable effects on FM and FFM (59). However, it is important to notice that the energy deficit was not equally between the three groups as all groups prescribed the same diet (5000-6000 kJ/day). In our study, percentage FM decreased and FFM increased by exercise alone and without reduction in body weight. This indicates that exercise as an independent intervention

can have beneficial effects on body composition changes, in absence of weight change, in these women. This is in line with others who have found exercise to have only modest effect on body mass alone, but with decreased FM and maintained FFM (29). Further, in a prospective exercise intervention study on overweight women with and without PCOS, Hutchinson et al. (50) reported that 12 weeks of moderate to high-intensity exercise (three times weekly sequentially altered between moderate-intensity at 75-85% HR_{max} and HIT 6x5 minutes intervals at 95-100% HR_{max}) reduced VF (measured by computer tomography) in both PCOS women and non-PCOS women, in the absence of body weight change. In our study, we found no significant difference in VF in any groups. This was possibly because we included both lean and obese women with PCOS, or due to difference in measuring methods. However, the HIT group in our study had a trend towards significant reduction in VF of -3.3 (95% CI: -6.9 to 0.3), and possibly this would have reached statistical significance if more subjects were enrolled.

Most of the previous exercise studies in women with PCOS have only reported changes in body weight, BMI and/or WC. In a non-randomized study, Vigorito et al. (75) found that a three months structured aerobic exercise program (three times weekly, 40 min cycling at 60-70% VO_{2max}) improved BMI and WC in overweight women with PCOS (*n*=45), compared to a non-exercise PCOS group (*n*=45). However, the participants in that study received a healthy balanced meal plan (without calorie restrictions), and therefore the isolated effect of exercise could not be determined. This is in line with other studies that have found similar effects in WC, weight and/or BMI after exercise interventions on women with PCOS (59, 75). Palomba et al. (51) found a reduction in WC and body weight after 24 weeks of either aerobic exercise (three times weekly, 30 min cycling at 60-70% VO_{2max}) or diet (800 kcal deficit/day) in 40 obese women with PCOS, with greater reduction in WC in the exercise group. The exercise program was adjusted to create the same energy deficit as the diet group (800 kcal deficit/day). However, treatments were self-selected in an unrandomized manner, which may have biased the results. In our study, we found no significant differences in body weight or WC between or within groups. This is not surprising giving that numerous short-term exercise studies have consistently shown that exercise alone induces modest weight loss (35, 50, 59). Further, the lack of weight loss in the present study may also be due to the small sample size, the increase in FFM and/or the fact that we included both lean and obese PCOS women. In addition, the HIT group in our study performed 4x4 minutes intervals, which gives an energy deficit of about 400 kcal, and probably even less in the 10x1 minute intervals. This leads to

an energy deficit of about 1000 kcal per week, which is much lower than the energy deficit in the study by Palomba et al. (51).

A randomized controlled trial by Slentz and colleagues (57) reported that eight months of low-amount/moderate-intensity (19.2 km/weekly at 40-55% VO_{2peak}) and low-amount/vigorous-intensity (19.2 km/weekly at 65-80% VO_{2peak}) endurance training were equally effective in reducing percent FM and WC in previously sedentary overweight adults with dyslipidemia. They also found that high-amount/vigorous-intensity (32 km/weekly at 65-80% VO_{2peak}) endurance training was more effective in reducing percentage FM compared with the low-amount training groups. The authors did not include a high-amount/moderate-intensity exercise group, and therefore had no opportunity to determine whether an interaction between training volume and training intensity existed. However, a dose–response relationship between training volume and amount of weight change was reported by using pooled analysis. To summarize, these data may indicate an interaction between training volume and training intensity for FM, WC and VF loss. Further, Irving and colleagues (55) reported that HIT (between lactate threshold level and VO_{2peak}) was more effective in reducing total abdominal fat and VF than low-intensity exercise training (at or below their lactate threshold level) when adjusted for energy expenditure during exercise, in obese women with metabolic syndrome. HIT can induce secretion of lipolysis hormones, including growth hormone and epinephrine, which can facilitate increased energy release and fat-oxidation after exercise (67). Further, it has been reported that under the same energy release, HIT can induce a greater negative energy balance compared to low-intensity exercise training (68). HIT may therefore be preferable to achieve changes in body composition, especially considering FM and VF loss in overweight women. However, we do not know if the effect of exercise in other population groups are comparable to women with PCOS.

As described above, studies on exercise in PCOS have found a reduction in BMI, WC (51, 75), VF (50), and FM (59) after moderate-intensity exercise or combined exercise intensities or types. Only one previous study (76) examined the effect of HIT as the only exercise mode (three times weekly, cycling and walking/running at 80-100% HR_{max} in intervals) on body weight and WC in overweight women with PCOS (n=17). They found a beneficial effect on body weight and WC after HIT. However, this study had a crossover design in combination with group counselling, and we do not

know whether it was the group counselling or the HIT that induced the greatest effects on body weight and WC.

Few studies have evaluated the effects of ST in women with PCOS. ST can induce hypertrophy of the skeletal musculature. FFM is an important component in the total energy metabolism because the muscle cells have a great ability to vary the energy metabolism relative to the activity, and regulate the energy balance (72). Therefore, change in FFM can have beneficial effects both in short – and long term. In our study, the ST group showed a significant increase in FFM and decrease in FM after intervention with 4.4% and 4.8%, respectively. Our results are in line with a study by Botero and colleagues (73) who found a significant increase in FFM and decrease in FM after 12 mounts of periodized ST in post-menopausal women. Similar results are seen in other high-risk groups after ST (58, 60). However, we do not know if the results on other populations are comparable to women with PCOS, as physiological factors may differ from other population groups.

The heterogeneity of exercise interventions studies in PCOS women, including differences in study design, diagnostic criteria, degree of symptoms and obesity, exercise type, duration, frequency, intensity, intervention length and supervision degree makes it difficult to conclude about the effects of exercise based on the current literature. Further, differences in primary and secondary outcomes, and different measuring methods, makes it difficult to compare the effect of exercise on body composition. The majority of studies on women with PCOS reported change in body weight without data on body composition changes, with the exception of two studies by Thomson et al. (59) and Hutchison et al. (50). As previously described, the study by Thomson and colleagues is the only one that had one group on ST. However, the ST was combined with diet and aerobic exercise in their study (59), making it difficult to determine the isolated effects ST had on body composition.

5.3 Methodological consideration

A strength in our study is that we conducted a randomized controlled trial (RCT). This study design is the “gold standard” to evaluate the effect of interventions. Such design reduces the importance of other known and unknown influencing factors, because these factors will, theoretically, be equally located to all groups.

PCOS is a complex and heterogeneous syndrome with highly variable presentation in symptoms and clinical and biological manifestations. Therefore, participants in our study were included based on the Rotterdam criteria. The Rotterdam criteria are currently the recommended and most commonly used definition of PCOS, and it is the criteria that diagnoses most PCOS women. Further, participants were stratified according to BMI < or ≥ 27 based on a previous study (89), and randomized to one of the three groups after baseline testing by a computer random number generator. This gives us an even distribution in BMI between groups. The analyses were done on an intention-to-treat basis, with outcome measures analyzed according to the treatment to which patient were randomized to, regardless of the amount of exercise performed.

Another strength in our study is that we compared HIT and ST as an independent intervention in women with PCOS. The exercise training in our study was well controlled, and documented through regular supervision with a trained exercise physiologist and/or physiotherapy student, and through monitoring of the exercise, using exercise diaries and heart rate monitors. The ST program included eight strength exercises for the whole body. This can provide a relatively large strain on muscles when performed three times weekly on untrained subjects. Therefore, we recommended one rest-day between sessions to ensure full recovery of the muscles. Each drill consisted of 10 repetition and three sets, based on the current literature for ST in untrained subjects (60). Most of the strength exercises were performed with strength machines to ensure good technique and to prevent injuries (as we were not able to supervise all exercise sessions). Participants in the HIT group achieved an adequate exercise intensity in the 4x4 minutes and 10x1 minute intervals. The compliance was high in all groups, and none of the participants experienced any problems during the training period.

InBody720 bioimpedance scale (BIA) was used to measure body composition, in addition to body weight and WC. This gave us valuable information on the distribution of FM, FFM and VF, compared to most studies who only reported changes in body weight and WC.

5.3.1 Study limitations

The study sample size was calculated based on the primary outcome measure of the whole study: insulin sensitivity. In this thesis, the primary outcome measurements is body composition, and the fact that the study sample size was calculated based on insulin sensitivity, is regarded as a limitation. Based on a previous study (59), the sample size needed to provide a statistical power of 80% with a 0.05 alpha level (two-tailed), to detect a difference in FM of 4% was 81 subjects. However, in our study we found a significant change in percentage FM based on the sample size calculated for the whole study (insulin sensitivity), but with no difference between groups. This may be due to our small sample size. The relatively small sample size of the present study is a limitation because of the increased risk of a type Π error, i.e. we were not able to detect any between group differences. PCOS is a heterogeneous group, and it may demand a larger sample size to detect a difference, than when studying a more homogenous population. However, we found no significant difference in baseline characteristics in our study. Compared to other studies on women with PCOS (50-52, 76, 78), our sample size was not much different. However, as other studies with small sample sizes, this study might be subject to selection bias (follow-up bias, participation bias, sample bias, non-blinded participation) regarding the representativeness in our study population. Selection bias may give us a study population that is not representative for all PCOS population, as women how enroll in an exercise study may have milder degrees of symptoms, higher fitness level and/or are more motivated to exercise than the general PCOS population. The statistical significant differences we found might have been more clinically significant with a larger sample size. A greater difference between groups are needed to achieve statistical significance with a small sample size, compared to a larger sample size. Therefore, an actual difference may be missed or disturbed because of confounding variables, caused by our small sample size.

Most previous exercise studies in PCOS have only included overweight or obese women. This is in contrast to our study, as we included both lean and obese women with PCOS. The fact that we included a comparatively large number of lean PCOS women, with WC and VF within the normal range, may possibly have influenced the fact that we did not found any significant effects in these parameters. With a larger data set, we could have created sub-groups analyses on participants with BMI $<$ and $\geq$ 27 to investigate the possibly different effects of exercise on body composition in lean and obese PCOS women.

As it is difficult to blind participants and treatment providers to behavior interventions, and we did not have enough research staff to allow for blinded assessments, the intervention was not blinded. Baseline measurements were, however, done before randomization. We argue, that most measurements in our study is objectively measured, therefore limiting the potential biases of a non-blinded assessor design.

Women were included in the study based on the Rotterdam criteria. These criteria are considered to have sufficient specificity and sensitivity to define PCOS. Not all women with PCOS need to undergo ultrasound of the ovaries if the women have both oligomenorrhea and evidence of hyperandrogenism, as polycystic ovaries are not requested to fit the criteria. Clinical and/or biochemical hyperandrogenism is obligatory in the NIH criteria and AE-PCOS task force criteria to define PCOS, but not in The Rotterdam criteria. Further, The NIH criteria require the presence of irregular menstrual cycles, while the other criteria do not. However, The Rotterdam criteria take greater account of the wide range of features PCOS is characterized by, as compared with NIH criterion. It may be that some of the women including in our study, based on the Rotterdam criteria, did not have polycystic ovaries. However, The Rotterdam criteria are currently the recommended and most commonly used definition of PCOS in countries outside the U.S. (9). Further, the Rotterdam criteria is the criteria that diagnoses most PCOS women. This may lead to that women in our study had a milder degree of PCOS, when compared to studies using other criteria to define PCOS. Further, some studies that have used the Rotterdam criteria required that all three diagnostic criteria (hyperandrogenism, irregular menses and polycystic ovaries) were fulfilled (29, 97).

A cluster of symptoms characterizes PCOS, and the participants in our study experienced varying degree of symptoms. The effect of exercise may be more difficult to achieve in women with milder degrees of symptoms. In addition, we included both lean and obese women with PCOS. This makes it difficult to determine the effect of exercise on body composition, as it may differ in lean and obese PCOS women. In the future, it might be informative to group the participants according to varying degrees of symptoms and different phenotypes of PCOS. Due to our small sample size and time concern, we did not have the opportunity to create sub-groups or to include women of only one phenotype (for example only obese or only insulin resistant). In addition, intra-individual variability in weight change is commonly observed after isolated exercise interventions, not including dietary advice or intervention (52).

We did not exclude regular use of oral contraceptive pills (OCP) before, during and after the intervention period, and the variation in use and type of OCP might have influence results on the effect of body composition changes by making these participants more or less susceptible to the adaption to exercise. In addition, ethnic variations are seen in association to PCOS (6). This was not determinated at inclusion, but the majority of participants were of Norwegian ethnicity. However, this must be accounted for when generalizing to other PCOS populations.

Another limitation in our study is that not all the training session were supervised, and we could not control the quality of all the sessions. However, the training sessions for the HIT were recorded with a heart rate monitor and registered through online training diary, and the ST group had to monitor their training sessions in a diary. In the 4x4 minutes intervals and 10x1 minute intervals, 8.9 minutes (19.8%) and 5.15 minutes (14.3%) of the total exercise session (including warm-up and cool down) was >90% of HR_{max}, respectively. This may indicate that the participants on average have reached >90% of HR_{max} in the last half of all intervals, indicating that they have completed interval sessions properly, considering that it takes time to reach the correct intensity in each interval. The ST sessions were conducted at a local fitness center with good accesses to equipment, and the HIT group could alternate between jogging and cycling to avoid strain injury.

The intervention period was short with a large training load. However, such a short intervention period seems to be sufficient to achieve significant difference in body composition changes in these women (29, 35, 36, 75). The short intervention period was due to time concern, and compliance to exercise with a large training load. However, compared to previous studies on exercise in PCOS, and in terms of compliance to exercise interventions, most studies had an intervention period between 10 and 24 weeks (29, 51, 75). However, longer intervention studies may be needed to find a potentially greater effect in body composition changes in these women. Further, we did not follow up the participants beyond the 10 weeks of intervention. A follow-up period to observe the effect of detraining would be of interest.

We used HIT, in contrast to most previous studies using moderate-intensity exercise. HIT has shown to have higher impact on body composition, especially on FM (57), FFM (66) and VF (55) under isocaloric conditions. Participants in our study were previous sedentary, and it may be that the high amount of vigorous exercise lead to an excessive training loads in relation to training status. On the other hand, it is important to notice that the compliance in our study was 90% and

87% in the HIT and ST group, respectively. This indicates good compliance to the exercise interventions, with small dropouts, and therefore that such programs can be well tolerated also in unfit subjects. It must also be considered whether this amount of exercise is feasible and realistic over time for women with PCOS who are not participating in an exercise study with close follow-up. In addition, an adaption period with gradual increase in intensity and resistance may be considered in the future to allow time for adequate cardiovascular and musculoskeletal adaption, and to achieve even greater compliance and quality of the exercise interventions.

The HIT group performed to types of intervals (4x4 and 10x1 minute intervals), which makes it difficult to distinguish between the two interval types. The 4x4 minutes interval has been found to positively affect fasting glucose levels, insulin sensitivity, fitness and fat metabolism in subjects with metabolic syndrome (63). Further, 10x1 minute interval has been found to improve glucose control and induce adaptions in skeletal muscle in DM2 patients, which is further linked to improved metabolic health (69). However, we are not able to say which interval was the most effective in improving body composition change in these women. In our study, we choose a combination of these to interval types because it is found to have good effect on insulin sensitivity, the main outcome of the whole study, and to add variety and reduce time consumption. In addition, both interval programs seems to have good compliance, and are time-efficient. However, in future studies, it may be preferable to distinguish between the two intervals to investigate the potential different effects on outcome measures.

We used a bioelectrical impedance scale, InBody720 (BIA), in addition to body weight and WC, to measure body composition. Although computer tomography (CT) and magnetic resonance imaging (MRI) is considered the most accurate method for assessing body composition and to examine fat distribution, and these are the "gold standard" methods to measure both VF and subcutaneous fat, these methods are expensive and not easily available. Dual energy X-ray absorptiometry (DEXA) is a more common form of measurement. However, this method is also expensive. Further, it has been shown that BIA measurements correlates well with DEXA (98). Although the BIA method is indirect, it is highly reliability, inexpensive, simple to operate and useful for determination of body composition and changes in body composition over time (geometrical assumption of the method is probably consistent within the same subject) (99).

BMI is the most common used method to measure body size and composition, and to diagnose overweight and underweight (100). However, WC has been suggested to be a better measure for abdominal obesity, and is superior to BMI in predicting risk factors like CVD and DM2 (100). WC is a major clinical parameter used for the indirect evaluation of increased VF. Nevertheless, WC alone does not help in distinguishing between subcutaneous fat and VF mass. This is a considerable drawback, given that VF and not subcutaneous fat plays a decisive role in the genesis of cardiovascular functions (42). However, WC is closely correlated with abdominal VF tissue accumulation and related CVD risk factors, and metabolic variables (100, 101). To summarize, the combination of WC and BMI is shown to be appropriate for determinate health risk (100).

A limitation in our study is that the energy expenditure between HIT and ST was not controlled for (not isocaloric), and it is most likely different in the two exercise groups. HIT can induce a greater acute energy expenditure, but increase in FFM in the ST group can result in increased post-training energy expenditure (72). We did not have the opportunity to control for isocaloric conditions in our study, and therefore, we do not know whether the energy deficit was different in the two exercise groups.

Diet was not controlled for during the study intervention. It would have strengthened our study if we had registered diet changes throughout the intervention period. Participants were asked to continue their regular diet pattern, but we did not registered whether some of the participants began a "healthier diet" or eat more calories as a result of the exercise performed. Food intake after exercise does not seem to lead to compensating for energy expended as a result of exercise performed (102). However, physical activity often results in disappointing effects, mainly because of inappropriate food choices and a desire for self-reward after exercise (102). Further, a misjudgment to which extent energy can be expended by exercise, or taken in by eating is observed (102). However, studies on exercise-induced suppression of appetite are conflicting in results, and a combination of physiological and psychological factors seems to influence the results (102, 103). A mapping of lifestyle changes in terms of increased or decreased energy intake and activity levels may be important in future research.

5.4 Conclusions

Structured exercise programs can be a helpful therapeutic strategy for management and treatment of PCOS. Our findings strengthens the recommendation that exercise should be included in treatment and management of PCOS.

In conclusion, our results suggest that women with PCOS can have some beneficial effects on body composition after both HIT and ST, even when body weight remains unchanged. Percentage FM decreased significantly after both HIT and ST, and FFM increased significantly after ST. However, we found no significant differences between groups. Although our results are unable to claim that one treatment was superior to another, the results from our study provide some information to suggest that lifestyle strategies, in the form of HIT or ST, may provide beneficial effects on body composition in women with PCOS. Further, the effect of exercise interventions in women with PCOS should not be judge solely on weight loss, as exercise can improve body composition without significantly altering body weight. These findings may have clinical relevance, as women with PCOS who exercise without losing weight, can be encouraged that they still are achieving health benefits.

5.5 Further Research

Studies on the effects of exercise as the only intervention on body composition in women with PCOS are limited. Further research and larger clinical studies are needed to confirm our findings, and to find the necessary dose, type, duration, intensity and frequency of exercise, and the health benefits of exercise, that can provide the greatest benefits for these women. Focus on lifestyle interventions over a longer time period, and with a larger sample size than in the present study should be emphasized to evaluate whether these findings may translate into long-term improvement in body composition. More studies are needed on the effect of HIT and ST on different health parameters in these women. Few studies have investigated the effect of exercise on lean PCOS women, and whether the beneficial effects of existing exercise intervention is due to degree of obesity or the syndrome itself remains unclear. Whether favorable changes in body composition, in absence of weight loss, can reduce the health risk associated with the syndrome should be

investigated further in this population. In addition, further research on the pathophysiology and causes of PCOS is needed to fully understand the syndrome and find proper treatment strategies.

REFERENCES

1. Rudenski AS, Matthews DR, Levy JC, Turner RC. Understanding "insulin resistance": both glucose resistance and insulin resistance are required to model human diabetes. Metabolism. 1991;40(9):908-17.
2. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. J Clin Endocrinol Metab. 1961;21:1440-7.
3. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. The Cochrane database of systematic reviews. 2011(7):CD007506.
4. McGowan MP. Polycystic ovary syndrome: A common endocrine disorder and risk factor for vascular disease. Curr Treat Options Cardiovasc Med. 2011;13(4):289-301.
5. Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarali H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. Hum Reprod. 2012;27(10):3067-73.
6. Jean Hailes Fundation for Women`s Health on behaf of the PCOS Australian Alliance M. Evidence-based guideline for the assessment and management of polycystic ovary syndrome. 2011.
7. Stein IF LM. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol. 1935;29:181 - 91
8. Garad R, Teede H, Moran L. An evidence-based guideline for Polycystic Ovary Syndrome. Aust Nurs J. 2011;19(4):30-3.
9. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2013.
10. Sherif K. Polycystic ovary syndrome. Women's health in clinical practice: A handbook for primary care. Totowa, NJ: Humana Press; US; 2008. p. 183-98.
11. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med. 2010;8:41.
12. Hudecova M, Holte J, Olovsson M, Larsson A, Berne C, Sundstrom-Poromaa I. Prevalence of the metabolic syndrome in women with a previous diagnosis of polycystic ovary syndrome: long-term follow-up. Fertil Steril. 2011;96(5):1271-4.
13. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2010;16(4):347-63.
14. Moran LJ, Lombard CB, Lim S, Noakes M, Teede HJ. Polycystic ovary syndrome and weight management. Women's health (London, England). 2010;6(2):271-83.
15. Deeks AA, Gibson-Helm ME, Paul E, Teede HJ. Is having polycystic ovary syndrome a predictor of poor psychological function including anxiety and depression? Hum Reprod. 2011;26(6):1399-407.
16. Deeks AA, Gibson-Helm ME, Teede HJ. Anxiety and depression in polycystic ovary syndrome: a comprehensive investigation. Fertil Steril. 2010;93(7):2421-3.
17. Giallauria F, Palomba S, Vigorito C, Tafuri MG, Colao A, Lombardi G, et al. Androgens in polycystic ovary syndrome: the role of exercise and diet. Semin Reprod Med. 2009;27(4):306-15.
18. Chen M, Andrew R. Obesity and Other Diseases. In: Williams G, Fruhbeck G, editors. Obesity Science to Practice. UK: John Wiley & Sons; 2009. p. 328-32.
19. Svendsen PF, Nilas L, Norgaard K, Jensen JE, Madsbad S. Obesity, body composition and metabolic disturbances in polycystic ovary syndrome. Hum Reprod. 2008;23(9):2113-21.
20. Marshall K. Polycystic ovary syndrome: clinical considerations. Altern Med Rev. 2001;6(3):272-92.

21. Carmina E, Ditkoff EC, Malizia G, Vijod AG, Janni A, Lobo RA. Increased circulating levels of immunoreactive beta-endorphin in polycystic ovary syndrome is not caused by increased pituitary secretion. Am J Obstet Gynecol. 1992;167(6):1819-24.
22. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab. 2006;91(11):4237-45.
23. Farrell K, Antoni MH. Insulin resistance, obesity, inflammation, and depression in polycystic ovary syndrome: biobehavioral mechanisms and interventions. Fertil Steril. 2010;94(5):1565-74.
24. Whitaker KN. Polycystic ovary syndrome: an overview. J Pharm Pract. 2011;24(1):94-101.
25. Casadei L, Madrigale A, Puca F, Manicuti C, Emidi E, Piccione E, et al. The role of serum anti-Mullerian hormone (AMH) in the hormonal diagnosis of polycystic ovary syndrome. Gynecol Endocrinol. 2013;29(6):545-50.
26. Smith JW, Taylor JS. Polycystic Ovary Syndrome: Evidence-based Strategies for Managing Symptoms and Preventing Long-Term Sequelae. Nurs Womens Health. 2011;15(5):402-11.
27. Wild RA. Obesity, lipids, cardiovascular risk, and androgen excess. Am J Med. 1995;98(1a):27s-32s.
28. Ahmadi A, Akbarzadeh M, Mohammadi F, Akbari M, Jafari B, Tolide-Ie HR. Anthropometric characteristics and dietary pattern of women with polycystic ovary syndrome. Indian J Endocrinol Metab. 2013;17(4):672-6.
29. Bruner B, Chad K, Chizen D. Effects of exercise and nutritional counseling in women with polycystic ovary syndrome. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme. 2006;31(4):384-91.
30. Zawadzki JK, Dunaif A. Diagsnostic criteria for polysystic ovary syndrome; Toward a rationale approach. In: Dunaif A, Givens JR, Hasseltine FP, Merrian GR, editors. Polycystic ovary syndrome. Boston: Blackwell Sientific Publications; 1992. p. 377 - 84.
31. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19(1):41-7.
32. Humphreys L, Costarelli V. Implementation of dietary and general lifestyle advice among women with polycystic ovarian syndrome. Journal of the Royal Society for the Promotion of Health. 2008;128(4):190-5.
33. Hoeger K, Davidson K, Kochman L, Cherry T, Kopin L, Guzick DS. The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials. The Journal of clinical endocrinology and metabolism [Internet]. 2008; 93(11):[4299-306 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/936/CN-00666936/frame.html

http://jcem.endojournals.org/content/93/11/4299.full.pdf.
34. Randeva HS, Tan BK, Weickert MO, Lois K, Nestler JE, Sattar N, et al. Cardiometabolic aspects of the polycystic ovary syndrome. Endocr Rev. 2012;33(5):812-41.
35. Harrison CL, Lombard CB, Moran LJ, Teede HJ. Exercise therapy in polycystic ovary syndrome: a systematic review. Hum Reprod Update. 2011;17(2):171-83.
36. Thomson RL, Buckley JD, Brinkworth GD. Exercise for the treatment and management of overweight women with polycystic ovary syndrome: a review of the literature. Obes Rev. 2011;12(5):e202-10.
37. Costello MF, Ledger WL. Evidence-based lifestyle and pharmacological management of infertility in women with polycystic ovary syndrome. Women's health (London, England). 2012;8(3):277-90.
38. Organization WH. Obesity and overweight 2013.

39. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res. 1998;6 Suppl 2:51s-209s.
40. Lim SS, Norman RJ, Davies MJ, Moran LJ. The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis. Obes Rev. 2013;14(2):95-109.
41. Escobar-Morreale HF, San Millan JL. Abdominal adiposity and the polycystic ovary syndrome. Trends Endocrinol Metab. 2007;18(7):266-72.
42. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, et al. Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care. 2010;33(4):920-2.
43. Rich-Edwards JW, Goldman MB, Willett WC, Hunter DJ, Stampfer MJ, Colditz GA, et al. Adolescent body mass index and infertility caused by ovulatory disorder. Am J Obstet Gynecol. 1994;171(1):171-7.
44. Karabulut A, Yaylali GF, Demirlenk S, Sevket O, Acun A. Evaluation of body fat distribution in PCOS and its association with carotid atherosclerosis and insulin resistance. Gynecol Endocrinol. 2012;28(2):111-4.
45. Battaglia C, Battaglia B, Mancini F, Paradisi R, Fabbri R, Venturoli S. Ultrasonographic extended-view technique for evaluation of abdominal fat distribution in lean women with polycystic ovary syndrome. Acta Obstet Gynecol Scand. 2011;90(6):600-8.
46. Cascella T, Palomba S, De Sio I, Manguso F, Giallauria F, De Simone B, et al. Visceral fat is associated with cardiovascular risk in women with polycystic ovary syndrome. Hum Reprod. 2008;23(1):153-9.
47. Kirchengast S, Huber J. Body composition characteristics and body fat distribution in lean women with polycystic ovary syndrome. Hum Reprod. 2001;16(6):1255-60.
48. Douchi T, Ijuin H, Nakamura S, Oki T, Yamamoto S, Nagata Y. Body fat distribution in women with polycystic ovary syndrome. Obstet Gynecol. 1995;86(4 Pt 1):516-9.
49. Borruel S, Fernandez-Duran E, Alpanes M, Marti D, Alvarez-Blasco F, Luque-Ramirez M, et al. Global adiposity and thickness of intraperitoneal and mesenteric adipose tissue depots are increased in women with polycystic ovary syndrome (PCOS). J Clin Endocrinol Metab. 2013;98(3):1254-63.
50. Hutchison SK, Stepto NK, Harrison CL, Moran LJ, Strauss BJ, Teede HJ. Effects of exercise on insulin resistance and body composition in overweight and obese women with and without polycystic ovary syndrome. J Clin Endocrinol Metab. 2011;96(1):E48-E56.
51. Palomba S, Giallauria F, Falbo A, Russo T, Oppedisano R, Tolino A, et al. Structured exercise training programme versus hypocaloric hyperproteic diet in obese polycystic ovary syndrome patients with anovulatory infertility: a 24-week pilot study. Hum Reprod. 2008;23(3):642-50.
52. Redman LM, Elkind-Hirsch K, Ravussin E. Aerobic exercise in women with polycystic ovary syndrome improves ovarian morphology independent of changes in body composition. Fertil Steril. 2011;95(8):2696-9.
53. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43(7):1334-59.
54. Penedo FJ, Dahn JR. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. Current opinion in psychiatry. 2005;18(2):189-93.
55. Irving BA, Davis CK, Brock DW, Weltman JY, Swift D, Barrett EJ, et al. Effect of exercise training intensity on abdominal visceral fat and body composition. Med Sci Sports Exerc. 2008;40(11):1863-72.
56. Slentz CA, Aiken LB, Houmard JA, Bales CW, Johnson JL, Tanner CJ, et al. Inactivity, exercise, and visceral fat. STRRIDE: a randomized, controlled study of exercise intensity and amount. Journal of applied physiology (Bethesda, Md : 1985). 2005;99(4):1613-8.

57. Slentz CA, Duscha BD, Johnson JL, Ketchum K, Aiken LB, Samsa GP, et al. Effects of the amount of exercise on body weight, body composition, and measures of central obesity: STRRIDE--a randomized controlled study. Arch Intern Med. 2004;164(1):31-9.
58. Stensvold D, Tjonna AE, Skaug EA, Aspenes S, Stolen T, Wisloff U, et al. Strength training versus aerobic interval training to modify risk factors of metabolic syndrome. J Appl Physiol. 2010;108(4):804-10.
59. Thomson RL, Buckley JD, Noakes M, Clifton PM, Norman RJ, Brinkworth GD. The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2008;93(9):3373-80.
60. Williams MA, Haskell WL, Ades PA, Amsterdam EA, Bittner V, Franklin BA, et al. Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2007;116(5):572-84.
61. Willis LH, Slentz CA, Bateman LA, Shields AT, Piner LW, Bales CW, et al. Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults. Journal of applied physiology (Bethesda, Md : 1985). 2012;113(12):1831-7.
62. Carroll S, Dudfield M. What is the relationship between exercise and metabolic abnormalities? A review of the metabolic syndrome. Sports Med. 2004;34(6):371-418.
63. Tjonna AE, Lee SJ, Rognmo O, Stolen TO, Bye A, Haram PM, et al. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. Circulation. 2008;118(4):346-54.
64. Johnson JL, Slentz CA, Houmard JA, Samsa GP, Duscha BD, Aiken LB, et al. Exercise training amount and intensity effects on metabolic syndrome (from Studies of a Targeted Risk Reduction Intervention through Defined Exercise). Am J Cardiol. 2007;100(12):1759-66.
65. Chicco AJ. Exercise training in prevention and rehabilitation: which training mode is best? Minerva Cardioangiol. 2008;56(5):557-70.
66. Vissers D, Hens W, Taeymans J, Baeyens JP, Poortmans J, Van Gaal L. The effect of exercise on visceral adipose tissue in overweight adults: a systematic review and meta-analysis. PLoS One. 2013;8(2):e56415.
67. Pritzlaff CJ, Wideman L, Blumer J, Jensen M, Abbott RD, Gaesser GA, et al. Catecholamine release, growth hormone secretion, and energy expenditure during exercise vs. recovery in men. Journal of applied physiology (Bethesda, Md : 1985). 2000;89(3):937-46.
68. Imbeault P, Saint-Pierre S, Almeras N, Tremblay A. Acute effects of exercise on energy intake and feeding behaviour. Br J Nutr. 1997;77(4):511-21.
69. Little JP, Gillen JB, Percival ME, Safdar A, Tarnopolsky MA, Punthakee Z, et al. Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes. Journal of applied physiology (Bethesda, Md : 1985). 2011;111(6):1554-60.
70. Alberga AS, Sigal RJ, Kenny GP. A review of resistance exercise training in obese adolescents. The Physician and sportsmedicine. 2011;39(2):50-63.
71. Schmitz KH, Hannan PJ, Stovitz SD, Bryan CJ, Warren M, Jensen MD. Strength training and adiposity in premenopausal women: strong, healthy, and empowered study. Am J Clin Nutr. 2007;86(3):566-72.
72. Tonkonogi M, Sahlin K. Physical exercise and mitochondrial function in human skeletal muscle. Exerc Sport Sci Rev. 2002;30(3):129-37.
73. Botero JP, Shiguemoto GE, Prestes J, Marin CT, Do Prado WL, Pontes CS, et al. Effects of long-term periodized resistance training on body composition, leptin, resistin and muscle strength in elderly post-menopausal women. J Sports Med Phys Fitness. 2013;53(3):289-94.

74. Figueroa A, Vicil F, Sanchez-Gonzalez MA, Wong A, Ormsbee MJ, Hooshmand S, et al. Effects of diet and/or low-intensity resistance exercise training on arterial stiffness, adiposity, and lean mass in obese postmenopausal women. Am J Hypertens. 2013;26(3):416-23.
75. Vigorito C, Giallauria F, Palomba S, Cascella T, Manguso F, Lucci R, et al. Beneficial effects of a three-month structured exercise training program on cardiopulmonary functional capacity in young women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2007;92(4):1379-84.
76. Roessler KK, Birkebaek C, Ravn P, Andersen MS, Glintborg D. Effects of exercise and group counselling on body composition and VO2max in overweight women with polycystic ovary syndrome. Acta Obstet Gynecol Scand. 2013;92(3):272-7.
77. Alexander CJ, Tangchitnob EP, Lepor NE. Polycystic ovary syndrome: a major unrecognized cardiovascular risk factor in women. Rev Obstet Gynecol. 2009;2(4):232-9.
78. Thomson RL, Brinkworth GD, Noakes M, Clifton PM, Norman RJ, Buckley JD. The effect of diet and exercise on markers of endothelial function in overweight and obese women with polycystic ovary syndrome. Hum Reprod. 2012;27(7):2169-76.
79. Teede HJ, Hutchison S, Zoungas S, Meyer C. Insulin resistance, the metabolic syndrome, diabetes, and cardiovascular disease risk in women with PCOS. Endocrine. 2006;30(1):45-53.
80. Teede HJ, Hutchison SK, Zoungas S. The management of insulin resistance in polycystic ovary syndrome. Trends Endocrinol Metab. 2007;18(7):273-9.
81. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes. 1989;38(9):1165-74.
82. Hutchison SK, Stepto NK, Harrison CL, Moran LJ, Strauss BJ, Teede HJ. Effects of exercise on insulin resistance and body composition in overweight and obese women with and without polycystic ovary syndrome. J Clin Endocrinol Metab. 2011;96(1):E48-56.
83. Kiddy DS, Sharp PS, White DM, Scanlon MF, Mason HD, Bray CS, et al. Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovary syndrome: an analysis of 263 consecutive cases. Clin Endocrinol (Oxf). 1990;32(2):213-20.
84. Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. Fertil Steril. 2009;92(6):1966-82.
85. Hoeger KM. Exercise therapy in polycystic ovary syndrome. Semin Reprod Med. 2008;26(1):93-100.
86. Giallauria F, Palomba S, Maresca L, Vuolo L, Tafuri D, Lombardi G, et al. Exercise training improves autonomic function and inflammatory pattern in women with polycystic ovary syndrome (PCOS). Clin Endocrinol (Oxf). 2008;69(5):792-8.
87. Tremblay A, Doucet E, Imbeault P. Physical activity and weight maintenance. Int J Obes Relat Metab Disord. 1999;23 Suppl 3:S50-4.
88. Stiegler P, Cunliffe A. The role of diet and exercise for the maintenance of fat-free mass and resting metabolic rate during weight loss. Sports Med. 2006;36(3):239-62.
89. Stepto NK, Cassar S, Joham AE, K. HS, Harrison CL, Goldstein RF, et al. Women with polycystic ovary syndrome have instrinsic insulin resistance on euglycaemic - hyperinsulaemic clamp. Human reproduction (Oxford, England). 2013;28(3):777-84.
90. Helsedirektoratet. Norske anbefalinger for ernæring og fysisk aktivitet. 2005(IS-1219).
91. Bioelectrical impedance analysis in body composition measurement: National Institutes of Health Technology Assessment Conference Statement. Am J Clin Nutr. 1996;64(3 Suppl):524s-32s.
92. Primeau V, Coderre L, Karelis AD, Brochu M, Lavoie ME, Messier V, et al. Characterizing the profile of obese patients who are metabolically healthy. Int J Obes (Lond). 2011;35(7):971-81.
93. Organization WH. Waist circumference and waist-hip ratio. Report of a WHO expert consultation. 2008.

94. Earnest CP, Lupo M, Thibodaux J, Hollier C, Butitta B, Lejeune E, et al. Interval Training in Men at Risk for Insulin Resistance. Int J Sports Med. 2012.
95. Gardner MJ, Altman DG. Confidence intervals rather than P values: estimation rather than hypothesis testing. Br Med J (Clin Res Ed). 1986;292(6522):746-50.
96. Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. BMJ. 2001;323(7321):1123-4.
97. Liao LM, Nesic J, Chadwick PM, Brooke-Wavell K, Prelevic GM. Exercise and body image distress in overweight and obese women with polycystic ovary syndrome: a pilot investigation. Gynecol Endocrinol. 2008;24(10):555-61.
98. Pateyjohns IR, Brinkworth GD, Buckley JD, Noakes M, Clifton PM. Comparison of three bioelectrical impedance methods with DXA in overweight and obese men. Obesity (Silver Spring, Md). 2006;14(11):2064-70.
99. Jebb SA, Siervo M, Murgatroyd PR, Evans S, Fruhbeck G, Prentice AM. Validity of the leg-to-leg bioimpedance to estimate changes in body fat during weight loss and regain in overweight women: a comparison with multi-compartment models. Int J Obes (Lond). 2007;31(5):756-62.
100. Organization WH. Waist circumference and waist-hip ratio. Geneva, Switzerland: 2008.
101. Pouliot MC, Despres JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol. 1994;73(7):460-8.
102. Blundell JE, King NA. Effects of exercise on appetite control: loose coupling between energy expenditure and energy intake. Int J Obes Relat Metab Disord. 1998;22 Suppl 2:S22-9.
103. Donnelly JE, Herrmann SD, Lambourne K, Szabo AN, Honas JJ, Washburn RA. Does increased exercise or physical activity alter ad-libitum daily energy intake or macronutrient composition in healthy adults? A systematic review. PLoS One. 2014;9(1):e83498.

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK midt	Øystein Lundestad	73597507	14.06.2013	2013/886/REK midt
			Deres dato:	Deres referanse:
			23.04.2013	

Vår referanse må oppgis ved alle henvendelser

Trine Moholdt
Institutt for sirkulasjon og bildediagnostikk

2013/886 Trening ved polysystisk ovariesyndrom

Forskningsansvarlig: NTNU
Prosjektleder: Trine Moholdt

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK midt) i møtet 24.05.2013. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikklovens § 4.

Prosjektomtale
Prosjektet skal undersøke effekten av ulik type trening på kvinner med polysystisk ovariesyndrom (PCOS). Livsstilsendring, inkludert fysisk trening, er ansett som første behandlingsalternativ. Det er usikkert hvilken type trening som gir best effekt på insulinsensitvitet, kroppssammensetning og reproduksjons-variabler (hormoner, eggløsning) hos disse kvinnene. Formålet med studien er å se om 10 ukers trening vil bedre insulinsensitivitet, kroppssammensetning, reproduksjonshormoner og eggløsning, samt kardiovaskulære variabler hos 30 kvinner med PCOS. Måling av vekt, høyde, kroppssammensetning, max. oksygenopptak og styrke, blodprøver og -trykk. Prosjektet skal munne ut i to masteroppgaver, og vitenskapelig, internasjonal artikkel. Det ønskes også å samle inn blodprøver for mulige senere undersøkelser (ikke nærmere spesifiserte).

Vurdering

Forsvarlighet
Komiteen har vurdert søknad, forskningsprotokoll, målsetting og plan for gjennomføring. Prosjektet framstår som forsvarlig, og hensynet til deltakernes velferd og integritet er ivaretatt.

Spesifikk forskningsbiobank
Det søkes om opprettelse av den spesifikke forskningsbiobank "PCOS Exercise". Forskningsbiobanken framstår som forsvarlig, og hensynet til deltakernes velferd og integritet er ivaretatt. Trine Moholdt er ansvarshavende person for biobanken.

Vilkår for godkjenning

1. Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, og etter de bestemmelser som følger av helseforskningsloven med forskrifter.
2. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter

innenfor helse- og omsorgssektoren». Prosjektdata skal oppbevares i minimum 5 år etter prosjektslutt.

3. Komiteen ber prosjektet knytte seg til en medarbeider med klinisk kompetanse innenfor enten gynekologi eller endokrinologi for å styrke den medisinskfaglige kompetansen knyttet til PCOS. Denne medarbeideren må være med i vurderinga av hvilke pasienter som er egnet for inklusjon i studien. Komiteen minner om at det finnes et veletablert klinisk fagmiljø innen PCOS ved St. Olavs Hospital.
4. I informasjonsskrivets kapittel B legges det opp til lagring og videre benyttelse av materialet (jfr. avsnitt "Biobank") samt utlevering av dette (jfr. avsnitt "Utlevering av materiale og opplysninger til andre"). Dette står i et visst spenningsforhold til følgende påstander i den generelle delen: "Prøvene tatt av deg og informasjonen som registreres skal kun brukes slik som beskrevet i hensikten med studien" samt: "Informasjonen slettes ved prosjektavslutning." Komiteen ber om at nevnte momenter i kapittel B reflekteres bedre i skrivets generelle del.
5. Komiteen ber om at REK midts navn korrigeres i avsnittet "Etisk og faglig vurdering" i skrivets kapittel B.
6. Komiteen forutsetter at det sendes inn separate søknader dersom innsamlet biologisk materiale skal benyttes i andre studier enn den anførte hovedstudien.
7. Materiale i forskningsbiobanker skal oppbevares og behandles forsvarlig. Oppbevaring og behandling skal skje med respekt for giveren av materialet, jfr. helseforskningslovens § 27. Dersom biobanken opphører, nedlegges eller overtas av andre, skal det søkes REK om tillatelse, jfr. hfl. § 30.

Vedtak
Regional komité for medisinsk og helsefaglig forskningsetikk Midt-Norge godkjenner prosjektet med de vilkår som er gitt. Regional komité for medisinsk og helsefaglig forskningsetikk Midt-Norge godkjenner opprettelsen av den spesifikke biobanken med de vilkår som er gitt.

Øvrige merknader

Regional forskningsbiobank Midt-Norge
Komiteen minner om at det eksisterer en regional forskningsbiobank. Regional forskningsbiobank Midt-Norge tilbyr lagring av helseopplysninger og biologisk materiale fra sykehuspasienter i helseregion Midt-Norge, til bruk i forskning.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK midt på eget skjema senest 01.10.2015, jf. hfl. 12. Prosjektleder skal sende søknad om prosjektendring til REK midt dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK midt. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK midt, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Sven Erik Gisvold
Dr.med.
Leder, REK midt

Øystein Lundestad
Rådgiver

Kopi til: rek-isb@medisin.ntnu.no; rek-midt@medisin.ntnu.no; biobankregisteret@fhi.no

Appendix A

Forespørsel om deltakelse i forskningsprosjektet

Utholdenhetstrening eller styrketrening ved polycystisk ovariesyndrom (PCOS)

Bakgrunn og hensikt:
Dette er et spørsmål til deg om å delta i en studie som undersøker effekt av utholdenhetstrening og styrketrening i forhold til blodsukkerregulering, fysisk form, blodårefunksjon, kroppssammensetning og mål på fertilitet hos kvinner med PCOS.

Hva innebærer studien?
Deltakerne vil trekkes tilfeldig til en av tre grupper. Det er to treningsgrupper, ei som trener styrke og ei som trener utholdenhet, samt ei kontrollgruppe. Treningsperioden er på 10 uker og alle deltakerne, både i treningsgrupper og kontrollgruppe, skal gjennom en del tester før og etter treningsperioden. Testene omfatter måling av kroppsvekt, BMI, kroppssammensetning, midjemål, maksimalt oksygenopptak, blodtrykk, blodårefunksjon og blodprøver. For nærmere beskrivelse av undersøkelsene og av treningen, se vedlegg A.

Mulige fordeler og ulemper:
Fordelene med å delta i studien, er at vi gjør en del undersøkelser av deg og at du kan få informasjon om resultatet av disse. Vi kjenner ikke til at testingen eller treningen i studien innebærer noen risiko for deg, bortsett fra noe ubehag/stølhet i forbindelse med oppstart av et nytt treningsopplegg. Det vil bli fokusert på anerkjente og anbefalte treningsformer, noe du som deltaker kan dra nytte av. For å kunne delta må du ha anledning til å sette av ca tre timer i uka på trening i perioden studien varer og til å komme på undersøkelsene i forkant av og etter treningsperioden.

Hva skjer med prøvene og informasjonen om deg
Alle opplysninger og prøver vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom navneliste. Dette betyr at opplysningene er avidentifisert. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres. Vi ber om å få oppbevare data i fem år etter prosjektslutt, og at blodprøvene som taes er tilgjengelige for eventuelle senere studier. Disse prøvene vil være avidentifiserte og koblingen til ditt navn vil da være slettet.

Frivillig deltakelse:
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte: Trine Moholdt, forsker ved NTNU: 97098594, trine.moholdt@ntnu.no

Ytterligere informasjon om studien finnes i kapittel *A – utdypende forklaring av hva studien innebærer.*
Ytterligere informasjon om biobank, personvern og forsikring finnes i kapittel B *– Personvern, biobank, økonomi og forsikring.*
Samtykkeerklæring følger etter kapittel B.

Appendix B

Kapittel B - Personvern, biobank, økonomi og forsikring

Personvern
Opplysninger som registreres om deg er kroppsvekt, BMI, kroppssammensetning, midjemål, maksimalt oksygenopptak, maksimal styrke i bein og bryst, blodårefunksjon, blodtrykk og resultat av blodprøver. Alle som får innsyn i opplysningene om deg har taushetsplikt. NTNU ved administrerende direktør er databehandlingsansvarlig.

Biobank
Blodprøvene som blir tatt vil bli lagret i en forskningsbiobank ved NTNU. Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Forsker Trine Moholdt er ansvarshavende for forskningsbiobanken. Det biologiske materialet kan bare brukes etter godkjenning fra Regional komité for medisinsk og helsefaglig forskningsetikk (REK).

Utlevering av materiale og opplysninger til andre
Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at prøver og avidentifiserte opplysninger utleveres til forskere ved samarbeidende institusjoner. Dette kan være land med lover som ikke tilfredsstiller europeisk personvernlovgivning.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi
Du må ikke betale for prøver som blir gjort på sykehuset i forbindelse med studien. De som trekkes til treningsgruppa vil få trene ved 3T treningssenter og ved St.Olavs hospital gratis i studieperioden. Du må imidlertid betale selv kostnader for transport og parkering i forbindelse med trening og testing. De som kommer i kontrollgruppa vil få et treningskort ved 3T treningssenter i etterkant av studien. Prosjektansvarlige mottar ingen spesiell finansiering til denne studien.

Frivillighet og samtykke
Deltakelse i prosjektet er frivillig. Alle deltakerne i prosjektet har rett til å trekke seg fra prosjektet når de måtte ønske, uten at dette får konsekvenser for videre oppfølging og behandling. All informasjon deltakerne gir i forbindelse med prosjektet, behandles konfidensielt. Deltakerne er dekket av Pasientskadeerstatningsordningen.

Etisk og faglig vurdering
Prosjektet er vurdert av Regional komite for medisinsk forskningsetikk, Region Midt-Norge, og komiteen har godkjent at prosjektet gjennomføres.

Ansvarlige prosjektleder er Trine Moholdt, forsker ved Det Medisinske Fakultet. Gynekolog Tone Løvvik er medarbeider i prosjektet.

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Appendix B

Time schedule from recruitment to submission of the master thesis

2013/2014	Mai	Jun.	July	Aug.	Sept.	Oct.	Nov.	Des.	Jan.	Feb.	Mars	Apr.	Mai
Protocol REK													
Recruitment													
Baseline													
Intervention													
Data, baseline													
Post-testing													
Method													
Background													
Introduction													
Data, post													
Analysis													
Results													
Discussion													
Submission													

= Intervention period. = Master thesis (analyze and writing).

Appendix C

Budget

Equipment	Price per unit	Number	Total
Polar RCX3 heart monitor	1100,-	10	11 000,-
Posters, printing expenses	6,- (A3)	100	600,-
			SUM: 11 600,-

Other expense in the study not related to this thesis are not taking into account in this budget.

Appendix D

Informasjon om testing

Takk for at du har sagt ja til å være med i studien! Det er en del tester som skal gjøres i starten og mot slutten av studien, og det er viktig at du leser gjennom informasjonen nedenfor. Bare ta kontakt hvis du har spørsmål om testinga!

Totalt tidsforbruk ca. 4 timer

Du må møte FASTENDE. Det vil si at du skal ikke ha spist eller drukket (litt vann er OK) siden kl 22.00 kvelden før. Du må heller ikke røyke eller bruke snus i dette tidsrommet. Siden fysisk aktivitet påvirker noen av målingene vi skal gjøre, må du ikke trene eller være i hard fysisk aktivitet de siste to dagene før testinga. Det er svært viktig at du er fastende, da dette påvirker prøvene i stor grad. Du må ha på eller ha med deg lette klær/treningsklær og gode sko, helst joggesko. Det er mulighet for å dusje her hos oss.

Blodårefunksjon
Vi måler hvor godt blodårene dine reagerer på en avklemming. Du ligger på en benk mens vi ser med ultralyd på en blodåre i overarma. Undersøkelsen tar ca 20 min. Vi måler også blodtrykk.

Undersøkelse av kroppssammensetning (InBody)
Vi vil også se på kroppssammensetningen (det vil si forholdet mellom fett- og muskelmasse) ved hjelp en spesiell vekt som heter InBody. Dette tar noen få minutter og innebærer ingen risiko. Du kan ikke ha pacemaker hvis du skal gjøre denne undersøkelsen, så si fra til oss om du har det.

Blodprøver
Vi tar noen blodprøver av deg. Noen av prøvene blir analysert med en gang og litt blod fryses ned for senere analyse. Du vil kunne få svar på blodprøvene som blir analysert i løpet av noen dager, hvis du ønsker det.

Etter disse testende skal du spise et lett måltid. Så vil du et spørreskjema som du skal fylle ut.

Test av oksygenopptak
Du skal gå på tredemølle med en maske eller munnstykke som måler hvor mye oksygen du klarer å ta opp og forbruke i kroppen. Dette er en test på kondisjon. Du skal holde på så lenge du orker.

Etter testingen blir det denne dagen trukket om du skal være i en av treningsgruppene eller kontrollgruppa.

Appendix E

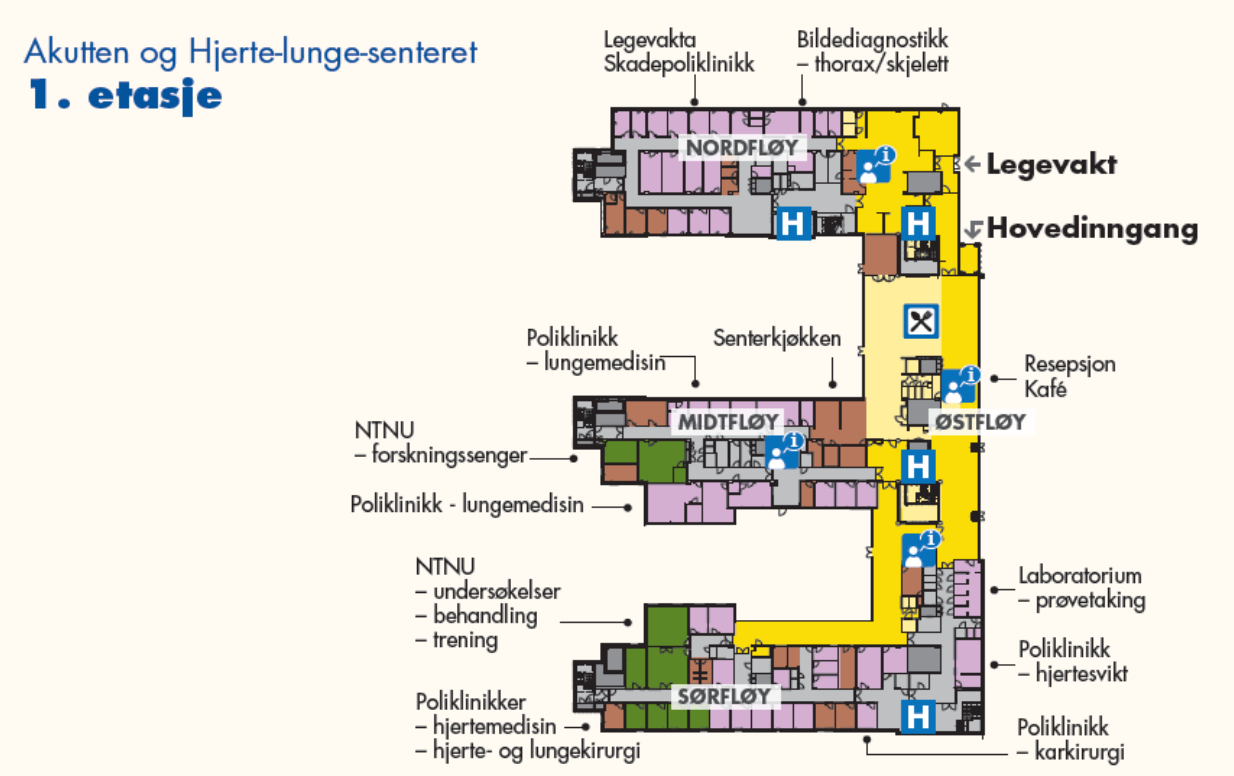
Tider for testing

Dato:

Kl:

Oppmøte: Akutten og hjerte-lunge-senteret, 1.etasje. Bygget ligger mot elva og brua over til Marienborg. Ultralyd av blodårefunksjon i overarmen. Gå inn til hjertepoliklinikken i sørfløya og sitt ned og vent utenfor undersøkelsesrommene til NTNU (Treningsenhet 1). Kontaktperson for denne undersøkelsen er…
Telefon nr du kan ringe om du ikke finner fram:...

HUSK AT DU SKAL VÆRE FASTENDE OG HA MED TRENINGSTØY!



EXPO

Treningsprogram: Høy-intensitets intervall trening

Navn:

Max HF:

Økt 1: 4x4 intervall

Hva	Tid	Intervall	Pause
Oppvarming	10 min 60-70% maxHF		
Hoveddel	45 min	4x4 min 90-95 % maxHF Hastighet:	3 min mellom intervallene < 70 % maxHF (gå)
Avslutning	10 min 50-70% maxHF		

Økt 1 skal gjennomføres 2 x pr. uke.

Økt 2: 10x1min intervall

Hva	Tid	Intervall	Pause
Oppvarming	10 min 60-70% maxHF		
Hoveddel	20 min	10x1 min Maksimal intensitet Hastighet:	1 min mellom intervallene. Rolig (gå)
Avslutning	5 min 50-70% maxHF		

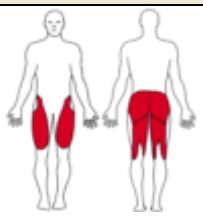
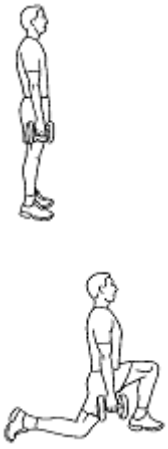
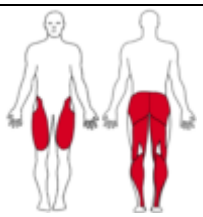
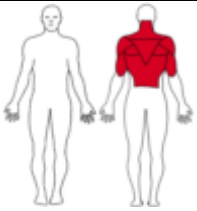
Økt 2 skal gjennomføres 1 x pr. uke.

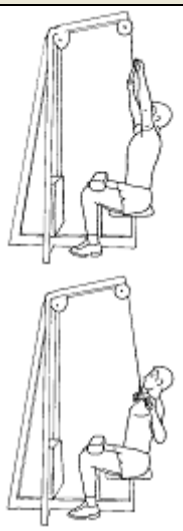
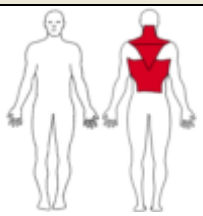
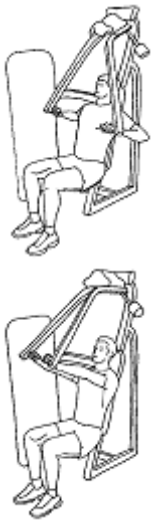
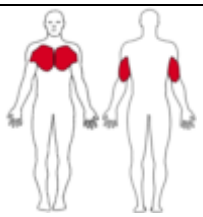
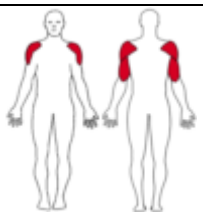
Appendix F

Styrketrening
EXPO

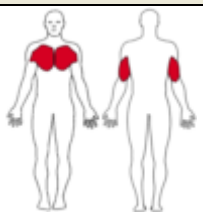
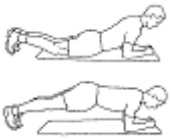
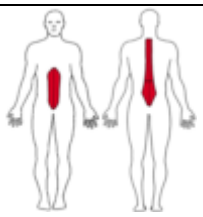
Navn:

Appendix G

Øvelse	Illustrasjon	Treningsfokus	Øvelsesdata	Kommentar
1 Beinpress			3 sets x 10 reps Ryggstøtte: Fotbrett: Kg:	Plasser føttene på fotbrettet med ca. skulderbreddes avstand. Sørg for at vinklen i knærne er 90 grader. Spenn opp i mage- og korsryggsmuskulaturen, og press benene framover. Stopp bevegelsen når benene er nesten strake, slik at du unngår å overstrekke knærne. Senk benene mot deg i et litt langsommere tempo.
2 Utfall			3 sets x 10 reps Kg:	Ha kneet på fremste fot rett over tå i 90 graders vinkel. Legg press på fremste fot under øvelsen. La armene henge rett ned langs siden.
3 Stående foroverbøyd roing			3 sets x 10 reps Kg:	Se rett frem. Ha en lett bøy i kne og hofte, og hold ryggen rett. Før stangen tett inntil kroppen under øvelsen. Press skuldrene sammen, og før stangen opp til navlen.

Øvelse	Illustrasjon	Treningsfokus	Øvelsesdata	Kommentar
4 Nedtrekk			3 sets x 10 reps Lårpute: Kg:	Ta et bredt grep, legg deg litt bakover og kikk skrått opp. Press brystkassen fram og trekk stangen ned til brystet. Før langsomt tilbake og gjenta.
5 Brystpress			3 sets x 10 reps Setehøyde: Kg:	Fest et godt grep om håndtakene. Trekk skulderbladene sammen og løft albuene til de er på høyde med grepet. Press armene framover til de er helt strake. Herfra føres håndtakene mot hverandre slik at armene samles. Senk litt langsommere tilbake til brystet og gjenta øvelsen.
6 Skulderpress			3 sets x 10 reps Kg:	Sitt på benken med hantlene i skulderhøyde. Skyv armene opp over hode. Gjenta.

Appendix G

Øvelse	Illustrasjon	Treningsfokus	Øvelsesdata	Kommentar
7 Armheving			3 sets x 10 reps	Hold kroppen rett under hele øvelsen. Ha litt bredere enn skulderbredde på armene. Alternativt: på kne.
8 Planken			3 sets x ____ reps Sek:	Stå på tær og albuer og la bekkenet hvile mot gulvet. Løft bekkenet opp fra gulvet ved å stramme opp i rygg og mage. Stabilisér kroppen i denne stillingen og hold 3-5 sek. Hvil tilsvarende og gjenta. Firfotstående bekkenhev

 20.08.2013