Master's thesis

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

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Isolated and combined effects of time-restricted eating and high-intensity interval training on glycemic control in reproductive-aged women with overweight/obesity: Preliminary findings from a randomized controlled trial

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Abstract

Introduction: Obesity and insulin resistance are associated with an increased risk of type 2 diabetes and cardiovascular diseases. Diet and exercise strategies are the first-line treatment in obesity, in order to prevent obesity-associated conditions, such as type 2 diabetes. However, most individuals find it hard to follow current recommendations of physical activity and healthy eating. Time-restricted eating (TRE) and high-intensity interval training (HIT) are two alternative strategies shown to improve glycemic control; however, it is still undetermined whether the combination TRE and HIT have additive effects. **Aim:** The main aim of the current thesis was to investigate the isolated and combined effects after seven-weeks of TRE and HIT on glycemic control in reproductive-aged women with overweight and obesity. A secondary aim was to examine the isolated and combined effects of TRE and HIT on other cardiometabolic health outcomes. **Methods:** This was a randomized controlled trial which included 50 women (33.4 ± 7.4 years; 32.1 ± 4.3 kg), who were randomly allocated to one out of four groups; TRE (eating window ≤ 10 h/d), HIT (3x/week), TRE and HIT (TREHIT), or a control (CON) group. At baseline, and after seven weeks of follow-up, blood sampling and cardiopulmonary testing were performed. **Results:** Thirty-three women completed the intervention (TRE; n = 9, HIT; n = 10, TREHIT; n = 9, and CON; n = 11). The daily eating window in TRE and TREHIT was 9.3±0.7 h/d and 8.9±0.6 h/d, respectively, and women allocated to HIT and TREHIT completed 89±11% and 94±16% of the scheduled training sessions, respectively. There was no between-group difference in glucose area under the curve (AUC) after a 2-h oral glucose tolerance test (p = 0.62), nor any significant within-group differences from baseline to after seven weeks in this outcome measure. There was a significant decrease in fasting glucose in the TREHIT group of -0.2 mmol/L (95%CI: -0.3,-0.01), without a significant between-group difference (p = 0.15). Diastolic blood pressure decreased in the TRE group (-5.0 mmHg, 95%CI: -9.1,-0.9). Maximal oxygen uptake (VO_{2max}) increased in the HIT and TREHIT group, with 1.6 ml/kg/min (95%CI: 0.9,2.3) and 2.7 ml/kg/min (95%CI: 0.6,4.9), respectively. **Conclusion:** The preliminary results of the current study suggest no changes in glucose AUC, however, promising tendencies for improvement in fasting glucose after TREHIT, in diastolic blood pressure after TRE, and in VO_{2max} after HIT and TREHIT. High adherence was reported in all the interventions, suggesting that TRE and HIT are feasible strategies for reproductive-aged women with overweight and obesity. However, long term adherence needs to be established.

Sammendrag

Introduksjon. Fedme og insulinresistens er assosiert med en forhøyet risiko for diabetes type 2 og kardiovaskulære sykdommer. Strategier som innebærer diett og trening står i front i behandlingen mot fedme, for å forhindre utviklingen av fedme-relaterte sykdommer, slik som diabetes type 2. Individer flest synes det er vanskelig å følge de nåværende anbefalingene for fysisk aktivitet og helsevennlig spising. Tidsbegrenset spising (TRE) og høyintensitetsintervaller (HIT) er to alternative strategier som har vist seg å forbedre glykemisk kontroll. Dog, det har fortsatt ikke blitt fastslått om kombinasjonen av TRE og HIIT kan ha noen tilleggsfordeler. **Mål**. Hovedmålet med denne oppgaven var å undersøke den isolerte og kombinerte effekten etter syv uker med TRE og HIT på glykemisk kontroll hos kvinner i reproduktiv alder med overvekt og fedme. Et andre mål var å undersøke den isolerte og kombinerte effekten av TRE og HIT på andre kardiometabolske helseutfall. **Metode**. Dette var en randomisert kontrollstudie som inkluderte 50 kvinner (33.4 ± 7.4 år; 32.1 ± 4.3 kg) tilfeldig fordelt på fire grupper; TRE (tidsvindu for inntak av mat ≤10 t/d), HIT (3x/u), TRE og HIT (TREHIT), eller kontrollgruppe (CON). Blodprøvetaking og kardiopulmonal belastningstest ble gjennomført på baseline og etter en syv-ukers intervensjon. **Resultat.** Trettitre kvinner fullførte intervensjonen (TRE; n = 9, HIT; n = 10, TREHIT; n= 9, og CON; n = 11). Det daglige tidsvinduet for inntak av mat i TRE og TREHIT var 9.3 ± 0.7 t/d og 8.9 ± 0.6 t/d. Kvinnene i HIT og TREHIT gjennomførte 89±11% og 94±16% av de planlagte treningstimene. Det var ingen forskjell mellom gruppene på glukose «area under the curve» (AUC) etter en 2-t oral glukosetoleransetest (p=0.62), heller ikke en signifikant forskjell innad i gruppene fra baseline til etter syv uker på dette utfallet. Det var en signifikant reduksjon i fasteglukose i TREHIT-gruppen på -0.2 mmol/L (95%CI: -0.3,-0.01), uten en signifikant forskjell mellom gruppene (p=0.15). Diastolisk blodtrykk sank i TRE-gruppen (-0.5 mmHg, 95%CI: -9.1, -0.9). Det maksimale oksygenopptaket (VO_{2maks}) økte i HIT- og TREHIT-gruppene, med 1.6 ml/kg/min (95%CI: 0.9,2.3) og 2.7 ml/kg/min (95%CI: 0.6,4.9). **Konklusjon**. De preliminære resultatene fra denne studien foreslår ingen forandringer i glukose AUC, men lovende tendenser til forbedringer i fasteglukose etter TREHIT, i diastolisk blodtrykk etter TRE, og i VO_{2maks} etter HIT og TREHIT. Høy tilslutning ble rapportert i alle intervensjonene, noe som foreslår at TRE og HIT er gjennomførbare strategier for kvinner i reproduktiv alder med overvekt og fedme. Dog, langsiktig tilslutning trenger å bli fastslått.

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I am sincerely grateful to everyone involved in this process, and I am incredibly proud of what I had accomplished during these last two years. I am completing this master's thesis, and looking forward to continue to participate and contribute to research.

Muchas Gracias

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List of Abbreviations

Akt/PKB	Protein kinase B
AMPK	AMP-activated protein kinase
ANCOVA	Analysis of covariance
ATP	Adenosine triphosphate
AUC	Area under the curve
BMI	Body mass index
CAMK	Ca^{+2}/calmodulin-independent protein kinase
CGM	Continuous glucose monitoring
GLUT4	Glucose transporter 4
HbA1c	Glycosylated hemoglobin
HDL	High-density lipoprotein
HIT	High-intensity interval training
HOMA-IR	Homeostatic model assessment for insulin resistance
HPLC	High-performance liquid chromatography
HR_{max}	Maximal heart rate
IRS-1	Insulin receptor signaling 1
LDL	Low-density lipoprotein
MICT	Moderate-intensity continuous training
OGTT	Oral glucose tolerance test
PCG-1alpha	peroxisome proliferator-activated receptor-gamma coactivator – 1 alpha
PIK3	Phosphatidylinositol 3-kinase
TRE	Time-restricted eating
VO_{2max}	Maximal oxygen uptake

1. Introduction

The prevalence of overweight and obesity has increased dramatically during the last decades, with an epidemic rise in the prevalence of obesity between the years 1975 and 2016 (1). In the adult population, 39% are overweight (39% of men and 40% of women), and 13% are obese (11% of men and 15% of women) worldwide (1), showing that women have higher rates of overweight and obesity compared to men. It has been estimated that 2.8 million people die every year due to the obesity epidemic (2). Obesity and type 2 diabetes are the biggest epidemic in human history and represent the major challenges to healthcare systems in the century (3).

Overweight and obesity are most commonly defined based on body mass index (BMI), which is calculated by dividing weight in kilograms by height in meters squared (kg/cm^2). BMI between 25.0 kg/cm^2 to 29.9 kg/cm^2 is defined as overweight, and a BMI of 30 kg/cm^2 and above is defined as obesity in adults (1). Increasing BMI has been associated with the incidence of cardiovascular disease and all-cause mortality (4). However, BMI, as a measure of adiposity, does not consider the amount of fat and its distribution within the body (5,6). The excessive fat storage in the body in subjects with overweight and obesity leads to numerous harmful effects on human health (7).

The increase in caloric intake and lack of physical activity are common causes that contribute to weight gain leading to overweight and obesity due to an energy imbalance (1). Additionally, increases in body weight can be influenced by genetics, metabolism, environment, behavior, and culture (8). In this regard, the industrialization of societies has reduced the need for physical activity, with concomitant changes in our dietary patterns. In parallel, we are now exposed to artificial light for a prolonged period, increasing the duration of the awake time and causing more extended periods of food intake (9). It has been seen in adults that more than 50% tend to have an eating window of 15 hours per day (10). Moreover, individuals who skip meals (most often breakfast), eat more at dinner time and prefer high-sugar meals late at night (10). Even though the diet composition is an essential factor, it has been shown that extended daily periods of food intake have a substantial contribution on the susceptibility to develop metabolic diseases, such as, type 2 diabetes, dyslipidemia, and fatty liver which the gain increases the risk of cardiovascular diseases (9–11).

Obesity has been classified as an independent risk factor in cardiovascular disease (12). Several cardiovascular risk factors, such as dyslipidemia, hypertension, insulin resistance, and

type 2 diabetes, are associated with obesity (13). It is well known that there is a relationship between obesity and type 2 diabetes due to the strong link between obesity and insulin resistance (14). Insulin resistance accounts for the impairment in insulin's ability to participate in glucose uptake, metabolism, and storage in the skeletal muscle, liver, and adipose tissue, leading to an alteration in glycemic control (14,15). The reason for the obesity-induced elevated risk is that obesity leads to an impairment in energy homeostasis in the different organ systems by altering the regulation of glucose and insulin levels, insulin sensitivity, cholesterol, and triglyceride levels (1,16,17).

1.1 Glycemic control

The concentration and balance of blood glucose levels, known as glycemic control, are important due to glucose's participation in energy metabolism in different organs (18,19). Glycemic control is regulated by two important hormones, glucagon and insulin, which are produced in the pancreas (19). Glucagon is produced by the alpha-cell in the pancreas when blood glucose is low (i.e., in the fasted state), activating glycogenolysis and gluconeogenesis in the liver to increase blood glucose. On the other hand, insulin is produced by the beta-cell in the pancreas when blood glucose is high (i.e., in the postprandial state), inhibiting hepatic glucose production and reducing blood glucose by mediating its transport into the cells (18,19). Additionally, insulin has important functions in adipocyte glucose uptake and lipid metabolism (i.e., fatty acid uptake, inhibition of lipolysis and lipogenesis) (19,20).

The main organs involved in the maintenance of glucose homeostasis are the liver, adipose tissue, and skeletal muscle. The skeletal muscle is one of the most important organs in glucose homeostasis due to its large distribution in the human body and its actions in glucose storage, uptake, and utilization (19). There are two ways skeletal muscle can regulate glucose levels. The first one is mediated by insulin through the phosphorylation of insulin receptor substrate (IRS)-1, which triggers phosphatidylinositol 3-kinase (PIK3), resulting in the activation of downstream protein phosphorylation. Further, this facilitates the translocation of glucose transporter 4 (GLUT4) to the sarcolemma and subsequent entry of glucose to the cell (18,19) (Figure 1.2.1). The second is independent of insulin and is mediated by skeletal muscle contraction-induced activation of different pathways that can involve two proteins; AMP-activated protein kinase (AMPK) and Ca^{+2}/calmodulin-independent protein kinase (CAMK) for

the translocation of GLUT4 (Figure 1.2.1). When glucose enters the skeletal muscle cell, it can be rapidly phosphorylated and directed to aerobic or anaerobic pathways to produce adenosine triphosphate (ATP) or to be stored as glycogen for later use (18,19).

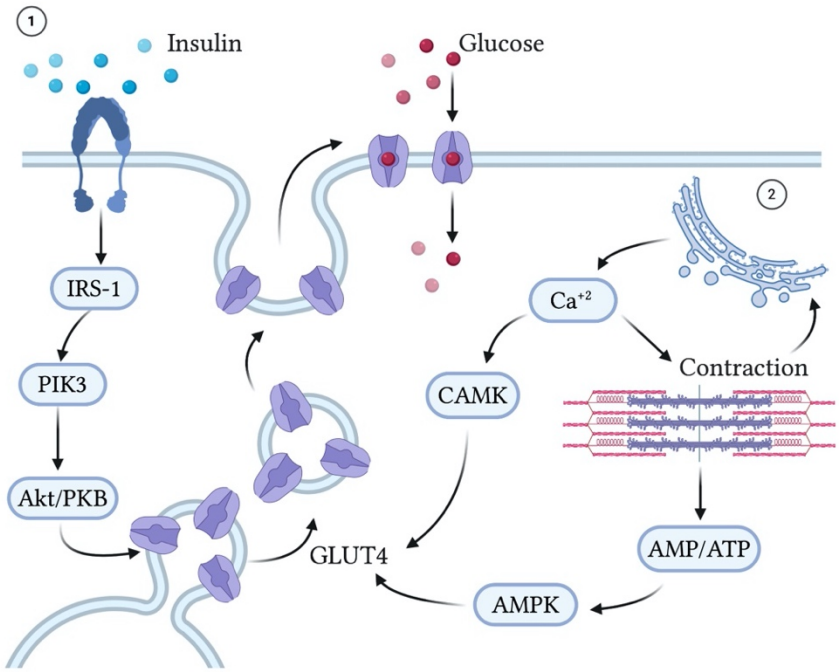


Figure 1.1.1. Skeletal muscle glucose uptake. 1) Insulin-stimulated glucose uptake and 2) Non-insulin stimulated glucose uptake. IRS-1 = insulin receptor substrate 1, PIK3 = phosphatidylinositol 3-kinase, Akt/PKB = protein kinase B, GLUT4 = glucose transporter 4, Ca^{+2} = calcium, CAMK = /calmodulin-independent protein kinase, AMP/ATP = adenosine monophosphate/adenosine triphosphate ratio, AMPK = AMP-activated protein kinase.

1.2 Obesity-induced alterations in glycemic control

The link between obesity and insulin resistance can be explained by an alteration in insulin-stimulated pathways that negatively affects glucose metabolism in the skeletal muscle and adipose tissue, and an impaired inhibition in hepatic glucose production (14,19,21). Alterations in insulin-mediated pathways for glucose uptake have shown to be impaired due to dephosphorylation of IRS-1 in the adipose tissue and PI3K in the skeletal muscle in subjects with obesity (21), which are important steps for GLUT4 translocation (18,19). These alterations in insulin-mediated pathways may lead to an increase in glucose blood levels that create a continued state of hyperglycemia. Such a constant state of hyperglycemia causes overstimulation of beta-cells that compensate by secreting insulin; however, the impairment of

insulin sensitivity makes this process ineffective, leading to a progressive reduction of beta-cell function (22). Therefore, it is believed that this vicious cycle contributes to the worsening of insulin resistance and lower beta-cell function leading to the development of type 2 diabetes (22).

Insulin resistance in the adipose tissue can also induce negative impacts on glycemic control. It has been reviewed that the excess of adipose tissue depots and decreased insulin-stimulated inhibitory lipolysis produce a rise in circulating fatty acids concentrations in the blood and subsequent accumulation in other organs (14,23,24). The increase of fat accumulation, mainly in hepatocytes and myocytes, cause alterations in insulin signaling pathways leading to a decrease in insulin sensitivity and glycogen synthesis (25,26). Excessive fat accumulation in skeletal muscle may be explained due to mitochondrial dysfunction and alterations in fat oxidative capacity, which has been found in individuals with obesity and type 2 diabetes (24,27).

1.3 Measures of glycemic control

Several glycemic markers are used to measure glycemic control for screening, diagnostic purposes, and research. One of the most common methods used to test alterations in glycemic control is fasting blood glucose (blood glucose levels following an overnight fast) and oral glucose tolerance test (OGTT) (monitor glucose levels after a 2-h 75-g glucose load) (28). Fasting glucose levels reflect glucose production from the liver and insulin secretion from the pancreas (29). Glucose tolerance shows the balance between glucose intake, insulin-mediated inhibition of glucose production in the liver, and glucose uptake in insulin-sensitive organs (30). Alterations in fasting glucose and glucose tolerance are conditions that play an essential role in the transition to type 2 diabetes (31). Another measure of glycemic control, important in the development of type 2 diabetes and the progression of its complications, is glycosylated hemoglobin (HbA1c) (28,32). HbA1c represents the average of long-term blood glucose levels (over one to three months), yet it does not show changes in blood glucose levels along the day (28).

Glucose area under the curve (AUC) is an index used to measure glucose tolerance and to quantify the whole blood glucose excursion after a glucose load (i.e., 2-h OGTT) or food intake (33). There are three different ways to estimate glucose AUC, such as the total AUC (including the baseline values), incremental AUC (subtracting baseline values), and positive

AUC (subtracting the baseline and below baseline values). Incremental and positive glucose AUC takes away the variance of baseline values, and have been used to estimate glycemic index and response to food (34).

Continuous glucose monitoring (CGM) is a technology that has been used lately to measure interstitial glucose levels fluctuations and magnitude during several days. This device uses a sensor inserted in the subcutaneous adipose tissue that receives glucose information and transfers it to a monitor. CGMs can also be used to see variations in glycemic control after exercise training. Therefore, CGM has been shown to be a better strategy compared to other traditional methods (i.e., Fasting glucose and 2-h OGTT) to detect impairments in glycemic control that could be missed (i.e., hyperglycemia and hypoglycemia) by measuring glucose once daily (35).

1.4 Obesity-induced cardiometabolic risks in women

Obesity in reproductive-aged women may lead to alterations in the menstrual cycle, which is related to impairments on cardiometabolic health (36). Hormones secreted during the menstrual cycle (i.e., estrogen and progesterone) are important in glucose and lipid metabolism, and the concentration of these hormones varies along with the different phases (follicular and luteal phase) (37,38) (Figure 1.5.1). Alterations of estrogen and androgens (i.e., testosterone) outside the normal range can have negative influences in glucose metabolism and insulin sensitivity in reproductive-aged women leading to alterations in the menstrual cycle (39).

In women with obesity, higher circulating levels of insulin have been related to dysfunctions in the menstrual cycle (40,41). Such an increase in circulating insulin induces alterations in the normal balance of hormones involved in the hypothalamic-pituitary-ovarian axis and thereby negatively affect the regulation of the menstrual cycle and the ovulatory process (41). Therefore, menstrual cycle irregularities, fertility alterations, and complications during pregnancy (i.e., gestational hypertension and gestational diabetes) are more common in women with obesity compared to their normal-weight counterparts (41). Additionally, obesity during pregnancy can affect the offspring's health and increase their risk of all-cause mortality as adults (41,42).

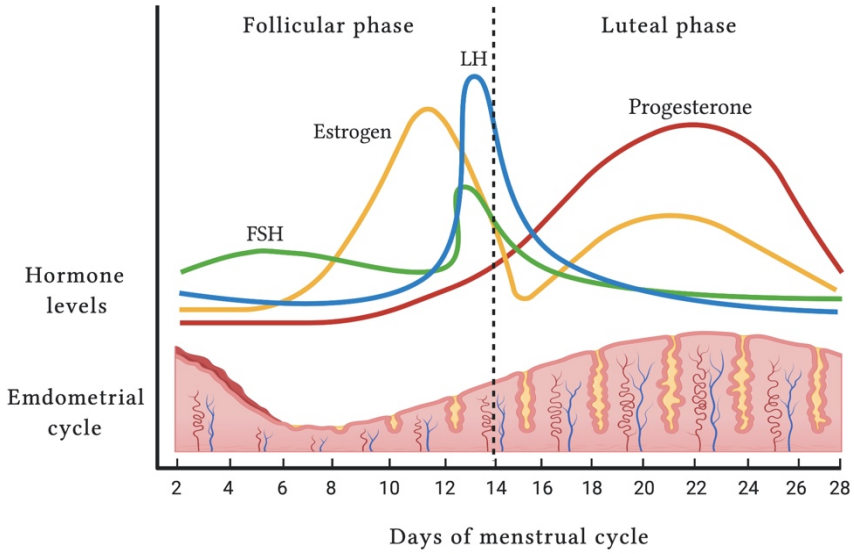


Figure 1.4.1. Illustration of the average duration of the menstrual cycle and hormone variation in women. FSH = follicle-stimulating hormone, LH = luteinizing hormone.

2 Lifestyle strategies to manage obesity

Several diet-exercise approaches have been proposed as a first-line strategy to prevent obesity and type 2 diabetes. Current guidelines propose a healthy diet (quality and quantity of food) and an adequate level of physical activity to reduce cardiovascular disease risk factors (43,44). The recommendations for a healthy diet, as proposed by the World Health Organization (43), are based on a restriction in caloric intake, low intake of saturated and trans-fats, sugar and salt, and a high intake of fruits, vegetables, and fiber. The current recommendations for physical activity for cardiometabolic health benefits suggest an increase of physical activity, such as 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity, or a combination of both (44). Moreover, the American College of Sports Medicine (45) proposes a larger volume (150 - 300 minutes) of moderate-intensity physical activity per week to reduce body weight. Therefore, increasing energy expenditure and decreasing energy intake will produce an energy deficit that will translate into a reduced body mass. It has been argued that between 5% to 10% of body weight loss is needed to induce improvements in cardiovascular and metabolic health (46,47). These improvements in health are reflected by an improvement in insulin sensitivity, lower lipid and glucose levels, decreased inflammatory markers, and lower blood pressure (48).

Most diet interventions have shown a decrease in body mass, which is accompanied by a loss in muscle mass of approximately 25% (8,49), resulting in unfavorable body composition. On the other hand, exercise has been shown to maintain or increase muscle mass, which has an essential role in muscle oxidative metabolism and cardiorespiratory fitness (49). Moreover, exercise is an effective strategy to attenuate muscle mass loss during caloric restriction (49). Skeletal muscle is one of the most important organs in the regulation of glycemic control and energy metabolism, and the amount of muscle mass is inversely correlated with the risk of type 2 diabetes (19,50). Additionally, subjects with obesity have shown lower muscle mass, and this can be exacerbated with advanced age (49). The loss of muscle mass may lead to low mitochondrial volume and oxidative capacity that negatively affects ATP synthesis, which may play a critical role in the development of insulin resistance (19,24,27).

A systematic review and meta-analysis by Clark et al. (56) showed that interventions combining diet and exercise are more effective than diet and exercise alone at improving cardiometabolic parameters. However, most individuals fail to meet the current recommendations for diet and physical activity, often reported due to a lack of time and motivation (51). Therefore, alternative approaches are needed to increase adherence and thereby improve health parameters in individuals who are at risk for cardiometabolic diseases.

2.1 Dietary approaches

Continuous caloric restriction is a dietary approach that has been implemented for the management of overweight and obesity (52,53). Continuous caloric restrictive diets are characterized by decreasing daily energy intake by 15% to 60% to induce a significant improvement in cardiometabolic risk parameters (52,53). Even though it is an effective weight loss strategy, subjects with obesity find it difficult to adhere to such diets due to the intensity of the energy restriction (54). Therefore, strategies with moderate or intermittent caloric restriction should be considered.

Another diet approach that has been studied during the last decade is known as intermittent fasting, which has been shown to induce similar improvements in cardiometabolic health (i.e., body mass, insulin sensitivity, glycemic control, lipids, and blood pressure) as continuous calorie-restricted diets (55). Intermittent fasting is characterized by an intervention that alternate periods of eating and fasting. The modalities of intermittent fasting are alternate-day fasting, modified alternate-day fasting (56), and periodic day fasting (5:2) (55). Alternate-day and modified alternate-day fasting are identified by the complete (100%) or partial (50% to 75% less of weight maintenance energy needs) food restriction respectively, every other day of the week followed by an ad-libitum (24-h) food consumption on the “eating days” (57). Periodic day fasting is characterized by an ad-libitum food consumption during five days of the week and a partial food restriction (75%) the other two consecutive or non-consecutive days (55). It has been proposed that the benefits in cardiometabolic health may be due to caloric restriction in the fasting days or by metabolic pathways and cellular processes induced by fasting (58,59). Even though intermittent fasting diets have no daily caloric restriction, individuals have reported that they are hard to follow due to the severe food restriction and calorie counting during fasting days (55,60).

2.2 Time-restricted eating (TRE)

A new type of intermittent fasting called time-restricted eating (TRE) has gained popularity lately. TRE is characterized by a reduction of the time-window for daily energy intake (preferably ≤10-12 h) and increasing the fasting periods (≥14 h), controlling the daily time of eating without deliberate changes in caloric intake (61). Therefore, TRE maintains a constant daily balance of feeding and fasting to support the daily variations in metabolism (circadian rhythms) (62). TRE studies in mice (63–66) and humans (61,67–70) have shown positive effects in adiposity, glucose and insulin levels, blood pressure, and inflammation markers (Figure 2.2.1).

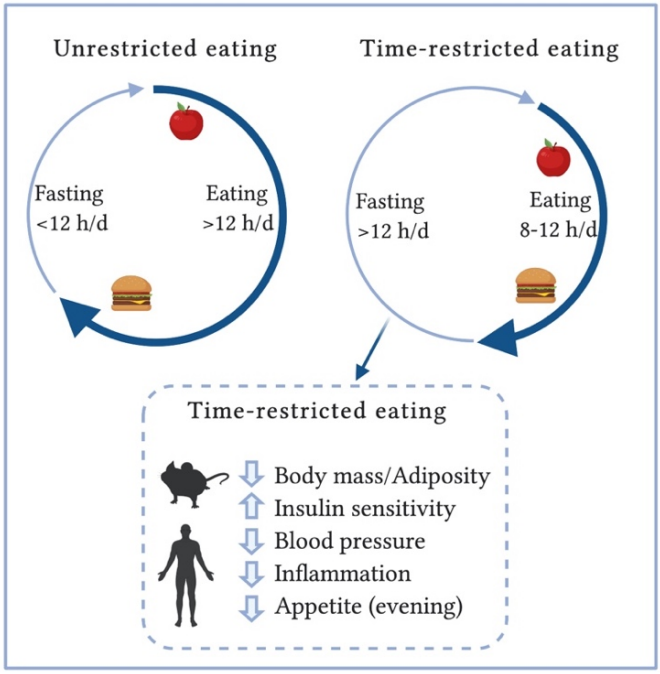


Figure 2.2.1. **Illustration of time-restricted eating (TRE) protocol.** Such protocols, where the daily time-window for energy intake is restricted, typically to 8-12 h/d, have shown cardiometabolic benefits in animal models and humans.

Gabel et al. (71) studied the effects of TRE in subjects with overweight and obesity (eating window 8 h/day). They found a ~3% decrease in body mass, without deliberate changes in the type of food consumed or counting the caloric intake. In that study, no changes in other cardiometabolic outcomes were seen after 12 weeks. In another study (eating window 10 h/d, 12-wk), the researchers reported a similar decrease in body mass (~3%) in subjects with metabolic syndrome, in addition to improvements on cardiometabolic parameters such as glucose tolerance, insulin and lipid levels, and HbA1c (70). Of note, the latter study showed that decreases in body weight were not correlated with improvements on cardiometabolic risk markers (70), suggesting that these changes may be independent of weight loss. In this regard, TRE with ≤ 10 hours window showed improvements in glucose tolerance measure as glucose area under the curve (AUC), insulin sensitivity and beta-cell function despite no significant changes in body mass in subjects with overweight/obesity (68), at risk of type 2 diabetes (72) and with prediabetes (67).

Studies on TRE (eating window mainly between 8- to 12 h/d) in mice have suggested that the timing of meals may be directly responsible for some of the metabolic mechanisms underlying the development of metabolic and cardiovascular diseases (63,64,66). Moreover, it has been seen that glucose control and energy metabolism changes throughout the day (circadian rhythms) (73), and alterations in these patterns due to longer periods of energy intake can lead to impairments in cardiometabolic health (10,74,75). Therefore, different eating windows during the day described as early- and late- TRE, have been used in humans to explain changes in cardiometabolic risk markers. Two studies using early TRE (eating window 6 h/d, with the last meal before 4 pm) found improved glycemic control and insulin sensitivity in subjects with overweight/obesity (69) and men with prediabetes (67). Studies where the TRE window was placed in the middle of the day (eating window 10 am – 6 pm, 8 h/d), have shown equivocal results; one study found no effects (71), another a tendency to improved glycemic control (76) and significantly improved glycemic control (68). Hutchinson et al (72) compared an early- (8 am to 5 pm) with a late- (12 pm to 9 pm) TRE (eating window 9 h/d) in men with overweight/obesity and risk of type 2 diabetes and found positive effects in glucose tolerance in both groups, yet greater improvements were seen in the early-TRE group.

It is still unknown if the mechanisms underlying the effects of TRE on metabolic risk parameters in humans are due to a change in food intake and appetite during TRE, the time of the day where the eating window is placed, or fasting length. The adherence to TRE has been reported to be sustained throughout the intervention approximately five to six days per week

(67,71,77), and participants have only referred difficulties to adapt to the TRE protocol at the beginning of the intervention (67,77,78). Of note, most of the studies in TRE are performed in men and mixed-populations, and only two in women (77,79). It has been seen that intermittent fasting in women has shown impaired glucose tolerance and insulin sensitivity compared to male counterparts after two weeks of alternate-day fasting (80). Therefore, more studies are needed in women to determine the effects of TRE on cardiometabolic health.

2.3 Exercise training

Physical activity is one of the key factors in the prevention of non-communicable diseases, such as obesity, cardiovascular diseases, type 2 diabetes mellitus, and certain types of cancer (81,82). Obesity and low cardiorespiratory fitness (measured as maximal oxygen capacity, VO_{2max}) are independent predictors of increased risk of cardiovascular morbidity and mortality (83,84). It has been seen that physical activity and increased cardiorespiratory fitness are associated with reduced cardiometabolic morbidity and mortality risk, regardless of changes in body mass (82,85,86). In this regard, subjects with obesity with low aerobic fitness have higher cardiovascular risk compared to fit counterparts (87). Additionally, exercise improves glycemic control due to an increase in glycogen synthesis and glucose metabolism, higher insulin sensitivity, and enhanced muscle-oxidative capacity (88,89). Improvements in glycemic control can be seen after only one bout of exercise due to stimulation of AMPK and IRS-1 phosphorylation, which translates to an increased translocation of GLUT4, that can be maintained for up to 72-h (89).

Several studies have demonstrated that moderate-intensity continuous training (MICT) and high-intensity interval training (HIT) have essential roles in improving cardiometabolic health (90–92). MICT is characterized by protocols used in public health guidelines (93); however, when comparing to HIT, intensities between 60-75% of maximal heart rate (HR_{max}) have commonly been used (88). HIT is characterized by brief bursts of intense exercise separated by short periods of recovery (rest or low intensity), and different HIT protocols have been proposed regarding the length of the work-bouts (high-intensity and active/passive pause). The most common protocols are sprint interval training (SIT) characterized by 10-30 sec at supramaximal intensity (intensity required to elicit 100% VO_{2max}) and HIT identified by one to four min with an intensity near maximal or between 80-100% HR_{max} (93).

MICT and HIT have shown to induce similar changes on body mass when they are matched for energy expenditure or workload (90–92,94). However, a meta-analysis showed that HIT induces greater improvements in VO_{2max}, insulin sensitivity, glucose tolerance, and muscle oxidative capacity compared to MICT (94). In this regard, Tjonna and colleagues (95) have demonstrated in subjects with overweight and the metabolic syndrome that 4x4 HIT (four minutes bout at 85-95% HR_{max} with three minutes of active recovery, repeated four times) induced more significant changes on insulin sensitivity, glucose levels, phosphorylation of IRS-1 in the muscle and adipose tissue, beta-cell function and, compared to MICT (60-70% HR_{max}) after a 16-weeks of intervention.

HIT among women has also shown benefits in glucose control, insulin sensitivity, and VO_{2max}. Gillen et al. (96) reported reductions on glucose total AUC (~4%), increase in GLUT4 and (~16%) in women with overweight and obesity after six weeks (three times per week) of 10x1 HIT (90%HR_{max}). Additionally, in women with polycystic ovary syndrome, 10-weeks of 10x1 (one min bout "all-out" with one min of active recovery repeated ten times) once a week and 4x4 (90%HR_{max}) two times a week has shown improvements in insulin resistance (~17%) measured with homeostatic model assessment (HOMA-IR) and VO_{2max} (~10%) (97). Kiel et al. (98), using the same HIT protocol (4x4 and 10x1), also showed improvements in insulin resistance (~23%) measured with hyperinsulinemic-euglycemic clamp and VO_{2max} (~8%) after 10-weeks in women with overweight and obesity. Improvements in glucose control and VO_{2max} (~6%) can be seen after only two weeks (five sessions per week) of 10x1 HIT (85-90%HR_{max}) in women with overweight and obesity (99).

Consequently, subjects performing HIT can achieve similar or superior health benefits and need shorter time per session compared to MICT, making HIT a more time-efficient method (90,91). Lack of time and motivation are two of the main reasons why individuals do not perform physical activity (51), and HIT compared to MICT have shown higher rates of adherence due to the higher enjoyment during HIT in men and women with obesity (100,101). In women with overweight and obesity, the adherence to three-weekly HIT sessions was 85-90% during 10-weeks intervention (97,98). Therefore, HIT is an appealing strategy to improve health parameters in reproductive-aged women with overweight and obesity.

2.4 Time-restricted eating (TRE) and high-intensity interval training (HIT)

As outlined above, TRE and HIT can independently induce improvements in body mass, glucose control, and insulin sensitivity. Additionally, positive changes in body mass, glucose and insulin levels, and muscle oxidative capacity have been seen after HIT without a significant change in caloric intake pre- to post-intervention (96,102). HIT also leads to substantial improvements in VO_{2max}, which is an essential factor due to its strong relation with cardiovascular risk and all-cause mortality (83). It is well documented that the combination of exercise and diet should be the first-line treatment for subjects with overweight and obesity (43,44), and the combination of both induce more significant benefits in cardiometabolic health (103). Therefore, TRE combined with HIT may be an appealing option to improve cardiometabolic health in individuals with overweight/obesity.

There are three studies to date that investigated the combination of TRE and strength training in resistance-trained men (57,78) and women (79). When TRE (1 pm – 8 pm, 7 h/d) was compared with an "unrestricted" isocaloric diet among resistance-trained individuals, it showed a decrease in body fat mass and maintenance of lean mass, reduction of glucose and insulin blood levels, and diminished inflammatory markers after eight weeks (57). TRE (eating window 12 pm – 8 pm, 8h/d) in resistance trained-women showed maintenance in lean mass yet no improvements in glucose, insulin, and lipid levels after eight weeks (79). Tinsley and colleagues (78) showed that even though young men who performed resistance training had a decrease in caloric intake of approximately 650 Kcal during the TRE days (4h/d, on the four non-exercise days per week), no negative effects in muscle mass cross-sectional area were seen after eight weeks.

To date, there are no published studies that combine TRE and aerobic exercise, leaving a gap in knowledge regarding the potential additive effects of these two diet-exercise interventions on cardiometabolic health (104). Furthermore, most of the studies on exercise training and diet have been undertaken in men, and less is known about how females respond (105). The complexity of female physiology, due to the possible effects of sex-hormones and hormonal contraceptives in the metabolism of different substrates, training adaptations, and exercise performance, may be the main reason why women are unrepresented in research (93,105,106). Additionally, women have shown higher rates of overweight and obesity compared to men (1), which leads to several alterations in cardiometabolic and reproductive

health outcomes (36,40,41). Therefore, more research is needed to find a more feasible diet-exercise strategy to induce improvements in cardiometabolic health in reproductive-aged women with overweight and obesity.

3 Aim and hypothesis

The primary aim of this study was to determine the isolated and combined effects of short-term (seven weeks) TRE and HIT on glycemic control in reproductive-aged women with overweight/obesity. Secondary aims were to determine the isolated and combined effects of TRE and HIT on blood pressure, blood markers of cardiometabolic health, and cardiorespiratory fitness. Additionally, adherence to TRE and HIT was recorded.

The hypothesis of the present study was that both TRE and HIT would improve glycemic control and cardiometabolic risk markers, with more significant changes after the combination of both interventions after seven weeks in reproductive-aged women with overweight/obesity.

4 Materials and methods

4.1 Study design

This study was carried out in the Next Move Core Facility and research laboratories located in St. Olav's hospital, in the Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU). The study was carried out following the ethical principles established by the Helsinki Declaration. This research project has been reviewed and approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REK no. 2019 / 851) and registered in Clinical Trials (Clinicaltrials.gov, identifier NCT04019860). All participants received an information letter before being considered for participation (Appendix A) and signed an informed consent before participating in the study. Participation was voluntary, and the participants had the opportunity to withdraw from the study at any time without having to state the reason. All data were treated confidentially to protect the participants' privacy.

This study was a randomized control trial with four parallel groups, where the subjects were allocated randomly in a 1:1:1:1 manner after the baseline testing to TRE, HIT, TREHIT, or control (CON) group. The lead investigator (T. M.) was responsible for the randomization of the participants in the different groups, and this allocation was carried out using a web-based system for random number generation developed and managed by the Unit of Applied Clinical Research, Institute of Cancer Research and Molecular Medicine, NTNU, Trondheim, Norway. Each participant was studied for eight to nine weeks, with one week of baseline measurements (no intervention) and seven weeks of intervention. Participants came for assessments in the laboratory on two separate days at the beginning of the study period and again after the intervention period (Figure 4.1.1).

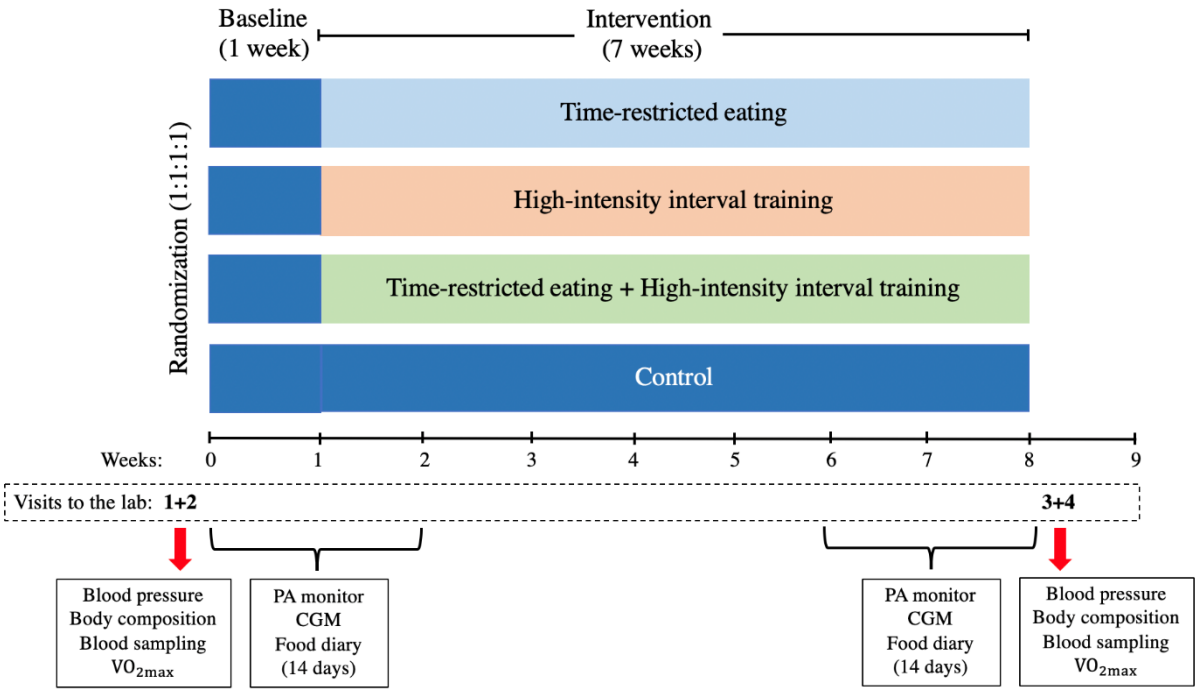


Figure 4.1.1. Study design. Participants attended four times to the laboratory to be tested (blood pressure, body composition, blood sample, cardiopulmonary exercise test, and questionnaires), two at the beginning and two at the end of the study. After all the outcome variables were measured at baseline, the participants were randomized in one of the four groups, fitted with physical activity (PA) monitors, continuous glucose monitor (CGM), and instructed to start writing in the food diary for 14 days. Two weeks before the end of the intervention the participants were fitted again with the PA monitors and CGM and started to register their energy intake in the food diary. VO_{2max} = maximal oxygen capacity.

4.2 Participants

The inclusion criteria used in the study were; aged between 18 and 45 years old, BMI ≥ 27 kg/cm^2, able to walk on a treadmill, or ride a bike at least 60 min. The exclusion criteria were; pregnancy, lactation within 24 weeks of the study commencement, known cardiovascular disease, type 1 or 2 diabetes, currently taking medication for hypertension or glucose- or lipid-lowering medication, habitual eating window < 12 hours, performing HIT more than once a week, weight variations > 4kg in three months prior the study commencement and shift work (that included night shifts). To see if the participants met the inclusion criteria to participate in the study, telephone calls were made for a pre-screening of the participants regarding the eligibility criteria.

4.3 Outcome measures and procedures

Participants received a letter with information regarding the test procedures (Appendix B). We requested the participants not to perform vigorous physical activity ≥ 48 hours before all test days. Participants with regular menstrual cycles were tested during the follicular phase of the menstrual cycle due to the variations on sex-hormone concentrations in the different phases.

4.3.1 Blood sampling

The primary outcome measure was glycemic control determined by glucose total area under the curve (AUC) after a 2-h 75g- oral glucose tolerance test (OGTT). Glucose total AUC was calculated using the trapezoidal method, with glucose fasting concentrations as baseline values. Participants were tested in the morning after an overnight fast for ≥10 h, between 8 to 10 am in the pre- and post-test. An in-dwelling venous cannula was placed in the antecubital vein of the participant, and the first blood sample (0 min) was taken. Then the participant drank 75-g of glucose diluted in 250 mL water. We sampled one Lithium-Heparin tube and one EDTA tube every 30 minutes for two hours (30 min, 60 min, 90 min, and 120 min). For the other outcome measures such as fasting glucose, 2-h glucose, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and HbA1c, two EDTA tubes were taken at 0 min. Serum and Lithium-Heparin tubes rested in a vertical position for 30 min before we centrifuged them at 2220g for 10-min at 20°C. EDTA tubes were centrifugated at 2220g for 10 min at 4°C.

We sent one EDTA tube (0 min), and all the Li-hep tubes to the St. Olav's hospital laboratory for analyses of glucose, total cholesterol, HDL, LDL, triglycerides, and HbA1c. Glucose levels, total cholesterol, HDL, LDL, and triglycerides concentration was measured using Roche Modular P. chemistry analyzer (Roche Diagnostics Ltd, Switzerland). The concentration of HbA1c was measured using high-performance liquid chromatography (HPLC) and analyzed with Cobas Integra 400 plus (Roche Diagnostics Ltd, Switzerland). In cases where HbA1c could not be measured by HPLC, an alternative analysis method was used on the DCA

Vantage analyzer (Siemens, Germany). We also aliquoted a part of all the blood samples, and these froze at - 80°C for future analysis of circulating insulin.

4.3.2 Blood pressure

Blood pressure and resting heart rate were measured before the blood test after 15 min rest in a seated position. We used an automatic blood pressure device (CASMED 740 MAXNIBP, CAS Medical Systems) and completed three measurements with a one-minute interval in-between. The average of the three blood pressure measures is reported.

4.3.3 Cardiopulmonary exercise test

Subjects were asked to restrain from alcohol consumption and vigorous physical activity for 24 hours before the measurements. The cardiopulmonary exercise test was performed on a treadmill (Woodway PPS 55, Waukesha, Wisconsin, USA) and was measured using direct analysis of expired gases (Metalyzer II, Cortex, Leipzig, Germany). The participant warmed up for ten minutes before the test started. After the warm-up, we used an individualized ramp protocol where the participants walked or ran at an increasing speed (0.5–1.0 km) or inclination (1-2%) every one to two minutes until they reached exhaustion or the VO_{2max} criteria were met; a plateau was seen regardless of increases in speed or incline, combined with a respiratory exchange ratio (RER) above 1.05 (107). VO_{2max} was measured as an average of the three highest values reached over 30 seconds. We used a heart rate monitor to measure the HR (measured with a HR monitor, H7, Polar Electro, Kempele, Finland) continuously during the test, and HR_{max} estimated was estimated as the highest HR at the end of the test (108). The post-test was performed two to four days after the last exercise session for participants who were allocated to HIT and TREHIT. The exercise test took place at the same time of the day, pre- and post-intervention, to reduce the effects of circadian rhythms on exercise performance (109).

4.3.4 Protocol adherence

Participants were given a handbook where they wrote the time of their first and last daily energy intake for eight weeks. Adherence to TRE was recorded as the average daily time-window for food intake and the number of days per week that participants adhere to a ≤ 10 h time window for energy intake. For HIT, adherence was be recorded as the percentage of the scheduled HIT sessions the participants completed.

4.3.5 Other measurements

The current thesis only includes some of the outcome measures that we obtained in the study. On the same day as the blood sampling, we also estimated the participants' body composition. Participants wore light clothing and no shoes for the estimation of body composition using bioelectrical impedance analysis (InBody720, Biospace CO, Korea).

During the baseline week, the first week of the intervention, and during the last two weeks before the post-test, the participants recorded their caloric intake using an online food diary (www.kostholdsplanleggeren.no). Additionally, appetite was registered after they woke up and before they went to bed during the same weeks.

Participants were fitted with an activity monitor (Sensewear Armband, BodyMedia) to estimate their physical activity level, energy expenditure, and sleep duration, as well as continuous glucose monitors (CGM) (FreeStyle Libre Pro Glucose Monitoring System, Abbott Diabetes Care) to measure the 24-hour glucose levels in the interstitial fluid. At baseline and after the intervention period, the participants also completed three questionnaires; International physical activity questionnaire (IPAQ), Pittsburgh sleep quality index (PSQI), Hornestberg morningness-eveningness questionnaire (MEQ).

4.4 Intervention

Subjects allocated in the TRE, HIT, and TREHIT group had an identical TRE and HIT intervention. It is important to mention that the two HIT modalities used (4x4 and 10x1) were not matched for volume or energy expenditure. The self-reported eating window was registered in a handbook during the baseline week and study period for all four groups.

4.4.1 Time-restricted eating (TRE)

Participants were asked to reduce their daily time-window for energy intake to a maximum of 10 hours in order to fast at least 14 hours every day throughout the intervention period. Participants were allowed to choose an eating window that suited them best, yet they were advised not to eat after 8 pm. There were no dietary restrictions, and participants were not guided about the quality and quantity of the caloric intake. During the fasting period, participants were allowed to consume non-caloric drinks (i.e., water, zero-calorie soda, black tea, and coffee). Participants were asked to continue with their habitual physical activity during the intervention period. Adherence and motivation support were provided weekly via phone call/sms/email or face-to-face by the investigators.

4.4.2 Exercise training

We used the same HIT protocol as in a previous study showing improvements in insulin resistance after 10 weeks in women with polycystic ovary syndrome (97). Participants came to the lab for a supervised HIT session three times per week for seven weeks. All sessions started with 10 minutes of warm-up at 60 - 70% of their HR_{max} and ended after three minutes of cool down at the same moderate intensity. Two of the weekly training sessions were of four times four minutes HIT at 90 – 95% of their HR_{max} interspersed by three minutes of moderate-intensity at 60 - 70% of their HR_{max} (Figure 4.4.1.A). The total exercise time for the four times four min sessions (4x4) was 38 minutes. The third session consisted of ten times one min HIT

at an intensity corresponding to ≥ 90% of their HR_{max} and one minute of low-intensity recovery (Figure 4.4.1.B). The total exercise time for the ten times one-minute (10x1) sessions was 33 minutes. All exercise sessions were supervised by the research staff, and the intensity was recorded using heart rate monitors (Polar M400, POLAR, Finland) to make sure the participants exercised with the correct intensity. Data was uploaded to an online personal training webpage (https://flow.polar.com), where the investigators also had access. The estimated at baseline after the cardiorespiratory test was used to prescribe the exercise intensity. We adjusted the workload to account for the improvement in fitness throughout the training intervention. Participants performed both HIT modalities walking or running on a treadmill, but if they reported discomfort or pain from walking/running, they could cycle instead.

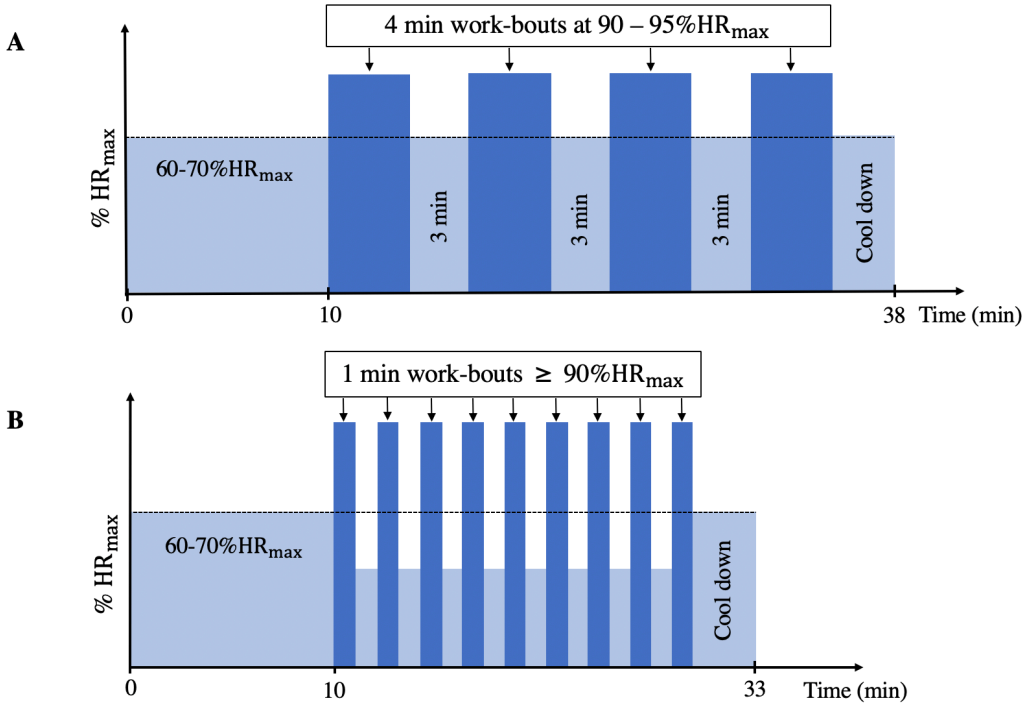


Figure 4.4.1. Hight-intensity interval training (HIT) study protocol. Participants performed two weekly sessions of 4 x 4 min HIT (A) and one weekly session of 10 x 1 min HIT (B). HR_{max} = Maximal heart rate.

4.4.3 Control group

Participants in the control group were asked to maintain their habitual diet, physical activity, and exercise routines during the intervention period. After the completion of the post-test, they were offered to have a "delayed treatment" where they chose which group they wanted to be allocated; TRE, HIT, or TREHIT group with interventions as outlined above for seven weeks. At the end of the seven weeks, they were offered the cardiopulmonary exercise test and body composition measurement. The data from that period are not included in the study.

4.4.4 COVID-19 pandemic and exercise training

The closing of the laboratory due to the COVID-19 pandemic in March 2020 had some consequences for our study, especially for participants enrolled in the HIT and TREHIT group. Participants who were close to finishing with the exercise training intervention were offered to continue with HIT, either unsupervised (using treadmill/bike) or as supervised outdoor uphill running/walking, based on their preferences. Participants continued with both HIT modalities, and the relative intensity was recorded with a heart rate monitor (Polar M400, POLAR, Finland) to corroborate that they exercised with the correct intensity.

5 Statistical analysis

This thesis project is a part of a large ongoing project and will only report preliminary findings. In the main project, the sample size was calculated based on a previous HIT study in women with overweight/obesity in their reproductive age, where they showed a decrease in glucose total AUC of -54 (standard deviation -64) mmol/L after six weeks (110). With a statistical power of 80% and an alpha level of 0.05 (two-sided), 12 participants are needed per group to detect such difference between the HIT and control group. However, there is no data regarding the effects of TRE nor of the combination of TRE and HIT in this population, hence to compare the four groups, the data is too scarce to perform a power calculation. Because of the COVID-19 pandemic, the main study will include 27 participants in each group to account for the expected dropout of 15% and possible missing measurements.

Every participant with at least one outcome measure in the pre- and post-test was included in the statistical analysis regardless of adherence to the intervention, and according to the group, the subject was allocated into (intention-to-treat analysis). Shapiro-Wilk test was used to assess the assumptions of normality and visually inspected normality from the histogram and Q-Q plots of residuals. It was assumed that there were no systematic differences between groups at baseline due to the randomization model used in the current study (111). To assess changes within groups, a univariate general linear model was used, and data were reported estimated mean difference (-EM) with a 95% confidence interval (CI). A univariate general linear model covariance analysis (ANCOVA) was used to test the differences between groups, with Bonferroni adjustments. The difference of change between pre- and post-test was used as the dependent variable in the analyses, and pre-test values were used as covariates. P-values < 0.05 were considered as significant. All descriptive data are presented as mean ± standard deviation (SD), with mean differences ± SD of differences between conditions. The statistical analysis was undertaken using SPSS Statistics program version 26 (IBM SPSS Inc., Chicago IL., USA) software for Mac.

6 Results

6.1 Participant characteristics

The participants were recruited from September 2019 to February 2020 through community advertisements and social media channels. A total of 140 women volunteered to participate in this study. Forty-nine women met the inclusion criteria and were able to participate; their characteristics at baseline are presented in Table 6.1.1. Eleven of them dropped out for different reasons (Figure 6.1.1). Thirty-nine participants completed the study period, their baseline and post-test characteristics are presented in Supplementary Table 6.1.2 (Appendix C). Results in total body mass and BMI were added in the current project as an exploratory outcome (Appendix C).

Because of the closing of the exercise laboratory at the Next Move Core Facility at St. Olav's hospital due to the COVID-19 outbreak, we could not measure six participants VO_{2max} in the post-test (TRE n = 2, HIT n = 1, TREHIT n = 2, and CON n = 1). Additionally, we excluded four participants from the analyses of VO_{2max}; three participants because of unreliable max test (technical difficulties) and one because of sickness.

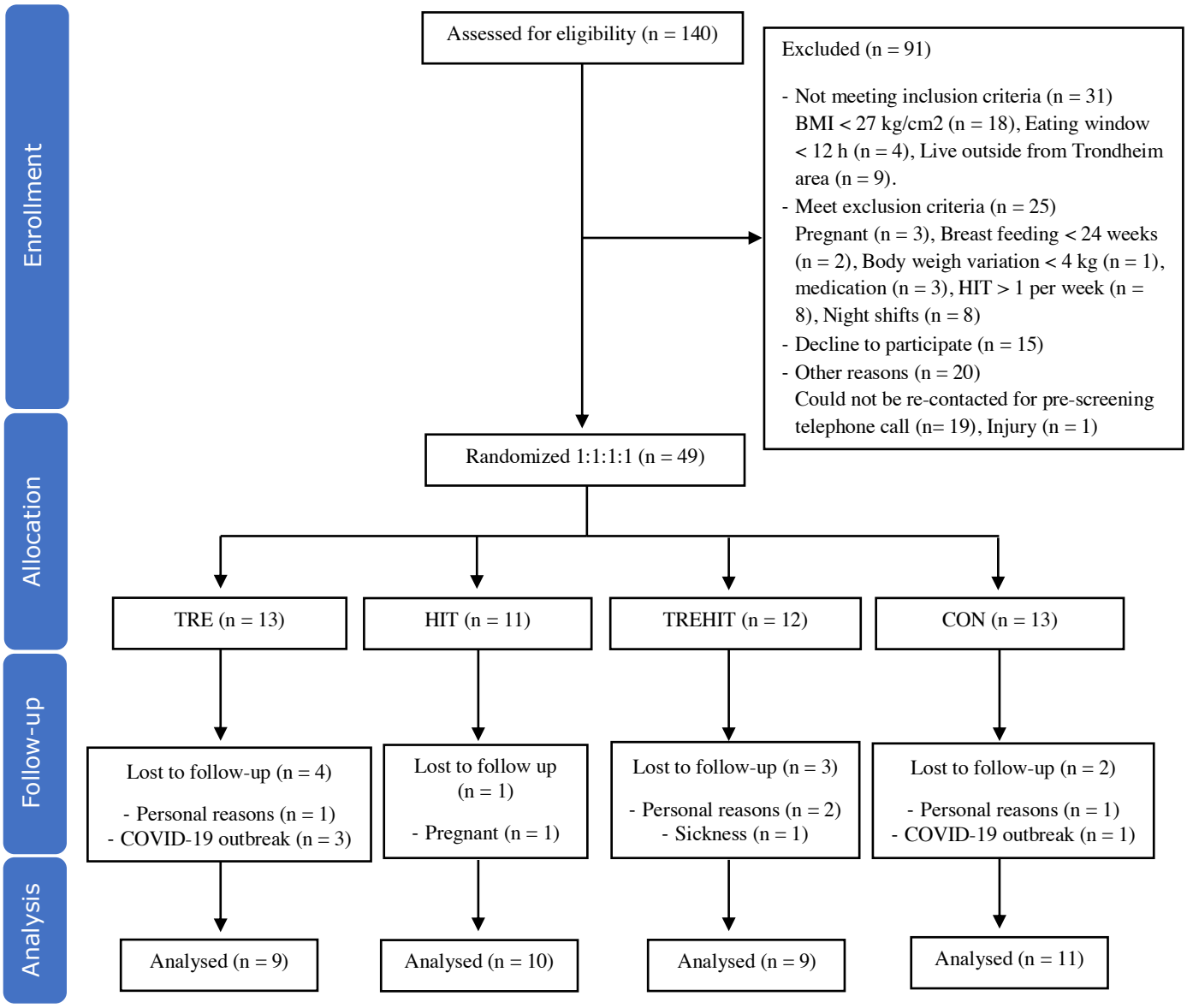


Figure 6.1.1. Flow chart of participant inclusion in the study

Table 6.1.1 Participant characteristics at baseline.

	TRE (n = 13)	HIT (n = 11)	TREHIT (n = 12)	CON (n = 13)
	Baseline	Baseline	Baseline	Baseline
Age, yr.	32.9 ± 11.9	30.8 ± 7.1	32.1 ± 8.4	34.2 ± 8.5
Weight, kg	92.04 ± 9.3	91.4 ± 15.1	87.4 ± 8.7	95.4 ± 9.5
Height, cm	170.5 ± 6.6	167.1 ± 3.4	169.0 ± 4.9	167.8 ± 5.5
BMI, kg/cm^2	31.2 ± 3.6	32.8 ± 5.5	30.6 ± 2.6	34.0 ± 4.2
SBP, mmHg	118.1 ± 1.4	121.1 ± 7.0	128.6 ± 12.9	119.1 ± 9.1
DBP, mmHg	77.4 ± 5.4	77.7 ± 8.1	86.8 ± 9.6	79.2 ± 7.8
Fasting Glucose, mmol/L	4.4 ± 0.8	4.9 ± 0.4	4.9 ± 0.3	4.9 ± 0.4
AUC, mmol/L	688.0 ± 108.0	699.6 ± 168.7	698.0 ± 145.8	807.1 ± 278.1
HbA1c, mmol/mol	33.5 ± 2.9	32.4 ± 4.0	34.4 ± 3.1	33.4 ± 2.6
Chol, mmol/L	4.5 ± 0.84	4.6 ± 0.6	4.5 ± 0.8	4.7 ± 1.29
HDL, mmol/L	1.4 ± 0.3	1.6 ± 0.2	1.5 ± 0.4	1.4 ± 0.4
LDL, mmol/L	3.0 ± 0.8	3.0 ± 0.7	2.9 ± 0.6	3.2 ± 1.2
TG, mmol/L	1.2 ± 0.4	0.9 ± 0.2	1.0 ± 0.4	1.2 ± 0.7
VO_{2max} L/min	3.3 ± 0.3	3.2 ± 0.5	3.1 ± 0.3	3.1 ± 0.5
ml/kg/min	35.7 ± 5.2	36.4 ± 7.5	35.9 ± 4.6	33.4 ± 6.2
ml/ min$^{0.75}$/min	110.2 ± 12.7	111.5 ± 8.5	109.0 ± 12.0	103.8 ± 17.9
HR_{max}, beats	189.3 ± 12.7	187.8 ± 8.8	188.4 ± 9.8	188.4 ± 11.5

Table 6.1.1. Participant characteristics at baseline. Data presented as mean ± SD, and percentage include all participants randomized at baseline (n = 49). BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, AUC = glucose total area under the curve, HbA1c = glycosylated hemoglobin, Chol = total cholesterol, TG = triglycerides, VO_{2max} = maximum oxygen uptake, HR_{max} = maximum heart rate.

6.2 Adverse effects

There were no serious adverse events reported by participants in the current study. During the blood sample testing, five participants were afraid of the procedure and reported fatigue and dizziness during the blood test. Two participants reported discomfort due to the implantation of the glucose sensor in the arm. In the TRE group, one participant reported fatigue and increased hunger in the evening during the first week of intervention, and resolved this by increasing water intake. All participants in the HIT and TREHIT group tolerated the exercise training well, and no injuries were reported. One participant in the TREHIT group reported worsening of migraines that led her to drop out of the study.

6.3 Adherence

The average daily eating window at baseline for the TRE, HIT, TREHIT and CON group was 13 ± 1.1 h/d (mean ± SD), 12.6 ± 1.8 h/d, 12.9 ± 0.8 h/d, and 12.4 ± 1.3 h/d respectively. The average daily eating window for the TRE and TREHIT group during the intervention was 9.3 ± 0.7 h/d and 8.9 ± 0.6 h/d, respectively (Figure 6.3.1), without between-group differences ($p = 1.0$). The TRE and TREHIT group showed a significant decrease in their eating window of 3.7 ± 0.2 h/d (95% CI: -4.2, -3.1) and 4.0 ± 0.2 h/d (95% CI: -4.5, -3.4) respectively. Significant differences were seen in the duration of the eating window between the TRE and TREHIT group compared to the HIT and CON group ($p < 0.01$). Participants in the TRE and TREHIT group adhere to the eating window 6.3 ± 0.8 and 6.6 ± 1.1 days per week, respectively, with no differences between both groups ($p = 0.48$).

Participants in the HIT and TREHIT group attended 18.8 ± 2.0 (89%) and 19.7 ± 1.2 (94%) of the 21 scheduled exercise sessions, with no difference between the groups ($p = 0.28$).

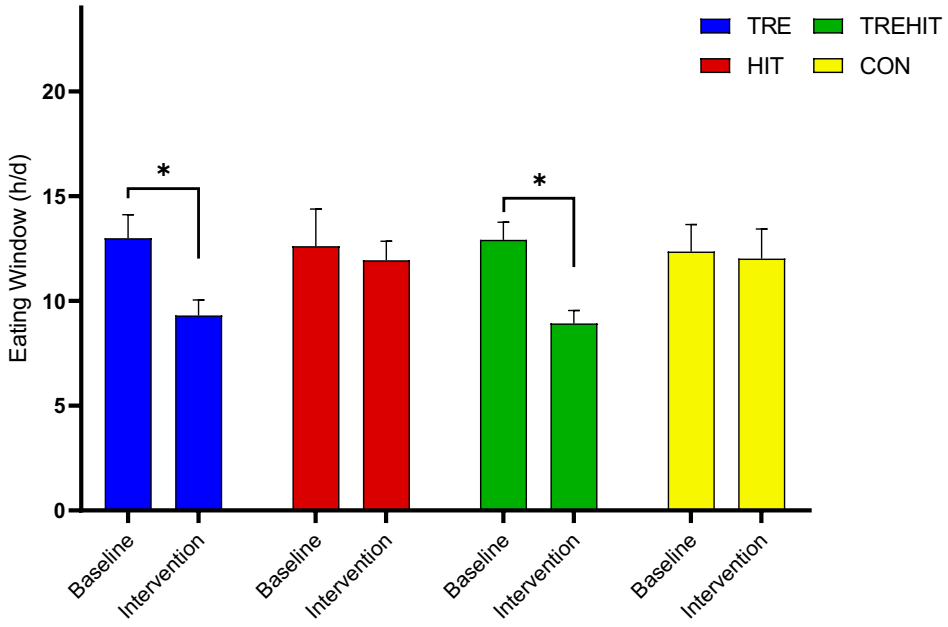


Figure 6.3.1. Eating window hours per day (h/d). This table shows the daily eating window in the four groups. Data presented as means ± standard error of the mean (SEM). (*) Significant differences within-group (95% CI does not include zero) from pre- to post-test.

6.4 Glucose total area under the curve (AUC), fasting glucose, and glycosylated hemoglobin (HbA1c)

Fasting glucose decreased in the TREHIT group only by 0.2 ± 0.4 mmol/L (95% CI: -0.3, -0.8) (Figure 6.4.1.A). There was no significant between-group difference in change in fasting glucose after the intervention (p = 0.15). No significant differences were seen in glucose total area under the curve (AUC), whether within or between the four groups (Figure 6.4.1.B). There were no significant changes in HbA1c within or between the four groups, yet a tendency of decreased values in the TRE group by 0.9 ± 0.5 mmol/mol (95% CI: -2.1, 0.4), HIT group 0.3 ± 0.3 mmol/mol (95% CI: -0.6, 0.5) and TREHIT group 1.0 ± 0.5 mmol/mol (95% CI: -2.2, 0.2) (Figure 6.4.1.C).

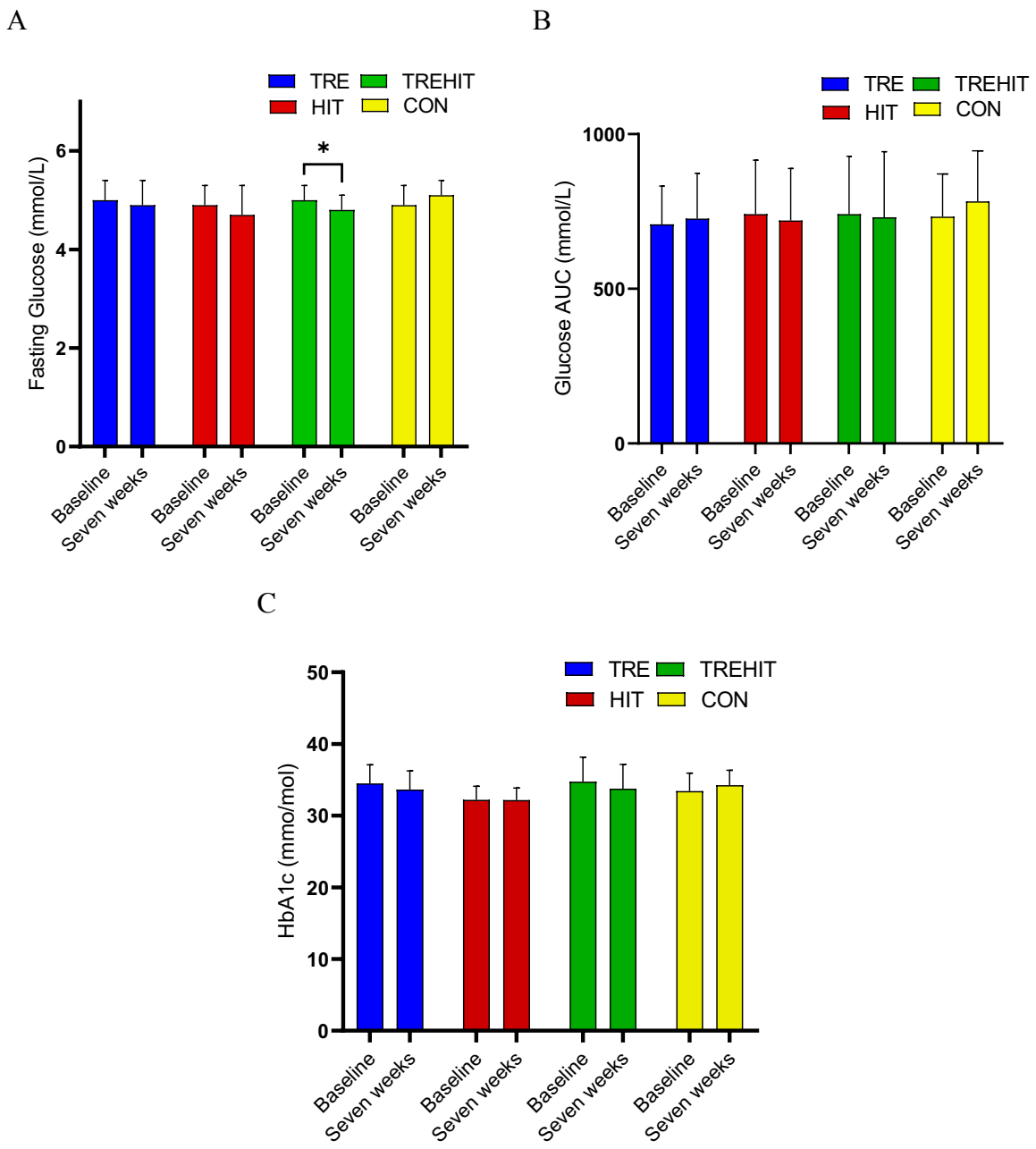


Figure 6.4.1. Glycemic outcomes. Changes in (A) fasting glucose, (B) Glucose total area under the curve (AUC), and (C) Glycosylated hemoglobin (HbA1c) after seven weeks. Error bars in the three panels (A, B, and C) are suppressed for visual clarity. Data presented as means ± standard error of the mean (SEM). (*) Significant differences within-group (95% CI does not include zero) from pre- to post-test.

6.5 Lipid levels and blood pressure.

There were no significant differences between the groups in total blood cholesterol (p = 0.08). Total blood cholesterol decreased in the HIT group by -0.4 ± 0.2 mmol/L (95% CI: -0.7, -0.1), whereas no significant changes were found in TRE 0.3 ± 0.3 mmol/L (95% CI: -0.5, 0.6), TREHIT -0.04 ± 0.2 mmol/L (95% CI: -0.5, 0.4) and CON 0.1 ± 0.1 mmol/L (95%CI: -0.2, 0.4) (Figure 6.5.1.A). Significant differences were found within HIT group regarding HDL-cholesterol -0.1 ± 0.04 mmol/L (95%CI: -0.2, -0.03), whereas no changes were seen in the other groups (Figure 6.5.1.B), and no differences between the groups (p = 0.31). LDL-cholesterol decreased only in the HIT group by -0.4 ± 0.1 mmol/L (95% CI: -0.7, 0.03) (Figure 6.5.1.C), however there were no differences between groups (p-value 0.10). In triglycerides levels no significant differences were seen within and between the groups (Figure 6.5.1.D).

There were no significant changes within or between groups regarding systolic blood pressure (Figure 6.5.2.A). In the TRE group diastolic blood pressure decreased by -5.0 ± 1.7 mmHg (95% CI: -9.1, -0.9) (Figure 6.5.2.B), yet, no differences between groups were found (p = 0.25).

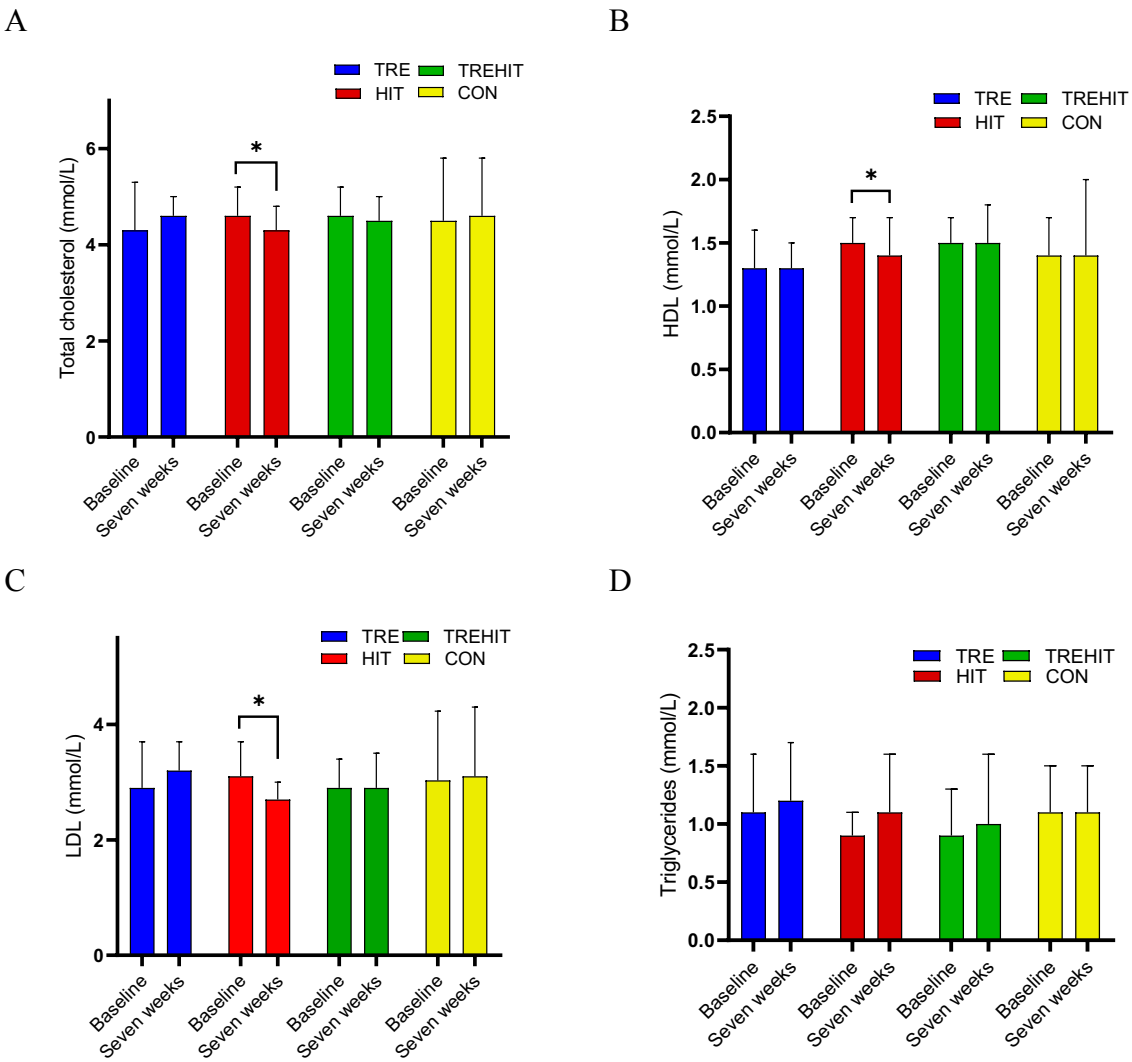


Figure 6.5.1. Lipid levels. Changes in (A) total cholesterol, (B) high-density lipoprotein cholesterol (HDL), (C) high-density lipoprotein cholesterol (LDL), and (D) triglycerides after seven weeks. Data presented as means ± standard error of the mean (SEM). (*) Significant differences within-group (95% CI does not include zero) from pre- to post-test.

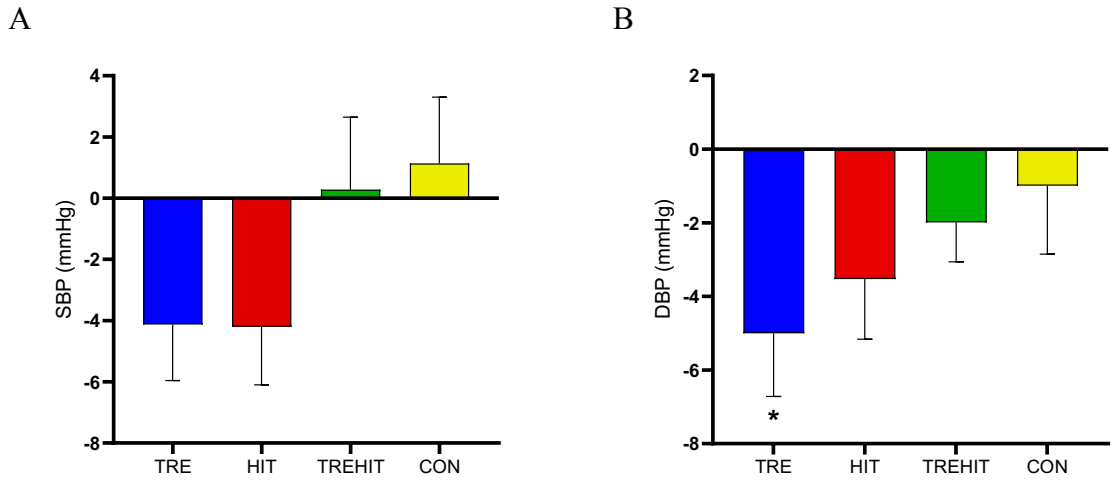
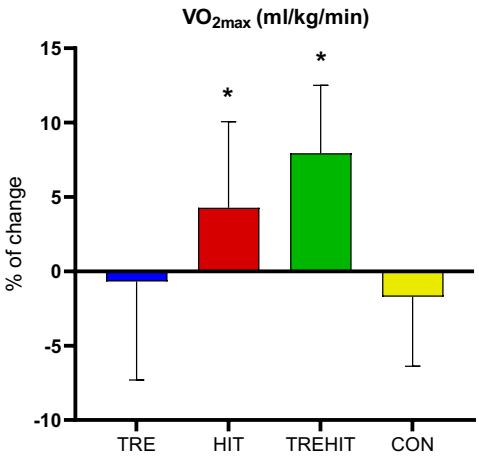


Figure 6.5.2. Blood pressure. Changes in (A) systolic blood pressure (SBP), (B) diastolic blood pressure (DBP) after seven weeks. Data presented as means ± standard error of the mean (SEM). (*) Significant differences within-group (95% CI does not include zero) from pre- to post-test.

6.6 Cardiorespiratory fitness

VO_{2max} (ml/kg/min) significantly increased in the HIT group by 1.6 ± 0.3 ml/kg/min (95% CI: 0.9, 2.3) and the TREHIT group 2.7 ± 0.7 ml/kg/min (95% CI: 0.6, 4.9), without between-group differences (p = 1.0) (Figure 6.6.1). There were significant differences in VO_{2max} (ml/kg/min) between the TREHIT and the TRE group (p = 0.01), and between the TREHIT and the CON group (p < 0.01).

A



B

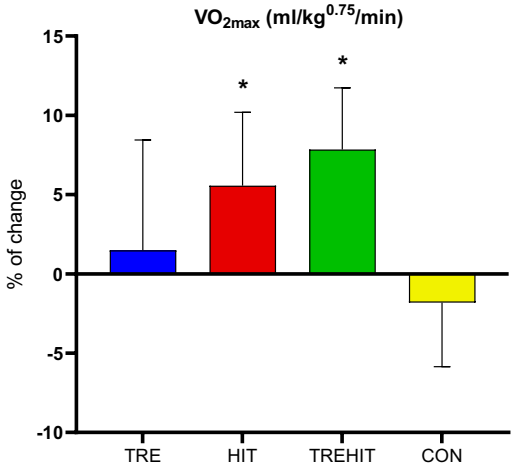


Figure 6.6.1. Mean percentage of change in maximal oxygen uptake (VO_{2max}) expressed as (A) ml/kg/min, and (B) ml/ $min^{0.75}$/min from baseline to post-intervention within the four groups (TRE, HIT, TREHIT, and CON). Data presented as means ± standard error of the mean (SEM). (*) Significant difference within groups (95% CI does not include zero) from pre- to post-test.

7 Discussion

The current master thesis reports from a larger study, aiming to determine the isolated and combined effects of TRE and HIT after seven-weeks intervention on cardiometabolic health in reproductive-aged women with overweight and obesity. The main findings were no between-group differences in any of the glycemic outcomes we measured, however, a tendency of decrease in glucose total AUC was seen in the HIT and TREHIT group, and a significant improvement in fasting blood glucose in the TREHIT group. Additionally, HbA1c in the TRE, HIT, and the TREHIT groups tended to decline, although not statistically significant. Significant increases in cardiorespiratory fitness (VO_{2max}, ml/kg/min) were seen in the HIT and the TREHIT group, without significant differences between these groups. The adherence was high in the three intervention groups, hence TRE and HIT isolated or combined may be a feasible intervention for reproductive-aged women with overweight/obesity.

7.1 Adherence and retention

Participants showed a high adherence to the TRE and HIT protocol in the respective intervention groups. We had a drop-out rate of 25%, with 10% due to the COVID-19 pandemic (Figure 6.1.1). Nevertheless, in the current study, adherence to the 10-h eating window was approximately 6.5 days a week in the TRE and the TREHIT group. In comparison, TRE studies have shown that compliance with the restricted eating window has been for 5 to 6 days per week (67,71,77). The high adherence to the TRE protocol in the current study can be explained by the fact that the eating window was not imposed, and participants chose where to place the eating window during the day, making it easier to adapt the intervention to their habitual lifestyle. In line with this, Wilkinson and colleagues (70), used a similar protocol of TRE (10 h/d) and found that participants can adhere to this regular TRE eating window with small variations of approximately one hour during the days in the week. The high adherence in the current study, may also be due to the fact that participants were contacted by phone call/sms/email weekly to review the protocol and give support. Because the TREHIT group had three exercise sessions a week, closer follow-up in this group might have influenced that higher

percentage of adherence to the 10-h eating window (~94%) compared to the TRE group (~89%). However, no significant differences in adherence rates were detected in the TRE and the TREHIT group.

Most of the participants in the TRE and TREHIT group reported difficulties to adapt to the restricted eating windows at the beginning of the study; however, this became easier after the first week. In line with other TRE studies where participants reported that it was easy to adapt to the restricted eating window after one to two weeks of TRE (67,77,78). Some participants in the TRE and TREHIT group stated that the main barrier which could make TRE challenging, was adapting TRE into their habitual lifestyle, and family life.

Similar to other TRE studies (61,76,78), the participants in the current study reported that it was harder to follow the TRE on the weekends compared to weekdays due to social activities. Participants with a family (mainly with small kids) found it harder to adapt the 10-h eating window to the family schedule (i.e., early breakfast and late last meal). In line with Parr et al. (68), who also reported that participants with a family tended to find it harder to adapt to TRE.

Adherence in the HIT and the TREHIT group to the exercise sessions was approximately 89% and 93%, respectively. The high adherence to the exercise training in the current study is similar to two studies with the same HIT protocol (4x4 combined with 10x1) performed three times a week in women with overweight (~85%) (98) and with polycystic ovary syndrome (~90%) (97). This could be explained by HIT being a time-efficient strategy (90,91) that generates higher enjoyment in women with obesity compared to MICT (101).

The combination of TRE and HIT (TREHIT) showed greater adherence compared with the two isolated interventions. However, there were no significant differences between the groups. Nevertheless, this implies that TRE and HIT combined is a feasible option in women with overweight/obesity in their reproductive age. Of note, the intervention period was relatively short (seven weeks); hence, studies with a longer duration should be performed to elucidate if TRE and HIT can be maintained long-term.

7.2 Glucose total area under the curve (AUC), fasting glucose and glycosylated hemoglobin (HbA1c).

After the seven weeks of intervention, the TRE group showed no significant changes in fasting glucose, glucose total AUC, or HbA1c. This is in line with several TRE studies (67,70,71,76) where they did not found improvements in glycemic variables. In contrast, other TRE studies (68,69,72), have reported improvements in glucose levels measured with 24-hr continuous glucose monitoring (CGM). However, protocols vary between TRE studies (i.e., controlled isocaloric meals vs. "free-living" conditions), hence making it hard to compare previous findings to our results. It is noteworthy, TRE in subjects with metabolic syndrome (70) and men with prediabetes (67), have reported that significant differences in fasting glucose and HbA1c were seen in participants who had elevated risk markers at baseline (i.e., hyperglycemia), suggesting that higher-risk patients with more severe metabolic diseases may have greater benefits compared to lower-risk individuals. Therefore, the lack of significant changes seen in the current study regarding fasting glucose, glucose tolerance, and HbA1c could be explained by metabolically healthy subjects at baseline. Nevertheless, in the current study, there was one participant in the TRE group who had impaired fasting glucose values (6 mmol/L) and showed an improvement of 11% (5.3 mmol/L) after the intervention. Most of the TRE studies are performed in subjects with normal baseline values; hence, studies investigating the effects of TRE in subjects with impaired glucose tolerance and fasting glucose are needed to determine if TRE can be a suitable intervention to reduce hyperglycemia.

The HIT group showed no significant changes in fasting glucose, glucose total AUC, or HbA1c after seven weeks. Previous research has shown contradictory results after HIT in women with overweight/obesity with normal fasting glucose values at baseline. Some studies report no improvements (96,97,99,112) and others a tendency to decrease (98,113). In this regard, a review by Jelleyman and colleagues (94), suggested that changes in insulin and glucose levels after HIT are related to the degree of disease, with greater changes in subjects with altered metabolic parameters (i.e., metabolic syndrome, and type 2 diabetes). Moreover, Alvarez and colleagues (114), found larger reductions in fasting glucose and fasting insulin levels in women with HOMA-IR > 5.0 at baseline compared to what was seen in these with HOMA-IR < 3.0 at baseline. Improvements in insulin sensitivity tend to be seen before 12

weeks compared to fasting glucose (94); hence the lack of changes seen in the current study may be due to the short intervention (seven weeks). However, a study in women with overweight/obesity after six weeks of 10x1 HIT (90%) three times per week reported no changes in fasting glucose levels, yet reductions in glucose total AUC (~4%) after a 3-h OGTT (96). These changes have been accompanied by an increase in GLUT4 translocation, and citrate synthase activity (a biomarker for mitochondrial density) in the skeletal muscle (96). These results in glucose tolerance deviate from the current study, which showed no significant differences in glucose total AUC after seven weeks of HIT. However, after two weeks of 10x1 HIT (90% HR_{max}) in women with overweight/obesity (99) and men with type 2 diabetes (115), improvements in glycemic variability in the 24-h CGM has been shown. In the current study, 24-h CGM data were not included; therefore, later analysis can indicate whether there was an improvement in glycemic control throughout the day. Nevertheless, the HIT protocol (10x1) used in the studies mentioned above (96,99,113–115) differs from the HIT protocol (the combination of two different HIT modalities; 4x4 and 10x1) used in the current study, hence comparing results is difficult. Of note, there are two studies performed in women with overweight (97) and with polycystic ovary syndrome (98) with the same training protocol as in the current study (4x4 and 10x1). Even though they did not measure glucose tolerance, they found significant improvements in insulin resistance measured as HOMA-IR after 10 weeks (97,98). Improvements in insulin sensitivity may potentially be translated into positive changes in glycemic control, due to insulin action in glucose uptake, glucose production, and inhibition in insulin-sensitive organs (18,19). However, insulin levels were not measured in the current project, but these analyses will provide further insight into the effects of TRE and HIT on glycemic control.

Significant improvements were seen in the TREHIT group, yet no significant changes in glucose AUC or HbA1c. Nevertheless, there were no significant differences between the four groups; hence it cannot be said that the combination of TRE and HIT produced larger improvements compared to isolated TRE and HIT. There are no studies to date that combine TRE and HIT; however, a study by Moro and colleagues (57), found significant decreases in fasting glucose blood levels (~11%) in resistance-trained man after eight weeks of TRE (8 h/d). However, such decreases were not evident in resistance-trained women (79). Moreover, in a study by Bhutani and colleagues (116), where they compared the isolated and combined effects of alternate-day fasting and MICT (75% HR_{max}), they showed no changes in fasting glucose levels after 12 weeks in subjects with obesity. It is hard to compare findings with the studies

mentioned above due to the variation in dietary and exercise modalities used. However, the significant decrease in fasting glucose seen in this study may be explained by the similar processes in which TRE and HIT improve glucose control. A decrease in fasting glucose accompanied by increased gene expression of Akt2/PKB (Protein Kinase B), which is an essential step via PI3K in the insulin-stimulated glucose uptake, was reported after one week of TRE (6 h/d) (69). Moreover, after HIT interventions it has been seen an increase IRS-1 expression in the skeletal muscle and adipose tissue, activation of AMPK, and GLUT4 translocation (95,115). Additionally, Little and colleagues (115) proposed that the reduction in insulin resistance and enhanced glycemic control may be due to increased mitochondrial capacity after HIT. In this regard, intermittent fasting approaches, similar to exercise, have been shown to stimulate mitochondrial biogenesis through the activation of AMPK and subsequent stimulation of the peroxisome proliferator-activated receptor-gamma coactivator – 1 alpha (PCG-1alpha, a marker of mitochondrial biogenesis) (59). However, possible improvements in hepatic glucose output after HIT could also be involved in the decrease on fasting glucose due to an increase in insulin sensitivity (117). Therefore, the combination of TRE and HIT may have synergistic effects that improve glucose control. However, the effect of this intervention over a longer period with a larger sample size should be investigated in future studies.

7.3 Lipid levels and blood pressure

After seven weeks of intervention, the TRE group showed no significant differences in lipid levels, such as total cholesterol, HDL, LDL, and triglycerides. This is in line with other TRE studies, where it was not possible to find differences in lipid levels in resistance-trained women (79) and men (57) and subjects with obesity (71). The lack of changes in lipid levels may be due to the normal baseline values of the subjects included in the current study. In contrast, some TRE studies have shown conflicting results, where they have seen a worsening effect on blood lipid levels (67–69). Differences in TRE protocols, the population studied, and intervention duration may explain the contradictory results between studies in lipid levels. Therefore, more TRE studies are needed to determine the effects of TRE on lipid metabolism.

On the other hand, the TRE showed significant improvements in diastolic blood pressure of approximately -5.0 mmHg (~6%). This is an important finding since high blood pressure is considered an important risk factor for cardiovascular disease and all-cause mortality (118). It

has been proposed that a decrease of 10 mmHg in systolic blood pressure or 5 mmHg in diastolic blood pressure is associated with approximately 40% and 30% reductions in the risk of stroke and ischemic heart disease deaths, respectively (119). In comparison with the current study, Gabel and colleagues (71) found a decrease only in systolic blood pressure of 7 mmHg (~5%) after 12 weeks of TRE (8 h/d) in subjects with overweight and obesity. Moreover, in subjects with metabolic syndrome, a significant decrease in systolic blood pressure (-5 mmHg, ~4%) and diastolic blood pressure (-6 mmHg, ~8%) after 10 weeks of TRE (10 h/d) were reported (70). Meanwhile, Sutton and colleagues (67), reported a significant decrease in systolic and diastolic blood pressure of 11 mmHg (~8%) and 10 mmHg (~12%), respectively, in men with prediabetes, after five weeks of TRE (6 h/d). However, in these last two studies mentioned (67,70), most of the subjects with metabolic syndrome and men with prediabetes were taking antihypertensive medication; hence, additive effects from the pharmacotherapy could have induced greater improvements (67,70). Additionally, Sutton el at (67), proposed that increases in insulin sensitivity could have also affected this enhanced improvement in blood pressure. It has been seen that insulin-mediated nitric oxide synthase production is important to induce a vasodilatory response; therefore, insulin resistance will hamper this process leading to a subsequent vascular dysfunction (25). Insulin sensitivity has not yet been measured in the current study to corroborate those findings, and the mechanisms underlying TRE's effects on blood pressure are still unknown.

The HIT group showed significant decreases in total cholesterol, HDL, or LDL, yet no significant changes in triglycerides. However, there were no significant differences between the groups. The decrease in total cholesterol and LDL can be explained due to an increase in insulin sensitivity in the adipose tissue (i.e., lipolysis inhibition and lipogenesis), mitochondrial volume, and fat oxidation in the skeletal muscle after exercise training (95,96,120). On the other hand, the results in HDL in the current project deviates from other studies that show a significant increase (95,97,120) or no changes in HDL after exercise training (98,112). It seems that HDL values show greater improvements when they are impaired at baseline or in combination with hyperinsulinemia (95,120). The decrease in HDL cholesterol post HIT intervention may be due to decreased energy intake or increased compensatory feeding. In this regard, after exercise, a tendency to an increased energy intake can be seen, resulting in an inappropriate food choice and a desire for self-reward (121). On the other hand, an increase in appetite suppression after exercise may lead to a change in the quality and quantity of food (i.e., "healthier diet") (104). Therefore, future analysis of the food diaries should be performed to

seek changes in eating habits. A decrease in HDL cholesterol may also be affected by the increased insulin sensitivity and decrease of glucose levels that affect the production of cholesterol and triglycerides (122). However, insulin levels and insulin resistance has not been measured in the current study; hence, changes in insulin levels and HDL cholesterol in this sample, and the correlation between them requires further investigation.

The HIT group showed no significant changes in blood pressure. In comparison, after 16 weeks of HIT, significant improvements have been reported in blood pressure in women with overweight and prehypertension compared with normotensive counterparts (123). Moreover, in subjects with metabolic syndrome, Tjonna and colleagues (95), found significant changes in systolic and diastolic blood pressure of -9 mmHg (~6%) and -6 mmHg (~6%), respectively after 16 weeks of HIT. These changes induced by exercise can be explained by improvements in nitric oxide bioavailability and a decrease of oxidized-LDL, improving endothelial function, and increasing flow-mediated dilatation (95,124). It is well known that exercise training has positive effects on blood pressure; however, the lack of significant changes in the current study may be due to the normal values at baseline, and the short intervention period.

The TREHIT group did not show any significant changes in lipid profile or blood pressure. Therefore, no positive additive effects were seen in these outcomes after the combination of TRE and HIT. Again, these results may be due to the participants having normal values at baseline, the short-term intervention, and small sample size.

7.4 Cardiorespiratory fitness

The HIT and TREHIT group showed significant improvements in relative VO_{2max}, 1.6 ml/kg/min (~5%), and 2.7 ml/kg/min (~8%), respectively. Only the TREHIT group showed significant differences compared to the TRE group ($p = 0.01$) and the CON group ($p < 0.01$). However, no between-group differences were seen between the HIT and the TREHIT group ($p = 1.0$). Therefore, we cannot say that the combination of TRE and HIT leads to more significant improvements in VO_{2max} compared to HIT alone. It is important to mention that VO_{2max} describes the body's ability to deliver and use oxygen to meet the metabolic demands during maximal exercise (125). The mechanisms underlying changes in VO_{2max} can be explained by the interplay of central and peripheral factors that account for the oxygen supply (cardiac output and blood oxygen-carrying capacity) and demand (muscle oxidative capacity, capillary, and mitochondrial volume) of the organism respectively (125,126). In the current study, we cannot

assess the mechanisms underlying the improvement in VO_{2max}. However, improvements in VO_{2max} after HIT may be as a result of enhanced stroke volume of the heart, hence improving oxygen delivery (95,107). Additionally, improvements in mitochondrial volume and oxidative capacity seen after HIT may be due to an increase in PCG-1-alpha expression and sarcoplasmic/endoplasmic reticulum Ca^{+2} ATPase activity in the skeletal muscle (95,124,127). Consequently, HIT can induce central and peripheral adaptations that lead to improvements in cardiorespiratory fitness. Cardiorespiratory fitness measured as VO_{2max} is an important factor due to its strong association with cardiovascular risk and all-cause mortality (83). It has been proposed that an improvement of one MET (metabolic equivalent task) approximately 3.5 ml/kg/min in cardiorespiratory fitness resulted in a reduction of approximately 12% to 17% on cardiovascular and all-cause mortality (83,128,129). However, in the current study VO_{2max} only improve by 1.6 ml/kg/min, and 2.7 ml/kg/min in the HIT and the TREHIT group, respectively. In comparison, two previous studies in women with overweight (98) and with polycystic ovary syndrome (97), that used the same HIT protocol, as in the current study, showed significant improvements in by 2.6 ml/kg/min (~8%) and 3.7 ml/kg/min (~10%) after 10 weeks, respectively. Therefore, a longer HIT intervention may have led to larger improvements in VO_{2max}, thereby inducing greater benefits in overall health.

8 Study strengths, and limitations.

The strength of this study is that it is a randomized control trial and the first investigation with the aim to determine the isolated and combined effects of TRE and HIT in reproductive-aged women with overweight/obesity. However, one important limitation of the current study is the small sample size. In the current project, preliminary findings from this on-going trial are reported. Due to the COVID-19 pandemic, several participants dropped out (10% of the total sample), and missing data is reported on several outcome variables. The laboratories got closed in March 2020, and we could no longer include new participants to the trial. Therefore, results should be interpreted with caution due to an increased risk of type II error. Additionally, there were five participants included in this study (TRE n = 1, HIT n = 1, TREHIT n = 2, and CON n = 1) who were affected by COVID-19 pandemic and subsequent quarantine period. Even though all the participants included in the current thesis reported that their eating habits and physical activity were not affected by the COVID-19 situation, further sensitivity analysis should be conducted. On the other hand, participants in the HIT (n = 1) and TREHIT (n = 1) group continued training outdoors under supervision, and one participant in the TREHIT group had a treadmill at work. The cardiopulmonary test was not performed in these participants due to the closing of the laboratory at St. Olav's hospital; therefore, future analysis of the possible effects of training outdoors on VO_{2max} should be investigated.

Another limitation in the current study was the lack of personnel (only two master students), making it difficult to blind participants and investigators in the testing procedures, training sessions, and follow-up. However, baseline tests were conducted before randomization. It is important to mention that all procedures were conducted objectively.

Another strength of the current study is that all workouts were supervised and recorded to make sure that the correct intensity was achieved during training. However, there were two participants (HIT n = 1, and TREHIT n = 1) that preferred to train on their own (i.e., local gym), one or two days of the week due to personal reasons. Nevertheless, their training sessions were recorded and checked. On the other hand, TRE was self-reported, which means that we cannot say if the time of the first and the last meal was accurate. Additionally, in TRE studies, others have found that even though this strategy does not prescribe a caloric deficit directly, individuals tend to reduce their daily caloric intake by approximately 20% while on TRE

(61,71). Moreover, studies report decreases in appetite and capacity to eat, and increased sensation of fullness (67,76), as well as changes in food preferences (68), have been seen during TRE interventions. The future analyses of data from the food diaries and appetite registration will give better insight regarding how this could affect the outcome variables and strengthen the study.

The self-selected eating window may appear to contribute to high adherence in the TRE and TREHIT group; however, this can also be considered as a limitation in the study. It has been suggested that an early TRE (eating before 5 pm) is more beneficial than a later TRE (eating the last meal at 9 pm) for improving cardiometabolic risk parameters (72). Therefore, it cannot be assessed if the time where the eating window is placed during the day may have affected the outcome measures. Nevertheless, with a larger sample size in the current study, subgroup analysis may be conducted to examine whether the time where the eating window is placed can have different effects on the outcome measures.

The combination of the two different HIT modalities (4x4 and 10x1) is a limitation because we cannot say if one form of HIT induces greater changes compared to the other modality. Of note, both the 4x4 HIT protocol studied in subjects with metabolic syndrome (95) and the 10x1 HIT studied in women with overweight and obesity (96) have been reported to induce improvements in glycemic control. Moreover, this HIT protocol (4x4 and 10x1) has been used before in two studies in reproductive-aged women with overweight (98) and with polycystic ovary syndrome (97), where they reported significant improvements in insulin sensitivity and high adherence (~85-90%) after 10 weeks.

Another limitation is that the participants joined the study voluntarily; therefore, they could have been more motivated to do exercise training and TRE intervention compared with the general population (i.e., women with overweight and obesity), leading to self-selection bias. However, there were no significant changes in the outcome variables in the control group, and this strengthens the study. This could be explained by the "delayed treatment" that was offered to the control group that could have worked as a motivational factor for them not to start TRE or exercise.

Another limitation of the study was that we only measured glucose levels in the morning and after a 2-h OGTT. Other studies investigating TRE (68–70,72) and HIT (99,115) have measured glucose levels throughout the day using a 24-h CGM. Therefore, future analysis of the 24-h CGM data used in the study can give a better understanding of the isolated and combined effects of TRE and HIT on glycemic control.

The current project lasted only seven weeks; hence, the study period can be a limitation with the consequences of missing important changes over time. Therefore, a longer intervention period with a larger sample size could have strengthened the study. Additionally, a follow-up period would be of interest to see if this intervention can be maintained for a longer period, without supervision and frequent follow-up by the research team.

9 Future perspectives

This study chose a sample of women with a range of ages from 19 to 45 years old, body weight from 76 to 116 kg, and BMI from 27 to 32 kg/cm^2 and can be generalized only to a population with similar characteristics. TRE and HIT showed to have good adherence, and low adverse effects were reported. Therefore, TRE and HIT isolated and combined are a feasible option in women with overweight and obesity. Nonetheless, the constant communication and support in the current study may have been important to maintain adherence in women. TRE and HIT have been implemented with various protocols, and in different populations, hence it is hard to compare between studies. It is noteworthy, studies in women are limited, leaving a gap for the understanding of the underlying mechanisms on glycemic control in this population. Future studies in TRE should determine whether it is the placement of the eating window or the time spent in the fasted state over each day that is more important to induce improvements in cardiometabolic health. It is still unknown which HIT protocol (i.e., volume, intensity, frequency) and time of exercise (i.e., morning/evening, pre/post-meal) is better for improvements in glucose control in women with overweight/obesity.

Strategies such as a smartphone application to record the energy intake and exercise session in real-time may be a helpful alternative to monitor and have a better understanding of day-to-day lifestyle variance. Additionally, the use of 24-h CGM to assess changes in glucose excursions throughout the day provides a better insight into the effects of meal timing and exercise training. Studies with larger sample size and during a longer study period than the current study are needed to evaluate if these findings in glycemic control are maintained or continue to change in a positive direction over time. Nevertheless, this project provides helpful information that can be used for future studies with the aim of research in women's physiology.

10 Conclusion

Alternative diet-exercise strategies are highly warranted to manage the obesity epidemic since current recommendations have low uptake. The preliminary results of our study suggest no changes in glucose total AUC in all four groups. However, there were promising tendencies for improvement in fasting glucose after TREHIT, in diastolic blood pressure after TRE, and in VO_{2max} after HIT and TREHIT. Additionally, HbA1c, which is an important measure to assess glycemic control over a period of time, was seen to change in the positive direction in all the intervention groups. Total cholesterol and LDL decreased in the HIT group, however, HDL cholesterol also decreased in this group.

Although these preliminary results are unable to show which intervention is best regarding cardiometabolic risk markers, the high adherence reported in all the interventions suggests that TRE and HIT are feasible strategies for reproductive-aged women with overweight and obesity for seven weeks.

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Appendix A

Information letter for the participants regarding the testing procedures.

Informasjon om testing

Takk for at du har sagt ja til å være med i studien! Det er en del tester som skal gjøres både i starten og i slutten av denne studieperioden, og det er viktig at du leser gjennom informasjonen nedenfor. Du vil få utdelt en studiehåndbok hvor du finner mer informasjon om studien første gang du kommer inn. Bare ta kontakt hvis du har spørsmål om testingen! trine.moholdt@ntnu.no, 97098594

TESTDAG 1	
Dag og dato	
Kl	
Hva skal gjøres?	**Test av kondisjon**
Oppmøtested	**Treningsenhet, 1.etasje Akutten Hjerte Lunge-senteret, se kart rød ring**
Totalt tidsbruk	**Ca. 45 min**

Sørg for å spise et lett måltid minst 2 timer før oksygenopptakstesten og drikk godt. Du bør ha på treningsklær/trøye uten lange armer, og gode sko, helst joggesko. Du skal gå eller jogge på tredemølle med en maske vi måler hvor mye oksygen kroppen din klarer å ta opp og forbruke. Dette er en test på kondisjon/fysisk form. Du skal holde på så lenge du orker. Vi måler også pulsen din underveis. Selve testen tar ca. 20 minutter. Du kan dusje her etterpå hvis du vil.

TESTDAG 2	
Dag og dato	
Kl	**(fastende)**
Hva skal gjøres?	**Kroppssammensetning, blodtrykk, blodprøver og glukosebelastning**
Oppmøtested	**Treningsenhet, 1.etasje Akutten Hjerte Lunge-senteret, se kart rød ring**
Totalt tidsbruk	**Ca. 2.5 timer**

Du må møte FASTENDE. Det vil si at du skal ikke ha spist eller drukket noe annet enn vann siden kl. 22.00 kvelden før. 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 bør drikke godt med vann før du kommer, for da blir det lettere å ta blodprøver.

Undersøkelse av kroppssammensetning

Vi vil undersøke kroppssammensetningen (det vil si forholdet mellom fett- og muskelmasse) ved hjelp av en kroppssammensetningsvekt som heter In Body.

Blodtrykk

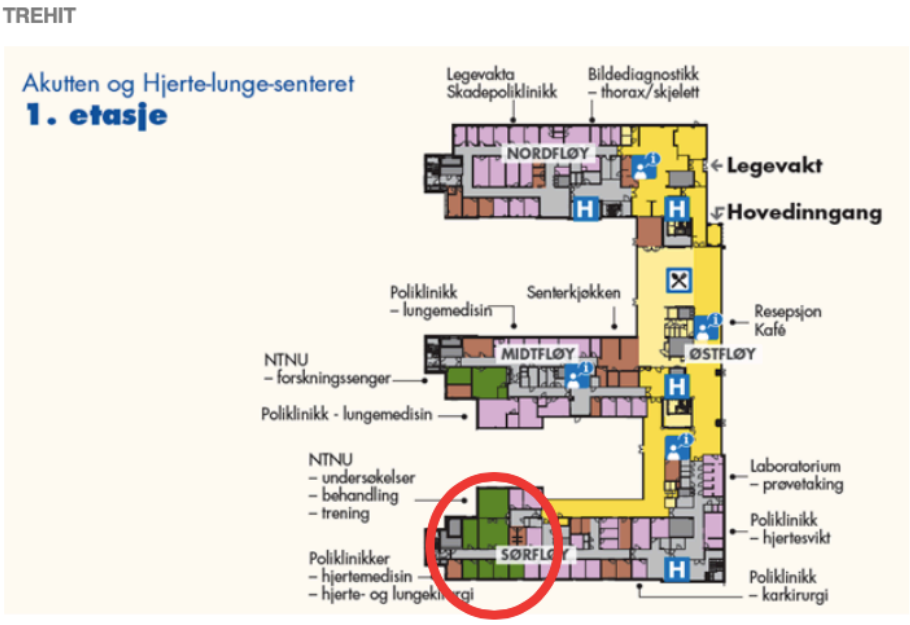
Hvilende blodtrykk vil bli målt i sittende.

Blodprøver og glukosebelastning

Vi vil ta en del blodprøver av deg. Vi måler insulinsensitivitet og glukose, det vil si blodsukker. Du sitter og slapper av under hele denne målingen. Du vil bli bedt om å drikke 2,5 dl sukkervann, og vi måler blodsukkeret ditt hver halvtime i 2 timer. Du vil få svar på blodprøvene. Det er lurt å ta med seg litt mat som du kan spise etter glukosebelastningen.

Etter testingen den siste dagen trekker vi hvilken gruppe du skal være i.

VELKOMMEN!



Appendix B

Information letter for the participants regarding the project.

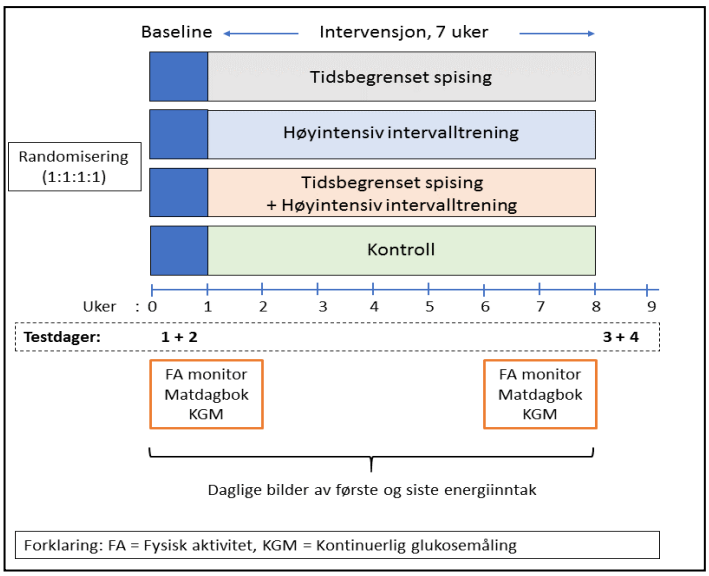
FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

INTERVALLTRENING OG TIDSBEGRENSET SPISING HOS KVINNER

Dette er et spørsmål til deg om å delta i et forskningsprosjekt for å undersøke effekter av intervalltrening med høy intensitet og såkalt tidsbegrenset spising vil bedre blodsukkerregulering hos kvinner med kroppsmasseindeks (BMI) på 27 kg/m^2 eller mer. For å delta må du være mellom 18 og 45 år og ha et tidsvindu for når du spiser som er på 12 timer eller mer per dag (det vil si at det går minst 12 timer fra du spiser det første måltidet for dagen til du spiser det siste). Du må også være i stand til å gå eller løpe på en tredemølle eller sykle på en spinningsykkel i minst 60 minutter og ikke trene intervalltrening med høy intensitet mer enn én gang i uka. Du må forstå muntlig og skriftlig norsk eller engelsk for å være med. Studien gjennomføres ved NTNU.

HVA INNEBÆRER PROSJEKTET?

Prosjektet innebærer at vi vil måle ditt blodsukker, insulin, fettstoffer i blodet, kroppssammensetning, fysisk form og blodtrykk ved oppstart og igjen etter sju uker. Du vil også bli bedt om å svare på noen spørreskjema (om blant annet fysisk aktivitet og søvn). Du må komme inn til undersøkelser på to separate dager i starten av studien og igjen etter åtte uker. Undersøkelsene varer i ca 2.5 time den ene av de to testdagene og ca 40 min den andre, både ved oppstart og avslutning av studien. Du må komme inn fastende på morgenen den ene av disse dagene ved oppstart og ved avslutning av studien.. De som blir med blir tilfeldig fordelt til én av fire grupper. Den ene gruppa skal begrense tidsvinduet for matinntak til maksimum 10 timer hver dag i sju uker. Den andre gruppa skal trene intervalltrening tre ganger i uka og spise som normalt. Den tredje gruppa skal både begrense tidsvinduet for matinntak til maksimum 10 timer hver dag og trene intervalltrening tre ganger i uka. Treningene vil foregå under veiledning ved St.Olavs hospital og du kan velge hvilken tid på dagen du vil komme inn og trene. Den siste gruppa skal være en kontrollgruppe som fortsetter å leve som vanlig. De som kommer i kontrollgruppa vil etter denne første perioden bli tilbudt å følge ett av programmene for de andre gruppene, etter eget ønske (se figur nedenfor). De vil bli tilbudt samme veiledning og oppfølging som de som først blir fordelt til disse gruppene, i sju uker etter at de har vært på den andre testdagen.



I prosjektet vil vi innhente og registrere opplysninger om deg. Dette omfatter: alder, vekt, høyde, kroppssammensetning (andel muskler og fett), hvor aktiv du er (spørreskjema og data fra aktivitetsmåler), blodtrykk, blodprøveresultater, fysisk form og kontinuerlig måling av blodsukker. Du vil også bli bedt om å besvare hvor sulten/mett du føler deg og tidsrommet for matinntak. Du blir bedt om å gå med en glukosemåler som er en liten sensor som festes med en liten nål på overarmen din og som måler blodsukkerverdiene dine automatisk og lagrer den. Denne måleren ber vi om at du går med i to uker i starten av prosjektet og i to uker på slutten. I disse periodene vil du også bli bedt om å gå med en aktivitetsmåler, et slags armbånd på overarmen, og registrere hva du spiser i en online kostholdsdagbok. Vi ber også om at du, i hele studieperioden, tar et bilde av det første og det siste måltidet du spiser hver dag og deler dette med oss. I blodprøvene vi tar av deg vil vi måle kolesterol og blodsukker. Vi vil også fryse ned blod som vi skal analysere senere (analyser av insulin og andre markører for stoffomsetning). Vi ber også om å få oppbevare noe av blodet til analyser som ikke er bestemt ennå men som trolig vil være appetitthormoner, andre markører for energiomsetning og for inflammasjon (betennelsesmarkører). Du må komme inn fastende på testdagene, det vil si at du ikke har spist eller drukket noe annet enn vann siden klokka 22.00 kvelden før. Etter at vi har tatt de fastende blodprøvene skal du drikke en sukkeroppløsning. Vi vil så ta blodprøver av deg hvert 30. minutt i to timer for å undersøke hvordan kroppen din responderer på dette. Vi vil måle fysisk form ved test av maksimalt oksygenopptak på tredemølle. Denne testen innebærer at du går eller løper til du ikke orker mer mens du puster i en spesiell maske. Vi øker farten eller stigningen på tredemølle slik at du blir utslitt etter ca 10–15 minutter.

MULIGE FORDELER OG ULEMPER

Fordelen for deg som deltaker er at du vil få undersøkt blodsukkeret ditt, kroppssammensetning, blodtrykk og fysisk form. Vi tror også det vil være en fordel for din generelle helse med veiledet trening og det å spise tidsbegrenset i en periode. Vi ser ikke at prosjektet innebærer noen ulemper for deg utover at du må avse tid til undersøkelsene og eventuelle ubehag du opplever med blodprøvetaking og festing av blodsukkersensoren.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte Trine Moholdt på telefon 97098594 eller trine.moholdt@ntnu.no.

HVA SKJER MED OPPLYSNINGENE OM DEG?

Opplysningene som registreres om deg skal kun brukes slik som beskrevet i hensikten med prosjektet. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg vil bli anonymisert eller slettet senest fem år etter prosjektslutt.

HVA SKJER MED PRØVER SOM BLIR TATT AV DEG?

Blodprøvene som tas av deg vil inngå i en spesifikk forskningsbiobank. Denne spesifikke forskningsbiobanken vil opphøre ved prosjektslutt. Ansvarshavende for denne er prosjektleder Trine Moholdt. Blodprøvene vil fysisk være lagret ved Institutt for Sirkulasjon og Bildediagnostikk, NTNU.

FORSIKRING

Deltakere er dekket av pasientskadeloven.

OPPFØLGINGSPROSJEKT

Det kan bli aktuelt med et oppfølgingsprosjekt. Vi ber derfor om å få beholde dine kontaktopplysninger i tilfelle vi ønsker å kontakte deg igjen senere. Du kan bli med på prosjektet uten å gi oss tillatelse til å kontakte deg senere.

ØKONOMI

Utgiftene til dette prosjektet vil bli dekket av NTNU og fra en NovoNordisk Foundation Challenge Grant. Det er gratis å delta i prosjektet.

GODKJENNING

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning (REK 2019/851)

Etter ny personopplysningslov har behandlingsansvarlig NTNU og prosjektleder Trine Moholdt et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6 nr. 1a, artikkel 9 nr. 2a og deltakernes samtykke.

Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet kan du ta kontakt med Trine Moholdt, 97098594, trine.moholdt@ntnu.no.

Du kan ta kontakt med institusjonens personvernombud dersom du har spørsmål om behandlingen av dine personopplysninger i prosjektet. NTNUs personvernombud er Tomas Helgesen, 93079038, personvernombud@ntnu.no.

JEG SAMTYKKER TIL Å DELTA I PROSJEKTET OG TIL AT MINE PERSONOPPLYSNINGER OG MITT BIOLOGISKE MATERIALE BRUKES SLIK DET ER

Vær vennlig og kryss av i en av boksene under:

*Jeg **godkjenner** at mine kontaktopplysninger kan beholdes i tilfelle forskerne vil kontakte meg for eventuelle oppfølgingsstudier:* ☐

*Jeg **godkjenner ikke** at mine kontaktopplysninger kan beholdes i tilfelle forskerne vil kontakte meg for eventuelle oppfølgingsstudier:* ☐

Sted og dato	Deltakers signatur
	Deltakers navn med trykte bokstaver

Appendix C

Supplementary table. Participant characteristics at baseline and after completing the seven weeks intervention.

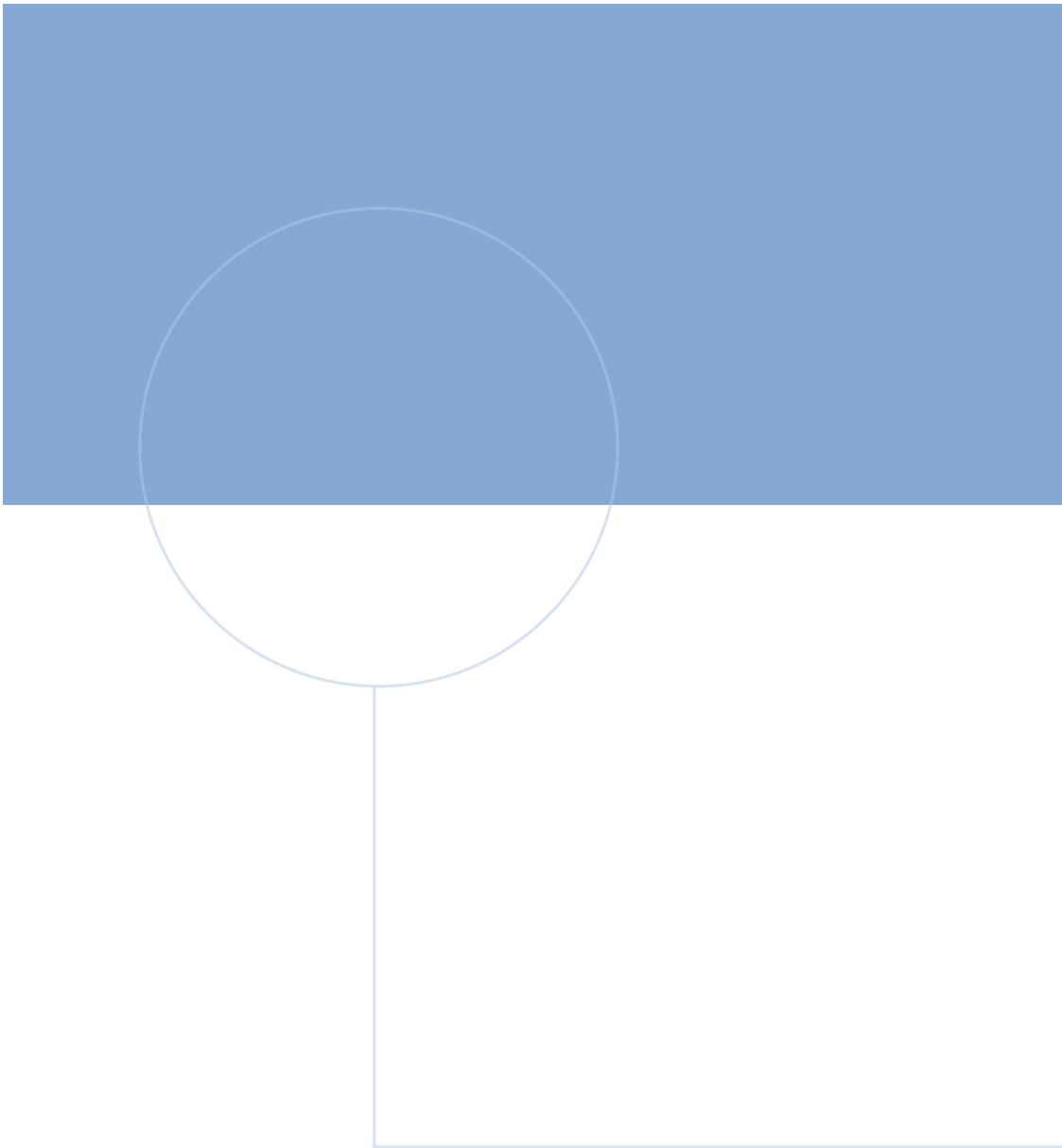
Table 7.4.1.

	TRE (n = 9)			HIT (n = 10)			TREHIT (n = 9)			CON (n= 11)			
	Pre	**Post**	**Δ - EM**	**Pre**	**Post**	**Δ - EM**	**Pre**	**Post**	**Δ-EM**	**Pre**	**Post**	**Δ-EM**	**p-value**
Age, yr.	35.8 ± 6.7	-	-	30.8 ± 7.5	-	-	34.9 ± 7.4	-	-	32.9 ± 8.2	-	-	-
Weight, kg	93.3 ± 11.1	91.5 ± 11.7	**-1.8 (-3.3, -0.4) ***	93.1 ± 14.7	91.2 ± 15.1	**-1.9 (-3.6, -0.1) ***	86.9 ± 9.6	83.6 ± 9.1	**-3.2 (-5.0, -1.5) ***	94.3 ± 9.5	94.2 ± 10.6	-0.02 (-1.08, 1.04)	**0.02****
BMI, kg/cm^2	31.3 ± 4.4	30.7 ± 4.6	**-0.6 (-1.1, -0.2) ***	33.3 ± 5.5	32.6 ± 5.5	**-0.7 (-1.3, -0.1) ***	30.5 ± 3.0	29.4 ± 2.9	**-1.1 (-1.7, -0.5) ***	33.1 ± 3.9	33.1 ± 4.3	0.01 (-0.4, 0.4)	**0.02****
SBP, † mmHg	118.1 ± 6.0	114.0 ± 7.9	-4.1 (-8.4, 0.1)	121.1 ± 7.3	116.8 ± 5.9	-4.2 (-8.5, 0.1)	126.5 ± 9.6	126.7 ± 7.3	0.2 (-5.5, 6.1)	118.8 ± 9.8	120.0 ± 10.3	1.4 (-3.7, 6.0)	0.06
DBP, † mmHg	78.1 ± 7.4	73.1 ± 8.5	**-5.0 (-9.1, -0.9) ***	78.0 ± 8.5	74.5 ± 8.5	-3.5 (-7.2, 0.2)	85. 4 ± 5.1	83.4 ± 5.2	-1.9 (-4.5, 0.6)	78.9 ± 8.4	77.9 ± 9.9	-0.9 (-5.1, 3.2)	0.25
FG, † mmol/L	5.0 ± 0.4	4.9 ± 0.5	-0.1 (-0.5, 0.6)	4.9 ± 0.4	4.7 ± 0.6	-0.3 (-0.7, 0.2)	5.0 ± 0.3	4.8 ± 0.3	**-0.2 (-0.3, -0.1) ***	4.9 ± 0.4	5.1 ± 0.3	0.2 (-0.1, 0.3)	0.15
2h Glucose,† mmol/L	5.6 ± 1.2	5.3 ± 1.7	-0.2 (-1.0, 0.4)	4.8 ± 1.2	5.1 ± 1.4	0.2 (-0.3, 0.9)	5.2 ± 1.6	5.3 ± 1.7	0.1 (-0.5, 0.8)	4.8 ± 0.7	5.1 ± 1.3	0.2 (-0.3, 0.9)	0.62
AUC, † mmol/L	708.2 ± 124.2	727.0 ± 146.6	16.0 (-71.8, 103.9)	741.7 ± 174.4	720.9 ± 168.4	-19.7 (-95.6, 56.2)	741.5 ± 187.0	731.2 ± 212.3	-9.18 (-96.8, 78.5)	733.2 ± 138.2	782.5 ± 163.3	49.4 (-18.4, 117.3)	0.52
HbA1c, † mmol/mol	34.5 ± 2.6	33.6 ± 2.6	-0.8 (-2.1, 0.3)	32.2 ± 1.9	32.1 ± 1.7	-0.3 (-0.5, 0.5)	34.7 ± 3.4	33.7 ± 3.4	-0.9 (-2.2, 0.2)	33.4 ± 2.5	34.2 ± 2.1	0.8 (-0.1, 1.7)	**0.03****
Chol, † mmol/L	4.3 ± 1	4.6 ± 0.4	0.3 (-0.5, 0.6)	4.6 ± 0.6	4.3 ± 0.5	**-0.3 (-0.7, -0.1) ***	4.6 ±0.8	4.5 ± 0.8	-0.04 (-0.4, 0.4)	4.5 ± 1.3	4.6 ± 1.2	0.1 (-0.1, 0.3)	0.08
HDL, † mmol/L	1.3 ± 0.3	1.3 ± 0.2	0.01 (-0.1, 0.1)	1.5 ± 0.2	1.4 ± 0.3	**-0.1 (-0.2, -0.03) ***	1.5 ± 0.4	1.5 ± 0.3	-0.04 (-0.1, 0.1)	1.4 ± 0.3	1.4 ± 0.6	0.0 (-0.1, 0.1)	0.31
LDL, † mmol/L	2.9 ± 0.8	3.2 ± 0.5	0.3 (-0.1, 0.7)	3.1 ± 0.6	2.7 ± 0.5	**-0.3 (-0.6, -0.03) ***	2.9 ± 0.5	2.9 ± 0.6	-0.03 (-0.4, 0.3)	3.03 ± 1.2	3.1 ± 1.2	0.1 (-0.2, 0.4)	0.10
TG, † mmol/L	1.1 ± 0.5	1.2 ± 0.5	0.1 (-0.1, 0.1)	0.9 ± 0.2	1.1 ± 0.5	0.1 (-0.04, 0.4)	0.9 ± 0.4	1.0 ± 0.6	0.1 (-0.1, 0.2)	1.1 ± 0.4	1.1 ± 0.4	0.1 (-0.01, 0.3)	0.73

Table 7.4.2. (Continued).

	TRE (n = 9)			HIT (n = 10)			TREHIT (n = 9)			CON (n= 11)			
	Pre	**Post**	**Δ-EM**	**Pre**	**Post**	**Δ-EM**	**Pre**	**Post**	**Δ-EM**	**Pre**	**Post**	**Δ-EM**	**p-value**
VO_{2max}, L/min †	3.1 ± 0.2	3.1 ± 0.1	-0.0 (-0.1, 0.1)	3.2 ± 0.5	3.3 ± 0.4	0.1 (-0.0, 0.2)	3.0 ± 0.2	3.1 ± 0.2	0.3 (-0.2, 0.9)	3.1 ± 0.4	3.0 ± 0.3	-0.0 (-0.1, 0.02	0.06
ml/kg/min †	35.0 ± 5.5	34.5 ± 4.0	-0.4 (-1.9, 0.9)	34.2 ± 8.2	35.8 ± 7.6	**1.6 (0.8, 2.3) ***	35.3 ± 5.7	38.1 ± 5.8	**2.7 (0.6, 4.8) ***	34.4 ± 6.2	33.8 ± 6.3	-0.6 (-2.1, 0.8)	**0.00****
ml/ $min^{0.75}$ /min †	105.5 ± 14.0	106.4 ± 9.6	0.9 (-3.8, 5.6)	105.8 ± 23.1	110.8 ± 20.3	**5.1 (2.9, 7.2) ***	107.0 ± 14.5	115.3 ± 15.1	**8.2 (2.4, 14.0) ***	106.2 ± 17.9	104.1 ± 17.6	-2.0 (-5.8, 1.7)	**0.01****
HR_{max}, † beats	185.7 ± 4.1	186. 4 ± 5.7	0.7 (-4.2, 5.6)	187.0 ± 9.6	182.7 ± 12.6	-4.2 (-10.2, 1.7)	190.6 ± 10.1	184.6 ± 9.2	-6.0 (-13.4, 1.4)	191.0 ± 12.0	189.4 ± 12.9	-1.5 (-3.7, 0.6)	0.07

Table 7.4.2. Participant characteristics at baseline and after completing the seven weeks intervention. Intention-to-treat analyses with all data presented as estimated mean ± and standard error (SE), and percentage. The difference of change of the estimated means (Δ-EM) between pre- and post-test, with 95% confidence interval (CI). The participants with missing data in the TRE group vary from 0 to 4, HIT group 0 to 3, TREHIT group 0 to 4, and CON group 0 to 2. BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, FG = fasting glucose, AUC = glucose total area under the curve, HbA1c = glycosylated hemoglobin, Chol = total cholesterol, TG = triglycerides, VO_{2max} = maximum oxygen uptake, HR_{max} = maximum heart rate, RER = respiratory exchange ratio. (*) Significant differences within group (95% CI does not include zero) from pre- to post-test. (**) Significant differences between groups p-value < 0.05. (†) Missing data.



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