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INTENSIFIED LIFESTYLE INTERVENTION WITH EXERCISE AS A TREATMENT OF SEVERE OBESITY AND PREVENTION OF CARDIOMETABOLIC RISKS

UNIVERSITY OF OULU GRADUATE SCHOOL;
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KAISU KAIKKONEN

INTENSIFIED LIFESTYLE INTERVENTION WITH EXERCISE AS A TREATMENT OF SEVERE OBESITY AND PREVENTION OF CARDIOMETABOLIC RISKS

Academic dissertation to be presented with the assent of the Doctoral Programme Committee of Health and Biosciences of the University of Oulu for public defence in the Wegelius Auditorium of Oulu Deaconess Institute (Albertinkatu 16) on 8 December 2023, at 12 noon

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Abstract

The prevalence of obesity is increasing worldwide despite a rise in therapeutic interventions to address this epidemic. However, there is a dearth of evidence-based non-surgical treatment guidelines for severe obesity. The aim of this three-year randomized, controlled trial was to elucidate the role of physical activity (PA) in the treatment of severe obesity. First, we studied the association of lifelong PA, aerobic fitness, and cardiac autonomic function by heart rate variability in severely obese adults. Secondly, we investigated the long-term effects of a three-month intensified behavioral modification (iBM) with exercise on glucose tolerance. Thirdly, we aimed to find out whether the timing of the exercise implemented at the weight loss phase of the intervention affects weight loss and waist circumference reduction (WC) from baseline. Finally, we evaluated whether a three-month exercise intervention combined with iBM has long-term effects on weight loss, weight maintenance, and reduction of WC over a three-year follow-up.

120 volunteers (mean BMI 36.8) were randomized into three intervention groups and a control group. All intervention groups were offered intensified behavioral weight loss guidance. According to previous studies, weight loss often stops and re-weighting begins after six months of intervention; we thus added exercise to the protocol of one group right at the beginning of the intervention and to another group after six months. Supervised three-month heart rate-controlled exercise training was implemented as circuit weight training. The weight loss period lasted 12 months, and the weight maintenance period lasted 24 months.

Lifetime physical activity and aerobic fitness were positively associated with cardiac autonomic function. During the trial, iBM alone and combined with exercise led to clinically significant weight loss and long-term weight control. Increasing exercise right at the beginning of the weight loss period reduced abdominal obesity, promoted weight management, improved glucose metabolism, and reduced cardiometabolic risk in severely obese adults. Circuit weight training was well suited for severely obese individuals.

As a conclusion of this thesis, we emphasize the importance of PA in the treatment of severe obesity in adults. More intensive lifestyle interventions including exercise at the onset of the treatment should be implemented for severely obese adults.

Keywords: behavior counseling, circuit training, glucose metabolism, heart rate variability, obesity, physical activity, physical fitness, waist circumference, weight loss

Kaikkonen, Kaisu, Tehostettu elämäntapaohjaus ja fyysinen harjoittelu osana vaikeasti lihavien aikuisten lihavuuden hoitoa sekä sydän- ja versisuonitautien riskitekijöiden vähentämistä.
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Oulun yliopistollinen sairaala; Medical Research Center Oulu; Oulun diakonissalaitoksen Säätiö sr.
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Tiivistelmä

Lihavuus yleistyy huolimatta erilaisten hoitomuotojen kehittymisestä. Vaikean lihavuuden hoitamiseen on vain vähän tutkitusti vaikuttavia ei-leikkauksellisia vaihtoehtoja. Tämän tutkimuksen tavoitteena oli selvittää fyysisen aktiivisuuden roolia vaikean lihavuuden hoidossa. Ensimmäiseksi tutkimme elinaikaisen fyysisen aktiivisuuden ja aerobisen kunnon yhteyksiä sykevaihtelulla mitattuun sydämen autonomiseen säätelyyn vaikeasti lihavilla aikuisilla. Toisessa osatyössä selvitimme 3 kuukauden liikuntaharjoittelun ja tehostetun elintapaohjauksen pitkäaikaisia yhteisvaikutuksia sokeriaineenvaihduntaan. Kolmannessa osatyössä selvitimme, vaikuttaako painonpudotusvaiheessa toteutetun liikuntaharjoittelun ajoitus painonpudotukseen ja vyötärönympärykseen. Lopuksi tutkimme, vaikuttaako elintapaohjaukseen yhdistetty 3 kuukauden harjoittelu pitkällä aikavälillä painonpudotukseen, painonhallintaan ja vyötärönympärykseen kolmen vuoden seurannan aikana.

120 vapaaehtoista aikuista (keskimääräinen BMI 36,8) satunnaistettiin kolmeen interventioryhmään ja kontrolliryhmään. Kaikille interventioryhmien jäsenille tarjottiin tehostettua elintapaohjausta painonpudotukseen. Aiempien interventiotutkimusten perusteella painonlasku usein pysähtyy 6 kuukauden kohdalla. Tämän vuoksi sisällytimme interventioprotokollaan liikuntaharjoittelun yhdelle ryhmälle heti intervention alussa ja toiselle ryhmälle 6 kuukauden kohdalla aloittamisesta. Ohjattu 3 kuukauden liikuntaharjoittelu toteutettiin sykeohjattuna kiertoharjoitteluna. Painonpudotusvaihe kesti 12 kuukautta ja painonhallintavaihe 24 kuukautta.

Elinikäinen fyysinen aktiivisuus ja aerobinen kunto olivat positiivisesti yhteydessä sydämen autonomiseen säätelyyn. Tehostettu elintapaohjaus yksin ja yhdessä liikuntaharjoittelun kanssa johti kliinisesti merkittävään painonpudotukseen ja pitkäaikaiseen painonhallintaan. Liikunnan lisääminen heti painonpudotuksen alussa pienensi keskivartalolihavuutta, edisti painonhallintaa ja paransi sokeriaineenvaihduntaa sekä vähensi kardiometabolista riskiä vaikeasti lihavilla aikuisilla. Sykeohjattu kiertoharjoittelu soveltui erittäin hyvin vaikeasti lihavien henkilöiden harjoittelumuodoksi.

Tämän väitöskirjan tulokset korostavat fyysisen aktiivisuuden merkitystä aikuisten vaikean lihavuuden hoidossa. Vaikean lihavuuden hoidossa tulisi toteuttaa intensiivistä elämäntapaohjausta, jossa liikuntaharjoittelu olisi heti alusta saakka mukana.

Asiasanat: elintapaohjaus, fyysinen aktiivisuus, fyysinen kunto, kiertoharjoittelu, lihavuus, painonlasku, sokeriaineenvaihdunta, sykevaihtelu, vyötärönympärys

To my family

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13.10.2023 in Oulu Kaisu

Abbreviations

ANS	autonomic nervous system
BMI	body mass index
CI	confidence interval
CON	control group
CRF	cardiorespiratory fitness
CVD	cardiovascular disease
CWT	circuit weight training
CWT1	group with supervised exercise (circuit weight training) during weeks 1 through 12
CWT2	group with supervised exercise (circuit weight training) during weeks 24 through 36
DBP	diastolic blood pressure
e.g.	exampli gratia, for example
ECG	electrocardiogram
HF	high-frequency
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
HOMA-β	Homeostasis Model Assessment of β-cell Function
HR	heart rate
HRV	heart rate variability
iBM	intensified behavioral modification
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IL-6	interleukin-6
LF	low-frequency
ln	natural logarithm of the absolute value
MET	metabolic equivalent total
PA	physical activity
RCT	randomized controlled trial
RM	repetitium maximum
RMR	resting metabolic rate
SBP	systolic blood pressure
SD	standard deviation
SDNN	standard deviation of all R-R intervals
SE	standard error
SNS	sympathetic nervous system

T2D	type 2 diabetes
TNF-α	tumor necrosis factor-alpha
ULF	ultra-low-frequency
VAT	visceral adipose tissue
VLF	very-low-frequency
VO_2 max	maximal oxygen consumption
VO_2 peak	peak oxygen consumption
W, W max	watts, maximal power output
WC	waist circumference
WHO	World Health Organization
WHR	waist-to-hip ratio
WhtR	waist-to-height ratio

List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

I Kaikkonen, K., Korpelainen, R., Tulppo, M., Kaikkonen, H., Vanhala, M., Kallio, M. & Keinänen-Kiukaanniemi, S. (2014). Physical activity and aerobic fitness are positively associated with heart rate variability in obese adults. *Journal of Physical Activity and Health. 11(8)*. 1614–1621. https//doi.org/10.1123/jpah.2012-0405

II Kaikkonen, K., Saltevo, S., Korpelainen, J., Vanhala, M., Jokelainen, J., Korpelainen, R. & Keinänen-Kiukaanniemi, S. (2019). Effective weight loss and maintenance by intensive start with diet and exercise. *Medicine and Science in Sports and Exercise*, *51(5),* 920–929. https://doi.org/10.1249/MSS.0000000000001855

III Kaikkonen, K.M., Korpelainen, R., Vanhala. M.L., Keinänen-Kiukaanniemi, S.M. & Korpelainen, J.T. (2022). Long-term effects on weight loss and maintenance by intensive start with diet and exercise. *Scandinavian Journal of Medicine & Science in Sports.* 33(3), 246–256. https//doi.org/10.1111/sms.14269

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1 Introduction

Obesity is a major health problem that poses a serious threat to public health worldwide. The global prevalence of overweight and obesity has considerably increased and nearly tripled over the last four decades (Bentham et al., 2017). According to the FinSote 2020 study, 72% of Finnish men and 63% of women over 30 years were overweight (body mass index [BMI] ⩾25 kg/m2), and every fourth of Finnish adults is categorized as obese (Koponen et al., 2018). Rates of obesity have increased, and rates of severe obesity and visceral obesity have increased even faster during the past decades (World Health Organization, WHO, 2021). Of Finnish men, 6% are severely obese (BMI>35), and 10% of women (Parikka et al., 2020). Obesity is known to reduce the life expectancy of up to approximately 20 years due to increased mortality from noncommunicable diseases, such as cardiovascular disease (CVD) and type 2 diabetes mellitus (T2D), as well as certain types of cancers (di Angelantonio et al., 2016; Fontaine et al., 2003; Guh et al., 2009). Individuals with a BMI above 35 are considered severely obese (grade 2), and to this degree the risk of developing obesity-related morbidities increases (di Angelantonio et al., 2016). As obesity increases, so do the rates of T2D. The estimated number of adults with diabetes has increased by 62% during the past 10 years (Saeedi et al., 2019). Without urgent actions, 578 million people are predicted to have diabetes in 2030 and the number will increase by 51% up to 700 million by 2045. Overweight and obesity are the most important modifiable risk factors for the development of T2D.

The development of obesity is a complex process. Environmental factors, such as energy-rich foods and their availability and accessibility, as well as low physical activity (PA) requirements in interaction with genetic susceptibility, cause weight gain (G. A. Bray et al., 2017). A growing proportion of adults are inactive and sedentary behavior is highly prevalent, even in those who are considered sufficiently active (Hallal et al., 2012). The pathology of obesity is strongly linked with body fat distribution. Visceral fat accumulation and abdominal obesity are known to be strong indicators of risks for cardiometabolic diseases.

There is a general agreement that the prevention of obesity would be the best strategy to treat obesity. When prevention fails, however, there are three principal tools to treat obesity: lifestyle modification, pharmacotherapy, and bariatric surgery (Lagerros & Rössner, 2013). Public health actions aim to prevent and reduce obesity by encouraging individuals to eat healthier and exercise more, but so far, not a single country has succeeded in reducing obesity rates in the past 30 years

(Ng et al., 2014). With increased prevalence of obesity, there has also been a rise in therapeutic interventions to address this epidemic. Surgical and nonsurgical options are available to individuals with severe or morbid obesity. Bariatric surgery generally results in clinically significant, sustained weight loss (Maggard et al., 2005) and remarkable improvement in some comorbid conditions, such as T2D (Sjöström et al., 2004). Despite its benefits, it is an unlikely public health solution because it causes high healthcare costs (Padwal & Sharma, 2009), the number of people requiring surgery exceeds the available surgical capacity, and there are surgical complications associated with bariatric surgery (Maggard et al., 2005). Access to bariatric surgery is limited, and less than 1% of eligible patients receive it (Padwal & Sharma, 2009), while lifestyle interventions are an accessible option for all adults with severe obesity (Lagerros & Rössner, 2013). Lifestyle intervention is always a part of the pre- and post-operative treatment of obesity. Obesity pharmacotherapy has evolved over the past decades and new anti-obesity medications are approved for the long-term treatment of obesity (Tchang et al., 2021). A few drugs, such as gastrointestinal peptide modulators are in various stages of development to meet the need for safe and effective pharmacotherapy to treat obesity. As in the treatment of other chronic diseases, medication should always be prescribed as part of a comprehensive treatment plan that always includes lifestyle modification. Diet, exercise, and behavior modifications remain the cornerstones of obesity treatment, regardless of the amount of obesity (Lagerros & Rössner, 2013).

A common strategy to treat obesity is to create a negative energy balance by decreasing caloric consumption, increasing PA or both. Many people are successful in losing weight in the short term, but long-term maintenance of the achieved results is often challenging. Success in obesity treatment is often judged only by weight loss, and health benefits without weight loss are not noticed. However, a minor weight loss (i.e., 3–5%) has been found to provide a clinically significant health benefits in terms of risk factors for CVD and T2D (Tuomilehto et al., 2001). In previous studies interventions combining diet, exercise, and behavioral therapy have been found to be an effective treatment for obese adults (Avenell et al., 2004). Weight-loss protocols utilizing exercise have been found to be more effective than those that employed just a hypocaloric diet (Clark, 2015), and this has also been shown in studies conducted on severely obese people (Hassan et al., 2016). Despite numerous studies, there is no consensus on what type of exercise is most effective for weight loss and weight management. However, there is a general agreement, that PA is beneficial not only for body mass reduction alone but also in bringing improvements in many health functions (Clark, 2015). A good question, then, is why so few severely obese people are physically active and why exercise is not more effectively utilized in the management the health of severely obese people.

There is a dearth of evidence-based treatment guidelines for severe obesity. As the number of obese people increases, there is a need for new, effective evidence-based, and accessible tools for the treatment and prevention of obesity and obesity-related diseases. In addition to the human burden through diseases, obesity also causes huge national economic challenges for society (Wang et al., 2011). More knowledge is needed on what is an effective program to lose weight and provide health benefits can be. However, there are only a few studies investigating intensified lifestyle interventions with exercise in individuals with a BMI>35, and studies with long follow-up are missing.

In the present study, we implemented a 36-month intensified lifestyle intervention for severely obese individuals. First, we studied the association between lifelong PA, aerobic fitness, and cardiac autonomic function measured by heart rate variability (HRV). Secondly, we examined the effectiveness of intensified lifestyle counseling with behavioral modification and a supervised three-month circuit weight training program (CWT) on weight loss, weight maintenance, and cardiometabolic risk factors such as abdominal obesity, and impaired glucose metabolism. Our aim was to find a new effective treatment protocol and lifestyle intervention tools for severely obese adults.

2 Review of the literature

2.1 Obesity and cardiometabolic health

Obesity is related to many illnesses, and there is a curvilinear increase in risk as a function of time (di Angelantonio et al., 2016). Diseases such as CVD and T2D are strongly associated with elevated BMI (Guh et al., 2009). According to the WHO, CVD is the leading cause of mortality worldwide, and obesity is an independent risk factor for CVD and all-cause mortality (WHO, 2000). The lowest mortality has been found with a BMI of 22.5 to 25.0, and for each five-unit increase in BMI, mortality rises by 30% (di Angelantonio et al., 2016). In individuals with a BMI of 35–40, all-cause mortality increases by 94% compared to those with lower BMI.

2.1.1 Definition and assessment of obesity

Obesity is a condition caused by a positive energy balance that has been sustained over an extended period. WHO defines obesity as "*abnormal or excessive fat accumulation that may impair health*" (WHO, 2021). The World Obesity Federation has declared obesity itself as a non-communicable, chronic, relapsing disease (G. A. Bray et al., 2017). Obesity is a result of a multi-factorial system in which genetics, environment, and behavior have influence. At the same time, it is a very heterogeneous and complex condition, a situation where individuals of the same weight may have accumulated fat in different areas of the body and have markedly different risk factor profiles (Després et al., 2001).

Various methods for assessing obesity have been used. WHO has adopted BMI as a criterion for defining obesity (WHO, 2000). BMI is a measure of body weight adjusted for height [weight (kg)/height (m^2)]. In adults, the classification system defines healthy body weight as a BMI between 18.5 and 24.9, overweight as between 25.0 and 29.9, and obesity as at least 30. In addition, obesity is divided into three categories: class I, BMI of 30.0–34.9; class II (severe obesity), BMI of 35.0–39.9; and class III (morbid obesity), BMI of ≥40. BMI provides a useful population-level measurement of overweight and obesity, and it is widely used in studies and obesity guidelines. However, there are two major limitations to using BMI alone to diagnose obesity in individuals. The first is related to the inability of BMI to distinguish weight associated with muscle versus fat (Okorodudu et al., 2010). The second is the inability to distinguish body fat distribution (Ross et al., 2020). For example, individuals with a normal BMI can have a proportion of body fat exceeding 30% (Oliveros et al., 2014). BMI is an insufficient biomarker of abdominal obesity, which is a much higher risk for obesity-related diseases than overall obesity. People with similar body weight or BMI values, can have substantially different comorbidities and levels of health risk. Despite these limitations, several obesity guidelines worldwide still recommend BMI alone as a measure characterizing obesity-related morbidity and risk of death (Jensen et al., 2014; Tsigos et al., 2008).

Several anthropometric techniques are available to estimate the distribution of body fat. The measurement of waist circumference (WC) by a WHO protocol (WHO, 1995) is a simple method to assess abdominal adiposity, and it is easy to standardize and clinically apply. WC is strongly associated with all-cause mortality (Cerhan et al., 2014) and cardiovascular mortality (Zhang et al., 2008) with or without adjustment for BMI. The threshold values of WC for white adults are >102 cm in men and >88 cm in women corresponding to a BMI of 30.0, which is the BMI threshold for obesity (Janssen et al., 2002). Although WC is a good proxy for central obesity, there are problems with setting cut-off values that can be used for all ethnic groups (Ashwell & Gibson, 2016). According to the previous statements the combination of BMI and WC identifies a high-risk obesity phenotype better than either measure alone (G. A. Bray et al., 2018; Ross et al., 2020). Alongside the previous sex-specific WC thresholds, a BMI category-specific WC threshold has been developed (Ardern et al., 2004), and previous studies suggest the use of BMI category–specific WC thresholds improve predictions of mortality compared with the traditional values (Staiano et al., 2013).

Other anthropometric techniques used are the ratio of WC divided by hip circumference (waist-to-hip ratio [WHR]) and the ratio of WC divided by height (waist-to-height ratio [WHtR]). The use of WHR is limited because both the numerator and denominator values usually change simultaneously in response to weight change (Després et al., 2001). However, narrow waist and large hips have been found to protect against CVD, and for this reason, WHR is also recommended for measurement (Seidell et al., 2001). WHtR is, in turn, a simple measure without the aid of a scale. The cutoff value for WHtR is 0.5, and it is the same regardless of sex and ethnicity (Ashwell & Gibson, 2016). For common health promotion, it offers a simple message that "your waist should not exceed half your height". Anthropometric measures can provide only rough information on body fat distribution. Imaging methods, such as computer tomography or magnetic resonance imaging, provide more specific and accurate data, and these two methods are considered gold standards to quantify fat distribution (Cornier et al., 2011). However, the availability of the types of equipment and the high costs of the measurements limits the use of these measurements.

2.1.2 Obesity and cardiometabolic health risks

Cardiometabolic disease has been described as a spectrum of conditions beginning with insulin resistance, progressing to metabolic syndrome, prediabetes, and finally to more severe conditions such as cardiovascular disease (CVD) and T2D (Guo et al., 2014). Obesity worsens most of the major cardiovascular risk factors, including impaired glucose metabolism, dyslipidemia, elevated blood pressure, and systemic low-grade inflammation, and it also negatively affects cardiac ventricular structure as well as cardiac ventricular systolic and diastolic function (Lavie et al., 2009).

Abdominal obesity

Adipose tissue is a highly metabolically active organ with many functions, such as lipid storage, mechanical protection, thermal insulation, immune responses, and endocrine functions (Chouchani & Kajimura, 2019). It can control its size and function in response to many internal and external stimuli and has an important role in regulating nutrient and energy homeostasis (Chouchani & Kajimura, 2019). For any given amount of body fat, a greater cardiometabolic risk has been associated with the localization of excess fat in the visceral adipose tissue (VAT) and ectopic depots, such as muscle, the liver, and the pancreas. VAT is an independent marker of cardiovascular morbidity and mortality, and abdominal subcutaneous adipose tissue is a much weaker indicator of cardiovascular risk (Hiuge-Shimizu et al., 2012).

VAT is also a marker of increased ectopic fat. Positive energy balance resulting from reduced energy expenditure – due to physical inactivity, excessive calory intake, or both – causes lipid depositions in tissues that are not originally designed for adipose storage, such as the liver, the heart, and skeletal muscle (Neeland et al., 2019). Individuals without the ability to respond to excess energy intake by recruiting new, healthy subcutaneous adipocytes will store excess fat in ectopic depots (Danforth E., 2000). Excess energy from food leads to an accumulation of fat in fat cells (Halberg et al., 2008). As fat cells reach their maximal storage capacity, the distribution of fat in visceral and ectopic fat may occur (Rosenbaum et al., 2015). The size of the fat cells increases, and they produce increased amounts of a variety of peptides, including leptin, cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), angiotensinogen, as well as metabolites such as free fatty acids and lactate (Arita et al., 1999). Adipose tissue produces an anti-inflammatory peptin called adiponectin, which improves insulin sensitivity and arterial function (Wang & Scherer, 2016). The circulating concentrations of adiponectin are inversely related to adipocyte size and visceral fat mass. The metabolic consequences of obesity result from the cytokines released from fat cells and from the inflammatory environment in which they live. In addition to the toxic effects of excess fatty acids, abnormalities in the hormonal functioning of adipose tissue may contribute to the development of metabolic diseases (G. A. Bray et al., 2017). Ectopic fat deposition might also increase the risk of developing atherosclerosis and cardiometabolic diseases (Després, 2012).

The number of people with metabolic syndrome has risen dramatically worldwide (Poirier et al., 2006). Metabolic syndrome is a cluster of cardiometabolic abnormalities with basic characteristics being visceral obesity and insulin resistance (Voulgari et al., 2011). An altered metabolic profile occurs in the individual as adipose tissue accumulates in excess amounts, even in the absence of comorbidities (Poirier et al., 2006). Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) constitute the category termed pre-diabetesand increase the risk of developing T2D. These disorders of glucose metabolism are also related to waist obesity and metabolic syndrome.

Obesity and heart rate variability

During the past decades, there has been an increase in the investigation of variability in autonomic modulation of cardiovascular parameters, such as HRV, as this form of analysis provides a method to evaluate cardiovascular autonomic function. Studies have shown that impairment in cardiac autonomic modulation is related to adverse cardiovascular events (Fang et al., 2020; Tsuji et al., 1994). Autonomic nervous system (ANS) dysfunction and obesity have been found to be intrinsically related to each other (Karason et al., 1999; Rossi et al., 1989), and inverse association of weight gain and obesity with alteration of HRV parameters have been demonstrated (Hirsch et al., 1991; Phoemsapthawee et al., 2019).

Obesity, metabolic syndrome, CVDs, and other cardiometabolic diseases have similar ANS characteristics and are associated with reduced HRV and baroflex sensitivity, impaired lipid and glucose metabolism, reduced insulin sensitivity, and increased circulating levels of inflammatory markers (Souza et al., 2021). Changes in glucose and insulin metabolism lead to changes in ANS control, characterized by reduced vagal modulation and/or increased sympathetic modulation (Souza et al., 2021). The autonomic imbalance between the parasympathetic and sympathetic nervous system (SNS) regulation of cardiovascular function currently accounts for part of mortality and morbidity rates in diabetes and obesity, and autonomic imbalance may independently predict the risk of sudden death (Gerritsen et al., 2001).

SNS plays a central role in cardiovascular system regulation, and the endothelium has a key role in the local regulation of peripheral vascular tone and structure. SNS has a vital role in maintaining cardiovascular health because of its effects on both short- and long-term regulation of blood pressure and blood flow to organs. SNS is a major vasoconstrictor system, and it can elevate arterial pressure by augmenting the force and/or rate of cardiac contraction; decreasing the diameter of resistance arteries; and reducing sodium and water excretion by the kidneys. A healthy endothelium preserves the balance between vasodilatation and vasoconstriction. Endothelium liberates the vasorelaxant gasotransmitter nitric oxide produced by endothelial nitric oxide synthase, thereby assuming a suitable adaptation and control of blood pressure (Sander et al., 1999). There is a reciprocal relationship between SNS and endothelium (Hijmering et al.,2002) and both are heavily involved in the development and prognosis of cardiovascular events and disease (Esler & Kaye, 2000)).

HRV measurement has been used as an index of sympathetic tone, and it is a useful non-invasive tool for the assessment of ANS. HRV refers to the beat-to-beatvariation in HR and is a marker of cardiac autonomic control (Kleiger et al., 1987). Referential indices of cardiac modulatory parameters were originally standardized by the European and American Cardiology Societies and later published by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), which is still used as a worldwide reference of autonomic parameters of HRV. Reduced HRV has been considered a marker of autonomic dysfunction and it is related to an increased risk of incident myocardial infarction, cardiovascular mortality, and all-cause death (Kleiger et al., 1987). Reduced HRV has also been associated with poor prognosis of CVD (Nolan et al., 1998) and it has been shown to be related to risk factors for CVDs (Felber Dietrich et al., 2008). In cardiometabolic diseases, an increase in circulating levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, may be responsible for the impairment in endothelial vasodilator function and a reduction in HRV.

Obesity and glucose metabolism

There is strong evidence that increased body weight, BMI, and central adiposity, and the increase in body weight predict future T2DM (de Fronzo, 2015). Enlargement of the adipose mass has pleiotropic effects on endocrine and metabolic events at the whole-body level that may contribute to the pathogenesis of the detrimental complications of obesity. Obesity is associated with impaired insulin sensitivity and glucose metabolism (Souza et al., 2021). Insulin sensitivity is a reference to how successfully blood glucose is lowered by blood insulin. In turn, insulin resistance means the diminished ability of skeletal muscle and liver cells to respons to the action of a given dose of insulin by transporting glucose from the blood into these tissues, or by reducing glucose production, respectively (Booth, 2012). The pancreatic beta cells compensate for impaired insulin sensitivity by secreting more insulin but with time this mechanism fails, and hyperglycaemia occurs (Stumvoll et al., 2005). Blood glucose levels are slightly increased already before T2D is diagnosed. Individuals with prediabetes who have raised fasting blood glucose levels are at risk of developing T2D (Tabác et al., 2012). Cardiometabolic diseases often begin with insulin resistance, and gradually lead into severe conditions such as T2D and CVD (Guo et al., 2014).

Overweight and obesity are the most important modifiable risk factors for the development of T2D, which is a complex metabolic condition caused by decreased insulin sensitivity and insulin secretion. However, progression to T2D among those with prediabetes is not inevitable. In the Finnish Diabetes Prevention Study, which was a randomized controlled lifestyle intervention study, T2D risk was reduced by 58% (Tuomilehto et al., 2001). Similarly, the U.S Diabetes Prevention Program showed that people who were at high risk for T2D could prevent or delay the disease by losing a modest amount of weight through lifestyle changes (Knowler et al., 2002).

2.2 Physical activity, fitness, and cardiometabolic health

2.2.1 Physical activity

PA is defined as 'any bodily movement produced by the contraction of skeletal muscle that increases/requires energy expenditure above a basal level' (Caspersen, et al., 1985; WHO, 2010). It has also been defined as a behavior that is a crucial part of healthy lifestyle habits (Pate et al., 1995). PA accounts for 15–30% of total daily energy expenditure; the major part, 60–75% is consumed by resting energy expenditure, and a small amount by the thermic effect of feeding, (10%) (Mc Ardle et al., 1991). Resting energy expenditure is the amount of energy required for 24 hours by the body in resting conditions. PA is the most modifiable component of total daily energy expenditure, and it is composed of both nonexercise activity thermogenesis, and the thermogenesis caused by the volitional activity of skeletal muscle (Mc Ardle et al., 1991). Energy expenditure from PA is directly related to body weight, particularly skeletal muscle mass.

PA can be undertaken in various ways and intensities, and it accumulates during the day through activities such as occupational activities, transportation and commuting, household and leisure time, or recreational activities and sports. Leisure-time activities, also named voluntary activity, refer to any activity that increases energy expenditure and that an individual prefers to engage in voluntarily (Bouchard & Shephard, 1994). Exercise is a subcategory of PA that is planned, structured, repetitive, and performed to improve fitness and health (Katch et al., 2011). Different domains of PA are associated differently with health outcomes (Holtermann et al., 2018) and energy expenditure in several metabolic, muscular, and cardiovascular parameters (Mc Ardle et al., 1991). Aerobic training, such as walking, cycling, cross-country skiing, and jogging utilizes mainly an aerobic energy-producing system and enhances cardiorespiratory fitness. Resistance or strength training enhances muscular strength, power, endurance, and mass (American College of Sports Medicine, 2000). Balance training improves the body's position throughout movement, and flexibility training improves the ability to achieve an extended range of motion.

Energy expenditure depends also on the frequency, duration, and intensity of the activity performed. The magnitude of the rate of energy expenditure needed to perform the activity is described by intensity. PA intensity can be expressed as an absolute term or a relative term. Absolute values commonly used are, e.g., oxygen uptake in liters per minute, power output in watts, HR in beats per minute, and metabolic equivalent (METs) (Physical Activity Guidelines Advisory Committee, 2018). One MET refers to the resting metabolic rate and it is considered to be approximately 3.5 mL of oxygen consumption per kg of body weight per minute (Ainsworth et al., 2011). In relative terms intensity values are commonly expressed as a percentage of the individual's maximum aerobic capacity, the subjective rating of perceived exertion, or the percentage of the maximum HR. A percentage of the one-repetition maximum (%1-RM) is often presented as a relative intensity of resistance training (Strath et al., 2013). In intervention studies, relative intensity is usually utilized. In the present study, both absolute and relative terms were used depending on the matter. Examples of standard definitions for both absolute and relative values are expressed in Table 1, modified from the U.S. Physical Activity Guidelines Advisory Committee summary of the scientific literature on physical activity and health (Physical Activity Guidelines Advisory Committee, 2018; Strath et al., 2013; U.S. Department of Health and Human Services, 1996).

Table 1. Classification and examples of physical activity intensity.

Relative intensity				Absolute intensity		
Intensity	Vo2 max, % Heart rate reserve, %	Maximal heart rate %	RPE (Borg scale 6–20)	Intensity	METs	Examples
Very light	<25	<30	<9	Sedentary	1–1.5	Lying down, sitting
Light	25–44	30–49	9–10	Light	1.6–2.9	Slow walking, light household tasks
Moderate	45–59	50–69	11–12	Moderate	3–5.9	Brisk walking, tennis, dancing, gardening
Hard	60–84	70–89	13–16	Vigorous	≥6	Running, shoveling snow, body pumping
Very hard	≥85	≥90	>16			
Maximal	100	100	20			

Vo2 max: maximal aerobic capacity, MET: metabolic equivalent, RPE: the rating of perceived exertion. Heart rate reserve = maximal heart rate minus heart rate at rest. Modified from Physical Activity and Health: A Report of the Surgeon General (U.S. Department of Health and Human Services,1996).

Circuit weight training

Circuit training was developed in 1953 at the University of Leeds in England (Gettman et al., 1978). The term 'circuit' refers to a series of selected exercises performed consecutively. The exercise program can be conducted, for example, with exercise machines or handled weights, or a combination of them. Usually, circuits range from 8 to 10 exercises, and circuits are repeated most often 2–3 times. All large muscle groups are engaged, and exercises can be performed at low (<60% of 1-RM), moderate (60–80% 1-RM), or high loads (>80% 1-RM) loads. In time-based programs, exercise is performed usually for 30–60 seconds; in rep-based programs, a certain number of repetitions is completed. Movement from one station to another is quick, with little or no break. When one circuit is completed, one begins the first exercise again. The total duration of one exercise session is short, often around 30 minutes.

Exercise training performed in low-resistance circuit training promotes muscular endurance, aerobic fitness, and neuromuscular and strength adaptations in one workout (Gettman & Pollock, 1981). According to previous studies circuit training can improve muscular strength and cardiorespiratory function (Marcos-Pardo et al., 2019; Wilke et al., 2019). The metabolic cost of circuit training has bee reported to be higher than that of general resistance training (Wilke et al., 2019) and the same or even higher than that of a combination of aerobic and resistance training (Gettman & Ayers 1978, n.d.; T. R. Myers et al., 2015). Due to the above-mentioned high metabolic cost of circuit training, it takes less time to achieve the goal required in the guidelines (450–750 MET-minutes/week) (Haskell et al., 2007). In addition to improving body weight, circuit training improves body composition (Batrakoulis et al., 2018), motivation to exercise, and the alleviation of cardiometabolic risk factors, such as inflammation and insulin resistance (Kolahdouzi et al., 2019).

Circuit training has been previously recommended as an appropriate training method for untrained individuals with a lower basal level of fitness (Willis et al., 2012), and it has been used as an intervention to lose body mass and fat mass and to increase muscle mass (Batrakoulis et al., 2018; Marcos-Pardo et al., 2019; Seo et al., 2019). According to a previous study, the degree of weight loss tended to be larger among individuals with higher BMI, and circuit training was argued to be more suitable for individuals living with overweight (Bocalini et al., 2012). Circuit training combined with other lifestyle intervention might have a beneficial effect on several cardiometabolic risk factors in obese individuals, even without weight loss (Eriksson et al., 2006). However, there are few studies examining the effects of circuit training on body weight in severely obese individuals and studies dealing with its effect on waist circumference are missing. Therefore, additional RCTs are warranted.

2.2.2 Physical fitness

In 1985 Caspersen and co-workers (Caspersen, 1985) defined physical fitness as 'a set of attributes that people have or achieve that relates to the ability to perform physical activity'. Physical fitness is divided into muscular, motor, metabolic, and cardiorespiratory fitness (Bouchard & Shephard, 1994) and includes several components, e.g., cardiorespiratory endurance, skeletal muscle endurance, strength, power, flexibility and balance. All these areas overlap and together constitute health-related and performance-related fitness.

Cardiorespiratory fitness (CRF) refers to the capacity of the cardiovascular (heart and blood vessels) and respiratory (lungs) systems to deliver oxygen to skeletal muscles and the capacity of the muscles to use oxygen to produce energy for movement (Bouchard & Shephard, 1994). The gold standard to determine CRF is to measure maximal aerobic capacity as described in the methods section (VO_2 max) (Mc Ardle et al., 1991). Peak power in absolute or relative watt values is an indicator of maximal muscular and cardiorespiratory capacity.

Physical fitness and PA are often mistakenly used as synonyms. They are closely interrelated and in general, physically active people tend to be fitter than those with a lower activity level and chronic PA increases physical fitness. Also, rapid changes in CRF can occur, and e.g., total physical inactivity can quickly decrease CRF (Saltin et al., 1968). For PA to improve fitness, exercise should have sufficient intensity (Sisson et al., 2009). Physical fitness is also influenced by genetics, and similar PA levels yield different fitness levels in different individuals (Bouchard et al., 1985; M. S. Bray et al., 2009).

2.2.3 The effects of physical activity and physical fitness on obesity-related cardiometabolic health risks

PA plays a critical role in improving cardiovascular health in both normal-weight and obese individuals (Haskell et al., 2007). Independent of weight loss, PA appears to be associated with improvements in body composition and metabolic conditions (Wadden, 2014). Good aerobic fitness and high PA in obese individuals have been argued to counterbalance obesity-related risks, and aerobic fitness and PA may be more important for cardiovascular health than for avoiding obesity (Blair & Brodney, 1999; Pedersen, 2007). PA lowers morbidity and mortality more in obese individuals compared with sedentary normal-weight individuals (Blair & Brodney, 1999).

High body fatness and low physical fitness are independent risk factors for cardiovascular morbidity and mortality, and low CRF is a strong and independent predictor for all-cause mortality in obesity and diabetes (J. Myers et al., 2002). Individuals who are physically less active have been found to have twice the rate of coronary artery disease compared to physically active ones (Thompson et al., 2003). PA has strong beneficial effects on cardiometabolic factors, such as WC (Duncan et al., 2003), visceral fat (Lee et al., 2005), ANS function, and glucose metabolism (Duncan et al., 2003).

Physical activity, physical fitness, and abdominal obesity

PA has considerable beneficial effects on cardiometabolic factors, such as WC (Duncan et al., 2003) and visceral fat (Lee et al., 2005), with or without significant weight loss (Shaw et al., 2006). Both caloric restriction and aerobic exercise training reduced visceral adipose tissue (Shaw et al., 2006, Verheggen et al., 2016), but PA also reduced it without significant weight loss (Shaw et al., 2006). When body weight was reduced by 5% by a hypocaloric diet, the reduction in visceral adipose tissue was 13.3%, whereas by exercise training the reduction was 21.3%.

A previous RCT among 300 abdominally obese adults showed that fixed amounts of exercise at any intensity resulted in similar reductions in abdominal obesity (Ross et al., 2015). Six months of commuting, and moderate intensity PA resulted in diminished intra-abdominal adipose tissue among obese and overweight adults. (Blond et al., 2019) The results of a recent 6 months randomized aerobic and resistance training intervention among 80 older individuals suggested that increased CRF did not mediate the effects of aerobic and resistance training on insulin sensitivity in older adults and that abdominal adiposity was a strong mediator of these effects independent of changes in total adiposity (Ko et al., 2016).

Physical activity, physical fitness, and heart rate variablity

Previous studies provide evidence that aerobic training improves ANS functioning measured by HRV (Pichot et al., 2005; Tulppo et al., 2003), and regular PA and good CRF reduce obesity-related health risks and morbidity (Blair et al., 1989; Haskell et al., 2007). Good cardiovascular fitness has been suggested to be associated with higher HRV in healthy young athletic men and senior sportsmen (Levy et al., 1998). Regular physical exercise has been found to have strong beneficial effects on cardiac ANS measured by HRV in obese individuals, and exercise may offset the negative effect of obesity (Felber Dietrich et al., 2008). In normal-weight individuals, aerobic fitness has been related to the regulation of cardiovascular system by ANS, with regularly physically active individuals demonstrating better HRV indices than their sedentary counterparts.

Different mechanisms underlying the beneficial protective effect of PA and physical fitness on cardiovascular health have been suggested, but the mechanisms are not entirely clear. One explanation could be the positive effect of PA on autonomic and endothelial function protecting from CVDs independent of traditional risk factors (Joyner & Green, 2009). Some studies have shown a beneficial effect of exercise on HRV, reflecting improved ANS function in physically active individuals in comparison to sedentary controls. An interesting question is whether PA is as protective from CVDs in severely obese individuals as in those with normal-weight individuals. In addition, it remains unclear whether these positive findings can be generalized to severely obese individuals as well.

Physical activity, fitness, and glucose metabolism

Physical inactivity and obesity have been shown to be independent risk factors for T2D (Hu et al., 2004), whereas PA and aerobic fitness have been found to protect against T2D (Carbone et al., 2019). A single exercise session has been shown to be associated with a marked improvement in insulin-stimulated glucose uptake (Mikines et al., 1988), and weight loss has been associated with improved insulin action (Rice et al., 1999). Improved insulin sensitivity may be an important explanation for the cardioprotective effects of PA (Gill & Malkova, 2006). PA has been found to improve insulin sensitivity particularly well among individuals with impaired insulin sensitivity (Gill et al., 2006), such as obese individuals. Whether PA is able to counterbalance the strong risk of impaired glucose tolerance or T2D caused by obesity remains is unclear (D. C. Lee et al., 2009).

A recent study found that higher sedentary time, lower PA, and lower aerobic fitness were associated with lower skeletal muscle glucose uptake among sedentary adults with metabolic syndrome. It also argued that body adiposity may be a more important determinant of skeletal muscle glucose intake than sedentary time, PA, or aerobic fitness (Garthwaite et al., 2022). Little is known about the relative roles of PA and fitness as determinants of glucose regulation in severely obese adults.

2.3 Treatment of obesity with lifestyle intervention

Managing obesity has three goals: 1) preventing weight gain, 2) achieving weight loss, and 3) maintaining weight loss (Hill et al., 2005). Regardless of the amount of obesity, lifestyle interventions including diet, exercise, and behavior modifications are the cornerstones of obesity treatment. There is a general agreement that weight loss will follow a negative energy balance. Weight loss can be achieved in numerous ways, and weight loss is reasonably easy to achieve but maintaining weight loss is much more demanding. Previous studies evaluating the effectiveness of lifestyle interventions in severely obese individuals have reported a greater reduction in weight in the lifestyle intervention groups compared to the control groups (Hassan et al., 2016). Lifestyle interventions with diet and exercise have been found to be the most effective (Goodpaster et al., 2010; Wadden, 2014). However, there are few lifestyle intervention studies among severely obese individuals, and there is a large heterogeneity between the components of lifestyle interventions used in these studies (Hassan et al., 2016).

Improved lifestyle interventions for adults with severe obesity can contribute to the successful management of severe obesity without bariatric surgery. However, lifestyle interventions have been shown to be ineffective in treating severely obese patients (Monkhouse et al., 2009). Weight loss counseling can be implemented as group or individual guidance. Group sessions may be more cost-effective than individual care and provide social support and weight loss results that are similar to individual and group counseling (Cresci et al., 2007). However, Seo and Sa (2008) found that the group approach was less effective than using a combination of individual and group approaches (Seo & Sa, 2008). Individual approaches allow more personalized tailoring. New possibilities, such as web-based programs, calculators, support forums, and coaching messages for delivering behavioral lifestyle guidance have become more common. Theoretically, they have the potential to overcome some of the limitations of traditional weight loss interventions (Lagerros & Rössner, 2013). They may reduce costs and can be reached at any time with convenient tools. However, it is not clear if the new technology helps to maintain motivation or reduce attrition rate.

One of the unclear issues is why individual responses of weight loss to any type of obesity treatment are different. Understanding the biological background of the different treatment responses can expand the option of the treatment in a more personalized medicine (M. S. Bray et al., 2009). Many genes affect the response to diets, PA, and changes in physical fitness. An algorithm that integrates dietary habits, anthropometrics, PA, blood parameters, and gut microbiota was argued to predict postprandial glycemic responses to real-life meals (Zeevi et al., 2015). Individual differences in risk factor responses to regular PA of the same volume of exercise have also been found (Rankinen & Bouchard, 2008). Should the content of weight loss interventions, especially in severely obese individuals, be designed to be more personal so that individual needs in both diet and exercise can be better considered? Although there has been a progress in understanding obesity, several impediments, such as stigmatization by the public and healthcare professionals (Brewis et al., 2018), and the consideration of obesity as a cosmetic issue, may negatively affect the advancements in clinical management (Bray et al., 2018).

Few people want to be obese. Our obesogenic environment promotes the development of obesity. Thus, obesity is not a surprising result in our obesogenic environment, but it perhaps should even be seen as a normal reaction (Lagerros & Rössner, 2013). Although obesity is defined as a disease (G. A. Bray et al., 2017), only a tiny proportion of obese people will get the healthcare attention they need (Lagerros & Rössner, 2013). Thus, there is a need for lifestyle interventions targeted specifically at individuals with severe obesity and a need for studies to determine the most effective components of lifestyle intervention to treat severe obesity.

2.3.1 Behavioral therapy

When we talk about obesity treatment, behavior therapy refers to a set of principles and techniques to modify eating, PA and thinking habits that contribute to excess weight (Wadden et al., 2007). The approach of this thinking model is that body weight is influenced by factors other than behavior, such as hormonal, metabolic, and genetic influences, and these predispose some persons to gain weight and set limits to what a person can achieve (Wadden et al., 2007). Behavioral treatment includes components such as problem-solving, relapse-preventing training, cognitive restructuring, and stimulus control in addition to diet, exercise, and self-monitoring (Diabetes Prevention Program Research Group, 2009).

Self-monitoring is considered the most important component of behavioral treatment, and records of food intake, PA, and body weight are kept in order to identify areas of success and areas in need of improvement (Wadden, 2014). Setting specific goals for behavior, such as what, when, where, how, and for how long, is typically included in behavior therapy. Cognitive approaches, such as problem-solving and cognitive restructuring, have been found to improve weight loss maintenance, and both cognitive and behavioral methods are recommended to maintain weight loss (Fabricatore et al., 2007). Behavioral therapy has been found to be effective in decreasing body weight (on average 7–10% over six months of intensive therapy), but maintenance of weight loss has been more challenging (Wing et al., 2011).

2.3.2 Diet

To achieve long-term weight loss, most obese people need to restrict their energy intake. The amount of energy obtained from food can be restricted by reducing portion sizes, decreasing the energy density of the diet, and/or counting calories. The most successful weight-reducing diet is one that an individual can adhere for several months (Wadden, 2003). The choice of diet should also address personal preferences to ease dietary adherence. According to the Finnish Current Care Guidelines for obesity the main effort in changing dietary habits is to improve eating control (e.g., regular eating, calm eating speed, eating vegetables, and sufficient protein intake), to reduce the intake of low-nutrient energy foods, and to secure an adequate intake of nutrients (vitamins, minerals, and trace elements, protein, and good-quality fat) (Obesity in Children & The Finnish Medical Society Duodecim, 2020). From the success of weight management viewpoint, calorie restriction and health-promoting diet may be more important than the nutrient composition of the diet.

The basic advice for a weight loss treatment diet according to the Finnish Care Guidelines (Obesity in children & The Finnish Medical Society Duodecim, 2020), is a low-energy diet with 1200–1500 kcal/d or a decrease of 500–1000 kcal/d in current energy intake. The advice for nutrient intake recommends total fat 25–35 E%, (saturated fat <10%), protein 15–25 E% and carbohydrates 40–60 E%. High protein intake has been found to be associated with better satiety, which may improve adherence to energy restriction (Larsen et al., 2010). Diets under 1200 kcal/d are not recommended except in the case of a very-low-calorie diet (VLCD). A VLCD with energy intake of 800 kcal/d might be used under the guidance of a healthcare professional for a maximum of 16 weeks. VLCD is especially suitable for obese adults with a BMI of over 30. The suitability of VLCD should be assessed before starting it and, if necessary, the suitability should be confirmed by consulting a physician.

2.3.3 Physical activity

Weight loss solely from PA has been generally modest, <3% of the initial body weight (Donnelly et al., 2009). However, even a minor weight loss, 3–5%, has been found to provide a clinically significant health benefits in terms of risk factors for T2D and CVD (Tuomilehto et al., 2001). Although clinically significant weight loss is not usually observed in exercise training trials, other favorable cardiometabolic changes have been observed following aerobic exercise without weight loss. Physical fitness improves as a direct response to aerobic training (Swift et al., 2013) but not with caloric restriction alone, having positive effects on cardiometabolic health. Compared with minimal or standard care (Hassan et al., 2016) or diet-only treatment (Chin et al., 2016; Goodpaster et al., 2010), lifestyle interventions with combined diet and exercise have proven to achieve the greatest weight loss also in severely obese patients as well.

According to previous studies and recommendations adults living with overweight and obesity require moderate-intensity PA for at least 150 minutes per week to improve or maintain health and over 250 minutes to lose weight significantly (Donnelly et al., 2009; Haskell et al., 2007). High levels of PA with an energy expenditure of 2,500 kcal/wk (achieved with brisk walking) have been shown to maintain significantly greater weight loss than with energy expenditure of 1000 kcal/wk (Jeffery et al., 2003). For most obese individuals, it might be difficult to find the time or motivation to engage in a high volume of activity. PA has been shown to be critical for long-term weight management and the primary predictor of weight maintenance (Donnelly et al., 2009; Tate et al., 2007). Weight regain is reduced by engaging in 60 min/d of brisk walking (Donnelly et al., 2009; Shaw et al., 2006). Also, opposite results have been found suggesting that higher levels of PA have no effects on short- or long-term weight loss (Jakicic et al., 2008). Thus, further high-quality intervention studies are needed to determine the effectiveness of PA as part of a lifestyle intervention in adults living with severe obesity.

Timing of exercise initiation within a weight loss program

Many people are successful in losing weight in the short term, but long-term maintenance of the achieved results is often challenging. We know from the multitude of studies that there is a plateau in weight loss and that weight regain often begins at six months (Jeffery et al., 1998). One explanation for cyclic patterns of weight loss success and failures is that weight loss efforts are rewarded by physical, psychological, and social benefits, but these benefits diminish their salience over time, and the motivation to continue efforts to control eating and exercise more is undermined (Jeffery et al., 2004). Over time, weight loss slows down or even stops, and positive rewards slow or even come to halt. Boredom with weight-loss techniques – even though these techniques were initially successful for weight loss – is common (Jeffery et al., 2004, 2009), and adherence to the treatment protocol declines over time (Jakicic et al., 1999; Wadden et al., 2005). Most weight loss programs recommend simultaneously a decrease in energy intake and an increase in PA. For many individuals with obesity, it may be difficult to sustain high levels of exercise with a simultaneous delivery of diet (Jakicic et al., 1999).

An alternative approach is to deliver exercise intervention in a different phase of the weight loss period. Few studies have considered the importance of the timing of an exercise intervention for long-term weight loss and maintenance (Table 2).

Table 2. Previous studies examining the association of changes in body weight and the timing of exercise within a behavioral weight loss program.

Reference, location	Study population	Design	Outcomes	Main results
Donnelly et al. (1994), Nebraska, USA	115 women living with obesity.	Matching design. A 12-week program consisting of a very-low-calory-diet (VLCD) and exercise. Group assignments: control with no exercise (C); endurance exercise (EE); weight training (WT); endurance exercise and weight training (EEWT); endurance exercise at weeks 5–12 (C4EE); weight training at weeks 1–4 and weight training and endurance exercise at weeks 5–12 (WT4EE).	Changes in body weight, fat free mass, resting metabolic rate, aerobic fitness, and muscular strength.	The delay or sequential onset of exercise during VLCD provides only slight differences between the groups. The WT4EE group showed favorable changes from the start compared to the other groups, but the differences were not significant.
Goodpaster et al. (2010), Pennsylvania, USA	130 individuals (87% women) aged 30–55 y living with obesity (BMI>35).	A single-blind randomized trial. 12-month intensive lifestyle intervention consisting of diet and PA. Group assignments: initial PA/PA for the entire 12 months; delayed PA: PA at 7–12 months; self-directed PA/300 minutes/week of moderate-PA.	Changes in body weight, waist circumference, visceral abdominal fat, and other cardiometabolic risk factors (e.g., blood pressure, insulin resistance).	Intensive lifestyle intervention resulted in significant weight loss and improvements in cardiometabolic risk factors in severely obese persons. The addition of PA, regardless of the timing of the initiation, promoted greater weight loss and long-term weight maintenance.

Reference, location	Study population	Design	Outcomes	Main results
Jakicic et al. (2015), Pennsylvania, USA	195 individuals with mean age 43.2 (SD 8.6) living with overweight or obesity (mean BMI 33.0, SD 3.4).	Randomized trial with 18-month weight loss program. Group assignments: Standard behavioral weight loss program (SBWP); SBWP plus intervention strategies for physical activity implemented over the initial nine months (ADOPT); SBWP plus additional intervention strategies for PA implemented between months 4–18 (MAINTAIN).	Changes in body weight, waist circumference, body composition, body fat distribution, cardiorespiratory fitness, PA, and dietary intake.	MAINTAIN improved 18-month weight loss compared to SBWP and ADOPT, with statistical trends that MAINTAIN resulted in greater improvements in fitness.
Catenacci et al. (2019), Colarado, USA	170 individuals (83% women) aged 18–55 yliving with overweight or obesity (BMI 25–42).	Randomized trial. 18-month weight loss program consisting of exercise, dietary intervention, and group-based behavioral support. Group assignments: standard group (STD)/supervised exercise at months 0–6; sequential group (SEQ)/supervised exercise at months 7–12; supervised exercise/300 minutes per week of moderate-intensity aerobic exercise.	Changes in body weight, waist circumference, fat mass, lean mass, and cardiorespiratory fitness.	Both groups showed clinically meaningful weight loss, with no significant between-group differences at 18 months. The STD group had greater weight-loss at six months. The SEQ group continued to lose weight during months 6–12.

3 Aims of the study

The overall purpose of this study was to examine the role of physical activity in the treatment of severely obese adults with a special interest in cardiometabolic risk factors.

The more specific aims were:

1. To investigate the cross-sectional association between lifetime physical activity, aerobic fitness, and heart rate variability (Study I)
2. To evaluate the long-term effects of a supervised three-month exercise intervention combined with intensified behavioral therapy on glucose metabolism over a two-year follow-up (Study II)
3. To find out whether the timing of the exercise intervention implemented during the weight loss phase affects weight loss and waist circumference reduction over a three-year follow-up (Study III)
4. To evaluate whether a three-month exercise intervention combined with intensive behavioral modification has additional long-term effects on weight loss, weight maintenance, and reduction of WC over a three-year follow-up (Study III)

4 Subjects and methods

The study is a part of the LILA study, the data collection of which data collection was carried out in the city of Oulu, Finland, in 2004–2011. The LILA study is a three-year RCT aiming to find effective exercise protocols to treat severe obesity in adults. The study was conducted in the Department of Sports and Exercise Medicine, Oulu Deaconess Foundation sr. in collaboration with the Unit of Population Health Research, University of Oulu, and Oulu University Hospital. Cross-sectional baseline data (Study I) and the follow-up data at 24 months (Study II) and 36 months (Study III) were utilized in this dissertation.

4.1 Study design

For the purpose of the study, both the cross-sectional study design (Study I) and RCTs (Studies II and III) were used.

The study was conducted according to the Declaration of Helsinki and was approved by the Ethical Committee of Northern Ostrobothnia Hospital District (83/2003). The participants took part voluntarily, and written consent was obtained from all the participants.

4.2 Subjects

The study participants were recruited by advertising in a newspaper, which attracted 489 responses (Figure 1). All those interested in the study were interviewed by phone with a standardized scheme. The inclusion criteria were age 18–64 years and BMI ≥30. The reasons that prevented participation in the study were the following: pregnancy, medication or a health reason that prevented exercise testing, participation in another exercise intervention or recent weight loss and previously diagnosed diabetes.

Altogether, 397 individuals met the inclusion criteria. Among them, 120 participants (94 women and 26 men) were randomly assigned to one of three different intervention groups or to a control group. The groups were (1) intensified behavioral modification (iBM), (2) iBM and supervised exercise during weeks 1 through 12 (circuit weight training group 1 [CWT1]), (3) iBM and supervised exercise during weeks 24 through 36 (CWT2), and a control group (CON). The baseline characteristics of the study participants according to group assignment are presented in Table 3.

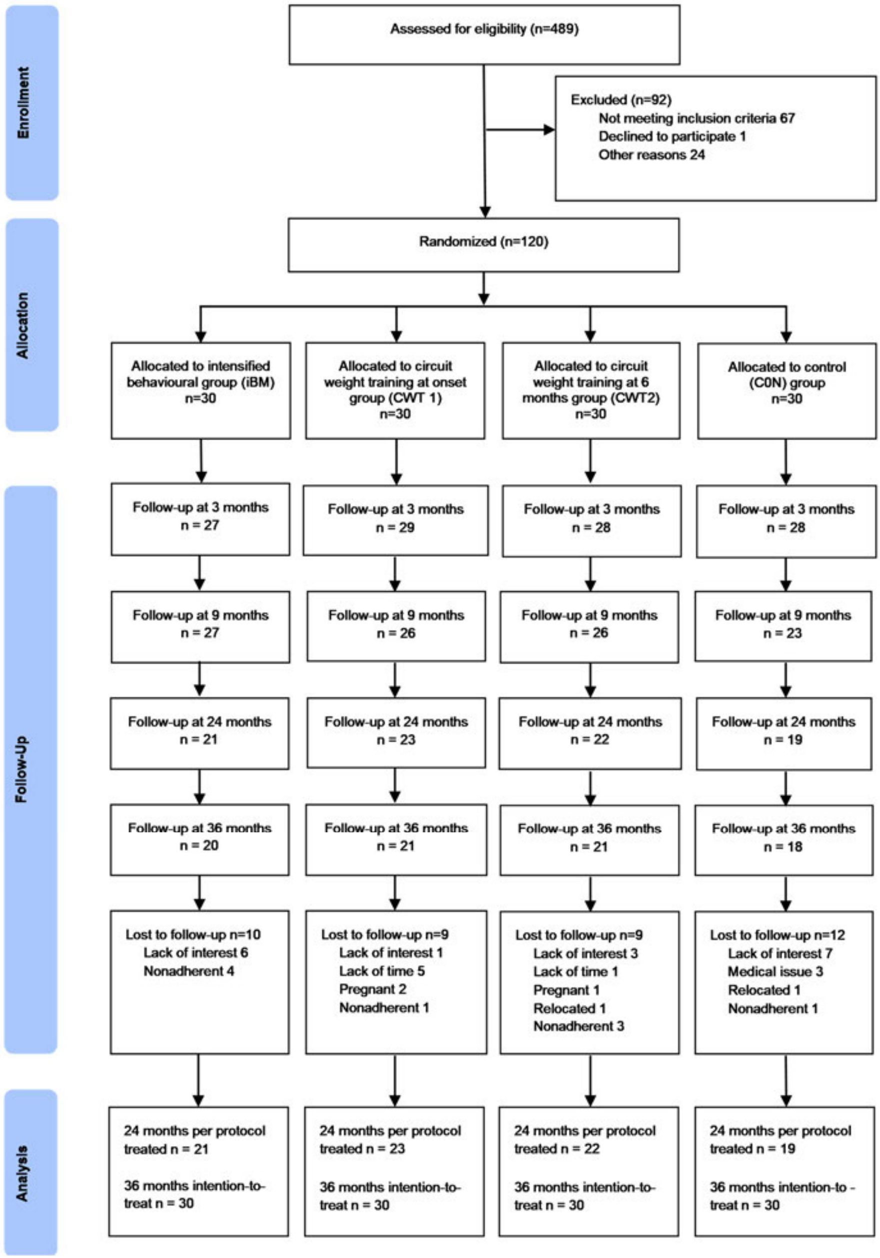

Fig. 1. The flow chart of the study participants in the LILA study. Modified from study III.

In Study I, cross-sectional data were used to investigate the associations of lifetime PA and aerobic fitness with HRV in obese adults. Complete data sets with technically sufficient HRV measurement (recordings >18 hours and recordings of sufficient quality) were gathered from 107/120 participants.

In Studies II and III, the data from a randomized control trial (RCT) were used. The number of participants at each phase of the studies and the reasons for withdrawal are presented in Figure 1: 85 participants completed the two-year follow-up (Study II) and 80 participants completed the whole three-year follow-up (Study III).

Table 3. Baseline characteristics in to the three intervention groups and the control group. Values are means (standard deviations) unless otherwise stated.

Characteristics	All n=120	iBM n=30	CWT1 n=30	CWT2 n=30	CON n=30
Female (n, %)	94 (78)	23 (77)	24 (80)	23 (77)	24 (80)
Men (n. %)	26 (22)	7 (23)	6 (20)	7 (23)	6 (20)
Age (years)	44.5 (10.5)	44.2 (10.3)	44.2 (11.0)	43.2 (11.1)	46.5 (9.9)
Weight (kg)	99.9 (15.0)	98.9 (13.5)	99.1 (12.2)	102.4 (17.6)	98.9 (16.7)
Height (cm)	164.7 (7.6)	165.8 (7.3)	164.7 (7.3)	164.5 (6.9)	164.7 (7.6)
BMI (kg/m^2)	36.8 (4.8)	35.9 (4.1)	36.6 (4.5)	38.0 (5.7)	36.8 (4.7)
Waist circumference (cm)	109.7 (11.1)	108.4 (10.8)	110.5 (9.3)	109.7 (11.5)	110.4 (12.8)
Hip circumference (cm)	120.7 (9.9)	122.3 (9.9)	121.8 (10.9)	119.9 (10.9)	119.9 (9.7)
Married or co-habitating (n, %)	87 (72.5)	26 (86.7)	25 (83.3)	19 (63.3)	20 (66.7)
Education years >12 (n, %)	75 (62.5)	18 (60.0)	22 (73.3)	18 (60.0)	17 (56.7)
Employed or studying (n, %)	92 (76.6)	22 (73.3)	23 (76.6)	21 (70.0)	26 (86.7)
Self-rated health as poor or very poor (n, %)	10 (8.3)	2 (6.7)	2 (6.7)	3 (10.0)	3 (10.0)
Self-rated fitness level as poor or very poor (n, %)	55 (45.8)	13 (43.3)	13 (43.3)	14 (46.7)	15 (50.0)
Current smoker (n, %)	23 (19)	4 (13)	8 (27)	8 (27)	3 (10)
Physical activity level low (n, %)	81 (67.5)	23 (76.7)	19 (63.3)	20 (66.7)	19 (63.3)
Measured fitness (Vo2 max ml/kg)	22.0 (5.5)	22.2 (5.3)	22.8 (5.4)	22.2 (6.7)	20.8 (4.3)

iBM = intensified behavioural modification group; CWT1 = intensified behavioural modification and supervised exercise from 0 to 3 months; CWT2 = intensified behavioural modification and supervised exercise from 6 to 9 months; CON = control group; BMI = body mass index; SD = standard deviation

4.3 Measurements

The data were collected using questionnaires and clinical measurements at the baseline and at 3, 9, 24, and 36 months. All the physiological measurements were performed by trained personnel in standardized conditions and procedures. The methods used for each variable are presented in Table 4.

Table 4. Variables measured in the original studies and methods used.

Variables	Studies	Methods
Anthropometry		
Height	I–III	Standard stadiometer
Weight	I–III	Mechanical scale (SOEHNLE S20, Soehnle Waagen, Germany)
Body Mass Index	I–III	Mass (kg)/height^2 (m)
Waist circumference	I–III	Standard tape measure
Hip circumference	I–III	Standard tape measure
Physical Activity		
Life-time-activity-score	I	Modified Paffenbarger questionnaire (Greendale et al., 1995; Paffenbarger et al., 1978)
Current activity-score	I–III	Modified Paffenbarger questionnaire (Paffenbarger et al., 1978)
Physical Fitness		
Self-rated	I–III	Standard five-scale questionnaire
Maximal oxygen consumption	I–III	Jaeger Oxycon Pro, Hoechberg, Germany (Mc Ardle et al., 1991)
Measured maximal oxygen consumption	I–III	Siemens Megacart -Ergoline 900 BP, Siemens-Elema AB, Electrocardiography Division, Sweden (American College of Sports Medicine, 2000)
Maximal power output	I	Siemens Megacart -Ergoline 900 BP, Siemens-Elema AB, Electrocardiography Division, Sweden (American College of Sports Medicine, 2000)
Maximal and minimal heart rate	I–III	Polar S810, Polar Electro Oy, Kempele, Finland
Self-rated health	I–III	Standard five-scale questionnaire
Health behavior		
Smoking	I–III	Standard three-scale questionnaire
Alcohol consumption	I–III	Seven-day food record
Dietary habits	II–III	Seven-day food record
Heart rate variability (R-R intervals and HRV)	I	Polar R-R recorder (Polar Electro Oy, Kempele, Finland) with Hearts software (Heart signal Co, Kempele, Finland)

Variables	Studies	Methods
Glucose metabolism		
Glucose	II	Hexokinase assay (Konelab analyzers, Thermo Electron Oy, Vantaa, Finland
Insulin	II	Chemiluminescent microparticle immunoassay (Abbot Diagnostic, Abbot Park, IL, USA)
Homeostatic Model Assessment for Insulin Resistance	II	Chemiluminescent microparticle immunoassay (Abbot Diagnostic, Abbot Park, IL, USA)
Matsuda Index	II	(Matsuda & DeFronzo, 1999)
Resting metabolic rate	II–III	Indirect calorimetry (Jaeger Oxycon Pro, Hoechberg, Germany)

4.3.1 Anthropometry

Weight and height were measured in light clothing without shoes. Weight was measured to the nearest 0.1 kg using a calibrated scale (SOEHNLE S20, Soehnle Waagen, Germany). Height was measured to the nearest 0.5 cm using a standard stadiometer. BMI was calculated as weight in kilograms divided by height in meters squared. WC was measured to the nearest 0.5 cm when the participant was standing with arms at the side and clear of the abdominal region. A stretch-resistant tape measure was placed around the body and located midway between the spina iliaca superior and the margin of the lowest rib. Hip circumference was measured to the nearest 0.1 cm at the level of the greater trochanters.

4.3.2 Physical activity

The modified Paffenbarger questionnaire was used (Greendale et al., 1995; Paffenbarger et al., 1978) to assess the frequency and intensity of lifetime and current PA. The participants were asked to recall their participation in physical activities during three time periods in their life, corresponding to the ages of 15 and 30, and to their current age. The participants reported the highest level of exercise performed for at least 15 minutes at a time. Options were given: 1) less than once a week, 2) once or twice a week, 3) three to five times a week, and 4) at least five times a week. Exercise intensity was categorized as light (e.g., quiet walking, slow cycling on the plains, weeding, housework inside), moderate (e.g., brisk walking, gymnastics, brisk cycling, carrying tree branches and water, horse riding), or strenuous (e.g., running, climbing stairs, fast rowing, cross-country skiing, clearing snow by hand). The lifetime exercise score represents the sum of the scores, ranging from 0 to 9, at the evaluated ages. In statistical analyses, the lifetime exercise score was divided into three categories: low (scores 0–2), moderate (3–7), and high (scores 8 and 9).

Participation in physical activities at the current age was used to evaluate the frequency and intensity of the current PA level. MET values for each intensity category were multiplied by the frequency of weekly activity, and the weekly MET minutes score was used to represent the overall level of current activity. The weekly MET minutes value was classified into six categories. In statistical analyses, two categories, low (cat. 1) and other (cat. 2–6), were used. Self-rated PA level was also asked, and the response options were ‘low’, ‘middle’, ‘high’ and ‘very high’.

4.3.3 Physical fitness

Self-rated physical fitness was assessed using a standardized five-scale questionnaire with the categories ‘very poor’, ‘fairly poor’, ‘satisfactory’, ‘fairly good’, and ‘very good’. In the statistical analyses, fitness categories were classified into two categories, poor (very poor, poor, and satisfactory combined) and good (very good and good combined). Satisfactory was included in the poor category since, according to our experience, those who report their physical fitness to be satisfactory are not fit when measured.

To determine the maximal HR, to measure the cardiorespiratory fitness, and to ensure the safety of the exercise intervention, the participants underwent a graded maximal exercise test under a physician’s supervision on a bicycle ergometer (Siemens Megacart -Ergoline 900 BP, Siemens-Elema AB, Electrocardiography Division, Sweden). In this thesis, physical fitness refers to CRF measured according to the existing gold standard, and VO2 max and absolute watt values were used. The workload at the beginning of the test was set at 25 watts (W) following a ramp protocol with the work rate increasing 25 W every two minutes (American College of Sports Medicine, 2000) until voluntary exhaustion or other symptoms limited the test. Symptoms that would terminate the test were: systolic blood pressure >240 mmHg, diastolic blood pressure >130 mmHg, arrhythmia, dizziness, and severe headache. The Borg rating scale (Borg, 1985) was used at each step throughout the test. The reason for ending the test was recorded. At this stage, the respiratory quotient was at least 1.0 in all participants, and all study participants fulfilled the maximum test criteria. Ventilation, gas exchange (Jaeger Oxycon Pro, Hoechberg, Germany), and HR responses (Polar S810, Polar Electro

Oy, Kempele, Finland) were monitored continuously during the ramp protocol. An electrocardiogram (ECG) was recorded with a standard 12-lead ECG (Siemens Megacart-Ergoline 900 BP, Siemens-Elema AB, Electrocardiography Division, Sweden). Ventilation and gas exchange were calculated on a breath-by-breath basis but were reported as mean values for 30 seconds. The highest value of oxygen consumption measured during the test was used as peak oxygen consumption (Mc Ardle et al., 1991). The values were categorized into seven sex- and age-specific fitness groups (very poor to excellent) according to international norms (Shvartz & Reibold, 1990).

The resting metabolic rate was measured by indirect calorimetry (Jaeger Oxycon Pro, Hoechberg, Germany) after an overnight fast of 10 hours. Resting blood pressure was measured in the seated position. Two readings separated by two minutes were averaged.

The participants were not allowed to eat or drink coffee for two hours before the exercise test, and heavy physical exercise and alcohol consumption were not allowed 24 hours before the day of testing. All the tests were performed between 10:00 a.m. and 3:00 p.m.

4.3.4 Health behaviors

The participants filled in a questionnaire including questions about demographic features, health and medication, obesity history, smoking, alcohol consumption, physical activity, and fitness. Alcohol consumption was reported as several portions (glasses of wine (12 cl), measures of spirits (4 cl), or bottles of beer (0.33 liter), each corresponding to 12 g of alcohol). In the statistical analyses, alcohol consumption was divided into two categories (fewer than six servings of alcohol per week, and six or more servings of alcohol per week). Smoking was reported as being a current smoker or a non-smoker. Those who had stopped smoking over two years ago were categorized as non-smokers. A seven-day food record was used to assess eating habits and to design the individual diet. A two-day diary was used to assess PA.

4.3.5 Measurement and analysis of heart rate variability

The R-R intervals were recorded over 24 hours with a Polar R-R recorder (Polar Electro Oy, Kempele, Finland) to an accuracy of 1 ms. The recording was performed during usual everyday activities. The analyses of the HRV were performed using the Hearts software (Heart signal Co, Kempele, Finland). The R-R intervals were edited by visual inspection based on ECG portions to exclude ectopic beats and artefacts. Measures of R-R interval dynamics were calculated from the entire 24-hour recording.

The mean HR and the standard deviation (SD) of all normal R-R intervals (SDNN), which is a summary measure of HRV, were used as time-domain measures of HRV. An autoregressive model was used to estimate the power spectral densities of RR interval variability, and the following frequency domain variables were calculated: ultra-low-frequency (ULF) power (<0.0033 Hz), very-low-frequency (VLF) power (0.0033–0.04), low-frequency (LF) power (0.04–0.15 Hz), high-frequency (HF) power (0.15–0.40 Hz), and the LF/HF ratio. HF power is an index of the parasympathetic modulation of the heart, whereas LF power is an index of the combined parasympathetic and sympathetic modulation of HR. The LF/HF ratio represents the sympathovagal balance.

4.3.6 Glucose metabolism

Ten-hour fasting venous blood samples were collected with a standardized procedure. After drawing the fasting blood samples, an oral glucose tolerance test with 75 grams of glucose was conducted, and glucose and insulin were measured at fasting (0 minutes), at 30 minutes, at 60 minutes, and at 120 minutes. The blood samples were centrifuged and stored in a freezer. The glucose values were analyzed from serum using a hexokinase assay (Konelab analyzers, Thermo Electron Oy, Vantaa, Finland), and insulin levels were determined using a (Jeffrey et al., 1998) using a chemiluminescent microparticle immunoassay (Abbot Diagnostic, Abbot Park, IL, USA). To measure insulin resistance, the indirect insulin resistance index was derived from the homeostasis model assessment (HOMA-IR). Insulin sensitivity was measured using the Matsuda Index, which was calculated as follows: (10,000/ [{fasting glucose level × fasting insulin level} × {mean glucose level × mean insulin level during the oral glucose tolerance test}]1/2) (Matsuda & DeFronzo, 1999).

4.4 Intervention (Studies II and III)

In this thesis, the intensified behavioral treatment was built around a certain frame and personal customization was done to achieve as much individual counseling as possible. Exercise training, even if it was carried out in a group, was based on personal performance and fitness level.

All members of the intervention groups (iBM, CWT1, and CWT2) were offered the same standardized basic procedure of intensified behavioral weight loss guidance. They also received a guidebook based on Finnish current care guidelines for obesity treatment (Suomen Sydänliitto ry., 2004). According to previous studies, weight loss often stops, and re-weighting often begins, about five to six months after starting a weight loss program (Jeffrey et al., 1998). Thus, we added exercise intervention to one group right at the beginning (CWT1) and to another group at six months (CWT2). The design and schedule of the intervention are presented in Figure 2.

	Weight loss period months 1–12							Weight maintenance period months 13–36				
Group	0	Weeks 1–13		Weeks 14–26	Weeks 27–39		Weeks 40–52	Months 13–24		Months 25–36		
iBM	Measurements and questionnaires	Counselling x 7	Measurements and questionnaires	Counselling x 3	Counselling x 2	Measurements and questionnaires	Counselling x 2	Counselling x4	Measurements and questionnaires	Counselling x 2	Measurements and questionnaires	Summary and feedback x 1
CWT1		Exercise intervention, counselling x 7		Counselling x 3	Counselling x 2		Counselling x 2	Counselling x 4		Counselling x 2		
CWT2		Counselling x 7		Counselling x 3	Exercise intervention, counselling x 2		Counselling x 2	Counselling x 4		Counselling x 2		
CON		Counselling x 1 (week 1)		No treatment	No treatment		No treatment	Counselling x 1 (month 24)		No treatment		

Fig. 2. The design and schedule of the intervention. iBM = intensified behavioural modification group; CWT1 = circuit weight training group 1, which received behavioral modification + supervised exercise from the baseline to three months; CWT2 = circuit weight training group 2, which received behavioral modification + supervised exercise from six to nine months; CON = control group. Modified from study III.

4.4.1 Intensified behavioral modification

The behavioral modification was based on a cognitive theory following the Finnish Current Care Guidelines for obesity (Obesity in Children & The Finnish Medical Society Duodecim, 2020), and the personal implementation was allowed to meet the individual needs of the participants. The intervention consisted of a 12-month intensified period followed by a 24-month follow-up period. The counseling protocol of the intensified behavioral modification is presented in Figure 3.

Time		Visits	Content of the counseling visit
Weight-loss period, weeks 0–52	0	1st visit, nutritionist	Preparing for weight loss: interview, dietary habits by a food diary, weight loss goal, meal plan.
	2	2nd visit, nurse	Going through the meal plan. Homework: Implementing the meal plan into everyday life.
	4	3rd visit, nurse	Principle goals of recommended eating. Meal rhythm, snacks, plate design, portion size, use of vegetables, berries, and fruits.
	6	4th visit, nurse	Health-promoting physical activity, benefits, and goal. What motivates you to move? Homework: Exercise diary.
	8	5th visit, nurse	Fats (quality and hidden fat), sugar. Homework: Where the fat lies? (Suomen margariinitiedotus).
	10	6th visit, nurse	Fiber and salt, energy content of foods. Homework: Salt test (The Finnish Heart Association), Fiber test (The Finnish Bread Information).
	12	7th visit, nutritionist	Going through the food diary, checking the meal plan, eating behavior. Homework: How emotions affect eating, self-assessment.
	16	8th visit, nurse	Eating control, difficult situations, binges. Homework: "A rambling diary".
	20	9th visit, nurse	Packaging labels, light products. Homework: The packaging speaks (Finnish Food Authority).
	24	10th visit, nurse	Special situations, treats, parties, alcohol.
	28	11th visit, nurse	Measurement and monitoring.
	36	12th visit, nutritionist	Going through the food diary, reviewing the meal plan.
	44	13th visit, nurse	Measurement and monitoring as well as encouragement and guidance.
	52	14th visit, nurse	Measurement and monitoring as well as encouragement and guidance.
Weight maintenance period, months 13–36	14	15th visit, nurse	Measurement and monitoring as well as encouragement and guidance.
	17	16th visit, nurse	Measurement and monitoring as well as encouragement and guidance.
	19	17th visit, nurse	Measurement and monitoring as well as encouragement and guidance.
	24	18th visit, nurse	Measurement and monitoring as well as encouragement and guidance.
	30	19th visit, nurse	Measurement and monitoring as well as encouragement and guidance.
	36	20th visit, nurse	Measurement and monitoring. Summary and further instructions.

Fig. 3. The counseling protocol of the intensified behavioral modification in all intervention groups (iBM, CWT1, CWT2).

During the first year, the intervention groups were offered 14 meetings of individual weight-maintenance counseling, three times by a nutritionist and 11 times by a qualified nurse. All meetings were individual and scheduled throughout the 12-month intensified intervention period. During the second year of interventions, groups met with their therapist four times every three months and, during the third year, two times. The counseling focused on a healthy diet, PA, self-monitoring, and risk situations in weight management. The participants were also given a guidebook based on current care guidelines for obesity treatment (Suomen Sydänliitto ry., 2004).

All the participants were individually instructed to reduce their daily energy intake to 500–1,000 kcal/d lower than their energy expenditure. The individual energy intake guidance was based on the measured resting metabolic rate, seven-day food diary, PA diary, and interviews. The participants were also requested to gradually increase their moderate aerobic PA to at least 150 minutes a week and to decrease their sedentary time. The participants were also advised to maintain these dietary and PA recommendations throughout the study period. The food and PA diaries were used to follow the accomplishment of the personal diet plan and the amount of daily exercise. The goal was to achieve a sustained 5% decrease in weight.

The participants in the CON group met with the personal therapist three times; at the beginning of the trial and at the 24-month and 36-month follow-up visits. They received basic weight-loss counselling, and they were also given a guidebook based on the current care guidelines for obesity treatment. Otherwise, they were asked to continue their normal lives.

4.4.2 Exercise intervention

The exercise intervention consisted of 12 weeks of heart-rate-controlled low-resistance CWT with air-resistance fitness equipment (HUR Ltd, Kokkola, Finland). The CWT sessions were offered three times a week, 40 minutes at a time. To determine the training loads for CWT and to ensure the safety of the training, the participants performed a 1-RM estimation test. They performed five repetition sets with increasing loads until they were unable to perform the sets properly. The test was performed in each exercise station. The 1-RM was theoretically calculated according to the knowledge of the person’s ability to perform five repetitions of 80% 1-RM, four repetitions of 85% 1-RM, and so on (McDonagh & Davies, 1984). Based on the results, the load was set at the level of 20% of 1-RM at each station. The target HR of the exercise was set to 70–85% of the measured HR maximum.

The training session included three resistance training circuits in 10 different stations: leg exten sion/curl, seated push-up/pull-down, seated body curl for abdomen/seated back extension, seated body twist left/right, and leg abduction/adduction. The work/rest ratio was 40/20 seconds. The participants were asked to keep up with a target HR of 70–85% of the maximum HR by modifying the repetition speed, and the heart rate monitor (Polar Edge NV, Polar Electro Oy, Finland) was set to alarm below and above the target HR zone. The training session started with a five-minute warm-up and ended with five minutes of cooling down and stretching. The circuit weight training program is presented in Figure 4.

Fig. 4. The circuit weight training program in intervention groups CWT1 and CWT2 by Kaikkonen.

The HR–controlled low-resistance CWT was chosen as an exercise protocol because it has been proven to be safe and effective to improve both aerobic and muscular endurance (Kaikkonen et al., 2000). The air-resistant equipment offers the possibility to control the intensity and the mode of training, and it is comfortable and safe for the joints. With light resistance, even physically inactive individuals and even those with BMI >35 are able to perform the exercises. Given that resting metabolic rate is related largely to the amount of fat-free mass and that the total fat-free mass is essential for the magnitude of resting metabolic rate (Ravussin et al., 1988; Schoenfeld, 2010), we assumed that low resistance strength training would help preserve both fat-free mass and resting metabolic rate during the weight-loss period.

4.5 Statistical analysis

Data were analyzed using the SPSS for Windows (SPSS Inc., Chicago, Illinois, USA) Version 15 in Study I and Version 24 in Study III and SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) in Study II. The normality of the variables was tested by the Kolmogorov-Smirnov goodness of fit test. The results of continuous normally distributed variables are presented as mean values with their SDs or 95% confidence intervals. The variables with skewed distributions were log-transformed by taking the natural logarithms of the absolute values. In tables and figures, the log-transformed values are presented as geometric means (SEs). The results of the categorical variables are percentages. Statistical significance was set at $p<0.05$.

The primary outcome of the original LILA study was weight loss at the end of the first year. The secondary outcomes were the change in body weight and waist circumference over three years. The sample size of 120 participants was calculated to observe over 20% difference in a weight change between the intervention groups and the control group at the end of the 12-month weight loss period. The drop-out rate was assumed to be 33% during follow-up. We estimated that we would require 30 participants in each group to give an 80% power of detecting the difference in body weight change at the end of the three-year follow-up. Block randomization was used as a randomization method.

In Study I, the associations of lifetime PA and physical fitness with HRV in adults living with severe obesity were studied. The primary outcome was HRV. For statistical analyses, the participants (n=107) were stratified into two age- and gender-specific fitness groups according to measured maximal power output. The unfit group included those in the lowest quartile of measured maximal power output, and the combined other quartiles (middle, high, and very high) were referred to as the fit group. The Student's independent samples t-test for continuous variables with normal distributions, the Mann-Whitney test for continuous variables with skewed distributions, and the Chi-squared test for categorical variables were used to evaluate the statistical difference between the two different fitness groups. The Pearson's or Spearman's correlation analysis was used to study intervariable relations between continuous variables with normal distributions and the Spearman's correlation analysis to study intervariable relations between continuous variables with skewed distributions. Because of the skewed distribution of frequency domain variables, the frequency domain HRV variables were log-transformed for the analyses. Multiple stepwise linear regression analysis was used to reveal the independent associates of the R-R interval dynamics. All explanatory variables that were significantly associated with HRV variables in univariate analyses were entered into multivariate models adjusted for age and HR.

In Study II, the primary outcomes were serum glucose and insulin values (0, 30, 60 and 120 min.), insulin resistance and sensitivity, and weight loss. The primary analysis was based on per-protocol-treated principles. The ANOVA was used for continuous variables and the Chi-square test for categorical variables. Changes in body weight, WC, fasting and two-hour serum insulin, HOMA-IR, and the Matsuda Index between the intervention groups over time were analyzed using a linear mixed-effects model for repeated measurements, including intervention group and time as a factor, baseline values of these parameters as a covariate, and group-by-time interaction. Glucose, insulin, HOMA-IR, and the Matsuda Index were also adjusted for weight change.

In Study III the primary outcome was weight loss, and the secondary outcome was a change in waist circumference at the end of the three-year RCT. The primary analysis was based on the intention-to-treat principles. The Student's independent samples t-test for continuous variables and the Chi-squared test for two independent proportions were used to evaluate the statistical difference between the groups at baseline. The means with 95% CIs were calculated for the changes in weight and WC within each group for the differences in changes between the groups. The statistical significance of the differences in changes in weight and waist circumference between the groups during the trial and follow-up was analyzed by the linear mixed-effects models. In post-hoc tests, the Bonferroni correction was used for the p-values.

5 Results

5.1 Baseline characteristics of the participants

A total of 80 participants (67% of the original study sample) completed the whole three-year intervention. Most of the participants were women (81%), the mean age was 44.8, and the median BMI was 35.7. The mean WC was 108.0 cm (89.0–138.0) in women and 114.8 cm (104.0–138.0) in men. Most (70%) of the 40 withdrawals dropped out due to a lack of interest. Those who dropped out of the study were younger (41 vs. 46 years, $p = 0.012$), heavier (104.6 vs. 97.3 kg), and more likely to be physically inactive (82% vs. 60%, $p = 0.023$) than those who continued until the end of the study. The completion rates in the different groups were as follows: iBM 67%, CWT1 70%, CWT2 70%, and CON 60%. The baseline characteristics of the participants in the original sample and studies I, II and III are presented in Table 5.

The average participation rate in the personal counseling sessions during the total three-year period was 18.6 (SD 10.9) (93%) times out of 20 sessions offered (93%). The mean participation rate in circuit weight training sessions in the CWT1 and CWT2 groups was 23 (SD 10.9) times out of 36 sessions offered (64%). No statistically significant differences were observed between the intervention groups in the frequency of sessions attended. There were no serious adverse effects related to the study interventions. The training method proved to be comfortable and safe for the joints, and only one mild strain injury to the Achilles tendon occurred during the intervention.

Table 5. The baseline characteristics of the obese adults in Studies I, II, and III.

Characteristics	Study I n=107	Study II n=85	Study III n=80
Female (n, %)	87 (81.3)	63 (75.3)	59 (73.8)
Age (years)	44.8 (10.8)	45.7 (10.4)	46.2 (10.0)
Weight (kg)	98.9 (14.0)	97.9 (13.4)	97.3 (13.1)
Height (cm)	164.2 (7.4)	164.3 (7.8)	164.4 (7.9)
BMI (kg/m^2)	35.7 (4.7)	36.3 (4.4)	36.0 (4.3)
Waist circumference (cm)	109.2 (10.2)	109.0 (9.9)	108.8 (9.6)
Hip circumference (cm)	120.8 (28.0)	119.7 (9.7)	119.0 (9.9)
Current smoker (n, %)	20 (9.7)	13 (15.3)	11 (14.0)

Characteristics	Study I n=107	Study II n=85	Study III n=80
Alcohol consumption more than six portions per week	21 (19.6)	18 (21.2)	18 (22.0)
Physical activity level low (n, %)	67 (63)	51 (60)	48 (60)
Measured maximal oxygen consumption (ml/kg/min)	21.8 (5.5)	22.6 (6.5)	22.7 (6.2)
SBP (mmHg)	140.8 (15.4)	142.0 (15.4)	141.0 (15.2)
DBP (mmHg)	89.4 (8.8)	89.6 (8.7)	89.7 (8.7)

Values are means (standard deviations) unless otherwise stated. BMI = body mass index, Vo2 max = maximal oxygen consumption, SBP = systolic blood pressure, DBP = diastolic blood pressure.

5.2 The association of lifetime physical activity and physical fitness with heart rate variability in severely obese adults (Study I)

The participants were stratified into four age- and gender-matched groups according to measured maximal power output values. For further analyses, the participants were stratified into two fitness groups. The unfit group included those in the lowest quartile of measured maximal power output and the combined other quartiles (middle, high, and very high) were referred to as the fit group. The characteristics of the 107 participants by the two age- and gender-stratified fitness categories are presented in Table 6.

Table 6. The characteristics of all 107 obese adults and the 27 unfit and 80 fit obese adults stratified by age and gender. Modified from study I.

Variable	All (n=107)	Fitness Category Unfit (n=27)	Fit (n=80)	*p*[a]
Gender				
Women, n (%)	87 (81.3)	22 (81.5)	65 (81.3)	0.979
Men, n (%)	20 (18.7)	5 (18.5)	15 (18.7)	
Age, years	44.8 (25–65)	45.4 (25–65)	44.6 (25–62)	0.755
Height, cm	164.2 (142.5–182.0)	162.0 (147.0–180.0)	165.0 (142.5–182.0)	0.071
Weight, kg	98.9 (72.9–150.6)	97.9 (79.9–129.0)	99.3 (72.9–150.6)	0.755
Women	97.6 (72.9–150.6)	95.8 (79.9–129.0)	98.2 (72.9–150.6)	
Men	104.8 (92.7–123.4)	106.7 (94.5–123.4)	104.1 92.7–118.8)	
BMI	35.7 (30.3–53.4))	36.4 (31.8–50.4)	35.4 (30.3–53.4)	0.401

Variable	All (n=107)	Fitness Category Unfit (n=27)	Fit (n=80)	p^a
Women	37.2 (30.3–53.4)	37.5 (31.8–50.4)	37.1 (30.3–53.4)	
Men	34.9 (31.5–44.6)	37.1 (33.2–44.6)	34.2 (31.5–40.4)	
WC, cm	109.2 (89.0–138.0)	111.1 (91.0–138.0)	108.6 (89.0–138.0)	0.281
Women	108.0 (89.0–138.0)	109.2 (91.0–129.0)	107.6 (89.0–138.0)	
Men	114.8 (104.0–138.0)	119.5 (105.0–138.0)	113.2 (104.0–124.0)	
Blood pressure, mmHg				
SBP	140.8 (107–185)	141.0 (117.5–172.0)	140.7 (107.0–185.0)	0.925
DBP	89.4 (68.0–110.0)	91.8 (80.0–110.0)	88.5 (68.0–110.0)	0.096
Alcohol >6 drinks/wk, n (%)	21 (19.6)	6 (22.2)	15 (18.8)	0.862
Current smokers, n (%)	20 (18.7)	5 (18.5)	15 (18.8)	0.997
Current physical activity low (<12.5 METh/wk), n (%)	19 (17.8)	10 (37.0)	9 (11.3)	0.002
Lifetime physical activity high, n (%)	17 (15.9)	3 (11.1)	14 (17.5)	0.552
Self-rated physical fitness level good, n (%)	13 (12.1)	0 (0.0)	13 (16.3)	0.025

Values are means (ranges) or numbers (percentages) of participants, except for BMI values, which are medians (interquartile ranges) due to its skewed distribution. Unfit = the lowest quartile of measured maximal power output (low), Fit = combined category of all other three quartiles of measured maximal power output combined (middle, high, and very high). BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, MET = a relative energy expenditure of physical activity expressed in metabolic equivalents

[a] *P*-value for the t-test and the chi-squared test (two independent proportions). Mann-Whitney nonparametric test was used to evaluate the statistical difference in BMI values.

Measures of 24-hour R-R interval dynamics showed that all the spectral components were higher in the fit group (Table 7). In the final model, lifetime PA and current physical fitness were positively and independently related to HRV in obese adults (Table 8). In multiple linear regression analysis, after adjusting for all the variables significant in the univariate analysis, lifetime PA explained 40% of the variance in SDNN. High measured VO_2 max explained 45% of the variance of LnHF ($p = 0.009$) and 25% of the variance in the LF/HF ratio ($p = 0.005$).

Lifetime PA explained 40% of the variance in normal R-R intervals (SDNN) adjusted for age and HR (Table 8). Each one-category increase in the lifetime PA index increased SDNN by 15.4 ($p = 0.009$) and 24% of the variance in the natural logarithmic value of ULF power (p = 0.050). High measured VO_2 max explained 45% of the variance in the natural logarithmic value of HF power (p = 0.009) and 25% of the variance in the LF/HF ratio (p<0.001).

Table 7. Age- and gender-stratified measures of 24-hour heart rate variation in all 107 obese adults and the 27 unfit and 80 fit obese adults. Modified from study I.

		Fitness		
Variable	All (n=107)	Unfit (n=27)	Fit (n=80)	*p-value*
Time and frequency-domain measures				
R-R Intervals, ms	817.3 (90.9)	791.2 (106.9)	826.2 (83.7)	0.084
HR, beats	74.3 (8.2)	77.0 (9.5)	73.4 (7.6)	0.045
SDNN, ms	154.1 (42.1)	137.7 (44.6)	159.6 (40.0)	0.018
HF, ln	5.71 (1.07)	5.62 (1.11)	5.89 (1.05)	0.262
LF, ln	6.58 (0.78)	6.46 (0.77)	6.68 (0.78)	0.213
VLF, ln	7.23 (0.61)	7.12 (0.65)	7.31 (0.59)	0.179
ULF, ln	9.53 (0.58)	9.31 (0.69)	9.62 (0.52)	0.016
LF/HF ratio	2.59 (1.44)	2.78 (1.78)	2.52 (1.31)	0.420

HR = heart rate; SDNN = standard deviation of R-R intervals; HF= high-frequency power, ln = natural logarithm of the absolute value in ms2, LF = low-frequency power, VLF = very-low-frequency power, ULF = ultralow-frequency power. The values are means (standard deviations) for variables with normal distributions, geometric means (standard deviations) for variables with skewed distributions corrected by natural logarithmic transformation, and p-values for differences in variables between unfit and fit obese adults from independent samples T-tests.

Table 8. The statistically significant predictors of 24-hour R-R Interval dynamics in all 107 obese adults from stepwise linear regression analyses. Modified from study I.

Variable	Regression coefficient (95% confidence interval)	*p*-value
SDNN, ms: Model R^2=0.403, p<0.001 [a]		
Lifetime activity level (per one category increase)	15.359 (3.852 to 26.866)	0.009
HFln: Model R^2=0.451, p<0.001 [a]		
High measured Vo2 max vs. low	-0.039 (-0.068 to -0.010)	0.009
ULFln: Model R^2=0.235, p<0.001 [a]		
Lifetime activity level (per one category increase)	0.181 (0.000 to 0.362)	0.050
LF/HF ratio: Model R^2=0.253, p<0.001 [b]		
High measured Vo2 max vs. low	0.096 (0.50 to 0.142)	<0.001

The values are unstandardized regression coefficients (95% confidence intervals) from linear regression models adjusted for a) age and heart rate and b) age, heart rate, and smoking, all of which were statistically significantly associated with measures of heart rate variation without adjustments. SDNN = standard deviation of R-R intervals, HF = high-frequency power, ln = natural logarithm of the absolute value in ms2, ULF = ultralow-frequency power, LF = low frequency.

5.3 The long-term effects of supervised three-month exercise intervention combined with intensified behavioral therapy on glucose tolerance over two years (Study II)

A total of 85 (70.8%) participants completed the 24-month follow-up: 64 (75.3%) were women, the mean (SD) of age was 45.7 (10.4) years of BMI 36.3, and of WC 109.9 (9.9) cm. Of the participants, 57 (67.1%) were normoglycemic. No statistically significant differences were observed between the groups in the baseline characteristics.

The mean changes in fasting serum insulin, 2-hour serum insulin, HOMA-IR and the Matsuda Index from baseline to three, nine, and 24 months in the three intervention groups and the control group are shown in Table 9. Compared with the CON group, the changes in fasting serum insulin levels and 2-hour serum insulin levels were statistically significantly different in all three intervention groups (p<0.001), and there were no statistically significant differences between these intervention groups. After the intensive three-month exercise period, both CWT1 (p = 0.004) and CWT2 (p = 0.033) showed a statistically significant decrease in fasting serum insulin value.

A statistically significant increase in the Matsuda Index from the baseline to three months (iBM p = 0.011, CWT1 p = 0.016, CWT2 p = 0.009) and to nine months (iBM p = 0.020, CWT1 p = 0.032, CWT2 p = 0.032) was observed in all the interventions groups. CWT1 showed the largest improvement in the Matsuda Index (p = 0.025) from baseline to 24 months.

Table 9. The changes in fasting serum insulin, 2-hour serum insulin, Homeostatic Model Assessment for Insulin Resistance, and the Matsuda Index from baseline to three, nine, and 24 months among 85 obese adults in the three intervention groups and the control group. Modified from study II.

Variable		iBM n=21	CWT1 n=23	CWT2 n=22	CON n=19
Fasting insulin mU·L^{-1}**	0 months	10.6 (5.5)	9.4 (4.7)	9.5 (4.5)	13.8 (8.5)
	3 months	-3.3 (4.5) *	-2.5 (3.6) *	-1.5 (3.5)	0.6 (4.8)
	9 months	-2.4 (4.8) *	-0.6 (4.8)	-1.8 (3.6) *	0.4 (6.8)
	24 months	-1.8 (5.0)	-0.9 (4.1)	-1.2 (3.7)	1.7 (6.2)
2 h insulin mU·L^{-1}**	0 months	59.1 (47.4)	57.0 (30.6)	58.8 (35.2)	80.7 (51.7)
	3 months	-17.0 (40.5)	-13.0 (23.3) *	-22.7 (31.1) *	17.6 (85.6)
	9 months	-16.4 (42.7)	-24.8 (22.6) *	-26.6 (31.5) *	17.2 (55.3)
	24 months	-15.3 (51.2)	-13.8 (31.7)	-19.9 (31.8) *	16.5 (44.0)
HOMA-IR	0 months	1.44 (0.72)	1.29 (0.67)	1.29 (0.59)	1.86 (1.09)
	3 months	-0.45 (0.59) *	-0.33 (0.50) *	-0.18 (0.48)	0.11 (0.63)
	9 months	-0.32 (0.64) *	-0.08 (0.65)	-0.23 (0.49) *	0.07 (0.83)
	24 months	-0.24 (0.66)	-0.10 (0.54)	-0.15 (0.51)	0.23 (0.82)
Matsuda Index	0 months	5.3 (3.0)	5.6 (3.1)	5.2 (2.2)	4.2 (2.9)
	3 months	1.1 (0.4) *	1.4 (0.5) *	1.9 (0.6) *	0.6 (0.6)
	9 months	1.7 (0.6) *	1.9 (0.8) *	1.4 (0.6) *	-0.4 (0.2)
	24 months	1.0 (0.7)	2.0 (0.8) *	1.4 (0.7)	-0.2 (0.3)

The values are means (standard deviations) for the baseline values and the mean changes in fasting serum insulin, 2-hour serum insulin, HOMA-IR, and the Matsuda Index from the repeated measures ANOVA.

* A statistically significant within-group mean change of fasting serum insulin, 2-hour serum insulin, HOMA-IR, or the Matsuda Index from baseline (p<0.05).

** A statistically significant difference in the mean changes in fasting serum insulin, 2-hour serum insulin, HOMA-IR, and the Matsuda Index across the four study groups from the repeated measures ANOVA.

The mean absolute changes in two-hour serum insulin values from baseline to three, nine, and 24 months are presented in Figure 5 and the mean absolute changes in Matsuda index in Figure 6. The mean two-hour insulin values decreased over the 24 months in all three intervention groups and increased in the control group over the trial period (p<0.001). CWT2 experienced the largest decrement in the two-hour serum insulin from baseline to nine months (p = 0.001). At the end of the 24 months the Matsuda Index in the CWT2 group was still slightly higher than the baseline value (p = 0.059). No statistically significant differences were found between the three intervention groups in HOMA-IR and HOMA-β.

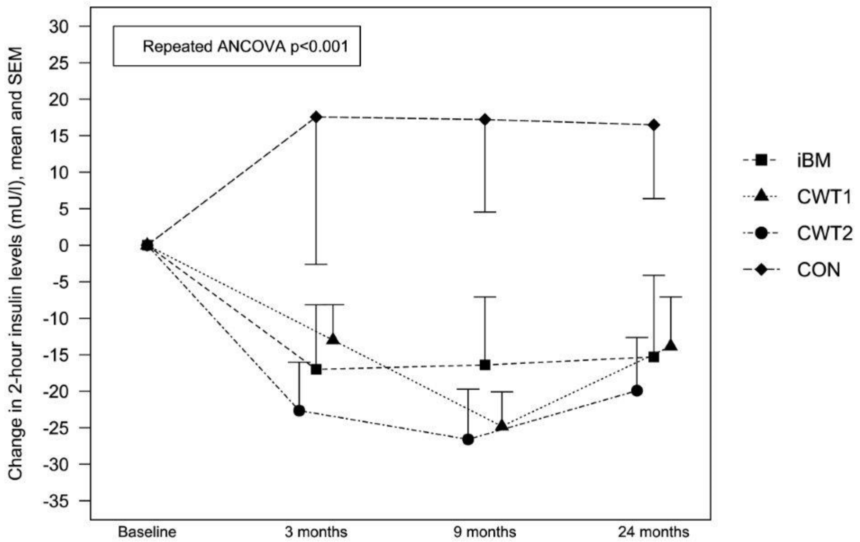

Fig. 5. The mean absolute changes in two-hour serum insulin from baseline to three months, nine months, and 24 months among 85 obese adults in the three intervention groups and the control group (n=85). iBM = intensified behavioural group; CWT1 = circuit weight training group with behavioural modification + supervised exercise from the baseline to three months; CWT2 = circuit weight training group with behavioural modification + supervised exercise from six to nine months; CON = control group. Reprinted with permission from study II © 2019 Wolters Kluwer.

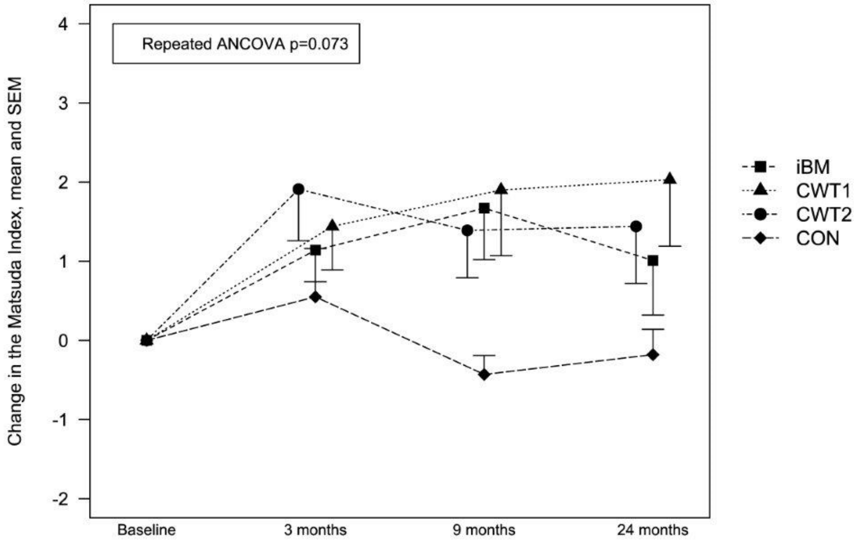

Fig. 6. The mean absolute changes in the Matsuda Index from the baseline to three, nine, and 24 months among 85 obese adults in the three intervention groups and the control group. iBM = intensified behavioural group; CWT1 = circuit weight training group with behavioural modification + supervised exercise from the baseline to three months; CWT2 = circuit weight training group with behavioural modification + supervised exercise from six to nine months; CON = control group. Reprinted with permission from study II © 2019 Wolters Kluwer.

5.4 The long-term effects of initial or delayed exercise intervention combined with intensified behavioral therapy on weight loss, weight maintenance, and waist circumference over three years (Studies II and III)

A total of 80 (67% of the original study sample) participants completed the three-year trial. Of them, 74% (n=59) were women. The average age was 46.2 (10.0) years, and the mean BMI was 36 (SD 4.3). The absolute values of weight at months 3, 9, 24 and 36 are shown in Table 10. Compared with the control group, all three intervention groups showed statistically significant weight loss over three years ($p<0.001$).

Table 10. Adjusted means (95% confidence intervals) of body weight at baseline, three months, nine months, 24 months, and 36 months among 80 obese adults in the three intervention groups and the control group. Modified from study III.

Variable	iBM	CWT1	CWT2	CON	*p-value*[1]
Weight (kg)					
Baseline	98.9 (93.8; 104.0)	99.1 (94.0; 104.2)	102.4 (97.3; 107.5)	98.9 (93.8; 104.0)	0.746
3 months	89.1 (83.7; 94.4)[3]	89.7 (84.4; 95.1)[3]	95.8 (90.4; 101.2)[3]	98.2 (92.8; 103.5)	0.046
9 months	90.3 (84.8; 95.7)[3]	89.6 (84.2; 95.0)[3]	95.2 (89.8; 100.6)[3]	98.9 (93.5; 104.3)	0.056
24 months	93.3 (87.8; 98.7)[3]	90.5 (85.0; 95.9)[3]	97.5 (92.1; 105.1)[2]	100.2 (94.8; 105.7)	0.063
36 months	92.2 (86.7; 97.7)[3]	93.3 (87.9; 98.8)[3]	99.6 (94.2; 105.1)	98.9 (93.4; 104.4)	0.137

Data are presented as means and 95% confidence intervals (CI).

[1] Difference between the groups, linear mixed model, [2] $p<0.01$, [3] $p<0.001$ Significance for the within-group difference from baseline, linear mixed model.

iBM = intensified behavioral modification group, CWT1 = intensified behavioral modification and supervised exercise from one to three months, CWT2 = intensified behavioral modification and supervised exercise from six to nine months, CON = control group.

The percentage weight loss from baseline to three, nine, 24, and 36 months is shown in Figure 7. The average percentage weight loss in kg from the initial weight for all the intervention participants was 8.3 (95% CI -9.5 to -7.0, $p<0.001$) at three months, 8.3 (95% CI -9.5 to -7.0, $p<0.001$) at 9 months, 6.2 (95% CI -7.5 to -4.8, $p<0.001$) at 24 months, and 5.0 (95% CI -6.3 to -3.6, $p<0.001$) at 36 months (for the difference between the intervention groups, $p = 0.035$). The achieved weight loss remained significant at 36 months in the iBM (-6.8%, $p<0.001$), the CWT1 (-5.8%, $p<0.001$), and the CWT2 group (-3.9%, $p<0.001$). Of the intervention participants, 62% reached clinically meaningful weight loss (>5%) at nine months, and 45% at 36 months. At 36 months, 32% of the subjects in the CWT1 group had their weight at least 10% lower than their initial weight; 25% of the completers in the iBM group, and 10% in the CWT2 group succeeded in maintaining their weight ⩾10% lower than their initial weight.

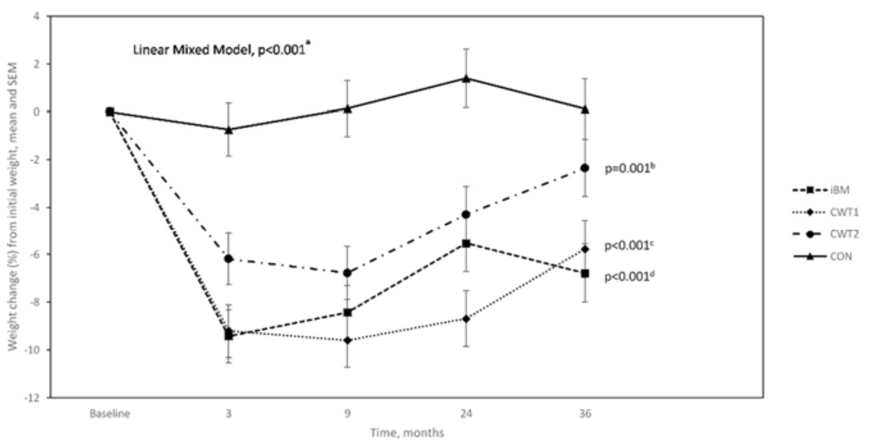

Fig. 7. The percentage changes in body weight from baseline to three, nine, 24, and 36 months among 80 obese adults in the three intervention groups and the control group. iBM = intensified behavioral group; CWT1 = circuit weight training group with behavioral modification + supervised exercise from the baseline to three months; CWT2 = circuit weight training group with behavioral modification + supervised exercise from six to nine months; CON = control group. Reprinted CC by 4.0 from study III © 2022 Authors.

[a] Group x time effect, [b] Difference between CWT2 and CON, [c] Difference between CWT1 and CON, [d] Difference between iBM and CON.

The percentage reduction in WC from baseline to 36 months is shown in Figure 8, and the absolute values of WC at months 3, 9, 24 and 36 are shown in Table 11. Compared with the control group, all three intervention groups showed a statistically significant decrease in WC over three years ($p<0.001$). The mean reduction in WC in all three intervention groups was 6.9 cm (95% CI -8.1 to -5.6, $p<0.001$) at three months, 9.5 cm (95% CI 10.8 to -8.2, $p<0.001$) at nine months, 6.2 cm (95% CI -7.6 to -4.9, $p<0.001$) at 24 months, and 5.0 cm (95% CI -6.4 to -3.7, $p<0.001$) at 36 months (for the difference between the intervention groups, $p = 0.017$).

CWT1 was most successful in WC reduction, and the mean difference in change from baseline was highest at nine months (mean change -11.2 cm, 95% CI -13.2 to -9.2). At 36 months, the mean change from baseline was -8.7 cm (95% CI -10.8 to -6.1). At 36 months, a statistically significant reduction in WC was also observed in iBM (mean change -5.0 cm, 95% CI -7.4 to -2.3, $p = 0.001$). In CWT2, the reduction in WC was statistically significant at nine ($p<0.001$) and 24 ($p = 0.004$) months.

Table 11. Adjusted means (95% confidence intervals) of waist circumference at baseline, three months, nine months, 24 months, and 36 months among 80 obese adults in the three intervention groups and the control group. Modified from study III.

Variable	iBM	CWT1	CWT2	CON	p^1
Waist circumference (cm)					
Baseline	108.4 (104.3; 112.5)	110.5 (106.4; 114.6)	109.7 (105.6; 113.8)	110.4 (106.3; 114.5)	0.882
3 months	101.2 (97.0; 105.4) [2]	103.2 (99.1;107.3) [2]	103.4 (99.3; 107.6) [2]	108.2 (104.0; 112.4)	0.118
9 months	99.3 (95.1; 103.5) [2]	99.2 (95.0;103.4) [2]	101.2 (96.9; 105.4) [2]	108.5 (104.2; 112.8)	0.008
24 months	103.2 (99.0; 107.5) [2]	101.7 (97.4;105.4) [2]	104.7 (100.4; 108.9) [2]	110.3 (106.0; 114.7)	0.031
36 months	103.5 (99.2; 107.8) [2]	101.8 (97.6;106.1) [2]	107.7 (103.5; 112.0)	109.9 (105.6; 114.3)	0.033

Data are presented as means and 95% confidence intervals (CI).

[1] Difference between the groups, linear mixed model

[2] $p<0.001$ significance for the within-group difference from baseline, linear mixed model

iBM = intensified behavioral modification group, CWT1 = intensified behavioral modification and supervised exercise from one to three months, CWT2 = intensified behavioral modification and supervised exercise from six to nine months, CON = control group.

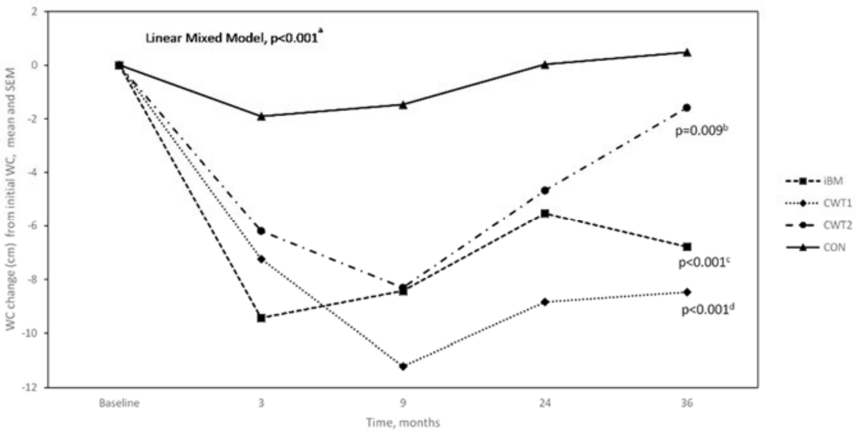

Fig. 8. The mean changes in waist circumference from baseline to three, nine, 24, and 36 months among 80 obese adults in the three intervention groups and the control group. iBM = intensified behavioral group; CWT1 = circuit weight training group with behavioral modification + supervised exercise from the baseline to three months; CWT2 = circuit weight training group with behavioral modification + supervised exercise from six to nine months; CON = control group. Reprinted CC by 4.0 from study III © 2022 Authors.

[a] Group x time effect, [b] Difference between CWT2 and CON, [c] Difference between iBM and CON, [d] Difference between CWT2 and CON.

6 Discussion

6.1 Study design and participants

The LILA study was RCT with an extended three-year follow-up. To our knowledge, LILA was the first RCT to investigate the long-term effects of the timing of the exercise program on weight loss and maintenance. The RCT design is the major strength of this study. In Study I we used a cross-sectional study design; hence, the causality cannot be inferred from existing associations. In Study II, the total follow-up time from the beginning of the trial was two years, and in Study III, three years.

The participants in the LILA study were recruited through local newspaper announcements. It may be that people who respond to announcements may be the most active in general and are more motivated to lose weight than obese people at the population level. This might have caused selection bias in our study sample. However, the participants were volunteers who were willing to receive guidance for weight loss and a lifestyle change and thus represented a typical person applying for counseling. The majority of those who responded to the announcement were women, and therefore the majority of those randomly assigned to the study groups were women. This is common in obesity treatment intervention studies and women tend to participate in such studies more actively (Johns et al., 2014; Soini et al., 2016). Because participants were mostly women, we could not determine the possible differences between sexes. The average age of the participants in the study was 44.5 years and the average BMI was 36.8. Thus, the participants were, on average, severely obese. Most of the obesity studies including exercise intervention have targeted participants with a BMI of less than 35; our results thus bring important new information to the guidance for the severely obese.

Initially, the sample size of the LILA study was 120 people. The sample size was calculated to detect a statistically significant difference between the intervention groups and the control group after three years of intervention. Small sample sizes (<20 participants per group) are typical for interventions that include guided exercise training, and they potentially lack the power to detect between-group differences (Keating et al., 2017). Attrition is a major limitation of most obesity management interventions; dropout rates vary from 10% to 80% (Yackobovitch-Gavan et al., 2015), and overall dropout tends to be higher in longer interventions. Our power calculation was based on a 33% dropout rate in the three-year follow-up. The attrition rate in the LILA study was 15% (18 participants) at nine, 29% (35 participants) at 24 months, and the originally estimated 33% (40 participants) at 36 months. Eighty (67%) participants continued until the end of the follow-up period. Compared to other obesity treatment interventions involving a long follow-up, compliance to the present trial was excellent and a major strength of the study. Most of the 40 participants who did not complete the three-year intervention dropped out because of a lack of interest. According to previous studies, poor compliance in the severely obese could be due to unrealistic expectations from the start (Lagerros & Rössner, 2013) and unsuccessful weight loss right at the beginning of the program (Yackobovitch-Gavan et al., 2015). Whether this was also the case in the LILA study remains to be analyzed.

There were three intervention groups in the LILA study: lifestyle guidance, lifestyle guidance plus exercise at onset (0–3 months), and lifestyle guidance plus delayed exercise (6–9 months). An interesting addition to the study would have been a group that was offered only an exercise intervention without other lifestyle guidance. Partly due to a lack of resources, the exercise-only group was left out of the research setting and the number of data collection points was limited to five. During the entire three-year intervention, surveys and measurements were repeated at baseline, three, nine, 24, and 36 months, but it may have been more optimal if the measurements could also have been conducted at six and 12 months.

The control group did not participate in the intensified lifestyle guidance or exercise intervention. Because of their severe obesity, they were offered normal primary care guidelines for the treatment of obesity. They received the same guidebook to read themselves, and they also participated in measurements and surveys. In addition, they received the laboratory results for their information. In studies where participants are measured and monitored regularly, a person's behavior can change, because of the so-called Hawthorne effect (Hassan et al., 2016). The Hawthorne effect is possible because those who choose to participate in trials are willing to change. It is possible that this also affected the results of this study, but for ethical reasons, the severely obese control group members could not be left completely without guidance. However, participants in all intervention groups showed a greater improvement compared to the control group. The RCT design allowed the estimation of the intervention’s effect over and above the Hawthorne effect to the mean.

6.2 Methods

Data collection in the study was comprehensive and we used questionnaires, diaries, and objective measurements. The persons randomized to the study went through a careful medical examination, which ensured safe participation in the study. To ensure the safety of the exercise intervention and to determine the maximum HR, a maximal graded exercise test was performed with a bicycle ergometer. Also, VO_2max was measured using a protocol that is standardized and recognized as the gold standard for measuring cardiorespiratory function (American College of Sports Medicine, 2000). In addition to measuring relative and absolute VO_2max, we used maximal power output in watts to describe the fitness of the participants. The precise measurements made in laboratory conditions are one of the strengths of this study.

As a non-weight-bearing test, the bicycle ergometer test was excellently suited for severely obese individuals. A previous study found that obese participants may not reach the maximal capacity level in exercise testing compared to lean participants (Hulens et al., 2001). It also suggested that the achieved maximal HR, respiratory exchange ratio, and rated perceived exertion were all lower in the obese group compared to the lean group. In the measurement of VO_2max and the measurement of resting energy consumption, we had problems fitting the mask to the faces of some subjects due to obesity. However, we were able to perform the measurements reliably by using different mask sizes. In our study, all the participants reached the maximal test criteria; thus, the results can be considered reliable. For statistical analyses, the 107 participants were stratified by age and gender into two groups of measured maximal power output. The unfit group included those in the lowest quartile of measured maximal power output, and the combined other quartiles (middle, high, and very high) were referred to as the fit group.

In Study I, information of lifetime PA questionnaires were combined with the measurements of HRV and measurements of physical fitness measured by maximal power. Ambulatory 24-hour recording of R-R interval is a widely used clinically useful method to assess the state of ANS. It has high reproducibility with no placebo effect (Task Force, 1996), but it also has certain limitations. Twenty-four-hour recordings of HRV during normal daily conditions have many potential confounding effects of non-stationary conditions due to breathing, PA, body posture, psychological stress and other factors. For the collected HRV data to be as reliable as possible, the data were carefully reviewed, and the R-R intervals were edited by visual inspection based on ECG portions to exclude ectopic beats and artefacts. Complete data sets were gathered from 107 participants (89%).

The questionnaires used in all the three studies included questions about demographic features, health habits, obesity history, health, medication, PA, and self-rated physical fitness. We mainly used validated and widely used questions to reduce weaknesses concerning self-reporting methods. The current PA and lifetime PA were assessed using a modified Paffenbarger Physical Activity Survey (Greendale et al., 1995; Paffenbarger et al., 1978). The survey has been used in previous studies finding relationships of lifestyle and current PA with health outcomes (Jokinen et al., 2010; Korpelainen et al., 2006; Volger et al., 2013), and having high reliability and predictive validity (Pereira et al., 1997). The use of self-reported data on PA may cause some recall bias and overestimation of the amount of activity (Hagstromer et al., 2010), but most questionnaires separate the most physically active participants from the sedentary participants. It may be that more goal-oriented physical exercise (skiing, running, brisk walking, etc.) is easier to remember than light commuting (walking and cycling to and from work, etc.) and everyday activities (gardening, household chores, etc.). Presumably, not all activities, especially the light ones, were not reported.

To examine current activity, we also used exercise diaries. Unfortunately, the diaries were so incomplete that we could not use them in analyzing the results. The participants' current activity was also assessed using wearable devices. We had to change the pedometers or accelerometera to the third measurement timepoint, and the reliability of the assessments in terms of repeatability decreased. We decided to leave the results of the wearable devices out of the analysis at this stage, but we intend to use them in our future studies. To assess central obesity, we used a simple measurement of WC. Due to financial reasons, dual-energy X-ray absorptiometry was not available in our pilot study, and the repeatability of the Bodystat® bioelectrical impedance and skin-fold assessments proved to be poor. Thus, we did not include these measurements in the study protocol, and the fat mass and fat-free mass of the participants were not measured.

6.3 Intensified behavioral modification

The intensive behavioral modification program was based on cognitive behavioral theory, and it followed the Finnish Current Care Guidelines for obesity (Obesity in Children & The Finnish Medical Society Duodecim, 2020). Lifestyle modification can be implemented individually or with group guidance and they may be equally effective. However, the results of the previous studies are contradictory. The Finnish guidelines recommend group counseling, based on the idea of getting and giving peer support, exchanging experiences, and learning together in the group cost-effectiveness may also favor the use of group guidance. For example, genetic differences can affect responses to exercise and food failure in different people, so personalized tailoring can improve long-term weight loss results (G. A. Bray et al., 2018). In our study all meetings were personal, and personal customization was allowed so that the guidance met each subject's personal needs. We wanted each person's own needs and opportunities to be considered as much as possible, and individual guidance was chosen instead of group counseling.

Cognitive-behavioral methods have had more favorable effects in some previous studies (Wadden, 2014) and are nowadays considered to be state-of-the-art by many researchers (Annesi et al., 2016). In counseling, we used both behavioral (goal setting, self-monitoring type of foods consumed, etc.) and cognitive strategies (barriers, problem-solving, etc.). The guidance followed the chapter division of the guidebook distributed to those involved in the interventions, and this ensured that the main theme of the guidance sessions was the same for everyone, regardless of the coach. The goal of the counseling was to change behavior. During the weight-loss period (first year), the participants met with a coach or nutritionist a total of 14 times. Frequent contact is critical for inducing clinically meaningful weight loss (Perri et al., 2008), and the latest recommendations state that an effective weight loss intervention includes at least 14 sessions of counseling during the first six months (Jensen et al., 2014; Wadden et al., 2020).

Our lifestyle guidance model proved to be successful when looking at the participants' commitment to the program. Participation in the guidance was very enthusiastic and, unlike in many other longer research interventions for the severely obese (Yackobovitch-Gavan et al., 2015), the participation activity remained high until the end of the intervention. The average participation rate for counseling sessions during the first trial year was 99%, 96% at the end of the second year, and 93% during the total three-year period. There was no difference between the intervention groups in the amount of participation in the guidance visits. However, high participation in counseling could have had a positive effect on the iBM group's success in losing weight.

6.4 Exercise intervention

We chose circuit training as the training model because it has been proven to be a safe and effective training method for previously untrained people with a lower basal level of fitness (Wilmore et al., 1978) and for those with higher BMIs (Seo et al., 2019). According to previous studies, it is an effective method to improve aerobic conditioning, muscular endurance, as well as neuromuscular and strength adaption (Gettman & Pollock, 1981; Kaikkonen et al., 2000). Supporting the findings of the previous studies the training model also proved to be safe for severely obese individuals. All participants randomized to the intervention were able to exercise according to the program, and no one had to stop the intervention due to adverse events (strain injury, injury, etc.). The training method proved to be comfortable and safe for the joints, and only one mild strain injury to the Achilles tendon occurred during the intervention. The heart-controlled CWT offered us the possibility to control the intensity and the mode of training and thus ensure that the exercises were done as planned. With light resistance, even the most inactive and obese participants could perform the exercises. The training equipment by Ab HUR Oy was well suited for the training of large persons.

The CWT sessions were offered three times a week, 40 minutes at a time. Previous studies have found that a longer exercise time can be a barrier to participating in exercise programs because a common reason for non-participation is a lack of time (Reichert et al., 2007). The 40-minute training session was short enough that participants in the exercise groups were able and willing to adhere to exercise sessions. The short exercise time may also enhance motivation to exercise more effectively than moderate aerobic exercise (Wilke et al., 2019). The mean participation rate in our study was 23 times for the total 36 sessions, on average 1.9 times a week. The goal was three training sessions a week and more than 1.9 times a week could have affected the research results. However, a previous study has shown that only two CWT sessions per week in active people may decrease body fat by 9.2% (Chtara et al., 2008). Since untrained participants most often have higher body fat mass, the range of improvement is usually much higher compared to trained participants, even after a shorter training period (Willis et al., 2012). The MET load of the training used in this study was approximately 7.5 (Ainsworth et al., 2011). For a person weighing about 100 kg, the energy consumption of one training session was about 500 kcal, depending on, for example, age, gender and body fat content. Three training sessions per week produced approximately 800 MET minutes per week. This dissertation did not examine the change in leisure time movement and diet, nor therefore the change in total energy intake and consumption. Based on our research, we can assume that even two training sessions per week can be sufficient for severely obese people to experience positive changes in body composition.

The CWT program we implemented was very much in line with the recent recommendation by Ramos-Campo et al. (Ramos-Campo et al., 2021), and we succeeded in building an impressive training model that was also suitable for severely obese people. This can be considered one of the significant findings of this study. The exercise program we implemented was supervised, and it may limit generalizability. On the other hand, a supervised program represents a strength of our study because adherence in individuals with overweight or obesity is typically low when exercise is unsupervised (Jakicic et al., 1999).

6.5 The association between lifetime physical activity, aerobic fitness, and heart rate variability in severely obese adults (Study I)

In our study, measures of 24-hour R-R interval dynamics showed that all spectral components were higher in the fit group. In the final models, aerobic fitness and lifetime PA were the most important associates of HRV. The level of lifetime PA explained 45% of the variance in 24-hour SDNN in severely obese participants. Results remained the same even after adjusting for mean HR, age, and other variables important in univariate analyses. In the Framingham study, SDNN was suggested to be related to future cardiac events (Tsuji et al., 1996), and reduction in SDNNwas found to be a significant independent predictor of death due to progressive heart failure (Kleiger et al., 1987; Nolan et al., 1998). Physically active obese people have been found to have a lower morbidity and mortality risk than inactive normal-weight people (Blair & Brodney, 1999). Barry et al. (Barry et al., 2014) and Ross et al. (Ross, Blair, et al., 2015) concluded in a meta-analysis that increased cardiorespiratory fitness in overweight and obese paricipants reduces their risk of mortality. Another previous study showed that increased PA was significantly associated with reduced adiposity rates and improved HRV variables related to vagal modulation in sedentary obese participants (Phoemsapthawee et al., 2019). In our study, lifetime PA and physical fitness were positively and independently related to HRV in severely obese adults. The results reflect the potential beneficial association between lifetime PA, good aerobic fitness and the risk of sudden cardiac events or premature death in severely obese adults. Our results are implying that regular PA is associated with structural and functional adaptations in the cardiovascular system.

Most of the previous studies investigating the association between PA and HRV have been conducted on populations with normal weight and BMI <30, or on patients with cardiovascular and metabolic diseases. Due to differences in study populations, methodological differences in recording and analyzing the HRV, and differences in the assessment of PA, results are difficult to compare. Only a few studies have analyzed the association of regular PA and physical fitness with HRV in obese and severely obese individuals. In a previous study, Felber Dietrich et al. (2008) found that middle-aged and older obese participants who were regularly physically active had a higher HRV than their sedentary peers (Felber Dietrich et al., 2008). Their results showed that exercise improves ANS function measured by HRV and the improvement in HRV induced by exercise was similar in obese and normal-weight participants. In their study, the PA data were collected over a relatively recent period and thus did not reflect lifetime PA. In the DREW study, moderate-intensity exercise was sufficient to improve HRV in sedentary overweight and obese postmenopausal women (Earnest et al., 2008). Our findings support the previous findings, and our data suggest that regular PA improves ANS function measured by HRV. We believe that long-term PA modifies the traditional risk factors of CVDs in obese people, but the protective effect is mainly a result of its impact on ANS. PA with or without weight change helps to maintain the ANS function, even in severely obese people.

6.6 The long-term effects of supervised three-month CWT combined with iBM on glucose tolerance in severely obese adults over two-years (Study II)

The results of our study showed that supervised CWT intervention was effective, and it produced positive effects on glucose metabolism in severely obese adults. The most significant improvement throughout the 24-month period was found in those who had the iBM together with the supervised CWT intervention at the very beginning of the weight management program, from baseline to three months (CWT1). Insulin sensitivity, assessed by the Matsuda Index, improved significantly in all the intervention groups during the first nine months, and a significant improvement was observed throughout the 24-month period in the CWT1 group. Our results show that the two-hour insulin values significantly improved in both exercise intervention groups (CWT1 and CWT2). The mean change from the baseline was similar in all the intervention groups and significantly differed from those observed in the CON group. Our findings are in accordance with previous studies suggesting that the decreased two-hour values are associated with PA (Healy et al., 2006).

The results of the previous studies have been conflicted about what kind and intensity of exercise is best for achieving improvements in health outcomes, as in glucose metabolism in obese people, and many unanswered questions exist. In a previous study, Ross et al. (2015) found that for reducing two-hour glucose level, high-intensity exercise is needed. Another study suggests that a low amount of moderate aerobic exercise with at least modest weight loss produces greater improvement in insulin sensitivity (Swift et al., 2018). Most of the newest guidelines suggest that no threshold need be exceeded before benefits begin to accrue in the least active population (Powell et al., 2019). In the present study, CWT exercises were performed at a low load (20% of one maximum repetition 1-RM), and the target HR of the exercise was set to 70–85% of the measured HR maximum. This kind of training proved to be an effective and well-implemented form of training to improve glucose metabolism in severely obese people.

An important finding was that the CWT1 group showed the most significant reduction in weight and abdominal obesity throughout the 24-month follow-up. There is much evidence that WC is strongly associated with intra-abdominal or visceral fat, the strongest indicator of health risks (Neeland et al., 2019). Both diet-induced (Goodpaster et al., 1999) and exercise-induced reductions (Ross et al., 2000) in visceral fat are related to improvements in insulin resistance in obese men and women. By maintaining favorable cardiometabolic parameters, such as insulin sensitivity and normal blood sugar, cardiometabolic diseases related to obesity may be prevented. Based on our study, an intensive start with CWT and lifestyle counseling right from the start are effective in reducing WC and improving glucose metabolism in the severely obese. These results are encouraging and provide an option for clinicians to treat severe obesity.

6.7 The effect of timing of exercise on weight loss and maintenance in a long-term weight management program (Studies II and III)

To our knowledge, this is the first RCT to evaluate the importance of the timing of exercise in a long-term (36-month) weight management program. Our results showed that the addition of supervised exercise training implemented with CWT right at the beginning of the program promoted long-term weight loss and reduction in waist circumference and cardiometabolic risk factors. Contradictory to our hypothesis, the six-month delay in the onset of the supervised exercise program did not bring any extra boost to weight loss or extra effects on long-term weight maintenance. CWT2 that started CWT at six months had the smallest absolute weight loss and WC reduction at each time point. The results were significantly better compared to the control group.

The effect of the timing of exercise in weight management programs has been studied very little. We found only three previous studies on the subject, and the follow-up time in them was shorter than in our study. Goodpaster et al. (2010) found that the addition of PA early in the weight loss program promoted a greater reduction in body fat and WC at six months compared with the delayed activity group, but at 12 months, the results did not differ between the groups. Unlike in our study, exercise training was not supervised in their study; thus, the results are not directly comparable. Based on their results, they argued that PA should be incorporated early in any dietary restriction approach to induce weight loss and reduce abdominal fat, but they also noted that additional studies are needed to determine long-term efficacy. A more recent study by Catenacci et al. (2019) found that both immediate and delayed exercise initiation within a behavioral weight loss program resulted in clinically meaningful weight loss at 18 months. Although their results indicated that weight loss at six months was greater when diet and exercise interventions were initiated simultaneously, there was no difference in long-term changes. Based on their results, they suggest that individual-specific factors may be used to guide the timing of exercise initiation within a behavioral weight loss program. Another study that combined a low-calorie diet with four weeks of delayed exercise training did not find any difference between the groups in weight loss (Donnelly et al., 1994).

Our results are partially consistent with previous observations. Like Catenacci (2019) and Goodpaster (2010) with colleagues, we found that the addition of exercise early in the weight loss program promoted the best weight loss and weight reduction at the intensive weight loss phase of 0–6 (9) months. The results of our study support the conclusions of the review by Chin et al. (2016) indicating that diet plus exercise combined interventions were more effective than diet-only interventions in weight loss at six months. Our results differ from the results of previous studies (Catenacci et al., 2019; Goodpaster et al., 1999) regarding the results of the follow-up period. In our study, the CWT1 group with initial exercise was the most successful until the end of the three-year follow-up in terms of both weight and waist circumference. In the present study, the follow-up time was notably longer than in previous studies and thus our findings have important implications.

An unexpected finding was that a six-month delay in the onset of CWT did not bring any additional benefits for weight loss or the maintenance and reduction of abdominal obesity. Previous research consensus indicates that the initial six months after treatment start is a time of weight loss, whereas beyond six months weight regain can be reliably predicted (Jeffrey et al., 1998). We assumed that after the first months of behavioral modification and diet-induced weight loss, the participants would have benefitted from structured CWT. We expected to see increased motivational boost on participants' weight loss plans as a result. However, we underestimated the power of a highly intensive start with a face-to-face meeting with healthcare professionals together with the CWT program from the very beginning. Improvements in weight loss and a feeling of ability may be associated with success in long-term exercise adherence. In a previous study by Annesi et al. (2016), they found that the use of manageable amounts of exercise can build self-regulatory skills and improvements in mood that promote a sense of control in overeating behaviors. Based on our study, an intensive start with high weight loss at the beginning seems to motivate obese participants to adopt a healthy lifestyle with diet and exercise in the long term.

6.8 The long-term effects of an intensified lifestyle intervention on weight loss, weight maintenance, and reduction of abdominal obesity in severely obese adults over three-years (Studies II and III)

The results of the present study showed that intensive lifestyle intervention can be effective in addressing severe obesity. Intensified behavioral modification alone and with exercise resulted in clinically notable weight loss and long-term weight maintenance in severely obese adults. Compared with the control group, all intervention groups sustained significant weight loss (iBM 6.8%, CWT1 5.8%, and CWT2 3.9%) at 36 months. At the end of the three-year follow-up, 45% of all the intervention participants sustained a clinically marked weight loss of >5% of initial weight. Our results directly counter the dogma that severely obese individuals do not respond to lifetime intervention and our findings are in accordance with the findings of Goodpaster et al (Goodpaster et al., 2010). They found that a lifestyle intervention with diet and PA resulted in significant weight loss and favorable changes in cardiometabolic risk factors in severely obese adults. The review by Chin et al (Chin et al., 2016) indicated that diet plus exercise combined interventions were more effective than diet-only interventions in inducing weight loss at six months. Our results support their findings. At nime and 24 months, the CWT1 group was most successful in weight loss. In the active treatment phase, exercise may improve body composition, metabolic profiles, and cardiorespiratory fitness, which may have particular importance in the prevention of cardiometabolic diseases (Ross, et al., 2015). However, at 36 months, both iBM and CWT1 groups had maintained a clinically significant weight loss result.

Although the iBM and CWT1 groups were most successful at long-term weight loss, the CWT1 group showed the most significant long-term effects on the reduction of abdominal obesity measured by WC. At 36 months, the mean change from baseline in the CWT1 group was -8.8 cm, -5.0 cm in the iBM group, and -2.0 cm in the CWT2 group. Previous studies have shown that a 5 cm reduction in WC is associated with a 9% lower risk for death in healthy middle-aged adults (Berentzen et al., 2010). A meta-analysis of studies showed that visceral adipose tissue was reduced by 6.1% by exercise and only by 1.1% by diet, while weight was held stable (Verheggen et al., 2016). The systematic review by Ross et al. (2020) concluded that decreases in WC are an important treatment target and that clinically relevant reductions in WC can be achieved by moderate-intensity exercise and dietary interventions. PA has proven to have the potential to improve fat distribution by reducing visceral fat, even without weight loss (Ross et al., 2000). Our study supports these previous findings. Importantly, a more favorable fat distribution has been associated with the maintenance of a metabolically healthy profile in obese adults and the elimination of excess risk of type 2 diabetes and CVD (Appleton et al., 2013).

Most weight loss programs recommend simultaneously a decrease in energy intake and an increase in PA. In weight maintenance studies, the role of PA has been indistinct. In a study by Soini et al. (2016), they identified characteristics of successful weight loss and maintenance of the lost weight (Soini et al., 2016). The successful ones were much more physically active, particularly in their leisure time but also in commuting, and they had a healthier lifestyle than the general population in Finland. Previous studies argue that it may be difficult for overweight and obese people to achieve and sustain high levels of exercise simultaneously with diet and exercise interventions (Tate et al., 2007). For severely obese people, exercise is often only associated with weight loss and not, for example, fitness improvement or the joy of exercise, and the focus of research has been on the treatment of obesity with the help of exercise (Bouchard et al., 1993). However, for many obese people, exercise involves social, physical, and psychological barriers, and they may avoid or do not dare to exercise at all, even if they are interested in it (McIntosh et al., 2016).

In this study, we succeeded in building a lifestyle guidance intervention in which personal guidance was combined with a personally tailored exercise intervention implemented in a group. The exercise intervention implemented as a circuit training was stimulating, and even previously inactive persons were willing to participate and continue with it. A personal approach can contribute to the promotion of healthy lifestyles and thus promote, e.g., cardiometabolic health in the severely obese. It remains interesting to consider whether the results of the exercise groups would have been even better if the exercise intervention had been repeated in the follow-up years.

The present study did not consider the amount or change in PA outside the study protocol, which is an interesting topic for further research. The participants in the study kept the seven-day food diaries and the diaries were utilized when planning the individual energy intake guidance and during the nurse and nutritionist sessions to follow the individual planning accomplishment. The present study did not analyze the diaries or the possible changes in diet.

6.9 Implications for future research

There is still a need for new high-quality studies with a randomized controlled design to investigate the effects of intensified lifestyle intervention with exercise training on weight loss and weight maintenance and the reduction of cardiometabolic risk factors in severely obese adults. Most of the previous studies have been conducted with small samples, they have often been underpowered and emphasizing the nutritional guidance. In addition, very few studies have been conducted on severely obese individuals. Moreover, waist circumference has often not been included in the review, and the endpoint variable is most often weight loss. A limitation of published research on the efficacy of exercise training has been reported to be the focus on group mean data, with the inter-individual variation in response often being overlooked (King et al., 2008). If such individual differences are present and predictors of individual response are identified, then targeted intervention strategies could be formulated to maximize weight loss for individuals. Finally, new strategies and interventions for motivating both obese individuals and health care professionals are needed.

The cost-effectiveness of the management of adults with severe obesity with the protocol we developed needs to be investigated. The effect of iBM with exercise on voluntary PA should also be investigated. In addition, the connection between changes in PA level and cardiometabolic risk factors should be clarified. Also, the phenomenon called healthy obesity and the effect of exercise, especially circuit training on it is an interesting topic for future research. Our results on the suitability of CWT for the treatment of obesity in severely obese people were promising, and research around this form of training should be continued. The intensified lifestyle guidance model with CWT at onset should be put into practice and become part of the treatment of severe obesity.

7 Conclusions

The overall purpose of this study was to examine the role of PA in the treatment of severely obese adults with a special interest in cardiometabolic diseases risk factors, such as abdominal obesity, glucose metabolism and heart rate variability. We also wanted to find out whether the timing of exercise combined with iBM has any effect on the results.

The main findings according to the study aims are presented below:

1. Lifetime PA and aerobic fitness are positively related to heart rate variability and have strong beneficial effects on cardiac autonomic function in obese working-age participants. Being physically active reduces obesity-related health risks by improving the autonomic nervous function measured by heart rate variability. Based on the study findings, lifetime PA should be emphasized in weight management strategies and interventions to reduce obesity-related health risks, and obese people should be encouraged to exercise regularly.
2. Intensified behavioral modification with three-month circuit weight training at the very beginning of the weight management program had the greatest effect on glucose tolerance in severely obese adults over a two-year follow-up. The treatment of severe obesity should include an intensive start followed by an extended follow-up with exercise and diet, regardless of weight status.
3. The addition of exercise right at the onset of the weight loss period promoted a greater reduction in waist circumference during the three-year follow-up time.
4. Intensified behavioral modification alone and with three-month circuit weight training resulted in clinically significant weight loss and long-term weight maintenance. Heart rate–controlled low-resistance circuit weight training was safe and effective even for physically inactive people and those with severe obesity. In the treatment of obesity, including severe obesity, more intensive lifestyle interventions with exercise should be incorporated.

The findings of this thesis underline the importance of PA in the treatment of obesity in adults, including severe obesity. Regardless of weight status, obese people should be encouraged to exercise regularly. Circuit weight training proved to be suitable and effective for previously inactive and severely obese participants, and it could be utilized more in the treatment of obesity. More intensive lifestyle interventions with exercise should be incorporated into the treatment of severe obesity. In addition to the Finnish Current Care Guidelines of obesity, for those with severe obesity, more individual and tailored behavior counselling is needed.

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