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Implications of Peak Oxygen Consumption and Visceral Adipose Tissue on the Metabolic Syndrome: A matter of intensity, duration and frequency?

A randomized controlled trial

Master's Thesis in Exercise Physiology and Sports Sciences

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Abstract

Background: The metabolic syndrome (MetS) is a socioeconomic concern on a worldwide scale. Visceral adipose tissue (VAT) accumulation is a fundamental component of the MetS, and the prevalence of abdominally obese individuals steadily increases. Cardiorespiratory fitness has shown to be an essential determinant in cardiometabolic health. Thus, it is a targeted remedy for improving the MetS. **Objective:** The present study aimed to assess how various loads of aerobic training (AT) would affect cardiorespiratory fitness, by means of peak oxygen consumption (VO_{2peak}); whether this would associate with a reduction in visceral adipose tissue (VATA), and furthermore if this would have an effect on the MetS. **Methods:** 38 subjects diagnosed with the MetS were randomized in three groups; continuous moderate exercise (CME; n=14), 1 • 4 min aerobic interval training (1-AIT; n=11) and 4 • 4 min aerobic interval training (4-AIT; n=13), and underwent a 16-week intervention. VO_{2peak} was measured by use of direct ergospirometry, and direct segmental multi-frequency bioimpedance analysis (DSM-BIA) was applied to determine VATA. **Results:** The alteration of VO_{2peak} did not differ significantly between groups at follow-up. However, CME increased VO_{2peak} ($p<0.05$), which was accompanied by a reduction in VATA ($p<0.05$). Furthermore, the alteration of VO_{2peak} and VATA inversely correlated ($p<0.01$). Body mass (BM) changed differently between groups ($p<0.05$). Coherently, there was a trend towards a dissimilar compliance between groups (CME compared with 1-AIT; p=0.056, 4-AIT; p=0.057). Finally, subjects that achieved the 25% highest positive alteration in either VO_{2peak} or VATA had the most profound improvements in features of the MetS, by means of waste circumference (WC), diastolic blood pressure (BPd) and triglycerides (TG). **Conclusion:** Aerobic intensity still seems to be most effective by means of augmenting cardiorespiratory fitness if carried out adequately. Augmented VO_{2peak} is associated with decreased VATA, and significantly affects the MetS.

Key words: Metabolic syndrome, visceral adipose tissue, aerobic training, peak oxygen consumption.

Frequently used abbreviations

AIT	Aerobic interval training
AT	Aerobic training
BC	Body composition
(DSM)-BIA	(Direct segmental multi-frequency)- Bioelectrical impedance analysis
BPd	Diastolic blood pressure
BPs	Systolic blood pressure
Cardiometabolic	Cardiovascular- and metabolic
CI	Confidence interval
CME	Continuous moderate exercise
CVD	Cardiovascular disease
FG	Fasting glucose
HDL-C	High-density lipoprotein-Cholesterol
HF_{max}	Maximal heart frequency
IDF	International Diabetes Federation
MetS	Metabolic syndrome
PA	Physical activity
RCT	Randomized controlled trial
ScAT	Subcutaneous adipose tissue
SD	Standard deviation
SMM	Skeletal muscle mass
TFM	Total fat mass
TG	Triglycerides
VAT	Visceral adipose tissue
VATA	Visceral adipose tissue area
VO_{2max}	Maximal oxygen consumption
VO_{2peak}	Peak oxygen consumption
WC	Waste circumference

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1. Introduction

1.1. Background

The metabolic syndrome (MetS) is the presence of multiple risk factors for cardiovascular disease (CVD) [1]. Although the pathogenesis of the MetS is complex and not fully clarified, the two major underlying components are insulin resistance (IR) and accumulation of visceral adipose tissue (VAT) [1]. Central- or abdominal obesity in the form of VAT accumulation appears to be strongly related to CVD and metabolic disorders [2-6]. It is an underlying- [7-9] and unifying [10, 11] risk factor seen among a majority of individuals with the MetS. VAT accumulation potentially exacerbates several features of the MetS [12], which emphasizes the role of body composition by means of specific fat distribution in the pathogenesis of the MetS.

In Europe, the MetS afflicts approximately one of four adults, with variations in different age- and ethnic groups, and geographical locations [13]. In the USA, recent results reveal that one-fifth of the U.S. population is classified as having the MetS [14]. Interestingly, due to an ongoing development in pharmacological treatment, a decrease in hypertension and dyslipidemia has been noticed from 1999 to 2010. However, the prevalence of abdominal obesity has increased from 45 – 56% in the same period.

The World Health Organization (WHO) revealed that 35% and 14% of women worldwide ≥20 years of age were overweight and obese respectively in 2008. This is almost a twofold increase if compared with the numbers from 1980 [15]. Furthermore, data from the Nord Trøndelag health study (HUNT) in Norway showed that the prevalence of obesity among men ≥ 20 years of age went from 6.7% to 15.5% from 1984 – 1997 [16]. It is estimated that 2.8 million people worldwide die as a direct result of being overweight and obese on a yearly basis, which accounts for approximately 5% of all deaths [17]. The growing prevalence of obesity in all age groups is a socioeconomic concern, in the way that it rises healthcare expenditures and diminishes the total work force. The world health report from the WHO in 2012 shows that health related expenditures, as a percentage of gross domestic product, has risen from 8.4 – 9.7% from 2000 – 2009 in Norway [17]. Coherently, per capita total expenditure on health has risen from 3155$ – 7533$. This trend is similar in other developed countries.

Inactivity is a central component in the development of the MetS. Our body wasn't created in an environment that allowed a sedentary lifestyle. It has been demonstrated that as little as 2 weeks of profound inactivity has the potential to increase visceral adipose tissue area (VATA) and plasma levels of triglycerides (TG) [18], in addition to decreasing peripheral insulin sensitivity and cardiorespiratory

fitness [19]. On a worldwide basis, it is estimated that 6 % of all deaths attributed to physical inactivity [17].

Physical activity (PA) is a salutary way of achieving caloric balance. However, of more importance is that regular PA in the controlled terms of aerobic training (AT), provides a systemic effect on the body with regards to cells and tissues that are involved in cardiovascular- and metabolic- i.e. cardiometabolic physiology [20]. It is substantially demonstrated that AT alters a variety of cardiometabolic risk factors and diseases [21-32]. Even small amounts of physical activity appear to provide substantially reduced risk of mortality, when compared with profound inactivity [33]. Indeed, intensity is an important factor in this regard, and high-intensity aerobic interval training (AIT) has shown to improve cardiorespiratory fitness and reverse several risk factors of the MetS more than continuous moderate exercise (CME) [21, 34]. The predictive value of cardiorespiratory fitness in relation to morbidity and mortality is strong [35-38]. Regardless, physical discomfort and lack of time to exercise, even though time spent in front of a screen has steadily increased over the last decades, are worrisome barriers to exercise [39]. Hence, the pursuit of an efficient and minimally time consuming method of performing AT has preoccupied researchers recently.

1.2. Theory

Exercise physiology

Physical fitness describes a person's ability to carry out daily tasks and challenges. To assess this, the term is operationalized into measurable components, including cardiorespiratory fitness, muscular fitness, body composition (BC), flexibility and neuromotor fitness [40]. Cardiorespiratory fitness describes the respiratory- and circulatory system's ability to supply oxygen to working skeletal muscles during prolonged physical activity. Fit individuals in this sense likely possess a proper cardiac- and endothelial function, as well as an adequate quantity of capillaries, mitochondria and metabolic enzymes [41]. Cardiorespiratory fitness serves as a favorable marker for cardiovascular health even when the MetS is present [35], and it has proven to be a robust predictor of morbidity and mortality [36]. It is even claimed to be as independent and consistent of a risk predictor for cardiovascular events as smoking [38].

Maximal oxygen consumption (VO_{2max}) is the golden standard for estimating cardiorespiratory fitness. It is defined as the highest rate at which the body can take up and utilize O_2 during strenuous exercise [42]. VO_{2max} is explained by Fick's law of diffusion, where it is stated that a gas diffuses through a tissue in proportion to its area, and inversely proportional to its thickness [41]. The Fick equation, as

illustrated below, estimates cardiac output (Q), which is a product of the stroke volume (SV) and frequency (HF) of the heart:

$$Q = \text{oxygen consumption } (VO_2) \bullet \text{arteriovenous oxygen difference } (a\text{-}vO_2\,diff)^{-1}$$

Reversing the equation ($VO_2 = Q \bullet a\text{-}vO_2\,diff$) illuminates that VO_{2max} is a product of the arterial content of O_2 and individual ability to pump oxygen-rich blood throughout the vascular system, together with the ability to extract and utilize the available O_2 from ambient air to lung capillaries, and further on into working skeletal muscles [43]. Limitations for VO_{2max} are pivotally related to cardiovascular conditions [44]. In fact, the circulatory system is the essential remedy between external- and internal respiration, i.e. from the moment O_2 enters the bloodstream until it diffuses into the targeted tissue. When power output increases, Q is the most important factor for augmenting VO_2. Indeed, it is also a determining factor for a sufficient removal of CO_2, which is required in order to maintain aerobic energy production and postpone the onset of lactate accumulation. The venous return to the heart is crucial for SV quantity, and consequently the end product of Q. It is fundamentally determined by conditions in the circulatory system, and therefore, cardiovascular fitness by means of VO_{2max} is an apparent reflector of cardiovascular health [41, 44].

Fat as a source of energy

Aerobic energy production happens in the mitochondrion of a cell, and requires oxygen in order for the electron transport chain to work. Through aerobic energy metabolism, a large amount of adenosine triphosphate (ATP) is produced from breaking down glucose- and fatty acid molecules. β-oxidation describes the process where lipids are utilized for ATP synthesis [45]. At low training intensities of approximately 60% of maximal heart frequency (HF_{max}), it is shown that β-oxidation is at its highest in relative terms. At that state, fat contributes to at least 50 % of the aerobic energy production [46]. However, although the proportion of energy derived from fat decreases at high aerobic intensities, it is claimed that β-oxidation per se increases further in absolute terms. This aspect is, however, controversial [47].

Aerobic training leads to increased beta-oxidation during rest as well as during submaximal exercise [41]. A high cardiorespiratory fitness is equivalent to a high absolute aerobic capacity. This makes the relative aerobic capacity high as well, which means that a greater workload can be maintained over a prolonged period of time at a low intensity. Thus, more fat is burned in cardiorespiratory fit persons [48].

Adipose tissue physiology

Cells that have the ability to store TG are described as adipocytes, and together they compose adipose tissue [45]. TG can constitute up to 95 percent of the total cell volume of an adipocyte. They are constantly kept in a liquid form, in order to maintain the ability to hydrolyze fat so it can be rapidly transported back into the blood. Adipocytes can also convert carbohydrates into TG for storage as a supplement to the synthesis in the liver, when glycogen storage capacity is reached and excess glucose is not immediately needed for energy production. This action requires the presence of insulin.

A better understanding of the role of adipose tissue, and specific fat distribution, has led scientists to progressively uncover the pathogenesis of obesity, and its impact on people's health. Earlier, adipose tissue was viewed merely as an energy storage depot, but recent discoveries have led to the fact that it is now recognized as an active endocrine- and paracrine organ that secretes cytokines, specifically referred to as adipokines [49]. These are cell to cell signaling proteins that affect the protein synthesis and thereby an array of cellular characteristics in various tissues.

Differences in the characteristics of adipose tissue are seen in relation to where it is located [50]. Hence, adipose tissue may be distinguished into the following three depots; lower body adipose tissue, upper body subcutaneous adipose tissue (ScAT) and VAT [51]. Around 53% of lean men and women's total body fat is located in subcutaneous areas of the upper body, i.e. the upper extremities and trunk, which makes up the largest depot of adipose tissue [52]. Intra-abdominal fat consists of ≈ 80% visceral adipose tissue that surrounds the internal organs in the abdominal cavity, and 20% adipose tissues in the mesentery, i.e. within the peritoneum. On average, this depot amounts to approximately 20% of the total body fat [53]. Upper body fat in obese individuals tends to consist of a higher proportion of VAT. In lean men compared to obese men, VAT has shown to differ from 10% to 25% [52]. With regards to the potential adverse effect of general obesity on cardiovascular health, results show discrepancies. Body mass index (BMI); a surrogate marker for total body fat calculated as $\text{weight(kg)} \cdot \text{height(m}^2\text{)}^{-1}$ [45], as well as direct measurements of total fat mass (TFM), fail to produce consistent results [5, 8, 54, 55]. This has elicited the need for more specific approaches, and with the invention of medical imaging techniques such as dual energy X-ray absorptiometry (DEXA), computed tomography (CT) and magnetic resonance imaging (MRI), research on adverse effects from specific fat distribution has been produced persistently in recent years. Accordingly, VAT turns out to have a notable influence on cardiometabolic health and the features of the MetS, as delineated in Figure 1.

Pathophysiology of Visceral Adipose Tissue

VAT differs from ScAT in several ways. Differences in cellular characteristics make VAT more sensitive to specific hormones that increase lipid accumulation and mobilization, and enlarges production of adipokines with pro-inflammatory properties [4, 53]. Thus, VAT has a higher metabolic activity. Furthermore, VAT tends to respond to prolonged positive caloric input with adipocyte hypertrophy rather than adipocyte hyperplasia and recruitment of new fat cells. The latter is indeed viewed as a protective quality of adipogenesis, for the reason that increased number of adipocytes augments the capacity for accumulating TG [4]. The development of obesity towards a pathological state is characterized by an increase in the relative amount of VAT, and an overall decrease in the total number of adipocytes [56].

Excessive VAT accumulation is suggested to be a consequence of dysfunctional- or pathogenic adipose tissue. An impaired ability to store excess fat in large depots like ScAT [5] eventually leads to elevated levels of serum lipids. Although VAT contribution of total circulating fat to the liver is modest, free fatty acids and TG from the visceral compartment are delivered directly via the portal vein in fluctuating magnitudes. Thus, the capacity for fat metabolism in liver- and muscle cells becomes strained, and fat may accumulate at these locations. This may consequently affect glucose metabolism and trigger insulin resistance [4]. In addition, these fluctuations might alter lipid processes in the liver, and thereby trigger dyslipidemia [56].

Furthermore, hypertrophied adipocytes in the visceral compartment may encounter space limitations. Hence, hypoxic conditions could develop due to a reduced potential for capillarization [57]. An increased amount of adipose tissue requires augmented blood supply, which only exacerbates the hypoxia and thus the adipocyte functionality [4]. This notion is elucidated in a study, showing that elevated serum levels of erythropoietin (EPO) are seen in abdominally obese individuals with the MetS, which, they claim, indicates an underlying adipose tissue hypoxemia [58]. Dysfunctional VAT ultimately brings about immune reactions and elevated secretion of inflammatory substances that affect the functionality of systemic adipose tissue [5, 57], and this pathological pathway eventually alters systemic production and secretion of adipokines.

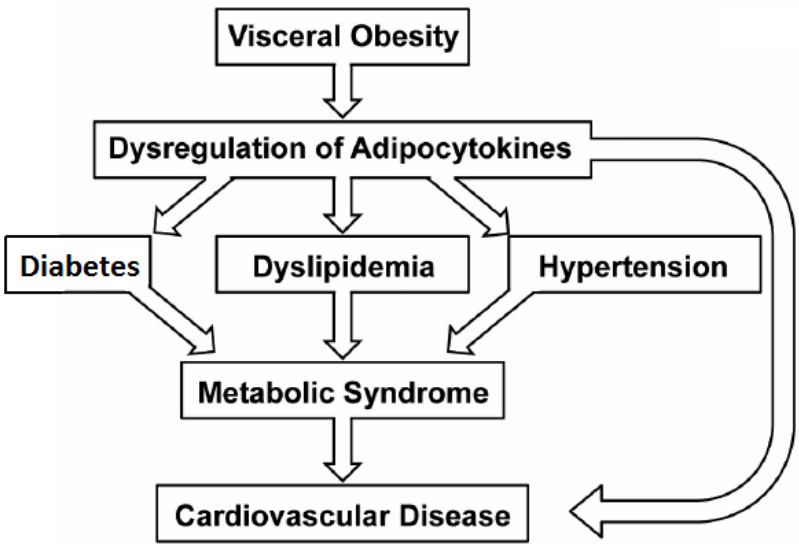

Figure 1. Outlined ripple effects from excessive visceral adipose tissue (VAT) obesity. (*Borrowed with permission from Matsuzawa et al.[8]*).

The Metabolic syndrome

The MetS is a cluster of the following features; augmented waste circumference (WC), hypertension, reduced high density lipoprotein cholesterol (HDL-C), raised levels of TG and raised fasting glucose (FG) in blood plasma. Wide agreement prevails with regards to that these features either alone or together, contributes to the development of CVD [1, 45, 59]. Briefly elaborated below, is each specific feature and its role in cardiovascular health.

Features of the MetS

The anthropometric measure of WC is a fair estimation of abdominal fat, and more importantly VAT [60]. The assessment of WC is both practical and reasonable. Thus, it is a suitable method in clinical settings. Increased values of WC correlates closely with the appearance of cardiovascular risk factors, and moreover, abdominal obesity plays a crucial role in the development and progression of the MetS [2-12].

Hypertension is abnormally high arterial blood pressure (BP), where systolic- (BPs) and diastolic (BPd) blood pressure exceeds a certain cutoff point, which in coherence with the MetS is 130 and 85 mmHg respectively. Hypertension strains the heart and vasculature, and can affect the endothelium towards a pathological state [45] However, it is not clear whether hypertension is a cause or a result of endothelial cell damage [61].

HDL-C are high density lipoproteins that consist of high proportions of protein and low concentrations of cholesterol and phospholipids [45]. This is contrary to other lipoproteins such as low density lipoprotein cholesterol (LDL-C), which carries a high amount of fatty acids and cholesterol. Lipoproteins transport cholesterol from the liver to peripheral tissue and vice versa, via the circulatory system. HDL-C has protective properties on the vasculature. Hence, it may prevent the development of atherosclerosis. An adequate amount of HDL-C, especially in relation to the ratio between HDL-C and LDL-C, is desirable.

Dyslipidemia is a pathological term that comprises abnormal levels of lipids in the plasma. In addition to an unfavorable lipoprotein profile; elevated levels of TG also features this definition. TG consists of three free fatty acid chains bound to a glycerol molecule [45]. They provide energy for metabolic processes, and are transported via chylomicrons in the circulatory system, after being derived from the intestines. TG are either transported directly to demanding tissue, or they are stored in adipocyte cells for subsequent usage. It is uncertain whether an elevated TG-level is independently pathologic, or rather an important biomarker for CVD [62].

Glucose homeostasis is regulated by insulin; an important regulatory hormone that also has a central role in lipid metabolism [63]. The reduction in a cell's insulin sensitivity, i.e. IR, is the primary cause of the development of raised FG, and this condition is viewed as a precarious component of the MetS as previously mentioned. If then, the pancreatic secretion of insulin fails to compensate for this reduction, a state of impaired glucose tolerance, or prediabetes, occurs [63]. This abnormal physiological condition predisposes type 2 diabetes mellitus (T2DM), which is a major risk factor for CVD [64]. Indeed, raised FG has shown to negatively affects various risk factors associated with CVD [45, 59] , although more moderately than T2DM. Progressively increased FG is associated with the appearance of obesity, hypertension and lipid disorders [64].

It is claimed that the MetS in relation to its respective features contributes to oxidative stress. This can potentially impair conditions in the circulatory system, and lead to endothelial dysfunction [65]. The endothelium, which is the inner lining of the vasculature, is considered a paracrine tissue. This is primarily due to its production and secretion of nitric oxide (NO) as a response to sheer stress [2]. NO regulates the medial tone by means of vasodilation, together with the vasoconstrictor effect of noradrenaline. Hence, under healthy conditions, the endothelium contributes to the regulation of vascular resistance. Furthermore, it controls the passage of fluids, electrolytes and other substances between the blood and its surrounding tissue, and it aids the regulation of blood clotting as well as the innate immune response [61]. In addition, it generates an antithrombotic surface on the inner walls of blood vessels, which is important for the transit of plasma and cellular components throughout the vasculature. A progression towards an endothelial dysfunction is characterized by a disability to maintain one or more of these functions [61]. This can have negative implications on cardiovascular

health, by means of the development of arteriosclerosis and furthermore CVD, which is symptomatically expressed through cardiorespiratory fitness.

The definition

It exists more than one definition of the MetS, and it is an ongoing discrepancy as to what might be the major underlying component of the syndrome [59]. The WHO together with the European Group for the study of Insulin Resistance (EGIR), claim that insulin resistance underlies the progression of the MetS. Others, such as National Cholesterol Education Program (NCEP) and the International Diabetes Federation (IDF), declares central obesity as the underlying component. The latter proposition is emphasized in this paper. To be diagnosed with the MetS according to the definition from the IDF [1], an individual needs have a WC specifically adjusted to a certain population- and country specific value, as shown in Table 4. In addition, one needs to obtain two of the four previously mentioned criteria. The specific cut-off values are presented in Table 1.

Table 1. Features of the metabolic syndrome

Waste Circumference	≥ 94 cm in European males ≥ 80 cm in European females (Ethnic specific values, see table WCC)
Raised blood pressure	Systolic BP ≥ 130 mmHg, or diastolic BP ≥ 85 mmHg, or treatment of previously diagnosed hypertension
Reduced HDL cholesterol	< 1.03 mmol/L in males < 1.29 mmol/L in females, or specific treatment for this lipid abnormality
Raised triglycerides	≥ 1.7 mmol/L, or specific treatment for this lipid abnormality
Raised fasting plasma glucose	≥ 5.6 mmol/L, or previously diagnosed type 2 diabetes

Cut-off values are defined by the international diabetes federation [1].

1.3. The study aspect

Current recommendations for AT

Current recommendations from the Norwegian directorate of health concerning PA [66], correspond with present recommendations from the British Association of Sport and Exercise Sciences (BASES) [67] and the American College of Sports Medicine (ACSM) [40]. The guidelines present that healthy individuals should participate in a minimum of 150 min • week^{-1} of moderate intensity aerobic activity, or 75 min • week^{-1} of vigorous intensity. Moreover, PA should be performed regularly [68], as results have demonstrated that alterations in endothelial adaptations usually subsides in less than 72 hours after training [24]. The effects, however, tend to be prolonged after vigorous- compared to moderate training. For overweight and obese individuals who want to extensively reduce their bodyweight, more PA; >250 min·week^{-1}, is desired [68].

AT as treatment

A complex combination of drugs is needed in order to ameliorate various cardiometabolic disorders and features of the MetS [63]. Needless to say, unknown side effects from specific drugs in combination with each other can come in addition. The IDF [1], with support from others [63], emphasizes that at present, no favorable pharmacological therapies are available. This is due to a lack of knowledge regarding the mechanisms of the MetS, and additionally; due to a number of adaptations that evidently occurs from improved cardiorespiratory fitness induced by AT, which provides treatment beyond today's pharmacological alternatives. Research has demonstrated that augmented cardiorespiratory fitness from AT can be achieved in subjects affected by CVD [22, 23, 69]. Often, cardiometabolic disorders per se has improved substantially, and it is in fact suggested that cardiorespiratory fitness should be incorporated as an independent feature of the MetS [37].

Intensity, duration and frequency in health and disease

A threshold below which PA does not protect against the MetS, has been identified in a prospective cohort study [70]. Higher walking speed and jogging seems to decrease the risk of having the MetS more than merely increased walking volume does. The conception that AIT is superior to CME when it comes to ameliorating cardiometabolic disorders is generally supported in the literature [32]. Indeed, recent studies have compared subsequent health effects after applying various durations and intensities of training.

Similar alterations in VO_{2max}, BP and FG, regardless of alteration of BC, have been demonstrated when comparing high- and low volumes of AIT [71]. Moreover, in relation to metabolism during training, decreased and increased skeletal muscle carbohydrate- and lipid oxidation respectively has been shown to a similar degree after CME and low-volume vigorous AT [25, 26, 72]. Thus, low-volume AIT has shown to potentially provide similar effects on cardiometabolic health compared to established recommendations, with regards the features of the MetS. Furthermore, low-volume AIT is claimed to augment resting glycogen content and the capacity for whole-body and skeletal muscle lipid oxidation, concomitantly with decreasing glycogen utilization [28].

AT of high intensity has the potency to increase mitochondrial capacity through activating key proteins, such as peroxisome proliferator-activated receptor-γ coactivator (PGC)-1ά, which regulates mitochondrial biogenesis in skeletal muscles. Thus, it is reasoned that high-intensity AT alters oxidative capacity, insulin sensitivity and glucose uptake as well as anti-inflammatory pathways in the muscles, which makes it a potential treatment strategy for insulin resistance and inactivity-related disorders [26, 28]. However, current research comprising low-volume AIT protocols are scarce. Therefore, the level of intensity and volume of training adequate for acquiring optimal health benefits remains uncertain.

AT in general, and particularly high-volume AIT, has proven to enhance peripheral vascular structure and function in healthy individuals [73], and in individuals with the MetS [24], which is fundamental in terms of preventing cardiometabolic disorders and the MetS. Indeed, it has been repeatedly demonstrated that AT improves features of the MetS [21, 29, 34] and other cardiometabolic disorders [27, 32]. A substantial decline in the presence of the MetS' features after receiving an AT intervention has often entailed the fact that individuals have no longer been diagnosed with the syndrome [21, 27].

Considering that VAT accumulation is viewed as one of the underlying components of the MetS [1], it is appropriate to scrutinize in isolated terms the effects that excessive VAT accumulation has on cardiometabolic health. Indeed, VAT has shown independent associations with all features of the MetS [7]. Needland with colleagues [74] specifically showed an association with T2DM, and Hiuge-Shimizu [9] in accordance with others [6], demonstrated a definite correlation between VAT reduction and a positive alteration of several cardiovascular risk factors including; hypertension, hyperglycemia and lipid disorders. The latter author further proposed that these results mainly occurred in Japanese individuals with VAT $\geq$ 100 cm² [75]. The role of VAT accumulation is pointed out in accordance with the development of glucose intolerance and hyperlipidemia, showing for instance that VAT obesity clearly induces greater insulin resistance than ScAT obesity [8]. Thus, VAT accumulation is closely associated with the development of CVD [5]. Furthermore, VAT is demonstrated as an independent predictor of all-cause mortality [54]. In this context, ScAT has not proven likewise [55]. However, some suggest that the association between VAT and mortality is not fully independent of

BMI [76], which supports that overall body fat probably is of some importance for the development of the MetS.

Unfortunately, the effects from AT on BC with specific regards to VAT, as well as other metabolic markers, are difficult to compare between studies due to considerable differences in training protocols. This has been elucidated in a meta-analysis [31], where representative studies that measured the alteration of VATA from AT were selected. The intensity ranged from 50% of maximal heart frequency (HF_{max}) to 85% $VO_{2\ max}$, equivalent to ≈ 30% VO_{2max} and ≈ 90% HF_{max} respectively [41], while frequency ranged from 2 – 7 times per week. The duration varied from 45 min at 75% VO_{2peak}, up to 90 min at 65 – 80% HF_{max}. Although evidence points towards a dose/response relationship between the amount of weekly training and weight reduction [68, 77], it is not always consistency in terms of reduction of BM- and VATA. Indeed, the intensity of AT has shown to be of definite importance for altering VATA [34, 78].

Although AT in general alters VATA and the features of the MetS, by means of improving cardiorespiratory fitness, previous findings seem to indicate that applying adequate intensity will have the greatest effects in this regard. Figure 2 summarizes the ripple effects on cardiometabolic health that AT potentially provides.

Figure 2. The potential cardiometabolic effects from applying training as treatment. Direction of arrows illustrates increment or decrement in physiological components.

Purpose of the Study

The primary aim of this study was to assess the effect from CME, low-volume AIT and high-volume AIT on peak oxygen consumption (VO_{2peak}) and VATA, in subjects with the MetS.

The secondary aim was to assess if improvements in VO_{2peak} or VATA after 16 weeks of AT alters the features of the MetS, and additionally BC.

We hypothesized that VO_{2peak} would have the largest increase in 4-AIT, and a similar increase in CME and 1-AIT after 16 weeks of AT. In addition, we hypothesized that a reduction of VATA would be in accordance with the increase in VO_{2peak}, and that this would favorably alter features of the MetS.

2. Methods and Materials

2.1. Subjects

Twenty nine middle aged individuals (mean age: 47.6 ± 8.2 years old) who were diagnosed with the MetS in accordance with the definition from the IDF [1] completed the16-week intervention of the present study. Subjects were recruited through advertisement by means of posters, at surgeries and various enterprises in the surroundings of Trondheim and in the local newspaper. The subjects were randomized into three groups, and stratified by age and gender into; 4 • 4 minutes aerobic interval training (4-AIT, n=10), 1 • 4 minutes aerobic interval training (1-AIT, n=8), and continuous moderate exercise (CME, n=11) in accordance with current recommendations from the Norwegian directorate of health with regards to PA [66]. Essentially, the subjects were excluded if they did not have the required WC and two additional features of the MetS. Other exclusion criteria were; precarious cardiovascular disease, kidney failure, orthopedic/neurological limitations, drug- or alcohol abuse, participation in another clinical trial and/or planned operations during the experimental period. In addition, it was required that at least 70% of the planned training sessions were carried out. Prior to participation, all subjects received detailed information about the study, before signing a consent form; approved by the Regional Committees for Medical and Health Research Ethics. During the experimental period, 8 subjects retreated from the study; 7 due to personal reasons and 1 due to prolonged illness. In addition, 1 subject was excluded from the analysis due to inadequate compliance of training sessions. Subject characteristics are presented in Table 2, and information about individual medical treatment is presented in Table 3.

Table 2. Subject characteristics at baseline

	CME (n = 11)	1-AIT (n = 8)	4-AIT (n = 10)
Age	50.1 ± 7.9	43.4 ± 9.2	48.2 ±7.1
Body composition			
Height (cm)	176.5 ± 11.9	174.9 ± 8.8	172.0 ± 10.1
BM (kg)	94.8 ± 19.7	99.8 ± 8.6	91.6 ± 10.3
VATA (cm^2)	133.5 ± 30.7	152.0 ± 17.8	132.0 ± 16.3
WC (cm)	103.7 ± 10.6	105.9 ± 4.5	103.4 ± 7.9
TFM (%)	33.8 ± 7.2	35.8 ± 5.9	34.0 ± 6.6
SMM (kg)	37.2 ± 9.0	36.2 ± 5.4	34.3 ± 6.5
Cardiorespiratory fitness			
VO_{2peak} ($mL \cdot min^{-1} \cdot kg^{-1}$)	30.6 ± 6.2	31.6 ± 6.1	32.7 ± 5.3
VO_{2peak} ($L \cdot min^{-1}$)	3.06 ± 0.95	3.17 ± 0.73	3.01 ± 0.66
Resting HF (bpm)	65 ± 11	70 ± 11	69 ± 11
BPs (mmHg)	132 ± 14	128 ± 14	146 ± 10
BPd (mmHg)	83 ± 9	79 ± 12	86 ± 5
Blood variables			
TG ($mmol \cdot L^{-1}$)	1.72 ± 0.55	1.98 ± 0.82	1.47 ± 0.73
HDL-C ($mmol \cdot L^{-1}$)	1.14 ± 0.24	1.11 ± 0.26	1.34 ± 0.27
FG ($mmol \cdot L^{-1}$)	5.8 ± 0.5	5.7 ± 0.4	6.1 ± 0.9

Data are presented as mean ± SD. CME; continuous moderate exercise, 1-AIT; 1 • 4 min aerobic interval training, 4-AIT; 4 • 4 min aerobic interval training, BM; Body mass, VATA; visceral adipose tissue area, WC; waste circumference, TFM; total fat mass, SMM; skeletal muscle mass, VO_{2peak}; peak oxygen consumption, HF; heart frequency, BPs; systolic blood pressure, BPd; diastolic blood pressure, TG; triglyceride, HDL-C; high-density lipoprotein cholesterol, FG; fasting glucose.

Table 3. Medical treatment

	CME (n = 11)	1-AIT (n = 8)	4-AIT (n = 10)
Angiotensin II blockers	5/11	2/8	1/10
Beta-blockers	0/11	1/8	0/10
Calsium antagonists	1/11	1/8	1/10
α-blockers	0/11	1/8	0/10
Statin	1/11	1/8	1/10
Acetylsalicylic acid	0/11	0/8	0/10
Metformin	0/11	0/8	1/10
Insulin	0/11	0/8	0/10
Total	7/11	6/8	4/10

Data are presented as the number of subjects taking the specific medication. CME; continuous moderate exercise, 1-AIT; 1 • 4 min aerobic interval training, 4-AIT; 4 • 4 min aerobic interval training.

2.2. Study design

In this randomized controlled trial (RCT), subjects were tested prior to- and after a 16-week training intervention comprising one of the following training regimens:

CME; performed 5 days per week for 30 minutes or more, at a moderate intensity of 60-70% of HF_{max}. 1-AIT and 4-AIT; performed 3 times per week and consisting of a 10 minute warm-up at 60-70% of HF_{max}, followed by 1- and 4 intervals of 4 minutes respectively at 85-95% of HF_{max}, and rounded off with a 5 minute cool-down at equal intensity as the warm-up. Between the intervals in 4-AIT, subjects carried out 3-minute intermissions at 60-70% of HF_{max}. Time expenditure on one training session was ultimately 19- and 40 minutes for 1-AIT and 4-AIT respectively. All training was performed as aerobic endurance training, primarily as walking up-hill or running on a treadmill, and the subjects were exhorted to perform two training sessions per week under supervised conditions in our lab at St.Olavs Hospital.

The study progressed as follows:

Baseline tests were performed in week 1. They involved a screening where anthropometric measures and blood samples were taken in order to assess for presence of the MetS' features. After receiving the test results (≈1 week), the subjects that met the inclusion criteria were randomized. Thereafter, body composition and VATA were measured, and a cardiopulmonary exercise test (CPET) was performed (week 2). Subsequently, each subject received training instruction both orally and written, in addition to a diary in which to record conducted training. Within two weeks subsequent to the 16-weeks training intervention (week 3 – week 19), the previously mentioned procedures were repeated in a follow-up (week 20). The study design is illustrated in Figure 3.

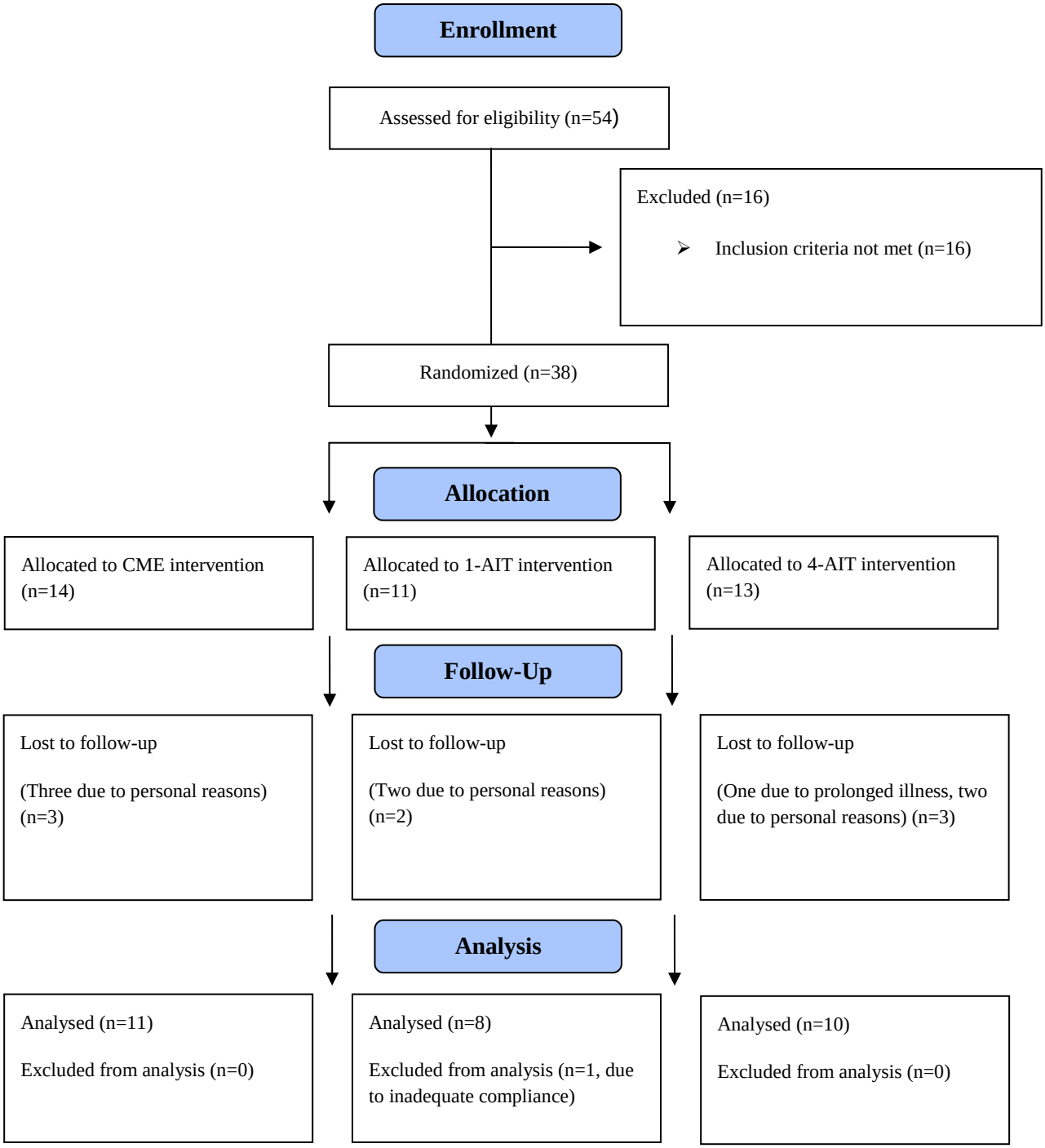

Figure 3. Flow chart of study design.

2.3. Procedures and equipment

Clinical Reference Form

Subjects answered a standardized questionnaire that involved questions related to general life style and anamnesis, in order to provide essential information on these aspects. Questions were answered orally, and the forms were filled out by the investigators. All papers were anonymous; marked with a screening- and randomization number for identifying each particular subject.

Anthropometric Measurements

WC-cutoff values are specific for certain ethnicities (Table 4). The measurement of WC was done on bare skin with a tape line that was parallel to the floor, and situated between the upper part of the iliac crest and the inferior costae, as illustrated in Figure 4. Simultaneous measurements of body height were performed. Body weight was measured during the bioelectrical impedance analysis (BIA).

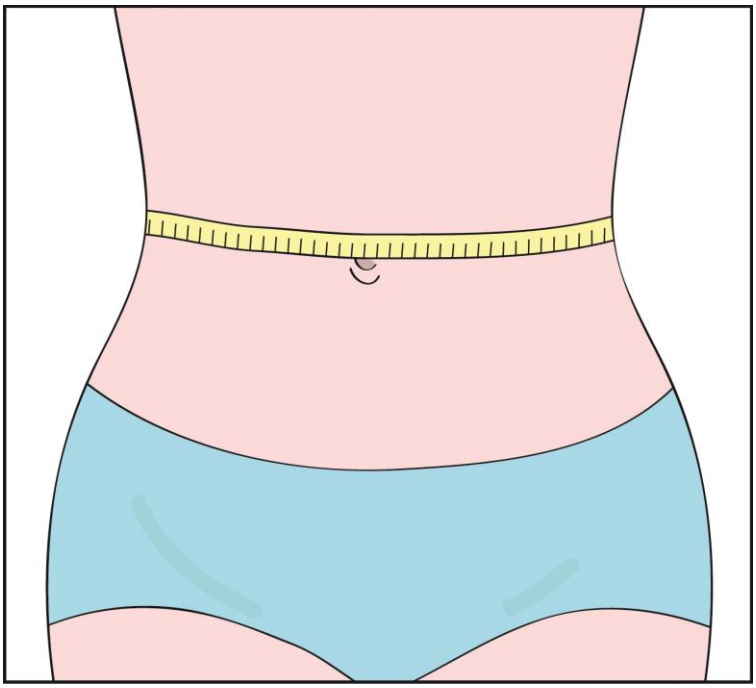

Figure 4. Illustration of the waste circumference measuring procedure.

Table 4. Specific values of waste circumference based on ethnicity

Region/Ethnic group		Waste circumference
Europeans	Male	≥ 94 cm
	Female	≥ 80 cm
South Asians	Male	≥ 90 cm
	Female	≥ 80 cm
Chinese	Male	≥90 cm
	Female	≥ 80 cm
Japanese	Male	≥ 90 cm
	Female	≥ 80 cm
Ethnic South and Central Americans	The same as South Asian recommendations until sufficient data are available	
Sub-Saharan Africans	The same as European recommendations until sufficient data are available	
Eastern Mediterranean- and Arab population	The same as European recommendations until sufficient data are available	

Blood pressure was measured noninvasively, with a Diacore Criticare 506N-2 (Criticare Systems Inc., Waukesha, WI, USA). Initially, the subject rested for ≥ 5 minutes in a sitting position with neither arms nor legs crossed. Thereafter, measurements were done three times on the subject's dominant arm, and each measurement was separated by 1 minute. If the value of the last two measurements differed above 15%, either in systolic or diastolic blood pressure, an extra measurement was taken. The mean blood pressure and the mean resting HF from the last two measurements were calculated and used further as standing values. The subjects were instructed to be quiet during the whole sequence, and the apparatus' display was put out of sight, in order to avoid any influence on the subject that possibly could affect the results.

Blood collection and processing

Standard biochemical analyses were carried out to assess TG, HDL-C and FG. Lithium heparin- and serum vacutainers were collected from each subject for the analysis. The 6-mL serum vacutainer was kept in room temperature for 30 minutes before being centrifuged. The 3-mL lithium heparin vacutainer was centrifuged immediately after collection, and stored on ice before it was sent for analysis. Both vacutainers were centrifuged at 1500 G for 10 minutes. Blood was obtained subsequently to 12 hours of fasting, preferably in the morning. In addition, the subjects had been instructed to avoid alcoholic beverages for 24 hours prior to the analysis, and they were inquired about their recent intake of medications.

Cardiopulmonary Exercise Test

VO_{2max} is accurately assessed by applying a CPET [79]. The test was performed on a treadmill (Woodway USA Inc., Waukesha, WI, USA), and VO_2 was measured by use of an ergospirometry system with a mixing chamber (Oxycon Pro, Erich Jaeger GmbH, Hoechberg, Germany). Prior to each test, the ergospirometry system was calibrated in accordance with ambient air and a high precision gas (16.00 ± 0.04% O_2 and 5.00 ± 0.1% CO_2, Reissner-Gase GnbH & Co, Lichtenfels, Germany), and the inspiratory flowmeter was calibrated by use of a 3 L volume syringe (Hans Rudolph Inc., Kansas City, MO, USA). The apparatus was regularly updated in correspondence with ambient temperature- and humidity conditions. A Polar T31 heart rate transmitter (Polar Electro, Kempele, Finland); compatible with the treadmill, was used to measure HF. The acquired HF at VO_{2max}- or $_{peak}$ plus a 5-beats estimated reserve was set as HF_{max}.

Before the test was initiated, each subject was informed about the procedure, and the use of rated perceived exertion (RPE), by means of the Borg scale [80]. Thereafter, two submaximal sequences of 4 minutes each, were conducted at a standardized load (4km • h^{-1}, and 0- and 4% inclination respectively) as a warm-up, as well as to familiarize subjects with the treadmill. When the test started, speed and/or inclination were increased with 1 km • h^{-1} or 2% respectively every one minute, in order to progress towards maximal effort and obtain VO_{2max}. HF, respiratory exchange ratio (RER); which describes the ratio of O_2 inspired and CO_2 expired, and the subjects RPE were documented immediately after ending the test. VO_{2max} was interpreted as a plateau in VO_2 despite an increase in work rate, and determined from the three continuously highest measurements at 10-sec intervals. In addition, RER ≥ 1.05, and RPE above 17/20 on the Borg scale was required in order to classify a value as VO_{2max}. If these requirements were not met, the term VO_{2peak} was applied; VO_{2peak} is frequently used in clinical settings that involve patients, or individuals, with exercise limiting disorders [79].

Bioelectrical Impedance Analysis

Direct segmental multi-frequency (DSM) BIA was applied for measuring specific parameters in relation to BC, on an Inbody 720 (Inbody 720, Biospace CO, Ltd, Seoul, Korea). This particular device measures BC by dividing the body into 5 segments; trunk, and upper- and lower extremities. It takes direct impedance measurements from each segment at six different frequencies using a tetrapolar eight-point tactile electrode system [81]. Empirical estimations are completely left out of the analysis, and this engenders crude measurements. The spectrum of electrical frequencies assesses intra- and extracellular water contents, from which BC parameters are further predicted. Finally, bare-skinned feet- and hands are placed in contact with electrodes for the analysis to be conducted.

Measurements of BC with DSM-BIA, by means of LBM and TFM, have shown to be valid in various size populations [82, 83], when compared to DEXA. Moreover, test-retest reliability has proven to be strong [82]. Furthermore, it is demonstrated that the particular device applied in this study, measured VATA accurately when compared with CT [84].

In order to avoid measurement biases, certain precautions were applied. Prior to the test, the subjects had fasted for a minimum of 12 hours, apart from drinking water ($\leq$ 0.5 L) on the day of the measurement. In addition, they were instructed to avoid physical exertion the day before the test. They were encouraged to visit the restroom if they felt the need, before the measurement was conducted. Furthermore, the subjects were instructed to remove shoes and socks, as well as all objects in contact with the body that contained metal, e.g. mobile phones, watches, jewelry, wallets, belts, etc. Normal indoor clothing was kept on. Upon entering the apparatus, each subject was instructed to stand in an upright position with no contact between the trunk and upper extremities, as illustrated in Figure 5. No talking was permitted during the measurement, to ensure a normal breathing pattern. The measurements were done in stable room temperature between 20-25˚C.

Figure 5. Illustration of subject posture during the BIA measurement.

2.4. Statistical analyses

The primary outcome variables were VO_{2peak} and VATA. Other specific data in relation to the MetS and BC served as secondary outcome variables. Extreme outliers were detected, by inspection of boxplots for values greater than 3 box-lengths from the edge of the box, and excluded from subsequent analyses. The data were considered as normally distributed, as assessed by Shapiro-Wilk tests and examination of quantile quantile (Q-Q) plots. Paired samples *t*-tests were ran in order to determine whether there were statistically significant mean differences between baseline and follow-up measurements within groups. The interaction of time and group on the outcome variables, i.e. training-induced effects, were determined by applying mixed-model design analyses of variance (mixed ANOVAs) with subsequent LSD post-hoc tests, in line with our hypothesis. If the assumption of sphericity was violated, Mauchly's test of sphericity was displaced by a Greenhouse Geisser correction. A Pearson's product-moment correlation was run in order to assess the relationship between alterations in the primary variables; VO_{2peak} and VATA. Preliminary inspection of a scatter plot confirmed the assumption of linearity. The degree of difference in each primary variable from baseline to follow-up (referred to as Δ) in the pooled sample was used to stratify the sample into3 groups, divided at the 25^{th} - and 75^{th} percentile. Hence, the primary variables served as independent variables in separate analyses. One-way ANOVAs and LSD post-hoc tests were ran in order to assess for differences between groups, with regards to MetS variables. Rearranging the data in this manner was applicable in order to test our additional hypothesis. Data are presented as mean ± standard deviation (SD) or confidence interval (CI), and a two-tailed $p < 0.05$ is considered to be statistically significant for all tests, unless otherwise stated. For statistical analyses, SPSS version 21 (IBM Corp., Armonk, New York, USA) was applied. Graphical illustrations were made in GraphPad Prism version 6 (GraphPad Software Inc., San Diego, California, USA).

3. Results

3.1. Subject characteristics

Modest differences between CME, 1-AIT and 4-AIT were observed at baseline, despite subsequent randomization. However, these differences were not statistically analyzed. VATA was somewhat higher in 1-AIT compared to CME (≈ 14%) and 4-AIT (≈ 15%), and VO_{2peak} was slightly higher in 4-AIT compared to CME (≈ 7%) and 1-AIT (≈ 3%). Also, blood variables had meagre differences between the groups (Table 2). As shown in Table 5, the number of subjects that had specific features of the MetS varied between the groups at baseline. Most notably, HDL-C varied from 20% to 64% (4-AIT compared to CME). In addition, all subjects in 4-AIT, whereas only 7/11subjects in CME, had elevated BPs. The presence of features of the MetS was reduced to a similar extent within the groups; 10.4% in CME, 8.6% in 1-AIT and 10.0% in 4-AIT. Medical treatment for each subject remained unaltered throughout the intervention period (see Table 3).

Table 5. Distribution of specific features of the metabolic syndrome

	CME (n = 11)		**1-AIT (n = 8)**		**4-AIT (n = 10)**	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
WC	11/11	11/11	8/8	8/8	10/10	9/10
BPs	7/11	7/11	7/8	6/8	10/10	10/10
BPd	8/11	5/11	5/8	4/8	7/10	5/10
TG	7/11	6/11	4/8	5/8	4/10	5/10
HDL-C	7/11	6/11	5/8	5/8	2/10	3/10
FG	8/11	8/11	6/8	4/8	7/10	4/10
Mean number	8.0	7.2	5.8	5.3	6.7	6.0

Data are presented as number of subjects. CME; continuous moderate exercise, 1-AIT; 1 • 4 min aerobic interval training, 4-AIT; 4 • 4 min aerobic interval training, WC; waste circumference, BPs; systolic blood pressure, BPd; diastolic blood pressure, TG; triglycerides, HDL-C; high density lipoprotein cholesterol, FG; fasting glucose.

3.2. Peak oxygen consumption

After 16 weeks of AT, VO_{2peak} increased 8.6% and 3.8% in CME and 4-AIT respectively and decreased 0.2% in 1-AIT, as illustrated in Figure 6. However, the changes were not significantly different between groups ($p = 0.209$), and LSD post hoc analyses for mixed ANOVA showed no significant difference between any group combination ($p > 0.05$).

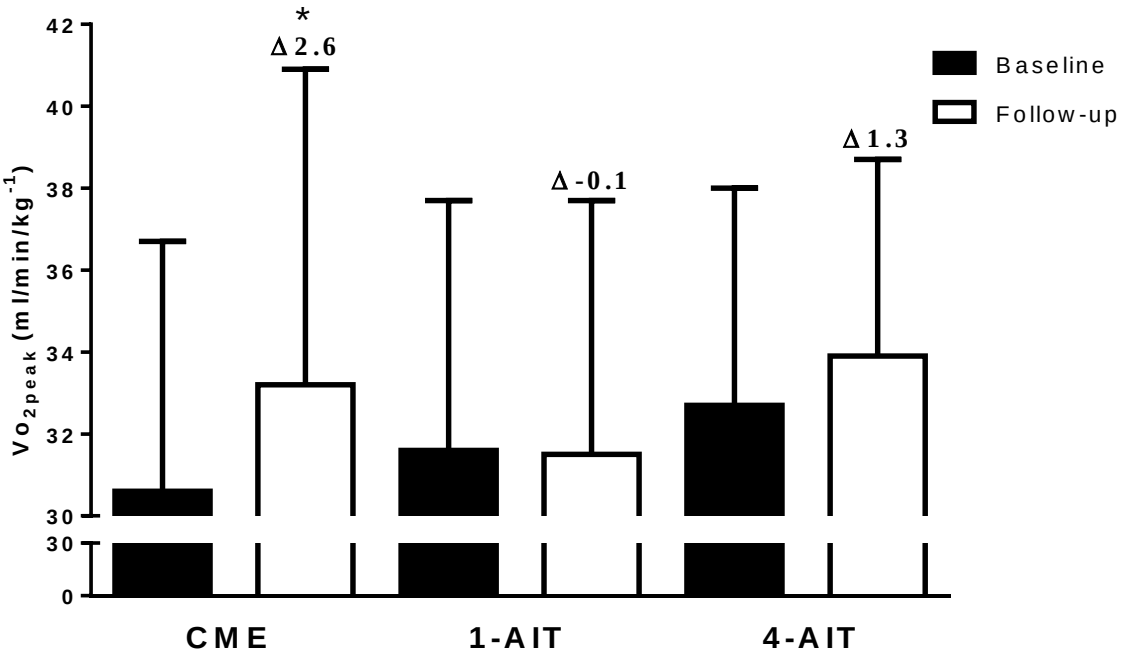

Figure 6. Peak oxygen consumption (VO_{2peak}) values at baseline and follow-up in continuous moderate exercise group (CME), 1 • 4 min aerobic interval training group (1-AIT) and 4 • 4 min aerobic interval training group (4-AIT). Data are presented as mean ± SD. Δ are presented as $mL \cdot min^{-1} \cdot kg^{-1}$. * statistically significant difference between baseline and follow-up ($p < 0.05$).

3.3. Visceral adipose tissue area

After 16 weeks of AT, VATA decreased 5.0% and 1.1% in CME and 4-AIT respectively and increased 0.6% in 1-AIT, as illustrated in Figure 7. The changes were not significantly different between groups ($p = 0.149$). However, LSD post hoc analyses for mixed ANOVA revealed that VATA was significantly decreased in CME compared to 1-AIT ($p = 0.047$), and trended towards a larger decrease in 4-AIT compared to 1-AIT ($p = 0.058$).

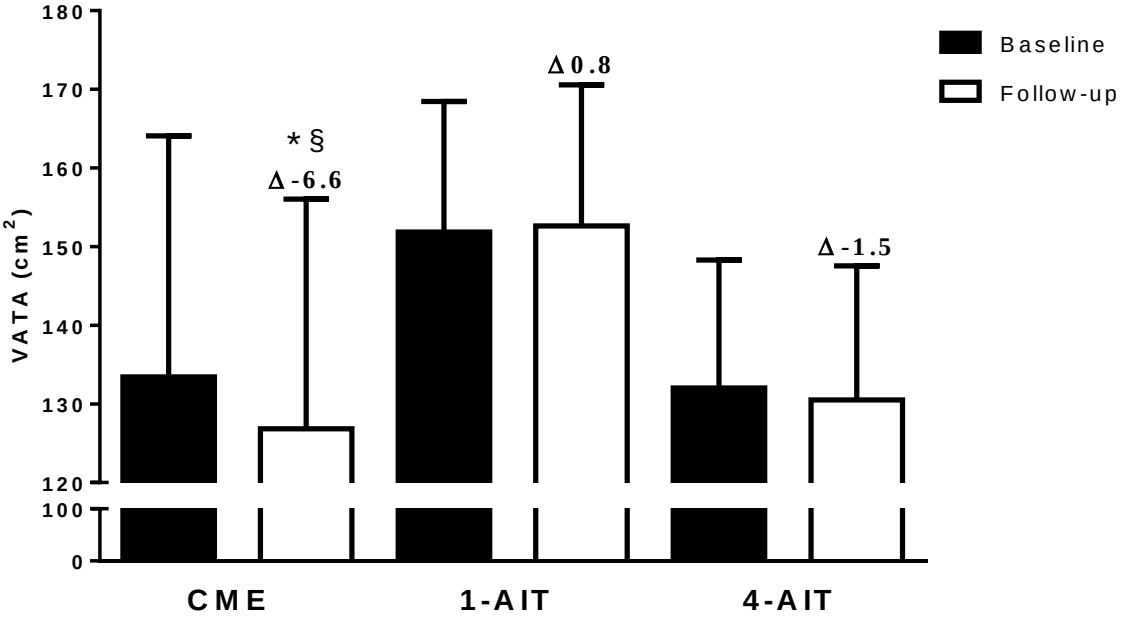

Figure 7. Visceral adipose tissue area (VATA) values at baseline and follow-up in continuous moderate exercise group (CME), 1 • 4 min aerobic interval training group (1-AIT) and 4 • 4 min aerobic interval training group (4-AIT). Data are presented as mean ± SD. Δ are presented in cm^2. * significant difference between baseline and follow-up ($p < 0.05$). § significantly different from 1-AIT.

The reduction in VATA correlated significantly with the reduction in WC ($r^2 = 0.556$, $p = 0.000$) (the results are not illustrated). Furthermore, there was a strong inverse correlation between the alteration of VO_{2peak} and the alteration of VATA from baseline to follow-up ($p = 0.001$), as illustrated in Figure 8. The increment in VO_{2peak} statistically accounted for 37.5% of the variability in VATA values ($r^2 = 0.375$).

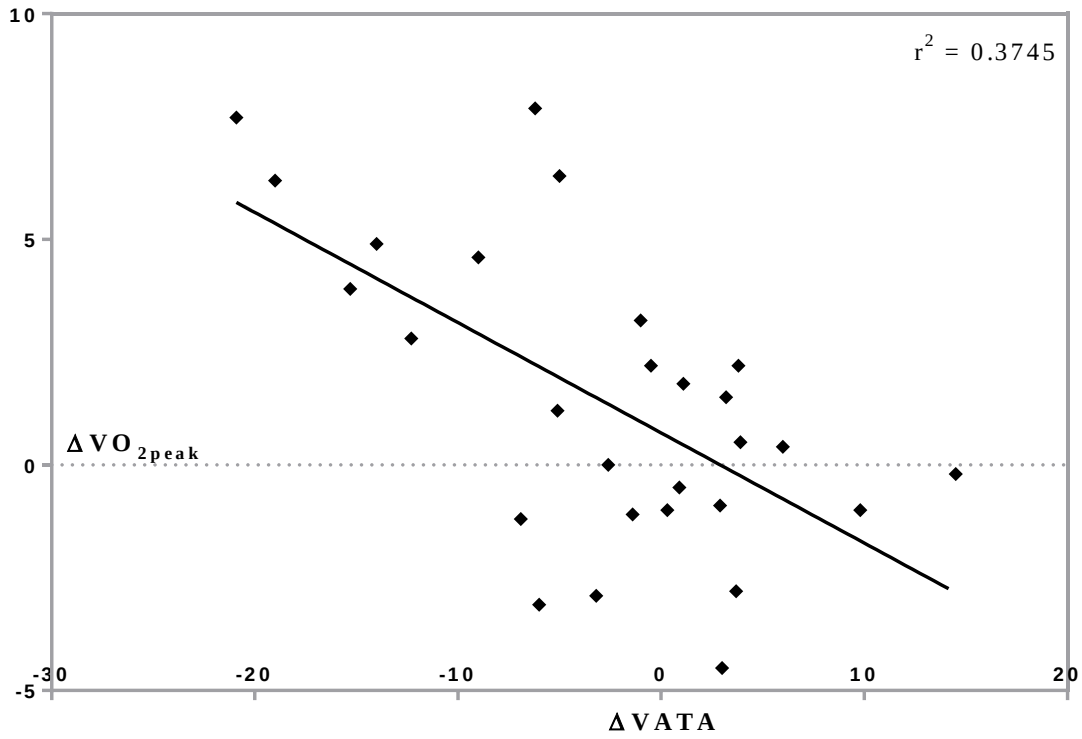

Figure 8. Linear relationship between the changes in peak oxygen consumption (VO_{2peak}) and visceral adipose tissue area (VATA).

3.4. The metabolic syndrome and body composition

After 16 weeks of AT, CME decreased WC (2.6%), BPd (7.9%) and TG (12.8%), and 1-AIT and 4-AIT significantly decreased FG by 8.5% and 6.3% respectively ($p < 0.05$). In addition, BPd was significantly different between groups ($p = 0.012$). Subsequent LSD post hoc analyses revealed significant differences in BPs in 4-AIT; compared to CME who had a higher value, and compared to 1-AIT who had a lower value ($p < 0.05$). Results are presented in Table 6.

Table 6. Changes from baseline to follow-up

	CME	1-AIT	4-AIT
The metabolic syndrome			
WC (cm)	-2.7 (-5.0, -0.3)	0.9 (-1.4, 3.3)	-1.8 (-4.7, 1.1)
BPs (mmHg)	-4 (-12.4, 3.9)	1 (-6.2, 7.7)	-2 (-9.1, 4.5)
BPd (mmHg)	-7 (-10.0, -3.1)	0 (-4.0, 4.8)	-1 (-4.5, 1.8)
TG (mmol • L^{-1})	-0.24 (-.43, -.05)	-0.16 (-.91, .60)	0.12 (-.36, .59)
HDL-C (mmol • L^{-1})	0.08 (-.06, .21)	0.03 (-.09, .15)	0.07 (-.06, .21)
FG (mmol • L^{-1})	-0.0 (-.36, .34)	-0.5 (-.94, -.03)	-0.4 (-.07, 2.76)
Body composition			
TFM (%)	-0.8 (-2.2, 0.5)	0.2 (-1.4, 1.9)	-0.1 (-1.3, 1.0)
SMM (kg)	-0.6 (-1.4, 0.2)	-0.4 (-0.8, 0.0)	0.1 (-0.3, 0.5)
Compliance			
Number of trainings	≈ 75/80	≈ 41/48	≈ 41/48

Data are presented as mean Δ values (95% CI). CME; continuous moderate exercise, 1-AIT; 1 • 4 min aerobic interval training, 4-AIT; 4 • 4 min aerobic interval training, WC; waste circumference, BPs; systolic blood pressure, BPd; diastolic blood pressure, TG; triglyceride, HDL-C; high-density lipoprotein cholesterol, FG; fasting glucose, TFM; total fat mass, SMM; skeletal muscle mass.

With regards to BC, CME decreased BM by 2.9% ($p < 0.05$), as illustrated in Figure 9. Furthermore, there was a significant interaction between type of AT and time on BM ($p = 0.014$), as assessed by a test of within-subjects effects in mixed ANOVA. No other significant differences with regards to BC were detected, as depicted in Table 5 ($p > 0.05$).

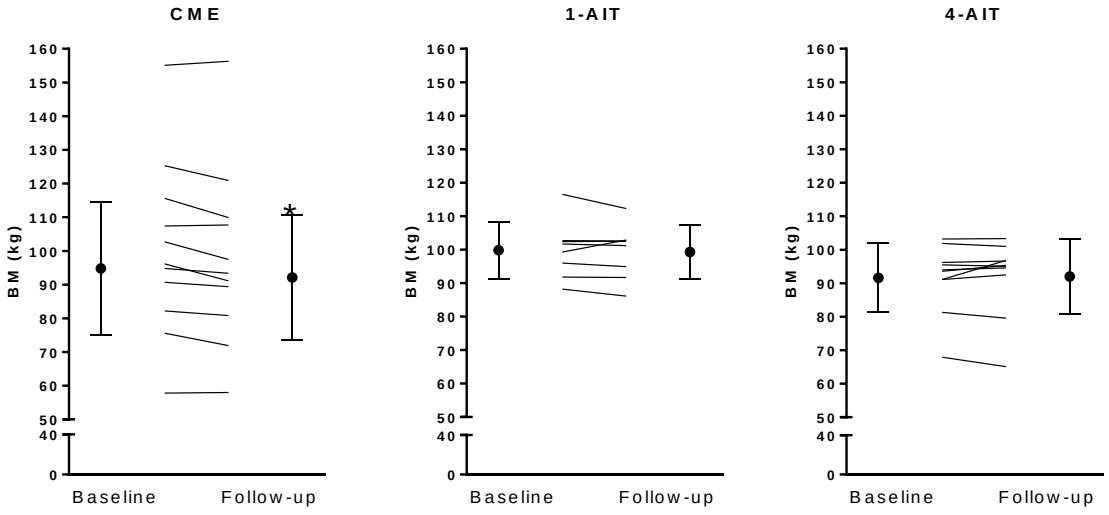

Figure 9. Individual changes in body mass (BM) from baseline to follow-up in continuous moderate exercise group (CME), 1 • 4 min aerobic interval training group (1-AIT) and 4 • 4 min aerobic interval training group (4-AIT). Data are presented in kg, as mean changes ± SD, and individual changes. * significant difference from baseline to follow-up.

3.5. Alternative stratification

A trend towards a significantly higher percentage of compliance of workouts in CME (93.3%), compared to 1-AIT (84.9%, p = 0.056) and 4-AIT (85.4%, p = 0.057), was discovered (see Table 6). Thus, in order to examine the effects from alterations in either VO_{2peak} or VATA on the MetS, we found it constructive to apply alternative groups for subsequent analyses. The groups are presented in Table 7. Thus, the subjects were stratified into 3 groups in accordance with their degree of VO_{2peak}- or VATA alteration. Cut-offs were set at the 25^{th}- and 75^{th} percentile. Accordingly, the standing variable was labeled chronologically as; [1], [2], or [3]. Statistically significant differences are only reported between percentiles [1] and [3].

Table 7. Percentile cut-offs of Δ values in the primary variables

	Percentiles		
ΔVO_{2peak} ($mL \cdot min^{-1} \cdot kg^{-1}$)	VO_{2peak}^{1}	VO_{2peak}^{2}	VO_{2peak}^{3}
	< 25%	25% – 75%	> 75%
	< -1.000	-0.999, 3.550	> 3.551
Mean change	-2.2	1.2	6.0
Most extreme value	-4.5	-	7.9
ΔVATA (cm^2)	$VATA^{1}$	$VATA^{2}$	$VATA^{3}$
	< 25%	25% – 75%	> 75%
	> 3.151	3.150, -6.725	< -6.726
Mean change	6.4	-1.6	-13.9
Most extreme value	14.5	-	-20.9

Data are presented as Δ cut-off values at the 25th and 75th percentile, for the variables VO_{2peak}; peak oxygen consumption, and VATA; visceral adipose tissue area.

Peak oxygen consumption

Significant differences between VO_{2peak}^{1} and VO_{2peak}^{3} in alterations of VATA, WC, and BPd were demonstrated, as illustrated in Table 8. Moreover, a visible trend was seen between augmented VO_{2peak} and decreased BPs- and TG.

Table 8. ΔVO_{2peak} in percentile groups

	VO_{2peak}^{1} (n=8)	**VO_{2peak}^{2} (n=14)**	**VO_{2peak}^{3} (n=7)**
Compliance (%)	≈ 90	≈ 85	≈ 93
VATA (cm^2)	-0.1	1.1	-12.8 (-19.9, -6.3) #
WC (cm)	0.2	-0.8	-3.9 (-7.7, -0.5) #
BPs (mmHg)	2	-3	-6 (-19.3, 2.0)
BPd (mmHg)	1	-3	-7 (-13.0, -2.2) #
TG (mmol/L)	-0.03	-0.05	-0.25 (-0.91, 0.48)
HDL-C (mmol/L)	-0.01	0.14	-0.00 (-0.17, 0.18)
FG (mmol/L)	-0.5	-0.1	-0.3 (-0.3, 0.8)

Data are presented as mean Δ values (95% CI in the difference between VO_{2peak}^{1} and VO_{2peak}^{3}). # statistically significant difference between VO_{2peak}^{1} and VO_{2peak}^{3} ($p > 0.05$). VATA; visceral adipose tissue area, WC; waste circumference, BPs; systolic blood pressure, BPd; diastolic blood pressure, TG; triglyceride, HDL-C; high-density lipoprotein cholesterol, FG; fasting glucose.

BC variables changed accordingly with VO_{2peak}^{3} compared to VO_{2peak}^{1}. BM and TFM% were decreased and increased respectively ($p < 0.05$). However, no changes occurred in SMM ($p > 0.05$).

Visceral adipose tissue area

Significant differences between $VATA^1$ and $VATA^3$ in alterations of VO_{2peak} and WC were demonstrated, as illustrated in Table 9. Moreover, a visible trend was seen between augmented VATA and the reduction of the following features of the MetS; BPs, BPd and TG.

Table 9. ΔVATA in percentile groups

	$VATA^1$ (n=7)	**$VATA^2$ (n=14)**	**$VATA^3$ (n=7)**
Compliance (%)	≈ 86	≈ 86	≈ 95
VO_{2peak} ($mL \cdot min^{-1} \cdot kg^{-1}$)	-0.0	0.6	4.1 (0.8, 7.4) #
WC (cm)	2.2	-1.4	-4.7 (-10.0, -3.9) #
BPs (mmHg)	3	-2	-7 (-21, 1)
BPd (mmHg)	1	-3	-5 (-12, -0) #
TG (mmol/L)	0.28	-0.20	-0.26 (-1.24, 0.15)
HDL-C (mmol/L)	0.14	0.06	0.01 (-0.33, 0.07)
FG (mmol/L)	-0.3	-0.3	-0.3 (-0.6, 0.5)

Data are presented as mean Δ values (95% CI difference between $VATA^1$ and $VATA^3$). # statistically significant difference ($p > 0.05$) between $VATA^1$ and $VATA^3$. WC; waste circumference, BPs; systolic blood pressure, BPd; diastolic blood pressure, TG; triglyceride, HDL-C; high-density lipoprotein cholesterol, FG; fasting glucose.

BC variables increased more in $VATA^3$ compared to $VATA^1$. BM and TFM% decreased and increased respectively ($p < 0.05$). However, no changes were detected in SMM ($p > 0.05$).

4. Discussion

Our primary aim was to assess the effect from 16 weeks of either CME, low-volume AIT or high-volume AIT on VO_{2peak} and VATA in subjects with the MetS. The main findings in the present study were: 1) VO_{2peak} and VATA did not differ significantly between CME, 1-AIT and 4-AIT. However, there was a significant difference in changes of BM ($p < 0.01$), 2) the subjects that improved either VO_{2peak} or VATA most, independent of AT modality, obtained largest improvements in features of the MetS. In accordance, VO_{2peak} and VATA had a significant inverse correlation ($p < 0.01$).

4.1. Peak oxygen consumption

4-AIT did not induce the largest increase in VO_{2peak} after 16 weeks of AT. Nor did VO_{2peak} increase to a similar extent in CME and 1-AIT. Thus, our hypothesis was rejected. Interestingly though; VATA changed inversely in accordance with VO_{2peak}.

CME displayed the largest increase in VO_{2peak} (≈ 9%), whereas 1-AIT actually decreased VO_{2peak} by 0.2%. 4-AIT had a ≈ 7% higher VO_{2peak} at baseline compared with CME, which subsequently was augmented by ≈ 4%. Thus, CME and 4-AIT had a similar VO_{2peak} after the intervention (33.2- and 33.9 $mL \cdot min^{-1} \cdot kg^{-1}$ respectively). Comparable data involving AT of various intensities on subjects with the MetS are, to our knowledge, scarce. However, in proportion to a previous RCT by Tjønna et al. [21], VO_{2peak} increments in the present study were, at best, modest. Baseline values for VO_{2peak} were similar, but after 16 weeks of AT, post measurement values increased to above 40 $mL \cdot min^{-1} \cdot kg^{-1}$ in both of their AT groups, with a 16%- and 35% increased VO_{2max} in CME and 4-AIT respectively.

A recent meta-analysis [32] involving 10 studies of patients with various cardiometabolic disorders, presented a mean increase of ≈ 10% and ≈ 19% in VO_{2peak} for CME and AIT respectively. Overall, VO_{2peak} increased 3.03 $mL \cdot min^{-1} \cdot kg^{-1}$ more in AIT compared to CME. Moreover, similar improvements in VO_{2peak} from CME compared to lower volumes of AIT have been demonstrated in sedentary populations at risk for cardiometabolic disorders [25, 27]. In these studies as well, VO_{2peak} increased by ≈ 10% in CME and low-volume AIT. Thus, based on the demonstrations of previous findings, our result seems reasonable with regards to the increase of VO_{2peak} in CME.

An important notion is that our study design imposed CME to perform a higher total amount of workouts (80 workouts), compared to 1-AIT (48 workouts) and 4-AIT (48 workouts). This is no more of a discrepancy than what has been applied in other RCT's that have investigated the effect on

VO_{2peak} from applying various intensities [21-23, 25, 27]. However, in our study, CME performed considerably more workouts in percentage of the prescribed total amount (≈ 93%) compared to both AIT groups (≈ 85%). The ACSM [68] emphasizes that overweight individuals need to surpass the currently recommended duration of AT for healthy individuals [40, 66, 67], in order to achieve appreciable weight loss. Basic knowledge implies that the principles of duration, frequency and intensity, makes up the total load of exercise training. Hence, the balance of these principles determines the degree of caloric output, as well as the sheer stress on the cardiovascular system. Obviously, a caloric imbalance primarily accounts for the level of weight alteration. This has been demonstrated by Slentz et al. [77] who clarified a linear relationship between the level of weight reduction and the total load of AT per week. As such, it is possible that the considerable group dissimilarities in duration and frequency which ultimately occurred in our study, contributed to the fact that BM decreased significantly more in CME compared to the AIT groups. Indeed, this has not been observed in other similar studies [21, 22, 27]. For instance, Earnest et al. [27] performed a study comprising a CME- and AIT group for 12 weeks on men at risk for insulin resistance. Albeit an eucaloric design, AIT reduced BM almost a twofold compared to CME, in fact to a similar degree as in our CME group. The comparison with previous work therefore indicates that in our study, the alteration in both 1-AIT and 4-AIT has been unusual with regards to VO_{2peak} as well as other outcomes of interest. One might speculate whether this is symptomatic to a failure of obtaining the necessary amount of training sessions. An interesting observation with this in mind, is that VO_{2peak} did not differ significantly between the groups ($p > 0.05$), despite a definite disparity in the total load of AT. Indeed, this could be an indication of the superior effect that AIT has on cardiorespiratory fitness, as previously demonstrated in unhealthy individuals [32].

4.2. Visceral adipose tissue area

VATA decreased most in the group in which the largest increase in VO_{2peak} occurred (CME), after 16 weeks of AT was seen. This was in accordance with our hypothesis. Briefly, it was reduced significantly in CME (5.0%) and modestly in 4-AIT (1.1%). However, it increased in 1-AIT (0.6%), albeit a ≈ 15% higher VATA at baseline compared with the other groups. The changes in CME were in fact significantly different from 1-AIT.

To our knowledge, no studies have been conducted where the reduction of VATA from AT has been measured specifically by use of DSM-BIA. However, DSM-BIA has shown fair conformity with established imaging techniques such as DEXA and CT [82, 84]. Kay with colleagues [85] reported the reduction in VATA from PA measured by use of CT, MRI and DEXA in a systematic literature

review. Among RCT's comprising AT, the mean VATA reduction was 27.4%; ranging from 5.8% to 48.5%. This is substantially more than what was achieved in our study. However, the mean reduction in WC was only 2.8% in this respective study, which in contrast is not far from our findings of 2.6% in CME. It is generally accepted that WC is a reliable surrogate marker for VATA [1], and indeed, we demonstrated that alterations of VATA and WC correlated strongly. The authors recognized the low coherence between the level of VATA- and WC reduction, and suggested that it could be attributable to subject differences such as age, gender, fat distribution and genetics, as well as methodological differences by means of WC measurement descriptions [85]. These are for sure confounding factors, and they can cause discrepancies when anthropometric measurements of WC are being compared with values of VATA that have been acquired by use of exact measurement techniques, such as DSM-BIA.

Vissers et al. [31] conducted a meta-analysis in which the effect of AT on the alteration of VATA, measured by use of CT or MRI, was investigated in overweight adults. Although training modalities varied, the investigated studies that contained only an AT intervention and presented their results in cm^2 (n = 10), had a mean reduction in VATA of 30.5 cm^2. Again, the findings of others are considerably higher than ours (6.6 cm^2 in CME). The authors found moderate- to high intensity to be most effective by means of reducing VATA. However, respectively these two levels of intensity were defined as 60 – 70% and ≥ 70% of HF_{max}, and this actually corresponds with our definition of CME. A closer inspection of two of the included RCT's with a study design similar to ours [34, 78]; they both employed moderate- and high intensity groups respectively at ≈ 60 – 70%- and ≈ 85 – 95% of HF_{max}, revealed that AIT reduced VATA significantly more than CME. For instance, Irving et al. [34] demonstrated a 25 cm^2 (14.5%) reduction after 16 weeks of AIT in obese women with the MetS. Although these findings are clearly different from ours, it is of particular interest that Irving et al. [34] reported an almost identical reduction in CME (7 cm^2 = 4.8%) as we did (6.6 cm^2 = 5.0%). Indeed, this is another sound indication towards that inadequate compliance may have engendered peculiar results in our AIT groups.

Albeit having a shorter duration, the majority of previous findings show that high volume AIT is superior in terms of reducing VATA. Mechanisms behind this are intricate. In relation to energy expenditure, it is known that β-oxidation decreases in relative terms at higher aerobic intensities [46]. However, in absolute terms it is deemed to increase. Thus, β-oxidation is elevated per time unit when an individual performs AIT. In addition, post exercise energy expenditure has proven to be significantly higher after AIT compared to CME, and this is even accompanied by a larger contribution of β-oxidation [86]. The fact that AIT is demonstrated to be superior by means of increasing VO_{2peak} compared to CME is essential, because an improved cardiorespiratory fitness augments lipid metabolism during rest and CME [41, 48]. Often, a remarkably higher reduction in VATA relative to overall BM has been demonstrated after a period of AT [31, 34, 78, 85]. This may descent from the fact that VAT appears to be the most lipolytically active adipose tissue depot [4],

which makes it sensitive to alterations in β-oxidation. Thus, when lipid metabolism is elevated, VAT instantly contributes. Our data demonstrated a significant inverse correlation between VATA and VO_{2peak}. This can hardly be interpreted as more than a vague sign, but nonetheless, it is a finding that supports the elaborated rationale.

4.3. The metabolic syndrome

Our results showed significant reductions in WC (≈ 3%), BPd (≈ 8%), and TG (≈ 13%) after 16 weeks of CME. Only FG was significantly reduced in both 1-AIT (≈ 9%) and 4-AIT (≈ 6%), and moreover, the reduction in BPd varied significantly between the groups ($p < 0.05$). These results stand in contrast to the findings of other analogous studies [21, 34]. Tjønna with colleagues [21] demonstrated that all features of the MetS apart from TG changed significantly in 4-AIT, whereas in CME, only WC (≈ 6%) and BPs (≈ 8%) were significantly altered. Furthermore, Irving et al. [34] demonstrated a significant reduction in WC (≈ 5%) after 16 weeks of AIT, but not CME. In both these studies, AIT had a greater overall effect on the MetS compared to CME. ≈ 21% decline in the number of MetS features in AIT was reported in one of the studies [21] , which is staggering compared to our findings of ≈ 10% overall decline. The results from a prospective cohort study [70], which stated that intensity is more important than volume with regards to ameliorating the MetS, confirms these findings. However, self-reported- and unorganized PA as assessed in this particular study, likely ensues a lower intensity compared to the defined terms in AT interventions of RCT's.

A distinct confounder when comparing these results are the notable differences in subject characteristics between studies. For instance, mean HDL-C- and FG values in the total sample of Tjønna et al. [21] at baseline, were 0.68 mmol/L and 6.4 mmol/L respectively. In our study, the same parameters had values of 1.20 mmol/L and 5.9 mmol/L respectively. This is one of the unfortunate consequences of a relatively small sample size. Obviously, an individual with abnormal values has a greater potential for positive alteration that an individual who already possess approximately normal values. This is concurred by a supplementary analysis from our sample (not presented in the results), which revealed that subjects with the highest 25% FG values at baseline reduced FG by ≈ 16% (6.9 – 5.8 mmol/L), whereas subjects with the lowest 25% FG values at baseline actually augmented FG by ≈ 6% (5.1 – 5.4 mmol/L). Indeed, it is shown that FG levels at 3.9 – 5.6 mmol/L is not considered to increase the risk of CVD to a notable degree [64].

The fact that FG was significantly reduced in both AIT groups, and HDL-C was augmented to a similar extent in CME (0.08 mmol/L) and 4-AIT (0.07 mmol/L), was an intriguing discovery in the present study. In addition, the decline in features of the MetS was similar between the groups. It is

presumed that certain features of the MetS contribute to endothelial dysfunction, primarily by means of oxidative stress and impaired NO bioavailability [61, 65]. Unfortunately, due to the lack of essential measurements, mere speculations of causal relationships with regards to these findings can be proposed. Nonetheless, improvements in FG as well as HDL-C, may very well be attributable to AIT considering that sheer cardiovascular stress administered from AIT in particular, has shown to increase blood glucose level and positively affect endothelial function [24]. However, after detecting notable differences in compliance of training sessions, the possibility of deluding results from various types of training in the present study could not be ruled out. Therefore, we did additional analyses were we pooled our data and investigated how changes in the primary variables; VATA and VO_{2peak} in three percentiles, altered the MetS in line with our aim and hypothesis.

4.4. Alternative stratification

It has been elucidated in a large prospective cohort study by Katzmarzyk et al. [35], that the risk for CVD- and all-cause mortality in individuals that are generally obese or have the MetS can be modified to a large extent by cardiorespiratory fitness. Briefly presented, our results show that $VO_{2peak}{}^{3}$ level with regards to improvement of cardiorespiratory fitness, was followed by a significant reduction in VATA (12.8 cm^2), which substantiate the previously mentioned correlation between VO_{2peak}- and VATA alteration. Furthermore, WC (3.9 cm) and BPd (7 mmHg) decreased significantly compared to $VO_{2peak}{}^{1}$ ($p < 0.05$). BPs and TG were also reduced considerably in $VO_{2peak}{}^{3}$; respectively by 6 mmHg and 0.25 mmol/L.

Cardiorespiratory fitness has proven to be a strong predictor of mortality [36], and is even claimed to be an equally independent CVD risk predictor as smoking [38]. Our pooled data showed that the subjects with the 25% greatest increase inVO_{2peak} ($VO_{2peak}{}^{3}$) had a mean increase of 6.0 $mL \cdot min^{-1} \cdot kg^{-1}$ ranging from 3.9- 7.9 $mL \cdot min^{-1} \cdot kg^{-1}$. At follow-up, these subjects had a mean VO_{2peak} of 37.8 $mL \cdot min^{-1} \cdot kg^{-1}$. In a cross-sectional study of 4631 healthy individuals, Aspenes et al. [37] portrayed that a 5 $mL \cdot min^{-1} \cdot kg^{-1}$ drop in VO_{2peak} induced an 11% higher odds for having hypertension and a 56% higher prevalence of CV risk factor clustering. Furthermore, a prospective cohort study of 2812 patients with coronary heart disease (CHD), possessing a rather low VO_{2peak} ($\approx$ 17 $mL \cdot min^{-1} \cdot kg^{-1}$), revealed a 15% reduced risk for CV- and all-cause mortality for every 1 $mL \cdot min^{-1} \cdot kg^{-1}$ increase in VO_{2peak} [87]. Thus, the level of augmented cardiorespiratory fitness that was seen in $VO_{2peak}{}^{3}$ potentially ameliorates cardiovascular health considerably.

Okhawara with colleagues [88] conducted a systematic review of clinical trials. They discovered a dose-response relationship with regards to VATA reduction from AT in obese but otherwise healthy

subjects, reported as metabolic equivalents • hours per week, i.e. the sheer load of frequency, duration and intensity. This is an argument towards that accounting for the total load of AT can be constructive when pursuing health effects from PA. Our results revealed that subjects with the 25% greatest reduction in VATA ($VATA^3$) had a mean reduction of 13.9 cm^2; ranging from 6.7 – 20.9 cm^2. Consequently, these subjects had a mean VATA of 129.9 cm^2 after 16 weeks of AT. It has been suggested that a VATA ≥ 100 cm^2 represents a threshold above which cardiometabolic abnormalities emerge more frequently [75]. However, this suggestion was based on findings in a Japanese population. Therefore, it might not be compatible for Caucasian individuals. Despres et al. [89] demonstrated significantly elevated levels of TG, HDL-C and blood glucose in women with high (≈ 187 cm^2)- compared to low (≈ 107 cm^2) VATA. In fact, the group with a mean VATA of 107 cm^2 did not fulfill the respective criteria's for the MetS. This implies that a certain threshold for VAT- induced cardiometabolic disorders probably varies with regards to ethnicity. Indeed, the reduction in $VATA^3$ in the present study was followed by detectable effects on the features of the MetS. BPs and BPd was reduced by 7- and 5 mmHg respectively, which corresponded with the findings in a meta-analysis comprising 7 clinical trials with AT interventions [29]. Furthermore, TG was reduced by 0.26 mmol/L in $VATA^3$, which is of notable contrast to the unexplainable mean increase of 0.28 mmol/L that was seen in $VATA^1$. However, HDL-C and FG did not change in accordance with VATA, although favorable alterations were expected based on previous demonstrations [7].

4.5. Implications for cardiometabolic health

In clinical terms; the magnitude of alterations in CVD risk factors that were demonstrated in the present study, have substantial effects on human health. This tendency, although randomly shown in our intervention groups, was clearest in the percentiles of our pooled sample as a consequence of a ≈ 6 $mL \cdot min^{-1} \cdot kg^{-1}$ increase in VO_{2peak} and a concurrent ≈ 14 cm^2 decrease in VATA Indeed, it has been shown that a 3 mmHg reduction of either BPs or BPd in hypertensive individuals diminishes the risk of having CAD, stroke and all-cause mortality by 5%, 8%, and 4% respectively [90]. Furthermore, it is claimed in a meta-analysis that 1 mmol/L increase in TG is associated with a 76%- and 32% increased risk for CVD in women and men respectively [91]. Certainly, our findings were lower than this, but nonetheless, this elucidated the potential ramifications on cardiovascular health from AT induced reduction of TG. Although HDL-C and FG were inconsistently altered in relation to VO_{2peak} and VATA, the largest induced improvements were 0.8 mmol/L (≈ 7%) and 0.5 mmol/L (≈ 9%) respectively. The NCEP expert panel on detection, evaluation and treatment of high blood cholesterol in adults has declared that a 1% decrease in HDL-cholesterol is associated with a 2-3% increased risk for having coronary artery disease (CAD) [92]. Moreover, a large meta-analysis of 102 prospective

studies revealed a 12% increased risk of having CHD for every 1 mmol/L increase in FG above 5.6 mmol/L [64]. Thus, our results show that AT in general has induced notable effects on cardiometabolic health and the MetS in the present study.

4.6. Study limitations

The outcomes in this study are highly affected by lifestyle factors, such as smoking, diet, sleep quality and alcohol consumption. These are not accounted for in the present analyses, and may have altered the results. In addition, the relatively small sample size may have made the data sensitive to extreme measurements. Furthermore, an isocaloric study design might have distinguished the effects from AIT to a greater extent. However, the elaborated lack of agreement in compliance between groups would still have remained a problem.

On the basis of feedback from individual subjects, a tendency towards a higher prevalence of fatigue in 4-AIT was observed. Indeed, fatigue may impair performance during training and presumably alter compliance of workouts, although this has not been noted in previous similarly designed studies. However, a preparatory training-phase might have been constructive in order to avoid this problem.

Subjects were recruited from various arenas, including local gyms in the surroundings of Trondheim. Our experience after feedbacks from individual subjects is that some of them actually performed AT regularly before they submitted to the study. Hence, they did not increase the load of AT during the intervention period. Indeed, results might have been different if a defined limit with regards to upper amount of weekly PA/AT was set as an exclusion criterion.

Finally, the fact that the subjects were familiarized with the treadmill from pre- to post measurements might have altered their ability to obtain maximal exertion.

4.7. Conclusion

The present study demonstrated that CME, 1-AIT and 4-AIT induced no significant differences in VO_{2peak} and VATA after 16 weeks of AT. However, the results may have been delusive, due to an inadequate compliance in both AIT groups. A trend was visible in relation to a compliance above ≈ 90% which seems necessary in order to obtain desirable effects from AT. Thus, if sufficiently carried out in accordance with today's recommendations, AT has a considerable effect on the MetS. Regardless, 4-AIT also induced detectable changes, which indicate that intensity also play an

important role in this regard. Although not demonstrated in the present study, AIT consistently has the most profound impact on cardiorespiratory fitness. In the present study; VO_{2peak} and VATA were inversely correlated, and separately, the degree of positive alteration of these two variables had a notable effect on the MetS. Thus, augmented cardiorespiratory fitness positively affects cardiometabolic health.

4.8. Perspectives

Larger sample sizes are warranted in similar future studies. Furthermore, cardiorespiratory fitness is established as a protector against the development of the MetS and CVD. In contradiction, a great body of evidence suggests that excessive VAT is a pathophysiologic condition in which leads to the development of the MetS and other cariometabolic disorders. However, the underlying causes of VAT accumulation are diffuse. Recently, the term adiposopathy was presented, which describes a condition of dysfunctional adipocytes. Indeed, AT is an ideal approach in terms of uncovering pathways that lead to cardiometabolic disorders. Hence, future research should explore how AT alters adipocyte characteristics, with emphasis on the progression of excessive VAT accumulation.

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