CARDIORESPIRATORY FITNESS, MUSCLE STRENGTH, AND BODY COMPOSITION RESPONSIVENESS TO WEIGHT LOSS IN ADULTS WITH DIFFERENT AGES OF OBESITY ONSET

Lucas Almeida

A Thesis

In

The Department

Of

Health, Kinesiology, and Applied Physiology

Presented in Partial Fulfillment of the Requirements

For the Degree of

Master of Science (Health and Exercise Science) at

Concordia University

Montreal, Quebec, Canada

December 2020

CONCORDIA UNIVERSITY

School of Graduate Studies

This is to certify that the thesis prepared

By: Lucas Almeida

Entitled: Cardiorespiratory fitness, muscle strength, and body composition responsiveness to weight loss in adults with different ages of obesity onset

and submitted in partial fulfillment of the requirements for the degree of

Master of Science (Health and Exercise Science)

complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

Signed by the final examining committee:

Dr. Geoffrey Dover Chair

Dr. Véronique Pepin Examiner

Dr. Angela Alberga Examiner

Dr. Sylvia Santosa Supervisor

Approved by Dr. Geoffrey Dover
Graduate Program Director

Dr. Pascale Sicotte
Dean of faculty

Date _____

ABSTRACT

Cardiorespiratory fitness, muscle strength, and body composition responsiveness to weight loss in adults with different ages of obesity onset

Lucas Almeida

Research shows that those who have had obesity from childhood have greater risk of cardiometabolic disease compared to those who only develop obesity in adulthood. A main way of mitigating the risk of cardiometabolic disease in obesity is with weight loss. Weight loss has been shown to positively affect cardiorespiratory fitness (CRF), muscle strength, and body composition of adults. However, it is unclear whether the response of the aforementioned outcomes to weight loss may be influenced by age of obesity onset. The current study investigated how CRF, muscle strength, and body composition of adults with childhood- versus adulthood-onset obesity are affected by weight loss. Measurements were conducted before, at 12 weeks, and after ~10% weight loss. In total, 37 adults completed the 12-weeks assessments (age=30.5±3.2 y; BMI=32.9±3.0 kg/m^2) and 23 participants with adulthood-onset (n=11) and childhood-onset obesity (n=12) reached 8.8±3.2% weight loss. The YMCA cycle ergometer test (YMCA) and the 20-m shuttle run test (20MSR) were used to measure CRF (ml.kg^{-1}.min^{-1}). A handgrip dynamometer was used to measure muscle strength. Body composition was assessed by DEXA and CT-scan. Overall, body composition and CRF improved (time effect: $p<0.05$) after 12 weeks and moderate weight loss and there was no group-by-time interaction for YMCA, 20MSR, muscle strength, and body composition variables. Age of onset of obesity does not affect the responsiveness of CRF, handgrip strength, and body composition at 12 weeks and after moderate weight loss in adults with obesity.

Keywords: Age of obesity onset; maximal oxygen consumption; static strength; behavioural weight loss protocol.

Acknowledgements

Firstly, I would like to thank my supervisor Dr. Santosa who accepted me as one of her graduate students. My supervisor's support throughout the last years was crucial for my academic performance and growth. I am grateful to her for this opportunity and now I feel prepared and motivated to continue my academic journey in an outstanding PhD program.

I would also like to thank Jessica Murphy for her great support and patience throughout the last two years. I would not have learned so much about research design and statistics without her unconditional support. I am grateful for her kindness and for turning my academic journey into a joyful experience.

Many thanks to Natalie Khor and Marie-Eve Rivard for their experience and willingness to help with anything in the clinical analysis suite. This environment was carefully organized where all lab work could be done smoothly.

I appreciate all the help and support of my lab mates. Thanks to Bjorn Tam, Kerri Delaney, Laurent Turner, and Niloufar Ghaderian for all the good memories.

My special thanks to Christina Weiss who provided outstanding guidance for all procedures on the conditioning floor at the PERFORM Center. She patiently supported me with the first steps to work with the participants on the conditioning floor, and my experience would not be as pleasant and enriching without her.

Lastly, I would like to reinforce the importance of my supervisory committee composed of Dr. Pepin and Dr. Alberga who kindly accepted my invitation and contributed to my academic progress.

Contents

List of figures

List of tables

Abbreviations

BMI	Body mass index
CVD	Cardiovascular diseases
CRF	Cardiorespiratory fitness
CT	Computed tomography
DEXA	Dual-energy X-ray absorptiometry
HR	Heart rate
HRR	Heart rate reserve
VO_2max	Maximal oxygen consumption
FM	Total body fat mass
%BF	Total body fat percentage
LM	Total body lean mass
RMR	Resting metabolic rate
SAT	Subcutaneous adipose tissue
VAT	Visceral adipose tissue
WHO	World Health Organization
YMCA	YMCA submaximal cycle ergometer test
20MSR	20-m shuttle run

1. THEORETICAL CONTEXT

1.1. Significance, prevalence, and treatment of obesity

According to the World Health Organization (WHO), obesity is defined as excessive fat tissue accumulation that leads to comorbidities and premature mortality[1], and the World Obesity Federation goes further, stating that obesity is a chronic relapsing disease[2]. Body mass index (BMI), a simple and inexpensive measurement, is the most used method to diagnose obesity. BMI is computed from the division of weight (kg) by height (m) squared and according to the WHO, an individual with a BMI of 25 kg/m^2 to 29.9 kg/m^2 and ≥ 30 kg/m^2 are considered to have overweight and obesity, respectively[1,3]. Recent evidence highlights the importance of integrating BMI and waist circumference in obesity diagnosis for a better understanding of adiposity-related complications[4]. Excessive body weight is associated with an increased incidence of several comorbidities including type 2 diabetes mellitus, cardiovascular diseases (CVD), hypertension, stroke, dyslipidemia, sleep apnea, chronic kidney disease, osteoarthritis, and several types of cancer in males and females[2,5-8]. For instance after analysing 57 prospective studies, Whitlock et al.[9] showed that an increase of 5 BMI units is associated with higher risk of diabetes mellitus, chronic kidney disease, and all-cause mortality in adults (by 120%, 60%, and 30%, respectively). Additionally, in 2002 the National Institutes of Health stated that a 10% increase in body weight is associated with 30% increased risk of developing coronary heart disease[10].

The etiology of obesity is a complex process that involves the interrelationships between genetics, and physiological, psychological and environmental factors[11]. The early 1970s marked the start of a rise in the prevalence of obesity in high income countries[11], and nowadays this scenario is also observed in medium and low-income countries[12,13]. The drastic alteration in the eating culture is a major driver for the rise in the rate of obesity incidence and prevalence in people from all ages, ethnicities, geographical localities, and socioeconomic statuses[14]. From 1980 to 2015, the worldwide prevalence of obesity rose from 5% to 10.1% in males and from 8.9% to 14.8% in females[14], and this trend has continued for the majority of countries[15-17]. In Canada, the prevalence of obesity has increased drastically, from 6.1% in 1985 to 18.1% in 2011[18]. The numbers are more alarming in the provinces of Quebec and Ontario where 25% of the population aged 6 to 79 years were classified as having obesity between 2007 and 2013[19].

However, there is recent evidence suggesting that the prevalence of obesity has levelled off from 2005 to 2015 in two high-income countries, the USA and United Kingdom, where the rates remained around 30-34% and 23-24%, respectively[14].

Weight loss has been shown to reduce obesity-related comorbidities. The Obesity Society recommends a 5-10% of weight loss to induce clinically meaningful reductions in some cardiovascular risk factors in individuals with obesity[3,20,21]. Several protocols have been suggested for weight loss, such as diet, physical activity, drug therapy, and surgical interventions[21]. However, the most recommended approach for weight loss is based on diet and physical activity[20,21]. In the short-term, losing weight in a behavioural weight loss protocol can be achieved through strict monitoring of the diet and the exercise components[22,23]. However, this is not the case in the clinical setting where individuals' lifestyle behaviours are not closely controlled[23]. Nevertheless, Santosa et al.[23] demonstrated that a 20-week weight loss protocol based on a self-selected diet and independent exercise sessions can promotes moderate weight loss (14.3%) comparable to studies that used more controlled approaches.

1.2. Age of obesity onset, disease risk and adipose tissue cellularity

An extensive body of research shows that increased body weight early in life leads to obesity in adulthood and its comorbidities[24-28]. Park et al.[24] pooled analyses of three cohort studies that tracked weight status and the prevalence of cardiovascular and metabolic diseases in individuals from childhood into adolescence and adulthood[24]. According to this study, compared to lean individuals, the odds ratio of developing type 2 diabetes was 12.6 in adults with obesity from childhood and 5.5 in adults who developed obesity in adulthood only[24]. In addition, a longitudinal cohort study suggested that a 1-unit increase in BMI *z* score at any age between 7 and 13 is associated with a higher risk of a CVD event in adulthood[29].

Evidence shows that, in humans, adipose tissue cellularity differs based on the age of onset of excessive fat tissue accumulation. Spalding et al.[30] assessed adipocyte number in children, adolescents (0.5-18 y), and adults (21-72 y) with obesity (n = 462) and their lean counterparts (n = 431). They showed that subcutaneous adipocytes number is established during childhood and

adolescence and remains constant during adulthood in individuals with and without obesity. In addition, a longitudinal study followed children and adolescents (4 months-19 years old) with obesity (n = 60) and their lean counterparts (n = 53) over 4 years[31]. The number of fat cells increased in both groups from 1-2 years and continued to increase from 2 years onward in the children with obesity only. Moreover, increases in fat cell size was reported in both groups, however, fat cell size was not statistically different until the age of 14. Therefore, it is suggested that fat tissue growth during infancy and adolescence occurs by increases in both adipocyte number (hyperplasia) and size (hypertrophy) but the former predominates[30-32]. Notably, Brook et al.[33] suggested that adults with adulthood-onset obesity tended to have larger cell size and less adipocytes compared to those with childhood-onset obesity. Larger adipocyte cell size is associated with local hypoxia, inflammation, disturbances in the expandability of adipose tissue, and fat cell dysfunction[34-41].

Furthermore, a study has shown that experimentally induced weight gain (15-20%) in adults resulted in adipose tissue expansion by hypertrophy and not hyperplasia[42]. In contrast, after weight loss total body fat mass (FM) reduction in these individuals was a result of decreases in adipocyte volume only[42]. In accordance with this study, Spalding et al.[30] have shown that FM reduction (18 ± 11%) after two years of bariatric surgery in adults was caused by decreases in fat cell volume, while adipocyte number remained constant. Overall, these findings suggest that the number of adipocytes is set during pre- and peri-puberty and remains relatively stable throughout adulthood[30,31,42,43].

Collectively, it is suggested that the age at which obesity develops plays an important role in disease risk and adipose tissue cellularity. Although it seems that the inflammatory profile, and the cardiovascular and neuromuscular systems are positively affected by weight loss[21,44-46], there is still much that remains unknown on how adults with childhood-onset and adulthood-onset obesity differ in the responsiveness of CRF, muscle strength, and body composition after weight loss.

1.3. Cardiorespiratory fitness

Cardiorespiratory fitness (CRF) is an important health-related component of physical fitness, which integrates the circulatory, respiratory, and muscular systems to supply oxygen to the active muscles during physical activity[47,48]. Maximal oxygen consumption (VO_2max) is the gold standard measure of CRF and is defined as the highest oxygen uptake by the working tissues despite increases in exercise intensity[49]. The direct measurement of VO_2max is obtained using a graded exercise test performed until volitional exhaustion, where the intensity increases gradually while a face mask measures the individual's oxygen consumption[50]. However, fatigue may occur before total exertion while measuring VO_2max in individuals with various diagnoses turning the test invalid[51]. In addition, besides being costly and time consuming, a maximal exercise test induces higher physiological stress, and requires highly trained personnel, well-equipped laboratory, and medical supervision [50,52,53]. As an attempt to overcome these drawbacks, nonmaximal exercise tests were developed for the prediction of VO_2max[51].

Submaximal graded exercise tests assume that there is a linear relationship between heart rate (HR) and VO_2[54]. By extrapolating VO_2 to age-predicted maximum heart rate, VO_2max can be predicted[54]. Several submaximal graded exercise and field tests have been shown to be effective in predicting VO_2max[52,55]. One such submaximal graded exercise test is the YMCA cycle ergometer. Beekley et al.[52] assessed the VO_2max measured by direct measurement and the YMCA test in adults from both sexes with normal weight to overweight. The VO_2max values from the two methods were strongly associated for males ($r = 0.63$) and females ($r = 0.90$), which suggests that the YMCA protocol may be an alternate method to predict VO_2max in this population. Furthermore, the 20-m shuttle run test (20MSR), also known as "*Course Navette*", "PACER" or "Multistage fitness test", has also been shown to be a validated field test to assess CRF[55]. A recent meta-analysis analyzed 57 correlational studies that compared the VO_2max predicted by the 20MSR and measured by a maximal laboratory-based incremental test[55]. This meta-analysis suggested that the 20MSR has a moderate-to-high mean correlation coefficient of criterion-related validity for estimating the VO_2max of apparently healthy adults from both sexes. Thus far, the YMCA and 20MSR validity studies have been conducted only on apparently healthy participants without obesity. Although these tests have not been validated in individuals with obesity, they seem to be reasonable alternative methods to assess CRF in this population.

The literature has consistently shown that low CRF is associated with increased risk of developing type 2 diabetes and CVD, and is a strong and independent predictor of all-cause mortality[56-59]. A cross-sectional study demonstrated that higher CRF is negatively associated with risk of developing CVD in the short-term and throughout lifespan in middle-aged adults classified as having overweight[59]. Furthermore, individuals who have obesity and are fit have lower risks of developing type 2 diabetes, hypertension, and CVD compared to those with obesity who are unfit[56,60]. Kodama et al.[61] also found that all causes of mortality and CVD events were reduced by 13% and 15% for every 1 MET (3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) increased in healthy males and females, respectively. These findings highlight the importance of CRF regardless of body weight on an individual's general health status.

1.3.1 Obesity and cardiorespiratory fitness

Excess body weight induces several physiological and functional changes in the cardiovascular system as obesity leads to increased blood volume, stroke volume, and cardiac output[60]. This additional cardiovascular work induces left and right ventricular concentric hypertrophy, and right atrial enlargement[60]. Other studies further demonstrated that adults with obesity have a thicker left ventricular wall compared to their lean counterparts[62-64]. Overall, this pathological hypertrophy of the cardiac muscles leads to cardiac dysfunction. Moreover, individuals with obesity have reduced expiratory reserve volume and functional residual capacity[65], which may also explain the negative effects of excessive body weight on CRF.

A cross-sectional study conducted by Fogelholm et al.[66] compared relative VO_2max ($ml.kg^{-1}.min^{-1}$) of adults with different BMI values. In this study, CRF was measured by a maximal cycle ergometer test and individuals with obesity had lower relative CRF compared to the participants with overweight. In addition, those pertaining to the overweight category also showed reduced relative CRF compared to normal weight participants[66]. Similarly, two other studies demonstrated an inverse correlation between increased body weight and relative CRF in young[67] (age = 19.3 ± 1.4 y; BMI = 22.4 ± 3.9 kg/m^2) and older adults[68] (age = 54.5 ± 6.1 y; BMI = 29.1 ± 4.3 kg/m^2). In addition, Bonney et al.[69] showed that adolescents girls without obesity

had a better overall performance in the 20MSR compared to participants with obesity, which reinforces the effect of obesity on CRF.

1.3.2 The effects of weight loss on cardiorespiratory fitness

Physical activity is often encouraged in a weight loss protocol. A systematic review showed greater improvements of CRF are observed when exercise training is added to an energy restriction intervention in adults with obesity[70]. The same was demonstrated in middle-aged women classified as overweight who followed an 8-week weight loss protocol[71]. In this study, relative VO_2max increased by 3.1 $ml.kg^{-1}.min^{-1}$ in participants who reached moderate weight loss induced by a diet-only program. Similarly, relative VO_2max increased by 4.8 $ml.kg^{-1}.min^{-1}$ in the participants who engaged in aerobic and strength training in combination with a calorie restricted diet after matched weight loss. In addition, a recent randomized clinical trial investigated the effects of three types of weight loss protocols (caloric restriction, aerobic exercise, and the combination of both) on CRF in females and males (n = 52; age = 57 ± 5 y; BMI = 27.7 ± 1.7 kg/m^2)[72]. In the calorie restricted group after the participants reached ~7% weight loss, absolute VO_2max was reduced by 6%. In the aerobic exercise group absolute VO_2max was increased by 15% and it did not change in the group who exercised and followed a caloric restricted diet[72]. Similarly, when matched for weight loss after a 12-month weight loss protocol (caloric restriction or aerobic exercise), those in the calorie restricted group also decreased VO_2max ($ml.min^{-1}$), whereas those in the aerobic exercise group had significant improvements[73]. When adjusted for body weight, VO_2max was still increased in the aerobic group and remained unchanged in the caloric restriction group[73]. These findings were consistent with those of Brinkworth et al.[74] who studied adults with obesity before and after moderate weight loss (age = 49.2 ± 1.2 y; BMI = 33.6 ± 1.5 kg/m^2).

Exercise stimulates capillary density and physiological adaptive hypertrophy of the myocardium, which improves the capacity to eject blood to the systemic circulation and to the delivery of oxygen to the working muscles[75,76]. Moreover, as a result of exercise training, increased mitochondrial density in the skeletal muscles enhances the use oxygen for energy production[76]. Indeed, exercise training has weight loss-independent effects on VO_2max[75].

However, there are also independent effects of weight loss on CRF. For instance, a prospective study demonstrated that adults diagnosed with class III obesity (BMI = 49.4 ± 5.4 kg/m^2) improved their relative CRF after weight loss induced by bariatric surgery even in the absence of exercise[45]. In this study, CRF was measured by the Bruce protocol and the participants were able to reduce their BMI by approximately 15 kg/m^2 after 6 months of surgery.

To our knowledge, only one study investigated the effects of age of obesity onset on CRF after weight loss. In this study, Rupp et al.[44] found that after 6 months of weight loss induced by diet and exercise, the adult-onset group had greater improvements in CRF compared to the childhood-onset group. However, the individuals from the adult-onset group had lower CRF at baseline and they engaged in more physical activity within the first 6 months, which may have contributed to the greater initial gains. Therefore, the only study on this topic has several limitations highlighting the necessity for further research.

1.4. Muscular strength

Muscular strength is fundamental in enabling an individual to perform daily activities and maintain functional independence, and the literature has suggested that muscle strength has an independent effect on the prevention of non-communicable diseases[77]. Hence, muscle strength is an important health-related fitness component along with CRF[54,77]. Static muscle strength is the capacity of a muscle group to produce maximal voluntary contractile force against an immovable resistance, which occurs through the integration of the neural, mechanical, and muscular systems[54,78]. Dynamometers are used to measure static strength and the handgrip dynamometer is largely used to evaluate handgrip static strength[54]. Despite the fact that the handgrip test provides specific strength values for the forearm muscles, this test has been largely conducted as proxy to evaluate overall muscle strength since it is an important predictor of muscular endurance and strength[79,80]. In addition, handgrip strength has been shown to have a strong inverse correlation with all-cause mortality in young and older adults[77]. For instance, a recent meta-analysis showed that adults with greater handgrip strength had 31% reduced all-cause mortality risk compared to individuals with similar characteristics, but with lower muscular strength[81].

1.4.1 Obesity and muscular strength

The consensus within the literature is that excessive adipose tissue has negative effects on the skeletal muscles of adults from all ages[82-86]. There are several factors that may explain the implications of obesity on muscle strength, and low-grade inflammation is one of them. It is suggested that the higher levels of pro-inflammatory cytokines, especially tumor necrosis factor-alpha and interleukin-6, have apoptotic effects on muscle cells[87]. In other words, these cytokines stimulate muscle protein catabolism to the detriment of synthesis, which affects muscle architecture, morphology, and signaling pathways. This systemic inflammation results in a decline in muscle mass and function, which is a common scenario observed in the pathogenesis of sarcopenic obesity[87-94]. Furthermore, skeletal muscle glucose uptake by GLUT-4 is negatively affected by this systemic inflammation, and muscle force production is in turn affected since it depends largely on carbohydrate to function at its maximal capacity[95]. Another plausible rationale is that weight gain leads to a process known as myosteatosis, which is the infiltration of adipose tissue in the skeletal muscles[88,95-97]. Goodpaster et al.[98] suggested that increased intramyocellular fat negatively affects muscle quality and strength. Overall, the literature clearly shows that excessive adipose tissue impairs the ability of an individual to perform maximal contractile force.

A recent review article reported that adults with obesity have higher absolute strength in the lower limbs compared to normal weight individuals, but the opposite is true when these values are adjusted for body weight[88]. For instance, Hulens et al.[99] showed that individuals with obesity (BMI = 37.8 ± 5.3 kg/m^2) had increased absolute muscle strength in the antigravity muscles compared to their lean counterparts (BMI: 22.0 ± 2.2 kg/m^2) and both groups did not differ in absolute handgrip strength. However, when the muscular strength of the knee extensors, oblique abdominals, and forearm were divided by fat-free mass, the group with obesity had lower strength compared to their lean counterparts.

1.4.2 The effects of weight loss on muscular strength

Different types of weight loss protocols have been implemented to examine the effects of weight loss on muscular strength. A study conducted by Weiss et al.[73] investigated the effects of

two different types of weight loss interventions (caloric restriction or aerobic exercise) on the muscular strength of adults (50-60 y) who were overweight. The exercise group increased their relative muscle strength significantly while strength remained unchanged in the calorie restricted group after matched weight loss (9.5 ± 1.5%; 10.7 ± 1.4%, respectively). A recent meta-analysis investigated the effects of weight loss induced by caloric restriction on absolute handgrip strength of adults with overweight or obesity [100]. In this study, absolute handgrip strength was reduced by 3.6% after approximately 8.8 kg of weight loss[100]. Similarly, Brinkworth et al.[74] showed that adults with class I obesity (age = 49.2 ± 1.2 y) had lower absolute handgrip strength after achieving ~7.5% weight loss following a diet-only weight loss protocol. Nevertheless, middle-aged adults with class II obesity (age = 56.9 ± 9.7 y) did not decrease absolute handgrip strength after weight loss (9.7 ± 2.1%) induced by a calorie restricted diet[101]. This finding is corroborated by another study in individuals with class III obesity (age = 45 ± 12 y) after achieving substantial weight loss (30 ± 7%) 12 months after bariatric surgery[102].

The literature lacks studies that investigate the effects of weight loss by diet in combination with exercise on handgrip strength. However, Kim et al. examined the effects of diet and exercise on leg muscle mass and strength in females[103] and males[104] who had overweight or obesity (age = 49.5 ± 9.2 y). Lower body muscle mass and absolute muscle strength were reduced after 12 weeks of weight loss induced by vigorous intensity aerobic exercise and resistance training in conjunction with a hypocaloric diet. However, relative lower body strength was increased after weight loss. Most studies that investigated the response of muscle strength to moderate weight loss considered only weight loss protocols based on calorie restricted diets suggesting that diet-only programs are not the best approach to maintain absolute strength or to improve relative handgrip strength[73,74,100]. Moreover, relative muscle strength of older adults with overweight increases with weight loss approach induced only by exercise[73]. Despite limited studies on weight loss modalities on muscular strength, the available evidence highlights the importance of the exercise component for individuals aiming to improve muscle strength after weight loss. However, the literature lacks studies that investigate whether age of obesity onset influence muscle strength responsiveness to weight loss.

1.5. Body composition

Body composition assessments are crucial for understanding underlying mechanisms that are associated with health risks and functional capacity, and for monitoring therapeutic interventions in obesity-related studies[105]. The three-compartment (3C) model is recommended for use in the research setting to assess body composition[105]. This model separates whole-body composition into fat mass, bone mineral content, and lean tissue mass[105]. Even though a 3C model is not able to differentiate total body water, fat-free dry mass, and remaining solids, such as protein and mineral residuals from the lean mass, the model is optimal for the research setting[106,107].

The dual X-ray absorptiometry (DEXA) technique for determining body composition uses a 3C model which provides an accurate body composition measurement without high-radiation exposure[105,108]. With the DEXA method, the participant lies on a bed where an X-ray beam emits high- and low-photon energy x-rays through the body. The two X-rays attenuate differently depending on the density and chemical composition of the tissues, while assuming that the hydration of the lean mass is constant[105,109,110]. The DEXA is the gold standard method to measure whole-body and regional bone mineral content and is widely used in the research setting to accurately estimate whole-body and regional fat and lean mass[110]. Several studies have demonstrated small precision error and a good reproducibility while conducting the DEXA assessment[108,111-113]. For instance, Tallroth et al.[112] have reported an intra-class correlation coefficient of 0.99 for repeated measures of abdominal fat and lean mass in healthy male adults (n = 37; mean age = 45.1 years; mean BMI = 26.2 kg/m^2).

Tomographic imaging techniques provide two-dimensional volumetric images of specific axial slices of the body in high resolution[114-116]. The computed tomography (CT) scan provides high quality images using radiographic measure, in which specific ranges of Hounsfield units distinguish tissue types. This method is commonly implemented to define visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) of the abdomen[117-120]. In the research setting, an axial single-slice image at the lumbar vertebrae can be used to accurately distinguish upper body SAT and VAT[117].

1.5.1 The effects of weight loss on body composition

The effects of weight loss on body composition varies according to the type of weight loss protocol[121]. The literature has shown that caloric restriction is effective in promoting significant weight loss within the first 6 months of intervention[70,71,122-124]. In the long-term, however, the magnitude and quality of weight loss is only augmented when aerobic and/or resistance exercises are added to a hypocaloric diet[71,72,113,122-130]. There is a greater body mass reduction while sparing or increasing total body lean mass (LM) in weight loss protocols that use a combination of diet and exercise[71,72,113,122-128]. For instance, with a 10 kg weight loss, fat-free mass is expected to decrease by 2.9 kg in males and 2.2 kg in females in response to diet-only programs[131]. However, when exercise is combined with a calorie restricted diet, for a 10 kg weight loss, fat-free mass is reduced by only 1.7 kg in males and females[131]. Interestingly, exercise-only weight loss protocols are not an effective approach to induce weight loss in the short- and long-term[122,123,131]. A meta-analysis suggested that body weight decreases only 0.2 kg/week in middle-aged adults with obesity following an exercise-only weight loss program. In comparison, a reduction of 1 kg/week is observed in individuals who engaged in a diet protocol with or without exercise[122]. Nevertheless, there is evidence that LM of premenopausal women is reduced similarly after 6 and 12 months of calorie restricted diet with or without strength and aerobic exercises[132].

Evidence shows that weight loss protocol type can impact changes in body composition. Overall, weight loss induced by diet in combination with structured aerobic exercise and/or resistance training promotes a greater body mass reduction while preserving LM in adults with obesity. Thus far, the literature lacks studies that investigate the influence of age of obesity onset on body composition and its responsiveness to weight loss, which highlights the importance of future research.

2. RATIONALE

Research shows that those who have had obesity from childhood have greater risk of cardiometabolic disease compared to those who only developed obesity in adulthood. A main way of mitigating the risk of cardiometabolic disease in obesity is with weight loss. Weight loss

has been shown to affect CRF, muscle strength, and body composition of adults. However, it is unclear whether the response of body composition and important health-related fitness components to weight loss may be influenced by age of obesity onset. Therefore, the proposed study aims to investigate how CRF, muscle strength, and body composition of adults with different ages of obesity onset respond to weight loss. The results from the current study will contribute to understanding whether obesity onset influences the treatment of obesity in adults, which will help inform the development of more effective approaches to treat adults with different ages of obesity onset.

3. OBJECTIVES

A. To investigate the effect of age of obesity onset on the changes in CRF as predicted by YMCA and 20MSR after weight loss.

B. To investigate the effect of age of obesity onset on muscle strength after weight loss.

C. To investigate the effects of age of obesity onset on changes in regional body composition after weight loss.

D. To investigate the relationship between changes in CRF, muscle strength and regional body composition after weight loss and to determine how these relationships are affected by age of obesity onset.

4. HYPOTHESIS

A. Adults with adulthood-onset obesity will have greater improvements in CRF after weight loss compared to adults with childhood-onset obesity.

B. Adults with adulthood-onset obesity will have greater improvements in muscle strength after weight loss compared to adults with childhood-onset obesity.

C. Adults with adulthood-onset obesity will have greater reductions in FM and VAT, and a lesser reduction in LM compared to adults with childhood-onset obesity.

D. Improvements in CRF and muscle strength will be positively correlated with decreases in FM and VAT and negatively correlated with decreases in LM. Moreover, adults with adulthood-onset obesity will present stronger correlations between changes in CRF and muscle strength with changes in FM and VAT compared to the childhood-onset group. However, correlations between changes in CRF and muscle strength with changes in LM will be stronger in the childhood-onset group.

5. METHODOLOGY

5.1 Study participants

Adult males and females were recruited through radio, poster, newspaper, and online advertisements. Eligibility of candidates to participate in the study was assessed through telephone screening. The study included sedentary males and females who were 25-40 years of age with a BMI of 30-39 kg/m^2 and did not smoke. To be included in the study, participants also had to provide a medical record or photographic evidence of their weight pre/-peri-puberty (~12-15 y for males and ~10-14 y for females). Exclusion criteria included (i) use of any medication known to affect metabolism; (ii) presence of any metabolic conditions that would affect body weight; (iii) any musculoskeletal condition that would prevent engagement in exercise; iv) participants who were not weight stable (+/- 2 kg) for at least 2 months at baseline; (v) menopausal women, and (vi) breastfeeding women. Eligible participants provided written informed consent (Appendix A) and also completed the Physical Activity Readiness Questionnaire – PAR-Q (Appendix B) to assess their readiness to perform the fitness tests and to engage in the exercise sessions of the weight loss protocol[133]. All study procedures were approved by the Concordia University Human Research Ethics Committee (UHREC).

Participants were categorized according to age of obesity onset based on their response to the Collins and Stunkard body rating scale[134,135] and confirmed by a picture from 12-15 years old and 10-14 years old for males and females, respectively[134]. The Collins scale (Appendix C) was

used to assess weight status during childhood and adolescence[134]. The Stunkard body rating scale (Appendix C) was used to assess weight status during adulthood [135]. Participants were considered to have childhood-onset obesity if they acquired obesity pre-/peri-puberty [134]. Participants were considered to have adulthood-onset obesity if they developed obesity after the age of 18 years[135].

5.2 Study design

The design of this study is presented in Figure 1. Baseline measurements were conducted in a two-week period while the participants maintained a stable weight (+/- 2 kg). Thereafter, all participants started the weight loss protocol, and the same measurements were conducted at 12 weeks into the weight loss protocol. Additionally, follow-up measurements were conducted during a two-week weight stabilization period on the participants who were able to achieve moderate weight loss of around 10%. In total, 37 participants (childhood (n = 19) versus adulthood (n= 18)) were measured at 12-weeks, and 23 participants (childhood (n = 12) versus adulthood (n = 11)) achieved moderate weight loss and underwent follow-up measurements (Figure 2).

Figure 1. Study design

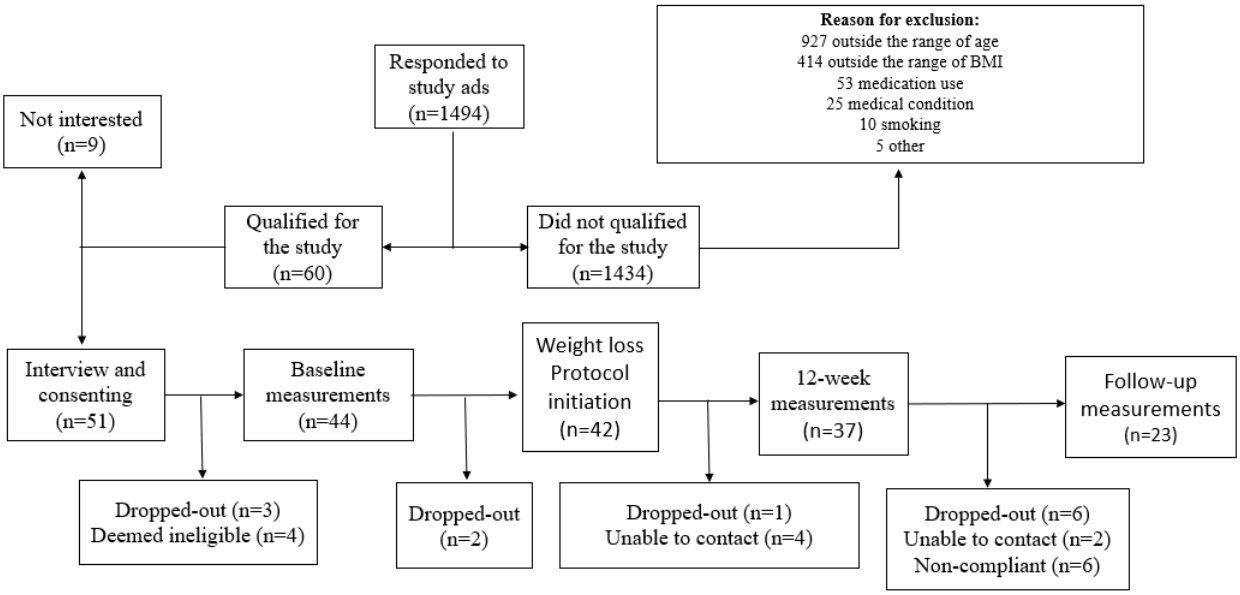


Figure 2. Flowchart of participants.

5.3 Weight loss protocol

The weight loss protocol aimed to achieve a 20% caloric restriction and a 10% increase in energy expenditure through exercise, resulting in a 30% total energy deficit as previously described[23]. Participants' usual eating habits were assessed through interview, a 24-hour recall, and 3-day food record. Resting metabolic rate (RMR) was measured by an indirect calorimeter at the three time-points, and total energy needs were quantified as RMR multiplied by an activity factor of 1.2-1.3. Participants were prescribed exchanges by a dietitian to meet recommended calorie intake based on exchange lists[136]. The diet was composed of 50-60% carbohydrates, 20-30% fats, and 20% proteins. The participants were weighed weekly, and individual meetings were arranged as needed to assist them in following the calorie restricted diet.

Participants were prescribed aerobic exercise on a treadmill and/or elliptical machine based on the guidelines of the Canadian Society of Exercise Physiology-Physical Activity Training for Health (CSEP-PATH). In the start-up phase (first 4 weeks), the participants were instructed to perform aerobic moderate intensity exercise three times per week for 10-25 minutes (Appendix D). The intensity corresponded to an exercise workload that could be sustained with 40-60% of

the participants' heart rate reserve (HRR)[137], which was predicted by the Karvonen method: HRR = [(220 - age - resting heart rate) x % intensity] + resting heart rate[138]. In the 2nd phase (week 4th-24th), participants increased to vigorous intensity exercise at 60-85% HRR[137]. During this phase, they were also instructed to increase their exercise frequency to 3-5 times per week for 20-40 minutes (Appendix D). After week 24 in the maintenance phase, the participants were instructed to engage in exercise sessions that lasted up to 60 minutes maintaining the exercise intensity at 70-85% HRR (Appendix D). At least one exercise session per week was monitored by an exercise specialist on the conditioning floor at the PERFORM Centre, Concordia University. At this visit, participants also reported their weekly exercise activity and were encouraged to self-monitor the rest of the week. There was a clear divide between participants who adhered or did not adhere to the exercise protocol. "Adherent" participants completed more than 80% of prescribed exercise session while "non-adherent" participants completed 0-1 exercise sessions every 2 weeks.

5.4 Cardiorespiratory fitness

5.4.1YMCA Submaximal Cycle Ergometer Test

VO_2max was estimated by the YMCA submaximal cycle ergometer test. The YMCA protocol consists of several stages, with each stage lasting at least 3 minutes[52]. Participants pedaled on a cycle ergometer (25 watts at 50 rpm) with gradual increases in the resistance based on their heart rate (HR) during the first stage (Figure 3).

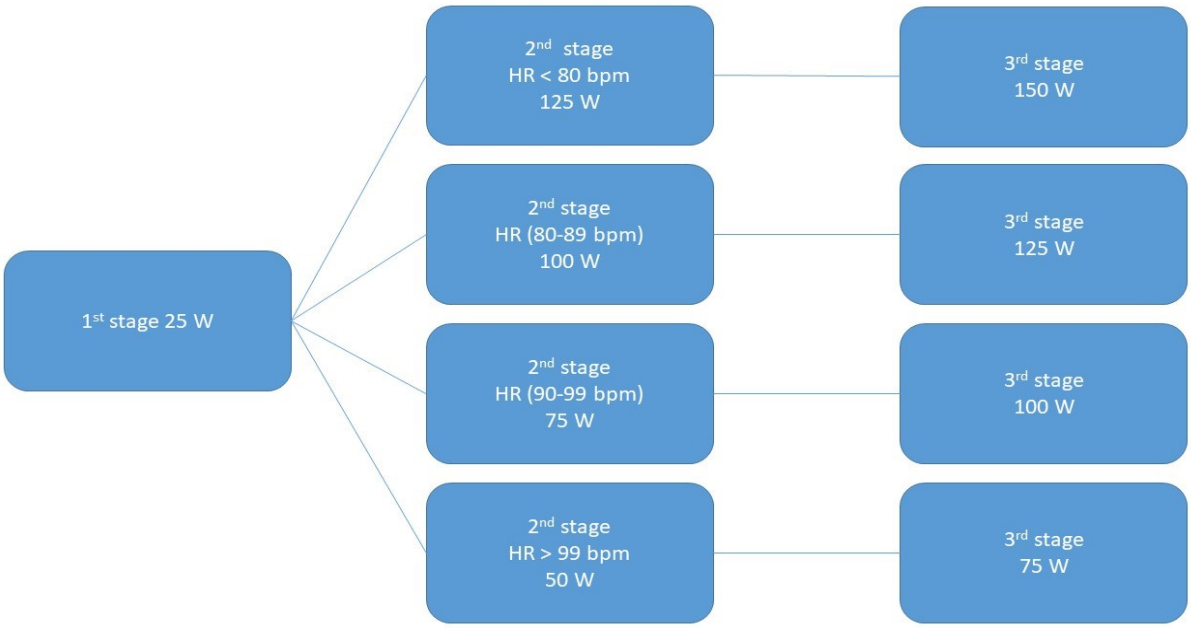


Figure 3. YMCA submaximal cycle ergometer test stages.

Figure 3 demonstrates that the HR response in the first stage determines the workload for the second stage. Thereafter, the workload increased by 25 watts for the subsequent stages until the participant's HR was within the range of 10 beats per minute of his or her 85% age-predicted maximum HR (220 - age). The participant's HR had to be within 5 bpm of the difference between the last two minutes of each stage. If the variation was higher, an additional minute was added to that stage until the HR was within ± 5 bpm. If the participant did not maintain a cadence of 50 revolutions per minute the test was considered invalid. The participants' blood pressure was measured by a sphygmomanometer between the 2nd and 3rd minute of each stage. The participants were asked to rate their perceived exertion (Borg scale)[139] before the end of each stage. The workload and HR encountered in the last two stages were used to estimate VO_2max. The following formula was used to calculate the sub-maximal VO_2 at the second-last workload (SM_1) and last workload (SM_2): [(workload (W)/weight (kg) x 10.8] + 7.0. Then, the slope (b) was calculated by the following formula: (SM_2 - SM_1) / (HR_2 - HR_1). This allowed the prediction of VO_2max: VO_2max (ml.kg^{-1}.min^{-1}) = SM_2 + [b (HRmax - HR_2)][52].

5.4.2 20-m Shuttle Run Test

The 20MSR was conducted on a non-split surface to predict the participants' VO_2max[140]. The test consisted of one-minute stages of continuous running with incremental increases until exhaustion. The participants ran between two cones that were 20-m apart while keeping the pace with sound beeps from a pre-recorded audio signal. The initial speed was 8.5 $km.h^{-1}$ and pre-recorded audio signals emitted by speakers guided increases in speed by 0.5 $km.h^{-1}$ per minute (level). The test ended whenever the participant failed to reach the end lines concurrent with the audio beeps on two consecutive occasions[141]. The equations $Y = 2.85 X + 25.1$ and $Y = 2.75 X + 28.8$ were used to predict the VO_2max for the female and male participants, respectively[140] with X being the last half-stage of the 20MSR completed[140].

5.5 Handgrip strength

An adjustable handgrip dynamometer (Jamar, Performance Health International LTD, Nottinghamshire, UK) was used to assess static muscle strength of the forearm muscles. The participants held the instrument in the hand to be tested at the level of the thigh with the elbows extended, and slightly away from the body[142]. The volunteers were asked to apply a maximum isometric effort to the apparatus and maintain it for 3-5 seconds. Encouragement was given to aid participants in achieving maximal effort[143]. The test was performed twice in each hand. The mean from the highest scores of each trial was recorded to estimate muscle strength.

5.6 Body composition

For the body composition measurements, participants were fasted for at least 8 hours, and wore light clothing, and no shoes. A calibrated DXA scanner (GE Lunar Corporation, Madison, WI, USA) with enCORE software (version 14.10.022) was used to measure total and regional body composition. For the DEXA assessments, the participants were positioned supine with the arms separated from their trunk. The abdominal region of interest was defined by the body segment between the greater trochanter and the 12^{th} rib and the forearm region was defined by the

body segment between the wrist and elbow[144]. In addition, a fixed-wall stadiometer (Seca 216, Seca Corp., Chino, CA) was used to measure height to the nearest 0.1 cm. BMI was then calculated by weight (kg) / height-squared (m^2).

A single-slice CT scan (GE Lightspeed 16TM, Milwaukee, WI) at the L2-3 vertebra with a slice thickness of 10 mm was conducted at baseline and follow-up time points. The Slice-O-Matic Software (version 5.0; Tomovision; Montreal, QC, Canada) was used for processing, segmentation, and measurements of compartments in cm^2. Total VAT mass (kg) was computed by the following equation: VAT[kg] = (VAT[cm^2] / Total abdominal fat[cm^2]) × DEXA total abdominal fat[kg][144]. The upper body SAT mass (kg) was calculated by subtracting VAT mass and leg fat mass from total fat mass (kg).

5.7 Statistical analyses

Descriptive data was expressed as means and standard deviations and the categorical variables were expressed as frequencies and percentages. The Shapiro-Wilk test was used to test normality and the Mauchly's test was applied to verify the sphericity of the data. If sphericity was violated, the Greenhouse-Geisser correction was adopted. The Levene's F test was used to test the homogeneity of variances. A mixed model ANOVA was conducted to assess the effects of age of onset of obesity on the outcome variables after 12-weeks and after 10% weight loss. For the analyses on the 10% weight loss data, weight loss duration was added as a covariate. When a significant effect was observed, the LSD post hoc was applied to identify differences between variables. Pearson's correlation coefficient was used to check the association between changes in fitness and body composition variables, from baseline to 12-weeks and from baseline to follow-up. For non-normal data, Spearman's correlation coefficient was used. The alpha level was set at 0.05 and the interval of coefficient was calculated as being 95%. All the statistical analyses were conducted using SPSS (version 22.0 for windows. IBM Corp., Armonk, NY).

6. RESULTS

6.1 Participants at 12-weeks

Table 1 shows that the participants who reached 12-weeks from both groups (n = 37) did not differ in age (p = 0.56) and BMI (p = 0.10). There were no between-group differences in exercise adherence, sex, weight, and %BF at baseline.

Table 1. Baseline characteristics by onset of obesity of participants who completed 12 weeks.

	Childhood-onset (n = 19)	**Adulthood-onset** (n = 18)	**p-Value**
Sex (n [% female])	13 [68.4%]	12 [66.7%]	0.90
Age (y)	30.2 ± 3.4	30.8 ± 3.1	0.56
BMI (kg/m^2)	33.6 ± 2.9	32.2 ± 2.0	0.10
Weight (kg)	94.6 ± 14.4	94.9 ± 9.8	0.94
BF (%)	42.9 ± 4.3	41.4 ± 6.9	0.43
Exercise Adherent (n [% adherent])	11 [57.9%]	15 [83.3%]	0.091

Abbreviations: BMI = body mass index; BF = total body fat.
Data are presented as means ± SD.

The childhood-onset and adulthood-onset group experienced similar (p = 0.97) %weight loss at 12-weeks (3.6 ± 2.7% vs 3.7 ± 2.4%, respectively). Over the 12-weeks period, both groups decreased (p < 0.001) weight, FM, %BF, and lower body SAT (Table 2). There was a time effect in LM (p = 0.007) and post-hoc analyses demonstrated that LM (p = 0.001) was reduced in the childhood-onset group only (Table 2; Figure 4). Moreover, a trend towards a significant group-by-time interaction effect was observed in %BF and LM (p = 0.066 and p = 0.051, respectively).

Table 2. Total body composition and anthropometric variables by onset of obesity at baseline and 12-weeks.

			p-value		
	Baseline	**12-weeks**	**Group**	**Time**	**Group x time**
Weight[a] (kg)			0.94	< 0.001	0.96
Childhood-onset	94.6 ± 14.4	91.0 ± 13.5*			
Adult-onset	94.9 ± 9.8	91.3 ± 9.2*			
FM[a] (kg)			0.43	< 0.001	0.21
Childhood-onset	40.4 ± 6.0	37.9 ± 5.5*			
Adult-onset	39.2 ± 7.2	35.7 ± 7.0*			
BF[a] (%)			0.29	< 0.001	0.066
Childhood-onset	42.9 ± 4.3	41.8 ± 3.9*			
Adult-onset	41.4 ± 6.9	39.3 ± 7.3*			
LM[a] (kg)			0.53	0.007	0.051
Childhood-onset	51.3 ± 10.3	50.3 ± 9.4*			
Adult-onset	52.6 ± 9.4	52.4 ± 9.5			
Lower body SAT[a] (kg)			0.78	0.001	0.60
Childhood-onset	13.5 ± 3.3	13.0 ± 3.2*			
Adult-onset	13.2 ± 3.7	12.6 ± 3.5*			

Abbreviations: FM = total body fat mass; BF = body fat percentage; LM = total body lean mass; SAT = subcutaneous adipose tissue.
[a]n = 19 for childhood-onset, n = 18 for adulthood-onset.
*Within-group difference from baseline to 12-week by post-hoc LSD tests.
Data are presented as means ± SD.

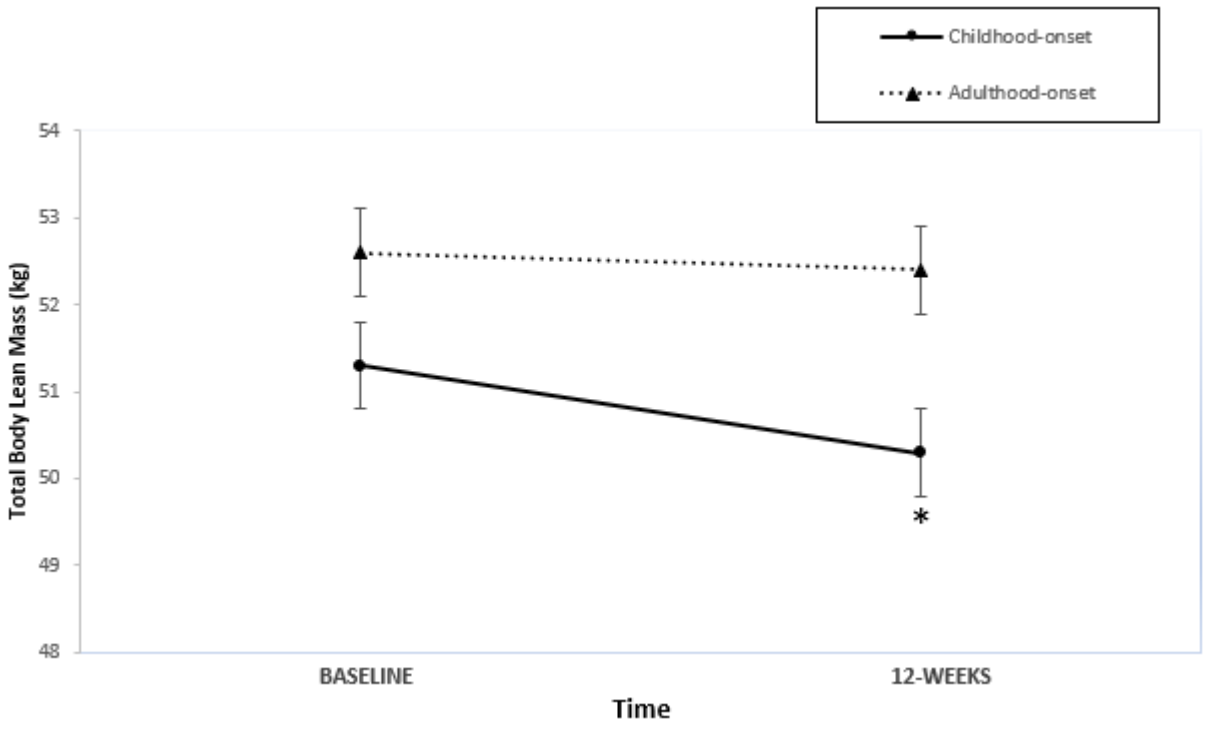


Figure 4. Time effect for total body lean mass from baseline to 12-weeks by onset of obesity; *: represents a difference from baseline to 12-weeks for the childhood-onset group. Error bars represent standard deviation of means.

There was a time effect ($p < 0.001$) for the YMCA test in the participants who completed 12 weeks (Table 3) and post-hoc analysis showed that only the adult-onset group improved ($p < 0.001$) in the YMCA test from baseline to 12-weeks. Both groups also experienced improvements ($p = 0.001$) in 20MSR. Moreover, there was a trend toward a significant effect of time in muscle strength in both groups ($p = 0.050$).

Table 3. Cardiorespiratory fitness and handgrip strength by onset of obesity at baseline and 12-weeks.

			p-value		
	Baseline	**12-weeks**	**Group**	**Time**	**Group x time**
YMCA VO_2max[a] (ml/kg/min)			0.80	< 0.001	0.11
Childhood-onset	32.0 ± 5.2	33.4 ± 5.7			
Adult-onset	31.6 ± 5.3	34.7 ± 6.2*			
20MSR VO_2max[b] (ml/kg/min)			0.86	< 0.001	0.94
Childhood-onset	32.5 ± 2.7	34.1 ± 2.8*			
Adult-onset	33.1 ± 5.5	34.8 ± 6.4*			
Muscle strength (kg)[c]			0.27	0.050	0.29
Childhood-onset	32.8 ± 10.3	34.5 ± 10.7			
Adult-onset	37.0 ± 10.6	37.7 ± 11.3			

Abbreviations: YMCA = YMCA submaximal cycle ergometer test; 20MSR: 20-m shuttle run test.
[a]n = 18 for childhood-onset, n = 18 for adult-onset.
[b]n = 18 for childhood-onset, n = 16 for adult-onset.
[c]n = 19 for childhood-onset, n = 18 for adult-onset.
*Within-group difference from baseline to 12-weeks by post-hoc LSD tests.
Data are presented as means ± SD.

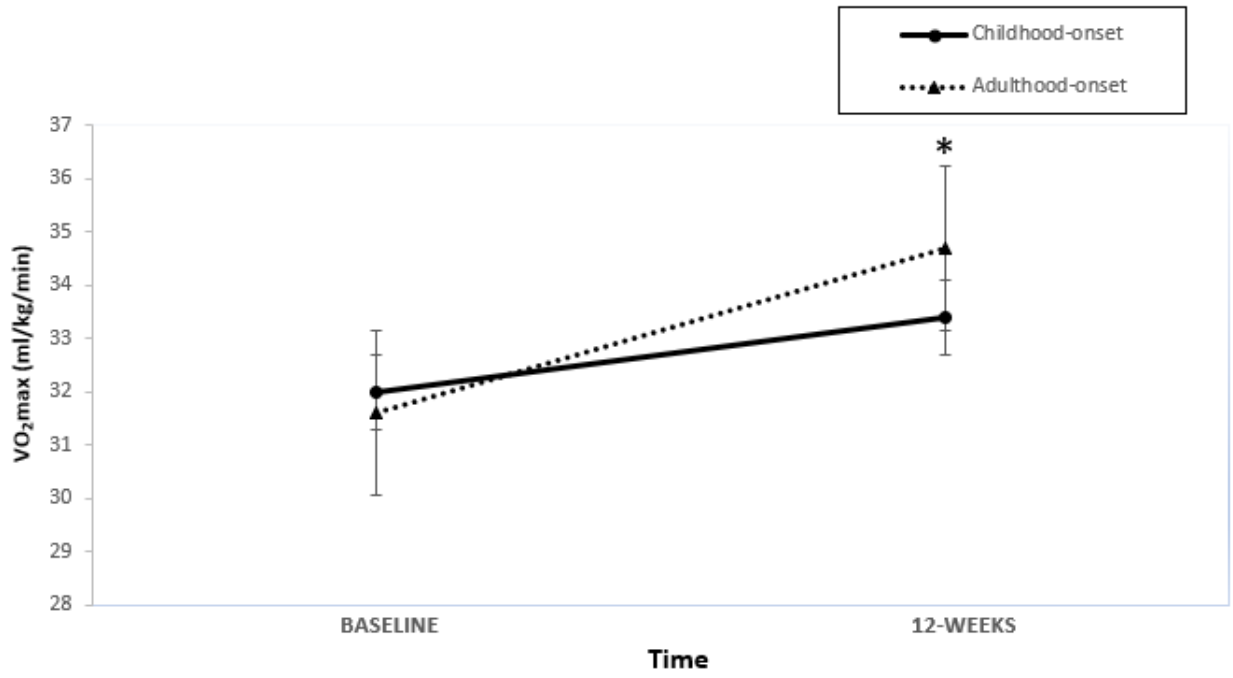


Figure 5. Time effect for cardiorespiratory fitness, predicted by the YMCA test, from baseline to 12-weeks by onset of obesity; *: represents a difference from baseline to 12-weeks for the adulthood-onset group. Error bars represent standard deviation of means. **Abbreviations**: VO_2max = maximal oxygen consumption.

6.2 Participants who achieved moderate weight loss

Table 4 shows that the average age and BMI of participants who achieved their weight loss goal was similar between groups ($p = 0.58$, $p = 0.37$, respectively). There were no differences in exercise adherence, sex, weight, and %BF at baseline. However, the childhood-onset group took longer ($p = 0.02$) to achieve around 10% weight loss compared to the adult-onset group.

Table 4. Baseline characteristics by onset of obesity of participants that achieved 10% weight loss.

	Childhood-onset (n = 12)	**Adulthood-onset** (n = 11)	**p-Value**
Weight loss duration (wks)	45.8 ± 23.0	27.7 ± 10.0	**0.02**
Sex (n [% female])	8 [66.7%]	7 [63.6%]	0.87
Age (y)	30.7 ± 3.6	29.9 ± 3.5	0.58
BMI (m/kg^2)	34.0 ± 3.0	32.8 ± 3.3	0.37
Weight (kg)	95.5 ± 15.7	94.6 ± 7.0	0.85
BF (%)	43.0 ± 3.7	42.0 ± 6.7	0.66
Exercise Adherent (n [% adherent)	8 [66.7%]	10 [90.9%]	0.31

Abbreviations: BMI = body mass index; BF = total body fat.
Data are presented as means ± SD.

In those that achieved moderate weight loss, percent weight loss between groups was similar at 12-weeks (childhood-onset = 4.3 ± 3.1%; adult-onset = 4.3 ± 2.5%; $p = 0.97$) and at the end of the study (childhood-onset = 9.3 ± 3.4%; adult-onset = 8.2 ± 3.0%; $p = 0.49$). Both groups decreased weight ($p < 0.001$) over time (Table 5) and post-hoc analyses showed that the two groups experienced significant weight reduction ($p < 0.001$) from baseline to 12-weeks, from 12-weeks to follow-up, and from baseline to follow-up (Table 5).

Table 5. Total body composition and anthropometric variables by onset of obesity at baseline, 12-weeks, and follow-up.

				p-value[b]		
	Baseline	**12-weeks**	**Follow-up**	**Group**	**Time**	**Group x time**
Weight[a] (kg)				0.85	< 0.001	0.17
Childhood-onset	95.5 ± 15.6	91.3 ± 14.2*	86.7 ± 15.6† ‡			
Adult-onset	94.6 ± 7.0	90.4 ± 6.5*	86.7 ± 5.9† ‡			
Weight loss[a] (%)				0.076	0.004	0.40
Childhood-onset		4.3 ± 3.1	9.3 ± 3.4†			
Adult-onset		4.3 ± 2.5	8.2 ± 3.0†			
FM[a] (kg)				0.97	< 0.001	0.42
Childhood-onset	40.8 ± 5.4	38.1 ± 5.1*	34.2 ± 5.7†‡			
Adult-onset	39.9 ± 7.1	36.0 ± 7.3*	33.2 ± 7.5†‡			
BF[a] (%)				0.83	< 0.001	0.81
Childhood-onset	43.0 ± 3.7	42.0 ± 3.9*	39.6 ± 3.7† ‡			
Adult-onset	42.0 ± 6.7	39.8 ± 7.2*	38.2 ± 7.9† ‡			
LM[a] (kg)				0.84	0.005	0.14
Childhood-onset	51.9 ± 11.2	50.4 ± 10.2*	49.7 ± 10.7†‡			
Adult-onset	51.7 ± 7.0	51.4 ± 6.9	50.5 ± 6.8‡			
Lower body SAT[a] (kg)				0.86	< 0.001	0.67
Childhood-onset	13.2 ± 2.5	12.5 ± 2.1*	11.1 ± 1.9† ‡			
Adult-onset	13.6 ± 4.2	12.7 ± 4.0*	11.7 ± 3.9† ‡			
Upper body SAT[a] (kg)				0.68	< 0.001	0.17
Childhood-onset	25.0 ± 3.4		21.0 ± 3.8‡			
Adult-onset	23.8 ± 4.1		19.6 ± 4.3‡			
VAT[a] (kg)				0.43	< 0.001	0.83
Childhood-onset	2.5 ± 1.4		2.0 ± 1.2‡			
Adult-onset	2.4 ± 1.0		1.7 ± 0.9‡			

Abbreviations: FM = total body fat mass; BF = total body fat; LM = total body lean mass; VAT = visceral adipose tissue.
[a] n = 12 for childhood-onset, n = 11 for adulthood-onset.
[b]Adjusted p-values controlling for weight loss protocol duration.
*Within-group difference from baseline to 12-weeks by post-hoc LSD tests.
†Within-group difference from 12-weeks to follow-up by post-hoc LSD tests.
‡Within-group difference from baseline to follow-up by post-hoc LSD tests.
Data are presented as means ± SD.

Table 5 shows that both groups decreased FM, %BF, and lower body SAT across the three-time points ($p < 0.001$). Post-hoc analyses showed that there was a reduction in FM, %BF, and lower body SAT ($p < 0.05$) in both groups from baseline to 12-weeks, from 12-weeks to follow-up, and from baseline to follow-up. There was an effect of time ($p = 0.005$) on LM and post-hoc analyses showed (Table 5; Figure 6) that LM declined ($p < 0.05$) across all three timepoints in the childhood-onset group. In contrast, LM declined in the adult-onset group ($p = 0.01$) from baseline

to follow-up only. There was also a time effect ($p < 0.001$) for upper body SAT and VAT and post-hoc analyses showed that upper body SAT and VAT was reduced ($p < 0.001$) from baseline to follow-up in both groups.

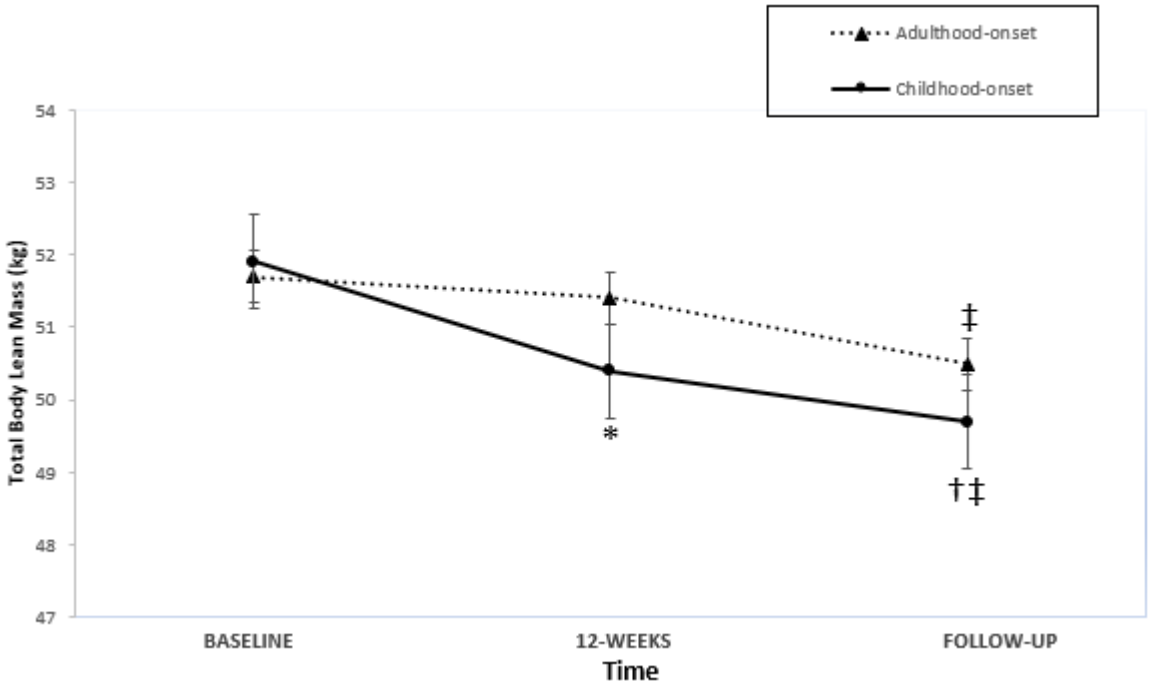


Figure 6. Time effect for total body lean mass from baseline to follow-up by onset of obesity; *: within-group difference from baseline to 12-weeks; †: difference from 12-weeks to follow-up; ‡: difference from baseline to follow-up. Error bars represent standard deviation of means.

Table 6. Cardiorespiratory fitness and muscle strength by onset of obesity at baseline, 12-weeks, and follow-up.

				p-value[d]		
	Baseline	**12-weeks**	**Follow-up**	**Group**	**Time**	**Group x time**
YMCA VO_2max[a] (ml/kg/min)				0.89	0.01	0.16
Childhood-onset	31.6 ± 6.4	33.2 ± 6.8*	36.0 ± 8.9† ‡			
Adult-onset	32.2 ± 6.2	36.1 ± 7.6*	35.6 ± 7.2			
20MSR VO_2max[b] (ml/kg/min)				0.68	0.18	0.85
Childhood-onset	32.4 ± 2.3	34.2 ± 2.9	36.3 ± 4.1			
Adult-onset	34.7 ± 6.0	36.3 ± 6.8	38.2 ± 6.7			
Muscle strength[c] (kg)				0.75	0.084	0.25
Childhood-onset	31.8 ± 12.3	34.1 ± 12.9	34.8 ± 11.0			
Adult-onset	34.7 ± 8.6	35.3 ± 9.0	36.0 ± 7.4			

[a]n = 11 for childhood-onset, n = 10 for adulthood-onset.
[b]n = 8 for childhood-onset, n = 9 for adulthood-onset.
[c]n = 12 for childhood-onset, n = 11 for adulthood-onset.
[d]Adjusted p-values for weight loss protocol duration.
*Within-group difference from baseline to 12-weeks by post-hoc LSD tests.
†Within-group difference from 12-weeks to follow-up by post-hoc LSD tests.
‡Within-group difference from baseline to follow-up by post-hoc LSD tests.
Data are presented as means ± SD.

Participants who achieved moderate weight loss experienced improvements (p = 0.01) over time in the YMCA test (Table 6). Post-hoc analyses showed that the childhood-onset group improved VO_2max based on the YMCA from baseline to 12-weeks (p = 0.04), from 12-weeks to follow-up (p = 0.02), and from baseline to follow-up (p = 0.003). However, the adult-onset group improved VO_2max based on the YMCA from baseline to 12-weeks only (p = 0.002; Figure 7).

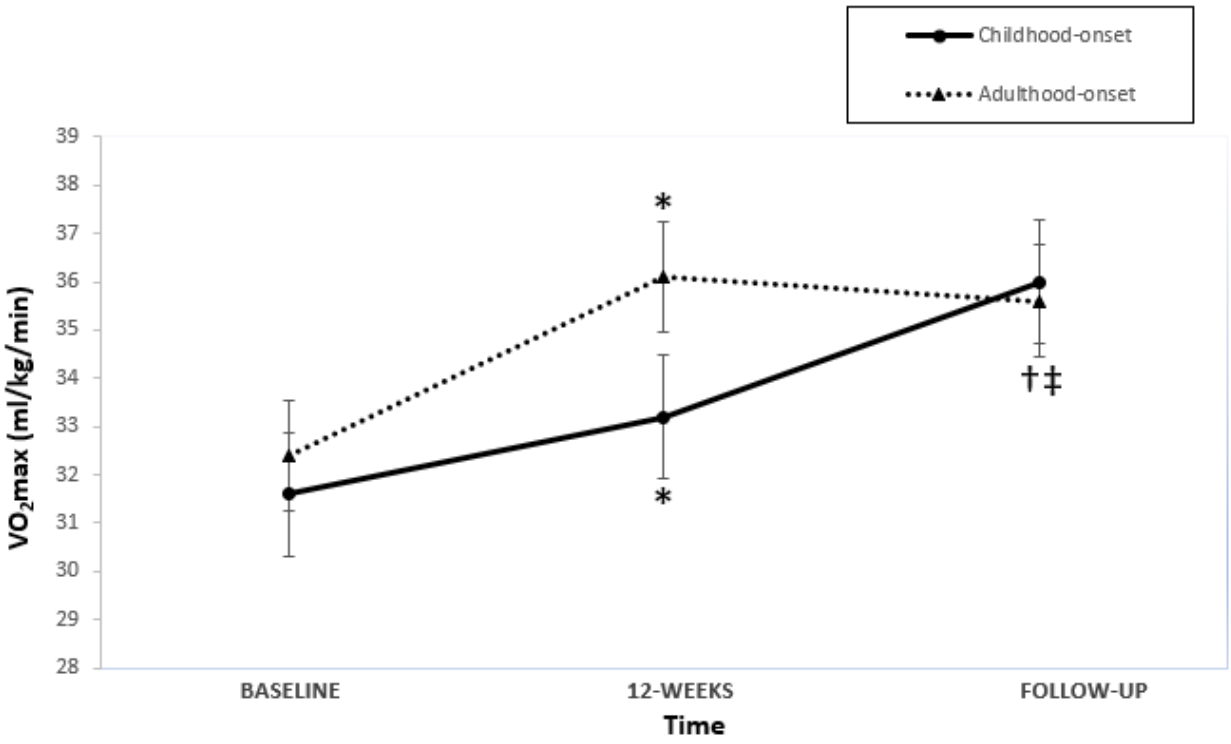


Figure 7. Time effect for cardiorespiratory fitness, predicted by the YMCA test, from baseline to follow-up by onset of obesity; *: within-group difference; †: difference from 12-weeks to follow-up; ‡: difference from baseline to follow-up. Error bars represent standard deviation of means. **Abbreviations**: VO_2max = maximal oxygen consumption.

6.3 Correlations between changes in cardiorespiratory fitness and body composition

Pearson's correlation analyses showed that from baseline to 12-weeks there was no association between Δ YMCA, Δ 20MSR, and Δ muscle strength with Δ FM, Δ %BF, Δ LM, Δ lower body SAT, Δ forearm fat mass, Δ forearm lean mass for the participants who reached 12-weeks (Appendix E; Appendix F; Appendix G). When the same analyses were examined from baseline to follow-up in those who reached their weight loss goal, there was a moderate negative correlation between Δ YMCA and Δ LM ($r = -0.44$; $p < 0.05$; Table 7; Figure 8) and between Δ YMCA and Δ VAT ($r = -0.54$; $p = 0.01$; Table 7; Figure 9)

Table 7. Correlations between changes from baseline to follow-up in fitness variables and changes in regional and total body composition.

	Δ FM[c]	Δ %BF[c]	Δ LM[c]	Δ Upper body SAT[c]	Δ Lower body SAT[d]	Δ Forearm fat mass[c]	Δ Forearm lean mass[c]	Δ VAT[c]
Δ YMC[a]	-0.19	-0.06	-0.44*	-0.26	0.24	-0.12	-0.40	-0.54*
Δ 20MSR[b]	-0.29	-0.40	0.00	-0.40	-0.03	-0.01	-0.15	-0.31
Δ Muscle strength[a]	-0.07	-0.10	-0.02	-0.03	-0.17	-0.01	-0.29	-0.03

Abbreviations: YMCA: YMCA submaximal cycle ergometer test; 20MSR: 20-m shuttle run test; FM: total body fat mass; BF: total body fat; LM: total body lean mass; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue.
[a]n = 23; [b]n = 18.
[c]Pearson's correlation coefficient (r).
[d]Spearman's correlation coefficient (r_s).
*$p < 0.05$.

Table 8. Correlations between changes from baseline to follow-up in fitness variables and changes in regional and total body composition in adults with adulthood-onset obesity.

	Δ FM[c]	Δ %BF[c]	Δ LM[c]	Δ Upper body SAT[d]	Δ Lower body SAT[d]	Δ Forearm fat mass[c]	Δ Forearm lean mass[c]	Δ VAT[c]
Δ YMCA[a]	-0.09	-0.01	-0.70*	-0.26	0.46	0.00	-0.67*	-0.58
Δ 20MSR[a]	-0.22	-0.22	0.03	-0.56	0.35	0.08	0.00	-0.06
Δ Muscle strength[b]	0.09	-0.04	0.79*	0.09	-0.15	0.04	0.92*	0.36

Abbreviations: YMCA: YMCA submaximal cycle ergometer test; 20MSR: 20-m shuttle run test; FM: total body fat mass; BF: total body fat; LM: total body lean mass; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue.
[a]n = 10; [b]n = 11.
[c]Pearson's correlation (r).
[d]Spearman's correlation (r_s).
*$p < 0.05$.

Table 9. Correlations between changes from baseline to follow-up in fitness variables and changes in regional and total body composition in adults with childhood-onset obesity.

	Δ FM[c]	Δ %BF[c]	Δ LM[c]	Δ Upper body SAT[c]	Δ Lower body SAT[c]	Δ Forearm fat mass[c]	Δ Forearm lean mass[c]	Δ VAT[d]
Δ YMCA[a]	-0.26	-0.24	-0.30	-0.26	0.06	-0.44	-0.29	-0.61*
Δ 20MSR[b]	-0.42	-0.65	0.06	-0.46	-0.51	-0.33	-0.24	-0.18
Δ Muscle strength[b]	-0.52	-0.29	-0.41	-0.44	-0.28	-0.45	-0.40	-0.32

Abbreviations: YMCA: YMCA submaximal cycle ergometer test; 20MSR: 20-m shuttle run test; FM: total body fat mass; BF: total body fat; LM: total body lean mass; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue.
[a]n = 11; [b]n = 8.
[c]Pearson's correlation (r).
[d]Spearman's correlation (r_s).
*$p < 0.05$.

Correlation analyses were run separately in individuals with different ages of obesity onset. Table 8 shows that there were negative correlations betweeen Δ YMCA and Δ VAT ($r = -0.61$; $p < 0.05$), Δ YMCA and Δ LM ($r = -0.70$; $p < 0.05$), and Δ YMCA and Δ forearm lean mass ($r = -0.67$; $p < 0.05$) in adults with adulthood-onset obesity (Appendix H). There were also positive correlations between Δ muscle strength and Δ LM ($r = 0.79$; $p < 0.05$), and Δ muscle strength and Δ forearm lean mass ($r = 0.92$; $p < 0.001$; Appendix M) in the adulthood-onset group. In contrast, Table 9 shows that adults with childhood-onset obesity had a negative correlation between Δ YMCA and VAT ($r = -0.61$; $p < 0.05$) only.

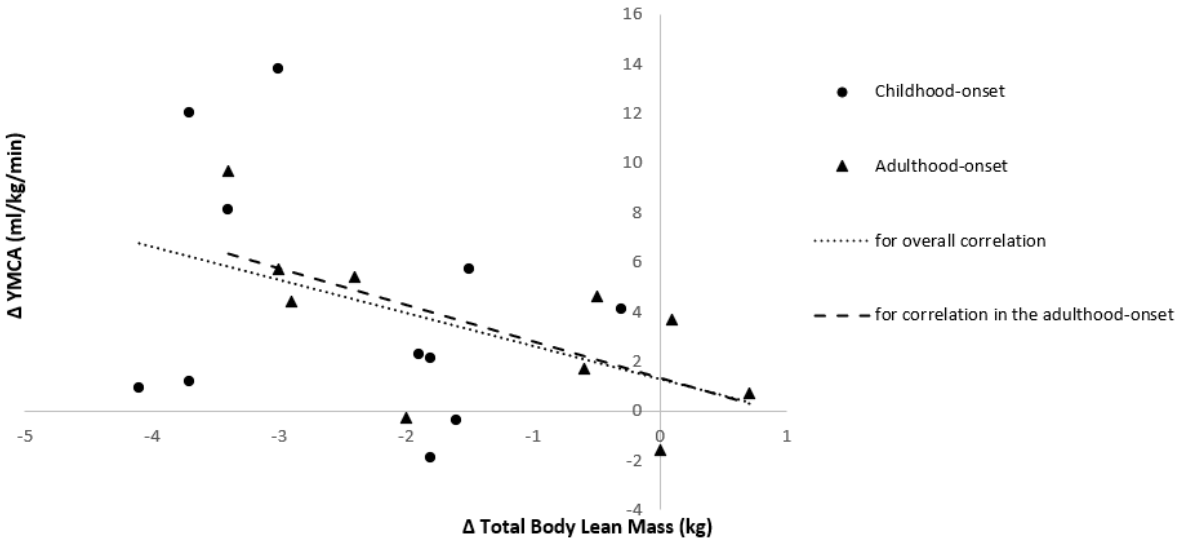


Figure 8. Scatterplot of the relationship between changes from baseline to follow-up in cardiorespiratory fitness and total body lean mass by onset of obesity. **Abbreviations:** YMCA = submaximal cycle ergometer test.

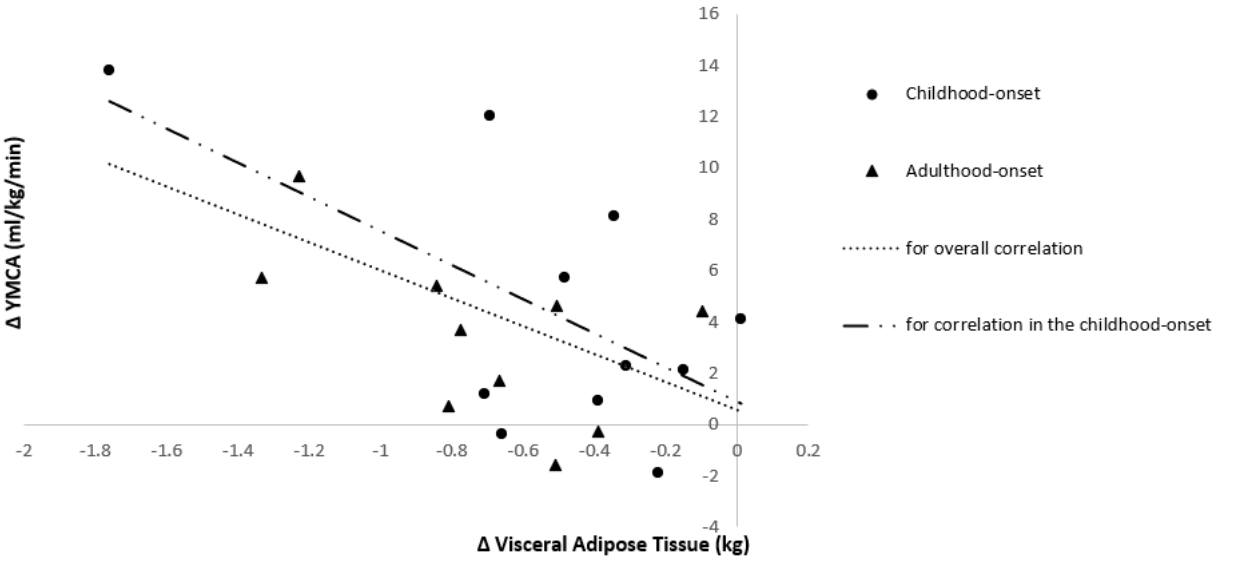


Figure 9. Scatterplot of the relationship between changes from baseline to follow-up in cardiorespiratory fitness and visceral adipose tissue by onset of obesity. **Abbreviations:** YMCA = submaximal cycle ergometer test.

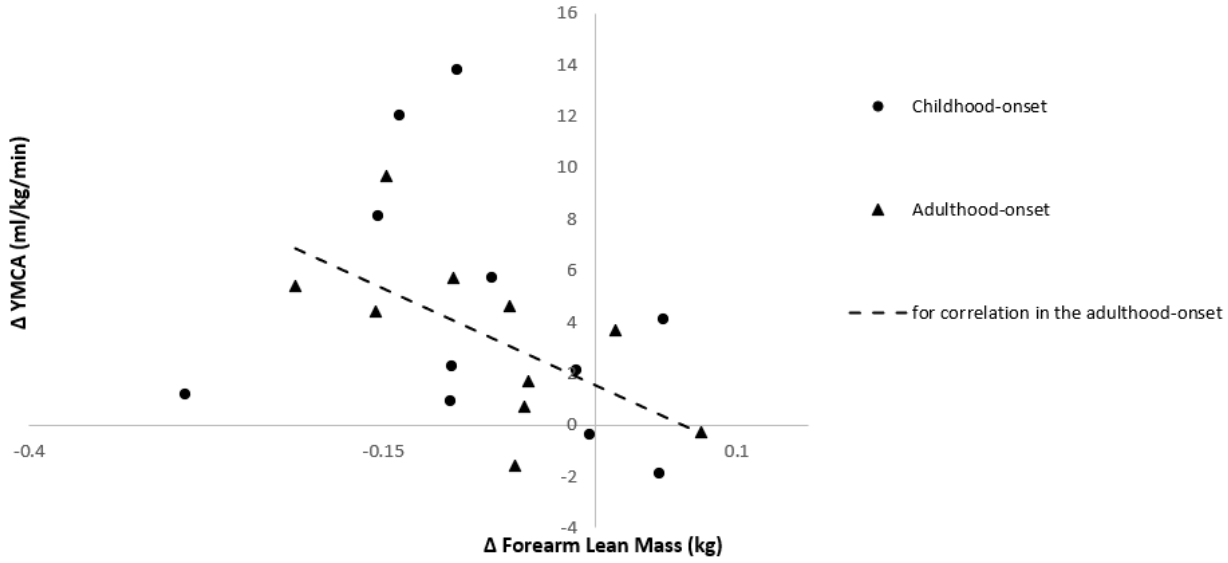


Figure 10. Scatterplot of the relationship between changes from baseline to follow-up in cardiorespiratory fitness and forearm lean mass by onset of obesity. **Abbreviations:** YMCA = submaximal cycle ergometer test.

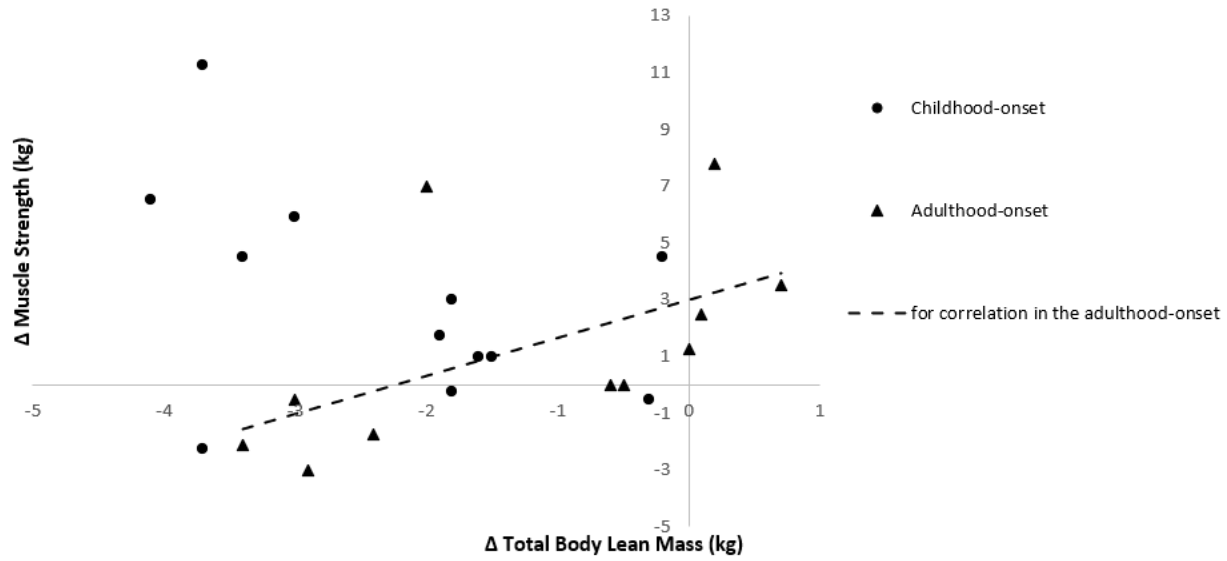


Figure 11. Scatterplot of the relationship between changes from baseline to follow-up in muscle strength and total body lean mass by onset of obesity.

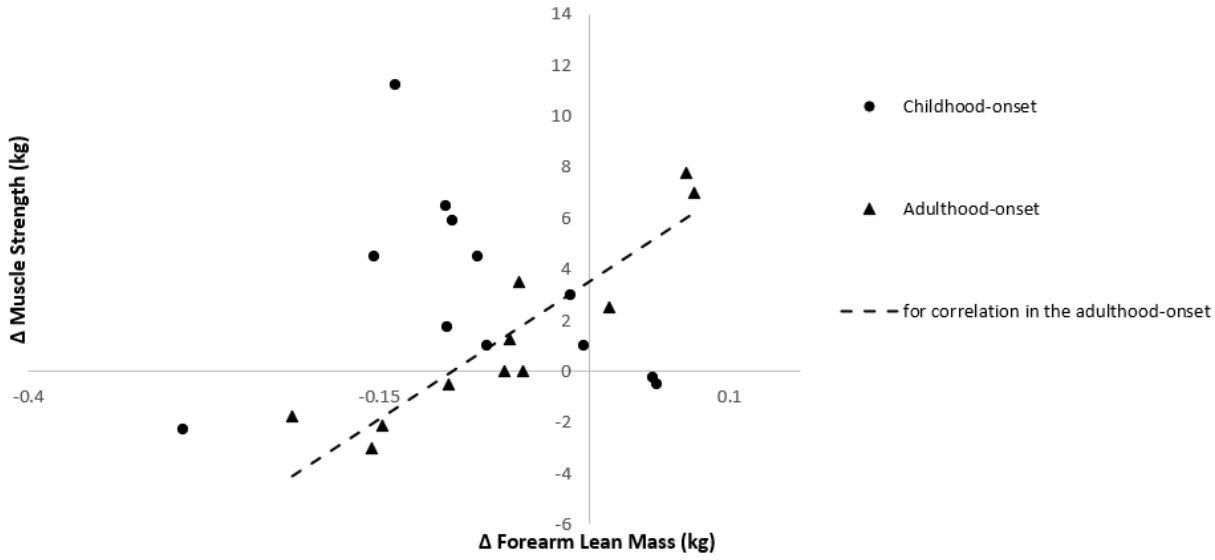


Figure 12. Scatterplot of the relationship between changes from baseline to follow-up in muscle strength and forearm lean mass by onset of obesity.

7. DISCUSSION

This is the first study to investigate whether CRF, muscle strength, and total and regional body composition of adults with childhood-onset obesity or adulthood-onset obesity are affected differently after weight loss. In addition, this study examined whether changes in CRF and strength correlated with changes in body composition after moderate weight loss and the influence of age of obesity onset on these correlations. In contrast to our initial hypothesis, the overall findings of the present study suggest that the age of onset of obesity does not play a role in the responsiveness of CRF, muscle strength, and total and regional body composition after a 12-week weight loss program or after moderate weight loss in adults with obesity. However, we did find that in the larger cohort that completed the 12-week measurement, those with adult-onset obesity showed improvements in CRF via both the YMCA and shuttle run test. In contrast, those with childhood-onset obesity only showed improved CRF in the shuttle run test. Moreover, in those that achieved moderate weight loss, we found that those with adult-onset obesity were able reach an earlier point of plateau in VO_2max at the 12-weeks measurement, whereas those with childhood onset obesity continued to improve their VO_2max to when they reached moderate weight loss.

In the present study, we found that in those that completed moderate weight loss, both adults with childhood and adulthood-onset obesity improved their CRF similarly, although those with adulthood-onset obesity reached an earlier plateau compared to those with childhood-onset obesity. Similarly, Rupp et al.[44] reported that CRF of adults with adulthood-onset obesity was rapidly increased within the first 6 months of a weight loss protocol; thereafter, CRF did not change even though they were still engaged in aerobic exercise. In contrast, those with childhood-onset obesity gradually increased CRF throughout 12 months in the protocol. Together, this evidence suggests that short-term weight loss protocols are sufficient to induce the most benefits in CRF in those with adulthood-onset obesity, whereas in adults with childhood-onset obesity, CRF seems to respond better to longer weight loss protocols.

Despite differences in the point of plateau, the present study showed no difference in CRF at baseline in adults with different ages of obesity onset. Only a study by Rupp et al.[44] examined the effects of obesity onset on CRF. Interestingly, after the prediction of CRF by a submaximal

treadmill test, in the Rupp et al.[44] study the adult-onset group was less fit compared to the childhood-onset group at baseline. The potential reasons for this divergence across studies is that, in the present study, the adults from the two groups were similar in age. In contrast, in the Rupp et al.[44] study the adults in the adulthood-onset group were almost 10 years older than the childhood-onset group. Therefore, it was not surprising that the adulthood-onset group in the Rupp et al.[44] study had lower fitness levels compared to the childhood-onset group since in both males and females, CRF starts declining 7-14% per decade after 20 years, regardless of physical activity level[145].

The changes in CRF between the childhood-onset and adulthood-onset obesity groups after 12 weeks or after achieving ~8-9% weight loss was not different. Rupp et al.[44] found that adults with adulthood-onset obesity had greater improvements in CRF compared to the childhood-onset group in the first 6 months of the protocol. From 6 to 18 months, however, there were no longer differences in changes in CRF between groups. There are many differences between our study and the Rupp et al.[44] study that may explain this lack of agreement. There were no differences in baseline CRF or exercise adherence in the current study, whereas in the study by Rupp et al.[44], the adulthood-onset group was less fit at baseline and they engaged in more exercise within the first 6 months compared to the childhood-onset group. The exercise training principle of "diminishing returns" states that as an individual becomes fit, greater effort is required to be applied for further fitness improvement[146]. In addition, higher engagement in exercise promotes physiological adaptations in the cardiovascular system to a greater extent[70,73,75,76]. Thus, a lesser improvement in CRF in the childhood-onset group, who performed less moderate-vigorous aerobic exercise and were fitter at baseline, would be expected.

Another difference between our study and the Rupp et al.[44] study was that early age obesity onset was defined differently. In the present study, age of obesity onset was defined as pre- or peri-puberty for childhood and over 18 in adulthood. In contrast, Rupp et al.[44] defined childhood-onset obesity as the development of obesity before 18 years old and adulthood-onset obesity as obesity acquired after 18 years old. The cut offs were chosen for our study because adipocyte cellularity responds differently to excessive fat tissue accumulation at different periods of life. The development of obesity during pre-/peri- puberty is associated with reduced fat cell size and increased number of adipocytes compared to obesity acquired after 18 years of age[30,33].

Moreover, in the study by Rupp et al.[44], obesity onset was self-reported. In contrast, in the present study the Collins[134] and Stunkard body rating scale[135] were used to aid the reporting of age of obesity onset by the participants and the participants were also required to provide evidence by way of documentation or picture proof from around their puberty to avoid recall bias. Thus, the method of classifying obesity used in the Rupp et al.[44] study was subject to recall bias.

The present study demonstrated that, in middle-age adults, age of obesity onset did not affect handgrip strength at baseline. The literature lacks studies that investigated the effect of age of obesity onset on handgrip strength. However, a study that compared handgrip strength of adults (average age 67 y) who developed obesity at 30, 40, and 50 y did not demonstrate any difference in handgrip strength between the groups after adjusting for age, sex, physical activity, smoking, and alcohol use[147]. Despite not considering childhood-onset obesity, this study seems to support and extend the findings from the current study to older adults.

The literature has mixed results regarding the effects of weight loss on handgrip strength. In our participants, absolute handgrip strength was not affected by moderate weight loss. This finding was corroborated by other studies that included middle-aged adults with overweight or obesity that achieved weight loss by caloric restriction alone[148-151] or in combination with aerobic exercise[151]. In contrast, two other studies reported decreases in absolute handgrip strength in middled-aged[152] and older adults[74] with obesity who achieved moderate weight loss only through calorie restriction. However, in a study conducted by Siervo et al.[101] adults with similar age and BMI as above improved absolute handgrip strength after comparable weight loss induced by diet. The potential reasons for this inconsistency across studies is unclear and requires additional examination.

Although adults with different ages of obesity onset have distinct risks of developing obesity-related comorbidities, the present study suggested that improvements in CRF and body composition occur similarly in adults with childhood- or adulthood-onset obesity after weight loss. An increase of 1-2 MET (3.5 $ml.kg^{-1}.min^{-1}$) is associated with a 10-30% lower risks of adverse cardiovascular events and reduced mortality[61,145]. In addition, metabolic risk factors and all-cause mortality rate are reduced as FM and VAT decreases[153,154]. Participants from the present

study were able to achieve this magnitude of CRF improvement as well as reductions in FM and VAT. Moreover, age of obesity onset did not influence these responses. From a clinical perspective, although adults with different ages of obesity onset appear to lose weight at different rates, these results imply that their risk of developing obesity-related comorbidities and all-cause mortality can be mitigated similarly after weight loss.

Even though body composition and fitness variables of adults with different ages of obesity-onset responded similarly after moderate weight loss, the present study showed that CRF and muscle strength of adults with adulthood-onset obesity were more sensitive to changes in body composition. Excessive fat tissue accumulation leads to increased serum concentration of several pro-inflammatory cytokines, which negatively affects the cardiovascular and neuromuscular systems[155-157]. Adults with adulthood-onset obesity likely experience the deleterious effects of pro-inflammatory cytokines on these systems for a shorter duration compared to those with obesity obesity dated to childhood. The shorter duration exposure of those with adulthood-onset obesity may explain the relationship between CRF and muscle strength to changes in body composition, whereas almost none were observed in the childhood-onset group. However, this hypothesis requires confirmation by further studies that investigate underlying effects of pro-inflammatory cytokines on the responsiveness of fitness variables to changes in body composition.

In this study, the exercise sessions were monitored once a week by an exercise specialist, and the participants self-reported whether they performed the prescribed exercises. Therefore, the classification of participants for exercise adherence might have been influenced by their perception and report bias. Furthermore, participants' CRF was predicted by a submaximal cycle ergometer test and a maximal field test (20MSR), which to our knowledge, has not yet been validated in people with obesity. Adults with excessive body weight have lower mechanical efficiency at a given submaximal workload on a treadmill or cycle ergometer compared with their lean counterparts due to the extra cardiovascular demand imposed by heavier body segments[158-160]. Therefore, the CRF values from the present study might have been underestimated. However, to attempt to overcome these limitations, CRF was measured by two (YMCA test and 20MSR) rather than one method. Since both methods provided similar results, it is likely that no differences were found because there were none to be found.

Our results are strengthened by the fact that both groups had similar baseline characteristics for age and BMI. There is an inverse correlation between BMI and relative VO_2max, and CRF declines with aging[66,145]. Accordingly, the two groups did not differ for YMCA, 20MSR, muscle strength, and body composition at baseline. Thus, differences in the response of CRF, muscle strength, and body composition to weight loss were not confounded by differences in baseline characteristics. Furthermore, both groups were able to achieve similar weight loss at all data collection points, which facilitated the investigation of the influence of age of obesity onset on CRF, muscle strength, and body composition responsiveness since they are affected by the magnitude of weight loss.

8. CONCLUSION

Findings from our study suggest that the age of onset of obesity does not play a role in the responsiveness of CRF, handgrip strength, and body composition at 12 weeks and after moderate weight loss induced by aerobic exercise and caloric restriction in adults with obesity. Moreover, adults with adulthood-onset obesity were able to achieve moderate weight loss quicker and preserved LM in the first 12 weeks, whereas adults with childhood-onset lost LM. Future studies should further investigate how weight loss rate can affect the responsiveness of CRF, muscle strength, and body composition and the underlying influence of pro-inflammatory cytokines on these responses.

REFERENCES

1. Organization WH. *Obesity: preventing and managing the global epidemic*: World Health Organization; 2000.

2. Bray G, Kim K, Wilding J, Federation WO. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. *Obesity Reviews.* 2017;18(7):715-723.

3. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. *Obesity research.* 1998;6 Suppl 2:51S-209S.

4. Ross R, Neeland I, Yamashita S, et al. Gri n BA, Zambon A, Barter P, Fruchart JC, Eckel RH, Matsuzawa Y, Després JP. Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. *Nature Reviews Endocrinology.* 2020;16(3):177-189.

5. Willet WC, Dietz WH, Colditz GA. Primary care: guidelines for weight. *N Engl J Med.* 1999;341:427-434.

6. Freedman DS, Dietz WH, Srinivasan SR, Berenson GS. Risk factors and adult body mass index among overweight children: the Bogalusa Heart Study. *Pediatrics.* 2009;123(3):750-757.

7. Mattsson N, Rönnemaa T, Juonala M, Viikari JSA, Raitakari OT. Childhood predictors of the metabolic syndrome in adulthood. The Cardiovascular Risk in Young Finns Study. *Annals of Medicine.* 2008;40(7):542-552.

8. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer—viewpoint of the IARC Working Group. *New England Journal of Medicine.* 2016;375(8):794-798.

9. Whitlock G, Lewington S, Sherliker P, et al. Prospective Studies Collaboration: Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet.* 2009;373(9669):1083-1096.

10. Wellman NS, Friedberg B. Causes and consequences of adult obesity: health, social and economic impacts in the United States. *Asia Pacific journal of clinical nutrition.* 2002;11:S705-S709.

11. Blüher M. Obesity: global epidemiology and pathogenesis. *Nature Reviews Endocrinology.* 2019;15(5):288-298.

12. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. *The Lancet.* 2011;378(9793):804-814.

13. Carden TJ, Carr TP. Food availability of glucose and fat, but not fructose, increased in the US between 1970 and 2009: analysis of the USDA food availability data system. *Nutrition Journal.* 2013;12(1):130.

14. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. *Metabolism.* 2019;92:6-10.

15. Meydani SN, Das SK, Pieper CF, et al. Long-term moderate calorie restriction inhibits inflammation without impairing cell-mediated immunity: a randomized controlled trial in non-obese humans. *Aging.* 2016;8(7):1416-1431.

16. Collaborators GBDO, Afshin A, Forouzanfar MH, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *The New England journal of medicine.* 2017;377(1):13-27.

17. Flegal KM. Commentary: the epidemic of obesity—what's in a name? *International journal of epidemiology.* 2005;35(1):72-74.

18. Twells LK, Gregory DM, Reddigan J, Midodzi WK. Current and predicted prevalence of obesity in Canada: a trend analysis. *CMAJ open.* 2014;2(1):E18.

19. Thielman J, Harrington D, Rosella LC, Manson H. Prevalence of age-specific and sex-specific overweight and obesity in Ontario and Quebec, Canada: a cross-sectional study using direct measures of height and weight. *BMJ open.* 2018;8(9):e022029-022018-022029.

20. Jakicic JM, Clark K, Coleman E, et al. Appropriate intervention strategies for weight loss and prevention of weight regain for adults. *Medicine & Science in Sports & Exercise.* 2001.

21. American Heart A, American College of C, Obesity S. Reprint: 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults. *Journal of the American Pharmacists Association : JAPhA.* 2014;54(1):e3.

22. Donnelly JE, Smith BK. Is exercise effective for weight loss with ad libitum diet? Energy balance, compensation, and gender differences. *Exercise and sport sciences reviews.* 2005;33(4):169-174.

23. Santosa S, Demonty I, Jones PJ, Lichtenstein AH. Moderate weight loss: A self-directed protocol for women. *Canadian Journal of Dietetic Practice and Research.* 2008;69(1):23-27.

24. Park MH, Sovio U, Viner RM, Hardy RJ, Kinra S. Overweight in childhood, adolescence and adulthood and cardiovascular risk in later life: pooled analysis of three british birth cohorts. *PloS one.* 2013;8(7):e70684.

25. Lakshman R, Elks CE, Ong KK. Childhood obesity. *Circulation.* 2012;126(14):1770-1779.

26. Berenson GS, Bogalusa Heart Study Research G. Childhood risk factors predict adult risk associated with subclinical cardiovascular disease: the Bogalusa Heart Study. *The American Journal of Cardiology.* 2002;90(10):L3-L7.

27. Serdula MK, Ivery D, Coates RJ, Freedman DS, Williamson DF, Byers T. Do obese children become obese adults? A review of the literature. *Preventive medicine.* 1993;22(2):167-177.

28. Singh AS, Mulder C, Twisk JW, Van Mechelen W, Chinapaw MJ. Tracking of childhood overweight into adulthood: a systematic review of the literature. *Obesity reviews.* 2008;9(5):474-488.

29. Baker JL, Olsen LW, Sørensen TIA. Childhood body-mass index and the risk of coronary heart disease in adulthood. *New England journal of medicine.* 2007;357(23):2329-2337.

30. Spalding KL, Arner E, Westermark PO, et al. Dynamics of fat cell turnover in humans. *Nature.* 2008;453(7196):783.

31. Knittle JL, Timmers K, Ginsberg-Fellner F, Brown RE, Katz DP. The growth of adipose tissue in children and adolescents. Cross-sectional and longitudinal studies of adipose cell number and size. *The Journal of clinical investigation.* 1979;63(2):239-246.

32. Arner P. Fat Tissue Growth and Development in Humans. *Nestle Nutrition Institute workshop series.* 2018;89:37-45.

33. Brook C, Lloyd JK, Wolf O. Relation between age of onset of obesity and size and number of adipose cells. *Br med J.* 1972;2(5804):25-27.

34. Goossens GH. The metabolic phenotype in obesity: fat mass, body fat distribution, and adipose tissue function. *Obesity facts.* 2017;10(3):207-215.

35. Choe SS, Huh JY, Hwang IJ, Kim JI, Kim JB. Adipose tissue remodeling: its role in energy metabolism and metabolic disorders. *Frontiers in endocrinology.* 2016;7:30.

36. Trayhurn P. Hypoxia and adipose tissue function and dysfunction in obesity. *Physiological reviews.* 2013;93(1):1-21.

37. Ye J. Gao Z, Yin J, He Q. *Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. Am J Physiol Endocrinol Metab.* 2007;293:E1118-E1128.

38. Makki K, Froguel P, Wolowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. ISRN Inflamm. 2013; 2013: 139239: 10.1155/2013/139239 PMID: 24455420; 2017.

39. Huh JY, Park YJ, Ham M, Kim JB. Crosstalk between adipocytes and immune cells in adipose tissue inflammation and metabolic dysregulation in obesity. *Molecules and cells.* 2014;37(5):365.

40. Jernås M, Palming J, Sjöholm K, et al. Separation of human adipocytes by size: hypertrophic fat cells display distinct gene expression. *The FASEB Journal.* 2006;20(9):1540-1542.

41. Tam BT, Morais JA, Santosa S. Obesity and ageing: Two sides of the same coin. *Obesity Reviews.* 2020;21(4):e12991.

42. Salans LB, Horton ES, Sims EA. Experimental obesity in man: cellular character of the adipose tissue. *The Journal of clinical investigation.* 1971;50(5):1005-1011.

43. Arner P. Fat Tissue Growth And Development in Humans. 2018;89:37-45.

44. Rupp K, Taverno Ross SE, Lang W, Jakicic JM. Response to a standard behavioral weight loss intervention by age of onset of obesity. *Obesity science & practice.* 2016;2(3):248-255.

45. De Souza SAF, Faintuch J, Sant'Anna AF. Effect of weight loss on aerobic capacity in patients with severe obesity before and after bariatric surgery. *Obesity Surgery.* 2010;20(7):871-875.

46. Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes–. *The American Journal of Clinical Nutrition.* 2013;97(3):505-516.

47. Lee D-c, Artero EG, Sui X, Blair SN. Mortality trends in the general population: the importance of cardiorespiratory fitness. *Journal of psychopharmacology.* 2010;24(4_suppl):27-35.

48. Bouchard CE, Shephard RJ, Stephens TE. Physical activity, fitness, and health: International proceedings and consensus statement. Paper presented at: International Consensus Symposium on Physical Activity, Fitness, and Health, 2nd, May, 1992, Toronto, ON, Canada; 1994.

49. McArdle WD, Katch FI, Katch VL. *Essentials of exercise physiology*: Lippincott Williams & Wilkins; 2006.

50. Bennett H, Parfitt G, Davison K, Eston R. Validity of submaximal step tests to estimate maximal oxygen uptake in healthy adults. *Sports Medicine.* 2016;46(5):737-750.

51. Noonan V, Dean E. Submaximal exercise testing: clinical application and interpretation. *Physical Therapy.* 2000;80(8):782-807.

52. Beekley MD, Brechue WF, Dehoyos DV, Garzarella L, Werber-Zion G, Pollock* ML. Cross-validation of the YMCA submaximal cycle ergometer test to predict VO2max. *Research quarterly for exercise and sport.* 2004;75(3):337-342.

53. Pescatello LS, Riebe D, Thompson PD. *ACSM's guidelines for exercise testing and prescription*: Lippincott Williams & Wilkins; 2014.

54. Gibson AL, Wagner D, Heyward V. *Advanced Fitness Assessment and Exercise Prescription, 8E*: Human kinetics; 2018.

55. Mayorga-Vega D, Aguilar-Soto P, Viciana J. Criterion-Related Validity of the 20-M Shuttle Run Test for Estimating Cardiorespiratory Fitness: A Meta-Analysis. *Journal of sports science & medicine.* 2015;14(3):536-547.

56. Wei M, Kampert JB, Barlow CE, et al. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. *Jama.* 1999;282(16):1547-1553.

57. Bouchard C, Rankinen T, Timmons JA. Genomics and genetics in the biology of adaptation to exercise. *Comprehensive Physiology.* 2011;1(3):1603-1648.

58. Carnethon MR, Gulati M, Greenland P. Prevalence and cardiovascular disease correlates of low cardiorespiratory fitness in adolescents and adults. *Jama.* 2005;294(23):2981-2988.

59. Swainson MG, Ingle L, Carroll S. Cardiorespiratory fitness as a predictor of short‐term and lifetime estimated cardiovascular disease risk. *Scandinavian journal of medicine & science in sports.* 2019;29(9):1402-1413.

60. Lavie CJ, McAuley PA, Church TS, Milani RV, Blair SN. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. *Journal of the American College of Cardiology.* 2014;63(14):1345-1354.

61. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *Jama.* 2009;301(19):2024-2035.

62. Alpert MA, Terry BE, Mulekar M, et al. Cardiac morphology and left ventricular function in normotensive morbidly obese patients with and without congestive heart failure, and effect of weight loss. *The American Journal of Cardiology.* 1997;80(6):736-740.

63. Alpert MA, Alexander JK. Cardiac morphology and obesity in man. *The heart and lung in obesity.* 1998:25-44.

64. Alpert MA, Terry BE, Kelly DL. Effect of weight loss on cardiac chamber size, wall thickness and left ventricular function in morbid obesity. *The American Journal of Cardiology.* 1985;55(6):783-786.

65. Salvadori A, Fanari P, Fontana M, et al. Oxygen uptake and cardiac performance in obese and normal subjects during exercise. *Respiration; international review of thoracic diseases.* 1999;66(1):25-33.

66. Fogelholm M, Malmberg J, Suni J, Santtila M, Kyröläinen H, Mäntysaari M. Waist circumference and BMI are independently associated with the variation of cardio-respiratory and neuromuscular fitness in young adult men. *International journal of obesity.* 2006;30(6):962.

67. Cc L, Udaya I, Vinutha Shankar S. Effect of body mass index on cardiorespiratory fitness in young healthy males. *International Journal of Scientific and Research Publications.* 2014:25.

68. Bertoli A, Di Daniele N, Ceccobelli M, Ficara A, Girasoli C, De Lorenzo A. Lipid profile, BMI, body fat distribution, and aerobic fitness in men with metabolic syndrome. *Acta Diabetologica.* 2003;40(1):s130-s133.

69. Bonney E, Ferguson G, Smits-Engelsman B. Relationship between Body Mass Index, Cardiorespiratory and Musculoskeletal Fitness among South African Adolescent Girls. *International journal of environmental research and public health.* 2018;15(6):1087.

70. Miller CT, Fraser SF, Levinger I, et al. The effects of exercise training in addition to energy restriction on functional capacities and body composition in obese adults during weight loss: a systematic review. *PloS one.* 2013;8(11):e81692.

71. Joseph G, Arviv-Eliashiv R, Tesler R. A comparison of diet versus diet+ exercise programs for health improvement in middle-aged overweight women. *Women's Health.* 2020;16:1745506520932372.

72. Weiss EP, Jordan RC, Frese EM, Albert SG, Villareal DT. Effects of weight loss on lean mass, strength, bone, and aerobic capacity. *Medicine and science in sports and exercise.* 2017;49(1):206.

73. Weiss EP, Racette SB, Villareal DT, et al. Lower extremity muscle size and strength and aerobic capacity decrease with caloric restriction but not with exercise-induced weight loss. *Journal of applied physiology.* 2007;102(2):634-640.

74. Brinkworth GD, Noakes M, Clifton PM, Buckley JD. Effects of a low carbohydrate weight loss diet on exercise capacity and tolerance in obese subjects. *Obesity.* 2009;17(10):1916-1923.

75. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart: a meta-analysis of cardiac structure and function. *Circulation.* 2000;101(3):336-344.

76. Coggan AR, Spina RJ, King DS, et al. Skeletal muscle adaptations to endurance training in 60- to 70-yr-old men and women. *Journal of applied physiology (Bethesda, Md.: 1985).* 1992;72(5):1780-1786.

77. Volaklis KA, Halle M, Meisinger C. Muscular strength as a strong predictor of mortality: a narrative review. *European journal of internal medicine.* 2015;26(5):303-310.

78. Suchomel TJ, Nimphius S, Bellon CR, Stone MH. The importance of muscular strength: Training considerations. *Sports Medicine.* 2018:1-21.

79. Bohannon RW. Muscle strength: clinical and prognostic value of hand-grip dynamometry. *Current Opinion in Clinical Nutrition & Metabolic Care.* 2015;18(5):465-470.

80. Trosclair D, Bellar D, Judge LW, Smith J, Mazerat N, Brignac A. Hand-Grip Strength as a Predictor of Muscular Strength and Endurance. *The Journal of Strength & Conditioning Research.* 2011;25:S99.

81. García-Hermoso A, Cavero-Redondo I, Ramírez-Vélez R, et al. Muscular strength as a predictor of all-cause mortality in apparently healthy population: A systematic review and meta-analysis of data from approximately 2 million men and women. *Archives of Physical Medicine and Rehabilitation.* 2018.

82. Blimkie CJR, Sale DG, Bar-Or O. Voluntary strength, evoked twitch contractile properties and motor unit activation of knee extensors in obese and non-obese adolescent males. *European journal of applied physiology and occupational physiology.* 1990;61(3-4):313-318.

83. Maffiuletti NA, Jubeau M, Agosti F, De Col A, Sartorio A. Quadriceps muscle function characteristics in severely obese and nonobese adolescents. *European journal of applied physiology.* 2008;103(4):481-484.

84. Maffiuletti NA, Jubeau M, Munzinger U, et al. Differences in quadriceps muscle strength and fatigue between lean and obese subjects. *European journal of applied physiology.* 2007;101(1):51-59.

85. Zoico E, Di Francesco V, Guralnik JM, et al. Physical disability and muscular strength in relation to obesity and different body composition indexes in a sample of healthy elderly women. *International journal of obesity.* 2004;28(2):234.

86. Rolland Y, Lauwers-Cances V, Pahor M, Fillaux J, Grandjean H, Vellas B. Muscle strength in obese elderly women: effect of recreational physical activity in a cross-sectional study. *The American Journal of Clinical Nutrition.* 2004;79(4):552-557.

87. Kewalramani G, Bilan PJ, Klip A. Muscle insulin resistance: assault by lipids, cytokines and local macrophages. *Current Opinion in Clinical Nutrition & Metabolic Care.* 2010;13(4):382-390.

88. Tomlinson DJ, Erskine RM, Morse CI, Winwood K, Onambélé-Pearson G. The impact of obesity on skeletal muscle strength and structure through adolescence to old age. *Biogerontology.* 2016;17(3):467-483.

89. Visser M, Pahor M, Taaffe DR, et al. Relationship of interleukin-6 and tumor necrosis factor-α with muscle mass and muscle strength in elderly men and women: the Health ABC Study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2002;57(5):M326-M332.

90. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *The Journal of clinical investigation.* 1995;95(5):2409-2415.

91. Mercier S, Breuille D, Mosoni L, Obled C, Patureau Mirand P. Chronic inflammation alters protein metabolism in several organs of adult rats. *The Journal of nutrition.* 2002;132(7):1921-1928.

92. Tallis J, James RS, Seebacher F. The effects of obesity on skeletal muscle contractile function. *The Journal of experimental biology.* 2018;221(Pt 13):10.1242/jeb.163840.

93. Molino S, Dossena M, Buonocore D, Verri M. Sarcopenic obesity: an appraisal of the current status of knowledge and management in elderly people. *The journal of nutrition, health & aging.* 2016;20(7):780-788.

94. Polyzos SA, Margioris AN. Sarcopenic obesity. *Hormones.* 2018;17(3):321-331.

95. Holten MK, Zacho M, Gaster M, Juel C, Wojtaszewski JF, Dela F. Strength training increases insulin-mediated glucose uptake, GLUT4 content, and insulin signaling in skeletal muscle in patients with type 2 diabetes. *Diabetes.* 2004;53(2):294-305.

96. Goodpaster BH, Theriault R, Watkins SC, Kelley DE. Intramuscular lipid content is increased in obesity and decreased by weight loss. *Metabolism.* 2000;49(4):467-472.

97. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harbor perspectives in biology.* 2014;6(10):a016295.

98. Goodpaster BH, Carlson CL, Visser M, et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. *Journal of applied physiology.* 2001;90(6):2157-2165.

99. Hulens M, Vansant G, Lysens R, Claessens AL, Muls E, Brumagne S. Study of differences in peripheral muscle strength of lean versus obese women: an allometric approach. *International journal of obesity.* 2001;25(5):676.

100. Zibellini J, Seimon R, Lee C, Gibson A, Hsu M, Sainsbury A. Effect of diet‐induced weight loss on muscle strength in adults with overweight or obesity–a systematic review and meta‐analysis of clinical trials. *Obesity Reviews.* 2016;17(8):647-663.

101. Siervo M, Nasti G, Stephan BC, et al. Effects of intentional weight loss on physical and cognitive function in middle-aged and older obese participants: a pilot study. *Journal of the American College of Nutrition.* 2012;31(2):79-86.

102. Alba DL, Wu L, Cawthon PM, et al. Changes in lean mass, absolute and relative muscle strength, and physical performance after gastric bypass surgery. *The Journal of Clinical Endocrinology & Metabolism.* 2019;104(3):711-720.

103. Kim B, Tsujimoto T, So R, Tanaka K. Changes in lower extremity muscle mass and muscle strength after weight loss in obese men: A prospective study. *Obesity research & clinical practice.* 2015;9(4):365-373.

104. Kim B, Tsujimoto T, So R, Zhao X, Oh S, Tanaka K. Changes in muscle strength after diet-induced weight reduction in adult men with obesity: a prospective study. *Diabetes, metabolic syndrome and obesity: targets and therapy.* 2017;10:187.

105. Kuriyan R. Body composition techniques. *The Indian journal of medical research.* 2018;148(5):648.

106. Albanese CV, Diessel E, Genant HK. Clinical applications of body composition measurements using DXA. *Journal of Clinical Densitometry.* 2003;6(2):75-85.

107. Withers RT, LaForgia J, Pillans R, et al. Comparisons of two-, three-, and four-compartment models of body composition analysis in men and women. *Journal of Applied Physiology.* 1998;85(1):238-245.

108. Mazess RB, Barden HS, Bisek JP, Hanson J. Dual-energy x-ray absorptiometry for total-body and regional bone-mineral and soft-tissue composition. *The American journal of clinical nutrition.* 1990;51(6):1106-1112.

109. Garg M, Kharb S. Dual energy X-ray absorptiometry: Pitfalls in measurement and interpretation of bone mineral density. *Indian journal of endocrinology and metabolism.* 2013;17(2):203.

110. Prior BM, Cureton KJ, Modlesky CM, et al. In vivo validation of whole body composition estimates from dual-energy X-ray absorptiometry. *Journal of applied physiology.* 1997;83(2):623-630.

111. Lohman M, Tallroth K, Kettunen JA, Marttinen MT. Reproducibility of dual-energy x-ray absorptiometry total and regional body composition measurements using different scanning positions and definitions of regions. *Metabolism.* 2009;58(11):1663-1668.

112. Tallroth K, Kettunen JA, Kujala UM. Reproducibility of regional DEXA examinations of abdominal fat and lean tissue. *Obesity facts.* 2013;6(2):203-210.

113. Volek J, Gomez A, Love D, et al. Effects of an 8-week weight-loss program on cardiovascular disease risk factors and regional body composition. *European journal of clinical nutrition.* 2002;56(7):585-592.

114. Yu L, Liu X, Leng S, et al. Radiation dose reduction in computed tomography: techniques and future perspective. *Imaging in medicine.* 2009;1(1):65.

115. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. *Journal of applied physiology.* 2000;89(1):104-110.

116. Seidell JC, Bakker C, van der Kooy K. Imaging techniques for measuring adipose-tissue distribution--a comparison between computed tomography and 1.5-T magnetic resonance. *The American journal of clinical nutrition.* 1990;51(6):953-957.

117. Shuster A, Patlas M, Pinthus J, Mourtzakis M. The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. *The British journal of radiology.* 2012;85(1009):1-10.

118. Micklesfield LK, Goedecke JH, Punyanitya M, Wilson KE, Kelly TL. Dual‐energy X‐ray performs as well as clinical computed tomography for the measurement of visceral fat. *Obesity.* 2012;20(5):1109-1114.

119. Thomas EL, Fitzpatrick J, Malik S, Taylor-Robinson SD, Bell JD. Whole body fat: content and distribution. *Progress in nuclear magnetic resonance spectroscopy.* 2013;73:56-80.

120. Murphy J, Bacon SL, Morais JA, Tsoukas MA, Santosa S. Intra‐abdominal adipose tissue quantification by alternative versus reference methods: a systematic review and meta‐analysis. *Obesity.* 2019;27(7):1115-1122.

121. Clark JE. Diet, exercise or diet with exercise: comparing the effectiveness of treatment options for weight-loss and changes in fitness for adults (18–65 years old) who are overfat, or obese; systematic review and meta-analysis. *Journal of Diabetes & Metabolic Disorders.* 2015;14(1):31.

122. Miller WC, Koceja D, Hamilton E. A meta-analysis of the past 25 years of weight loss research using diet, exercise or diet plus exercise intervention. *International journal of obesity.* 1997;21(10):941-947.

123. Johns DJ, Hartmann-Boyce J, Jebb SA, Aveyard P, Group BWMR. Diet or exercise interventions vs combined behavioral weight management programs: a systematic review and meta-analysis of direct comparisons. *Journal of the Academy of Nutrition and Dietetics.* 2014;114(10):1557-1568.

124. Hernández-Reyes A, Cámara-Martos F, Molina-Luque R, Romero-Saldaña M, Molina-Recio G, Moreno-Rojas R. Changes in body composition with a hypocaloric diet combined with sedentary, moderate and high-intense physical activity: a randomized controlled trial. *BMC Women's Health.* 2019;19(1):167.

125. Cava E, Yeat NC, Mittendorfer B. Preserving healthy muscle during weight loss. *Advances in nutrition.* 2017;8(3):511-519.

126. Swift DL, Johannsen NM, Lavie CJ, Earnest CP, Church TS. The role of exercise and physical activity in weight loss and maintenance. *Progress in cardiovascular diseases.* 2014;56(4):441-447.

127. Donnelly JE, Honas JJ, Smith BK, et al. Aerobic exercise alone results in clinically significant weight loss for men and women: midwest exercise trial 2. *Obesity.* 2013;21(3):E219-E228.

128. Trouwborst I, Verreijen A, Memelink R, et al. Exercise and nutrition strategies to counteract sarcopenic obesity. *Nutrients.* 2018;10(5):605.

129. Layman DK, Evans E, Baum JI, Seyler J, Erickson DJ, Boileau RA. Dietary protein and exercise have additive effects on body composition during weight loss in adult women. *The Journal of nutrition.* 2005;135(8):1903-1910.

130. Benito PJ, López-Plaza B, Bermejo LM, et al. Strength plus Endurance Training and Individualized Diet Reduce Fat Mass in Overweight Subjects: A Randomized Clinical Trial. *International Journal of Environmental Research and Public Health.* 2020;17(7):2596.

131. Garrow J, Summerbell C. Meta-analysis: effect of exercise, with or without dieting, on the body composition of overweight subjects. *European journal of clinical nutrition.* 1995;49(1):1-10.

132. Miller CT, Fraser SF, Selig SE, et al. Fitness, Strength and Body Composition during Weight Loss in Women with Clinically Severe Obesity: A Randomised Clinical Trial. *Obesity facts.* 2020;13(4):307-321.

133. American College of Sports M. *ACSM's health-related physical fitness assessment manual*: Lippincott Williams & Wilkins; 2013.

134. Collins ME. Body figure perceptions and preferences among preadolescent children. *International Journal of Eating Disorders.* 1991;10(2):199-208.

135. Stunkard AJ. Use of the Danish Adoption Register for the study of obesity and thinness. *Res.Publ.Assoc.Res.Nerv.Ment.Dis.* 1983;60:115-120.

136. Wheeler ML, Franz M, Barrier P, Holler H, CRONMILLER N, Delahanty LM. Macronutrient and energy database for the 1995 exchange lists for meal planning: a rationale for clinical practice decisions. *Journal of the American Dietetic Association.* 1996;96(11):1167-1171.

137. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Medicine and science in sports and exercise.* 2011;43(7):1334-1359.

138. Karvonen MJ. The effects of training on heart rate: A longitudinal study. *Ann Med Exp Biol Fenn.* 1957;35:307-315.

139. Borg GA. Psychophysical bases of perceived exertion. *Medicine and science in sports and exercise.* 1982;14(5):377-381.

140. Stickland MK, Petersen SR, Bouffard M. Prediction of maximal aerobic power from the 20-m multi-stage shuttle run test. *Canadian Journal of Applied Physiology.* 2003;28(2):272-282.

141. Leger LA, Mercier D, Gadoury C, Lambert J. The multistage 20 metre shuttle run test for aerobic fitness. *Journal of sports sciences.* 1988;6(2):93-101.

142. Kuzala EA, Vargo MC. The relationship between elbow position and grip strength. *American Journal of Occupational Therapy.* 1992;46(6):509-512.

143. Fess E. Clinical assessment recommendations. *American society of hand therapists.* 1981:6-8.

144. Jensen MD, Kanaley JA, Reed JE, Sheedy PF. Measurement of abdominal and visceral fat with computed tomography and dual-energy x-ray absorptiometry. *The American Journal of Clinical Nutrition.* 1995;61(2):274-278.

145. Hawkins SA, Wiswell RA. Rate and mechanism of maximal oxygen consumption decline with aging. *Sports medicine.* 2003;33(12):877-888.

146. Hoffman J. *Physiological Aspects of Sport Training and Performance*: Champaign, Illinois: Human Kinetics 2002.

147. Stenholm S, Sallinen J, Koster A, et al. Association between obesity history and hand grip strength in older adults—exploring the roles of inflammation and insulin resistance as

mediating factors. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences.* 2011;66(3):341-348.

148. Uusi-Rasi K, Rauhio A, Kannus P, et al. Three-month weight reduction does not compromise bone strength in obese premenopausal women. *Bone.* 2010;46(5):1286-1293.

149. Geliebter A, Maher MM, Gerace L, Gutin B, Heymsfield SB, Hashim SA. Effects of strength or aerobic training on body composition, resting metabolic rate, and peak oxygen consumption in obese dieting subjects. *The American journal of clinical nutrition.* 1997;66(3):557-563.

150. Beavers KM, Gordon M, Easter L, et al. Effect of protein source during weight loss on body composition, cardiometabolic risk and physical performance in abdominally obese, older adults: a pilot feeding study. *The journal of nutrition, health & aging.* 2015;19(1):87-95.

151. Pargman D, Feldschuh J. Muscle strength in obese adult females during weight loss. *The American journal of clinical nutrition.* 1967;20(7):790-794.

152. Wycherley TP, Buckley JD, Noakes M, Clifton PM, Brinkworth GD. Comparison of the effects of weight loss from a high-protein versus standard-protein energy-restricted diet on strength and aerobic capacity in overweight and obese men. *European journal of nutrition.* 2013;52(1):317-325.

153. Andersson DP, Eriksson Hogling D, Thorell A, et al. Changes in subcutaneous fat cell volume and insulin sensitivity after weight loss. *Diabetes care.* 2014;37(7):1831-1836.

154. Allison D, Zannolli R, Faith M, et al. Weight loss increases and fat loss decreases all-cause mortality rate: results from two independent cohort studies. *International journal of obesity.* 1999;23(6):603-611.

155. Schmidt FM, Weschenfelder J, Sander C, et al. Inflammatory cytokines in general and central obesity and modulating effects of physical activity. *PloS one.* 2015;10(3):e0121971.

156. Tuomisto K, Jousilahti P, Sundvall J, Pajunen P, Salomaa V. C-reactive protein, interleukin-6 and tumor necrosis factor alpha as predictors of incident coronary and cardiovascular events and total mortality. *Thrombosis and haemostasis.* 2006;96(03):511-518.

157. Zoico E, Roubenoff R. The role of cytokines in regulating protein metabolism and muscle function. *Nutrition reviews.* 2002;60(2):39-51.

158. Lafortuna CL, Proietti M, Agosti F, Sartorio A. The energy cost of cycling in young obese women. *European journal of applied physiology.* 2006;97(1):16.

159. Lafortuna CL, Agosti F, Galli R, Busti C, Lazzer S, Sartorio A. The energetic and cardiovascular response to treadmill walking and cycle ergometer exercise in obese women. *European journal of applied physiology.* 2008;103(6):707.

160. Lafortuna C, Agosti F, Busti C, Galli R, Sartorio A. The energy cost of cycling and aerobic performance of obese adolescent girls. *Journal of endocrinological investigation.* 2009;32(8):647-652.

APPENDIX A: Consent form.

INFORMATION AND CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title:

Acute and Chronic Effects of Obesity

Researcher:

Sylvia Santosa, PhD

Associate Professor

Department of Health, Kinesiology and Applied Physiology

Researcher's Contact Information:

Science Pavilion 165.21

Concordia University

7141 Sherbrooke Street West

Montreal, QC, H4B 1R6

514.848.2424 ex. 5841

s.santosa@concordia.ca

Source of funding for the study:

Canada Research Chair, Tier 2 – Clinical Nutrition, Natural Science and Engineering Research Council of Canada, and Heart and Stroke Foundation of Canada

You are being invited to participate in the research study mentioned above. This form provides information about what participating would mean. Please read it carefully before deciding if you want to participate or not. If there is anything you do not understand, or if you want more information, please ask the researcher.

A. PURPOSE

You have been invited to take part in a study on aging, fat tissue risk factors for disease, and weight loss. By participating, you will help us to better understand whether weight loss changes disease risk differently depending on the age when a person develops overweight.

B. PROCEDURES

If you participate, your involvement in the study will last about 6 months or shortly after you lose around 10 % of your starting body weight. The study includes a screening period, a pre-weight loss stabilization period ending with assessments, a weight loss period, and a post-weight loss stabilization period ending with assessments.

The description below provides a general outline of the study protocol. It is possible to schedule several assessments at a given visit. Please note that there may be times where assessments and sample collection (e.g. a blood draw) occur outside of the usual timeline for reasons such as scheduling conflicts.

Information Session, Screening, and Health Assessment

- ***Maximum of 2 visits of up to 1.5 hours each***

The screening process will determine whether you are eligible for the study, and the health assessment will provide information for designing your weight loss protocol.

- ✓ ***Information Session and Screening.*** You will meet with members of the research staff to discuss the study and have your questions answered. If you agree to enter the study you will sign the consent form and provide medical records of height and weight and/or pictures from childhood (around the age of puberty). You will also be asked to review and sign a behavioural contract agreeing to do your best to engage fully in the research project. A member of the research team will confirm your eligibility for the study by reviewing the information you provided via email or telephone, and by measuring your height and weight.

- ✓ ***Health Assessment.*** You will be interviewed and complete questionnaires about your demographic characteristics, medical history, weight history, dietary habits, and physical activity level.

Pre- and Post-Weight Loss Stabilization Periods

You will be instructed to follow your usual diet to maintain a stable weight for 2 weeks both before and after the weight loss protocol. To ensure that you are weight stable, you will be weighed at every study visit during this time period. You will also record your food intake for 3 days (2 weekdays and 1 weekend day).

Weight Loss Protocol

◆2-4 visits a week for approximately 5 months

During this period you will follow a protocol to help you lose weight by diet and exercise. You will be instructed on how to decrease the amount of calories you eat in your diet by 20 % and increase the number of calories you burn by 10 % through moderate intensity exercise. You will be required to keep a record of your daily diet periodically throughout the study. All exercise will be performed on cardio equipment at the study site at a self-selected frequency (2-4 visits) that will meet your weekly target. In addition, your weight will be measured and your weight loss progress will be monitored on a weekly basis. Optional educational and support group sessions

will be offered occasionally. *You will follow the weight loss protocol until you lose around 10 % of your starting body weight, which is estimated to take approximately 5 months.*

Assessments

◆***Approximately 2-3 fasted visits and 2 non-fasted visits per time point***

You will have assessments at the following 3 time points:

(1) Towards the end/after pre-weight loss stabilization period

(2) 12-weeks after starting weight loss protocol

(3) Towards the end/after post-weight loss stabilization period

The following assessments will be conducted at time points (1), (2) and (3):

Non-fasted Assessments. These assessments can occur at any time of day.

- ✓ ***Fitness Assessment.*** The fitness assessment will involve 3 tests.

    - You will undergo a submaximal fitness test on a bike. You will pedal on a stationary bike for approximately 15 minutes. Throughout this time, the resistance will be gradually increased, and your heart rate and blood pressure will be periodically assessed.

    - You will perform a shuttle run/walk test. You will run/walk back and forth between two lines in time with an audio 'beep'. The period of time required to reach the line will get progressively shorter. The test will end when you can no longer continue or when you do not reach the line before the 'beep' on 2 consecutive occasions. The test takes approximately 10 minutes.

- You will perform a handgrip strength test. You will squeeze your fist for around 5 seconds around a device that measures your strength. The test will be conducted 2 times per hand with at least 30 seconds rest between each test. The total time for the test is around 10 minutes.

Fasted Assessments. These assessments must occur in the morning after an overnight fast of at least 8 hours. Water is allowed.

- ✓ ***Body Composition Assessment by Dual Energy X-ray Absorptiometry (DEXA).*** For the DEXA scan you will be positioned on the table and be asked to lie still as the DEXA arm passes over you. Total scan time is usually about 15 minutes.

- ✓ ***Circumference Measurements.*** The circumferences of different parts of your body (e.g. waist, hip, chest, arm, thigh) will be measured with a measuring tape. This process takes approximately 15 minutes.

- ✓ ***Energy Expenditure Assessment by Indirect Calorimetry.*** You will rest comfortably for 90 minutes before the test. You will breathe normally under a clear, plastic canopy for around 30 minutes while lying down. This will allow us to measure the rate at which your body burns calories (your energy expenditure). Information from this assessment will help us determine how many calories you need to maintain weight or to lose weight at a certain rate. Your blood pressure and heart rate will be measured after the test.

- ✓ ***Blood Draw.*** *A sample of* your blood will be drawn. This procedure takes approximately 15 minutes.

The following assessments will be conducted at time points (1) and (3) only:

Non-fasted Assessments. These assessments can occur at any time of day.

- ✓ ***Questionnaires.*** You will be asked to complete questionnaires about your health, eating behaviour, and quality of life. The questionnaires take approximately 30 minutes to complete.

- ✓ ***Arterial Measurement.*** You will be asked to not consume caffeine or alcohol for at least 12 hours prior to this visit. On the day of this visit, exercise or strenuous physical activity should be avoided before the assessment. The hardening of your arteries will be measured while you are resting using a pen-like pressure sensor that will be placed on your skin on top of your pulse at three sites (wrist, neck, and crease of the leg). The procedure takes approximately 30 minutes.

Fasted Assessments. These assessments must occur in the morning after an overnight fast of at least 8 hours. Water is allowed.

- ✓ ***Body Composition Assessment by Computed Tomography (CT).*** If you are female, a urine pregnancy test will be conducted prior to this test to ensure you are not pregnant. During this test, you will lie on a table that will be passed through a large, open circular tube. The CT machine will take pictures of your abdomen. The scan takes approximately 5-10 minutes to complete.

- ✓ ***Biopsies.*** This procedure takes approximately 90 minutes. You will also be asked to not consume caffeine or alcohol for at least 24 hours prior to this visit. Exercise or strenuous physical activity should also be avoided for at least 24 hours before the procedure. You will provide a small urine sample prior to the procedure.

    - ***Fat.*** A sample will be taken from the fat in your stomach and thigh region. The procedure will be performed by a physician. The physician will first clean your skin

to remove any germs, numb your skin by injecting a local anesthesia (to freeze the area) with a thin needle, and injecting fluid (water and salt solution) similar to the composition of your body just below your skin. The physician then makes a small nick incision and suctions out the fluid that was injected using a small hollow tube attached to a syringe. As the fluid is removed, a small amount of fat tissue just below the skin will be removed as well. The procedure will not require stitches, as the incisions are small; the physician will simply place sterile tape to close the incision. After the biopsies are done, post-biopsy care will be explained and you will be provided with written instructions.

- ***Muscle.*** A sample will be taken from the muscle on the outside side of your thigh. The procedure will be performed by a physician. The physician will first clean your skin to remove any germs, numb your skin by injecting a local anesthesia (to freeze the area) with a thin needle, and make a small incision. A needle (hollow tube) will be inserted to remove a small piece of muscle. The procedure will not require stitches, as the incisions are small; the physician will simply place sterile tape to close the incision. Firm pressure will be applied to the area for 10 minutes to prevent bruising. After the biopsy is done, post-biopsy care will be explained and you will be provided with written instructions.

A typical timeline of study visits and assessments is shown in the table below:

Study Visit Timeline														
Time Point	**(1)** Screening/Pre-Weight Loss Stabilization Period						**(2)** 12-weeks into Weight Loss Protocol			**(3)** Post-Weight Loss Stabilization Period				
Visit #										***0***	***1***	***2***	***3***	***4***
Procedures														
Screening														
Health Interview														
Questionnaires														
Bike Fitness Test														
Shuttle Test														
Handgrip Strength Test														
Energy Expenditure														
DEXA Scan														
Circumferences														
CT Scan														
Arterial Measurement														
Blood Draw														
Biopsies														
Exercise/Diet Overview														

*Your weight will be measured at every visit and weekly throughout the weight loss protocol

*You will complete cardio exercise sessions 2-3 times per week throughout the weight loss protocol

C. RISKS AND BENEFITS

You might face certain risks by participating in this research. These risks include:

◆***Blood Draws.*** There is a risk of discomfort, pain, fainting, bruising or infection (rare) from the blood draw. The amount of blood drawn at each time point will vary. Total blood drawn throughout the study will not exceed 2 cups (~500 mL). It is recommended that you avoid taking aspirin 3 days before and after the blood draws, and that you don't donate blood for up to 8 weeks following your participation in the study.

◆***Fat and Muscle Biopsies.*** The most common risks of fat and muscle biopsies include pain, a small dent or bump and bruising at the site where the sample was taken. The bruising may last one to two weeks. Less common risks of biopsies include bleeding, infection, a small scar, and numbness of the skin around the biopsy site. The chance of these risks is less than 1% (1 in 100). There is also a chance of an allergic reaction to the lidocaine used for local anaesthesia. Care will be taken to reduce the chances of these risks. Aspirin should be avoided 3 days before and after the biopsies. It is not advised to participate in any vigorous activities for 3 days before and after the biopsies. Exposure to water for prolonged periods should be avoided (e.g bathtubs, hot tubs or swimming) for 5 days after the biopsies. Showering is permitted; however, band-aids must be changed afterwards. Normal daily activities will not be affected.

◆***Indirect Calorimetry***. There is a slight risk of discomfort and hyperventilation from claustrophobia when under the clear, plastic hood. Staff will be present and the hood is easily removable.

◆***DEXA and CT Scans.*** You will be exposed to some radiation with the DEXA and CT scan. The amount of radiation used is considered too low to cause any harmful side effects. Radiation exposure from the DEXA scan is similar to the amount you would receive from sun exposure on a sunny day ($1/10^{th}$ that of a chest x-ray). The amount of radiation you are exposed to from the CT scan is less than your exposure from one return transatlantic plane flight (about 2-3 chest x-rays). The radiation does not remain in the body after the scan. Should you have any concerns, the research team will be happy to address them with you.

◆***Fitness Tests and Exercise.*** You may experience some discomfort from physical exertion during the fitness test and the exercise component of the weight loss protocol.

Your assessments will be supervised by experienced research staff who will make every effort to keep you comfortable during the study.

Although the assessments conducted as part of this protocol are not expected to provide you with any direct benefits, the results will tell you more about your health and metabolism and you may see positive changes in your health during weight loss.

D. CONFIDENTIALITY

We will gather the following information as part of this research: demographic information, contact information, and the results of all study procedures described above.

We will not allow anyone to access the information, except people directly involved in conducting the research, and except as described in this form. We will only use the information for the purposes of the research described in this form.

The information gathered will be coded. That means that the information will be identified by a code. The researcher will have a list that links the code to your name.

All of your paper-based information will be kept in a filing cabinet in a secure and private research office. All of your electronic information will be stored on a password-protected research computer. The urine, blood, fat and muscle samples will be coded and safely stored at Concordia University. Any samples or data the are sent to external collaborators is coded.

We intend to publish the results of the research. However, it will not be possible to identify you in the published results.

E. BIOLOGICAL SAMPLES

You will be asked to provide the following biological samples as part of the research: urine, blood, fat and muscle.

Taking these specimens involves urinating into a plastic container, blood draws, and fat and muscle biopsies as described in the procedures section above.

We will use your urine sample to assess your overall health with a standard urinalysis, and to do a pregnancy test for female participants. We will use your blood samples to measure things like sugar, cholesterol and inflammatory markers. We will use the biopsy samples to assess the health of your fat and muscle. This includes things like the size of your fat cells, the amount and type of inflammatory markers in your fat, and how well your muscle uses energy.

We will keep the specimens for up to 25 years after the end of the study. After that, they will be destroyed.

If we find anything that might be relevant to your health, we will contact you and direct you to the appropriate service.

F. CONDITIONS OF PARTICIPATION

You do not have to participate in this research. It is purely your decision. If you do participate, you can stop at any time. You can also ask that the information you provided not be used, and your choice will be respected. If you decide that you don't want us to use your information, you must tell the researcher before withdrawing from the study. In addition, the research team may withdraw you from the study if you are not compliant.

As a compensatory indemnity for participating in this research, you will receive $500. If you withdraw before the end of the research, you will receive an amount proportional to your

progress in the study and the assessments you completed, as assessed by the research team. To make sure that research money is being spent properly, auditors from Concordia or outside will have access to a coded list of participants. It will not be possible to identify you from this list.

We will tell you if we learn of anything that could affect your decision to stay in the research.

There are no negative consequences for not participating, stopping in the middle, or asking us not to use your information.

We will not be able to offer you compensation if you are injured in this research. However, you are not waiving any legal right to compensation by signing this form.

G. PARTICIPANT'S DECLARATION

I have read and understood this form. I have had the chance to ask questions and any questions have been answered. I agree to participate in this research under the conditions described.

NAME (please print)

_____

SIGNATURE

_____

DATE

_____

If you have questions about the scientific or scholarly aspects of this research, please contact the researcher. Their contact information is on page 1.

If you have concerns about ethical issues in this research, please contact the Manager, Research Ethics, Concordia University, 514.848.2424 ex. 7481 or oor.ethics@concordia.ca.

H. FUTURE RESEARCH PROJECTS?

Do you agree that your research data may be used to carry out other research projects?

These research projects will be evaluated and approved by the Research Ethics Board at Concordia University prior to their realization. Please note that your research data will be kept securely by the researcher responsible for this research project. In order to preserve your identity and the confidentiality of your research data, you will only be identified by a unique numerical code. The code key will be kept by the researcher responsible for this research project.

Your research data may be published or be part of scientific discussions, but it will not be possible to identify you.

Your research data will be retained for as long as it can be useful for the advancement of scientific knowledge. When it is no longer needed, your research data will be destroyed. Please note that at any time you may request that your research data not be used by contacting the researcher responsible for this research project or the ombudsman office at Concordia University.

The Research Ethics Board of Concordia University will monitor and control the data that is collected. In addition, for monitoring, control, protection, and security purposes, your research data may be accessed by a person appointed by regulatory bodies, as well as representatives of the granting agency, Concordia University or the Research Ethics Board of Concordia University. These individuals and organizations adhere to a privacy policy.

Do you agree that your research data will be used under these conditions?

□ Yes □ No

Do you agree that the principal investigator of this research project or a member of his research staff may contact you again to suggest that you participate in other research projects? Of course, during this call, you will be free to agree or refuse to participate in the research projects suggested.

□ Yes □ No

APPENDIX B: Par-Q Questionnaire

Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO		
☐	☐	1.	**Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	2.	**Do you feel pain in your chest when you do physical activity?**
☐	☐	3.	**In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	4.	**Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	5.	**Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	6.	**Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	7.	**Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

Supported by: Health Canada Santé Canada

continued on other side...

APPENDIX C: Body Rating Scales

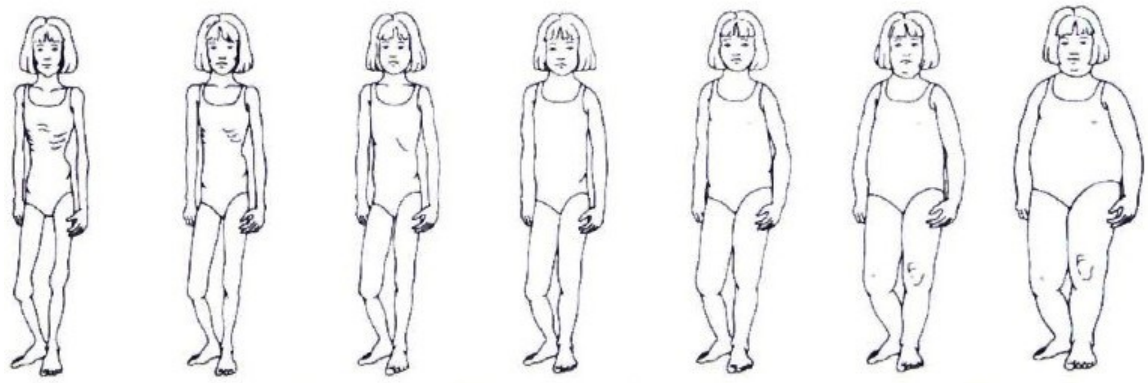
Body Rating Chart

Participants will be asked to report how their body status was at 5 years old, 10 years old, puberty, and 20 years old by comparing the figure drawings in the age- and sex-specific body rating scales below.

	Figure number								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Age 5	☐	☐	☐	☐	☐	☐	☐		
Age 10	☐	☐	☐	☐	☐	☐	☐		
Puberty (Age ____)	☐	☐	☐	☐	☐	☐	☐		
Age 20	☐	☐	☐	☐	☐	☐	☐	☐	☐
Currently (Age ____)	☐	☐	☐	☐	☐	☐	☐	☐	☐

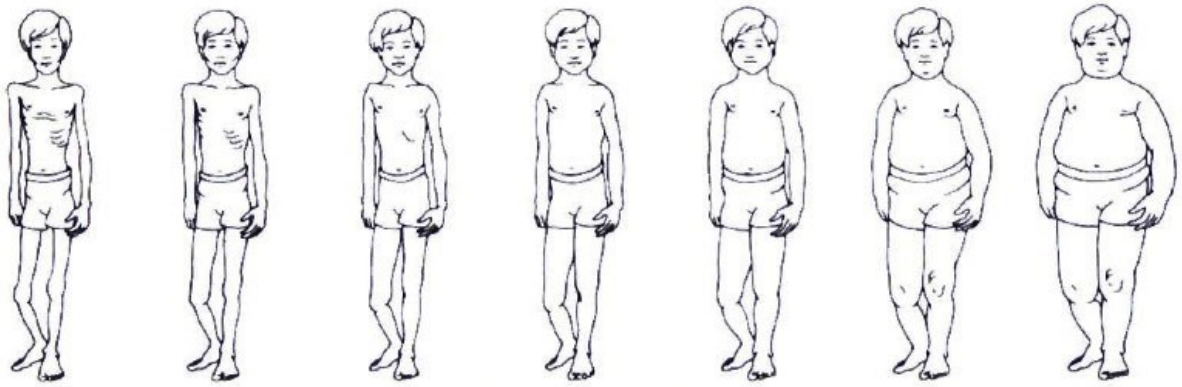
Childhood Body Rating Scale: Collins' Figure Drawings

Girls



1 2 3 4 5 6 7

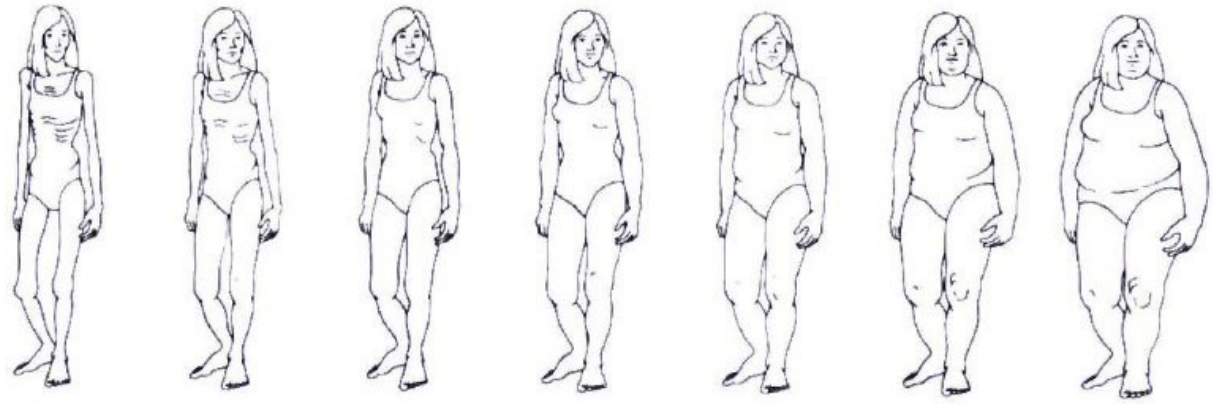
Boys



1 2 3 4 5 6 7

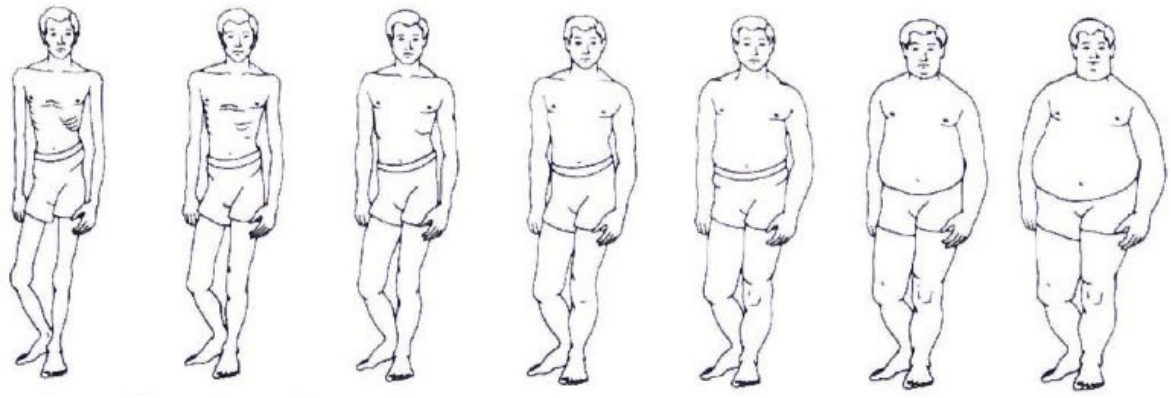
Adolescent Body Rating Scale: Collins' Figure Drawings

Girls



1 2 3 4 5 6 7

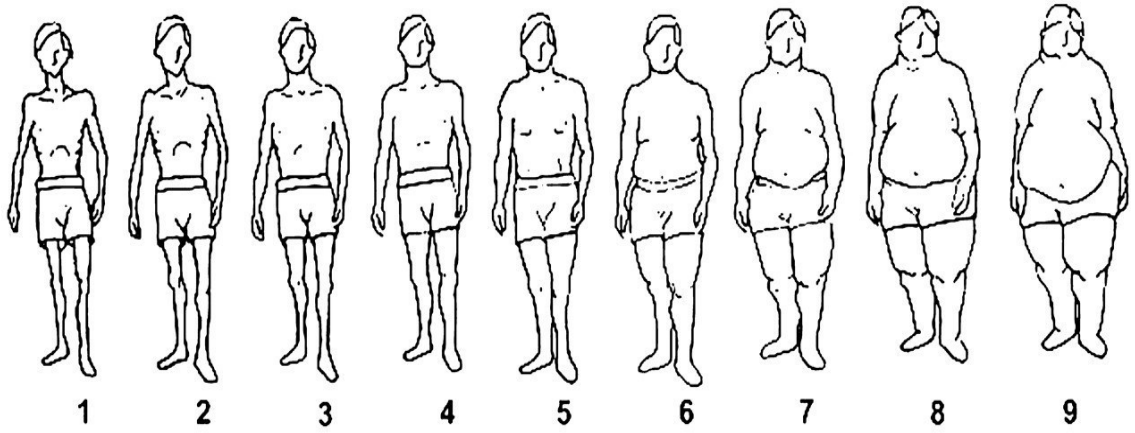
Boys



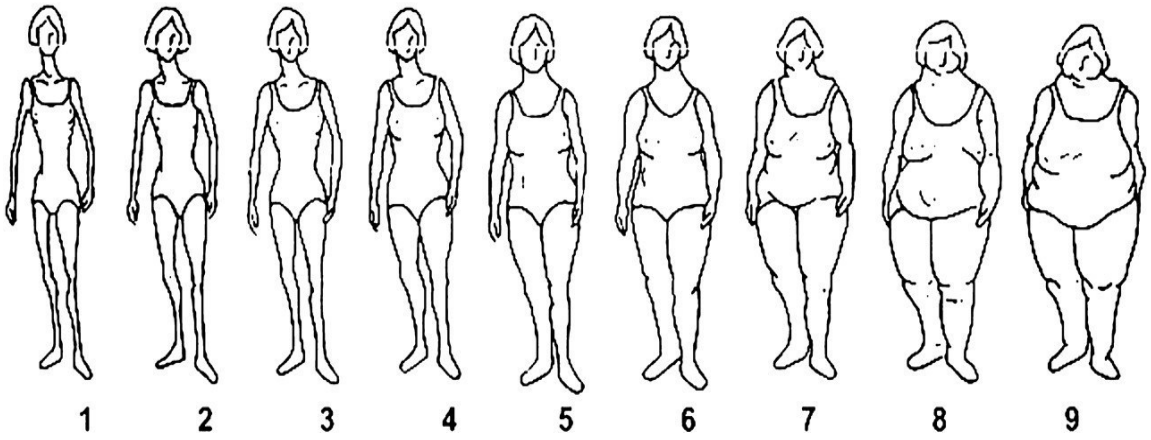
1 2 3 4 5 6 7

Adulthood Body Rating Scale: Stunkard Body Rating Scale

Men



Women

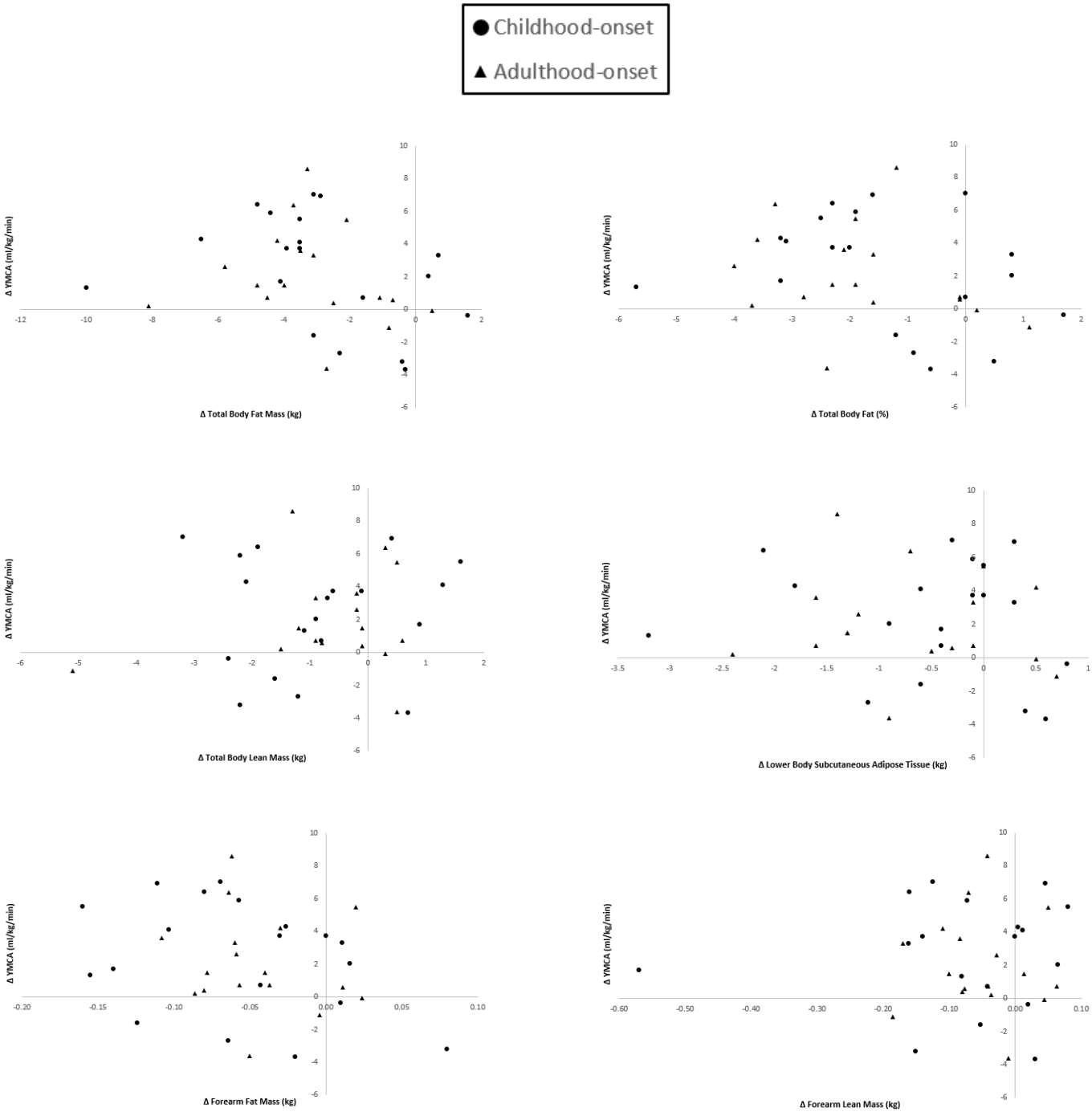


APPENDIX D: Aerobic Training Prescription and Progression

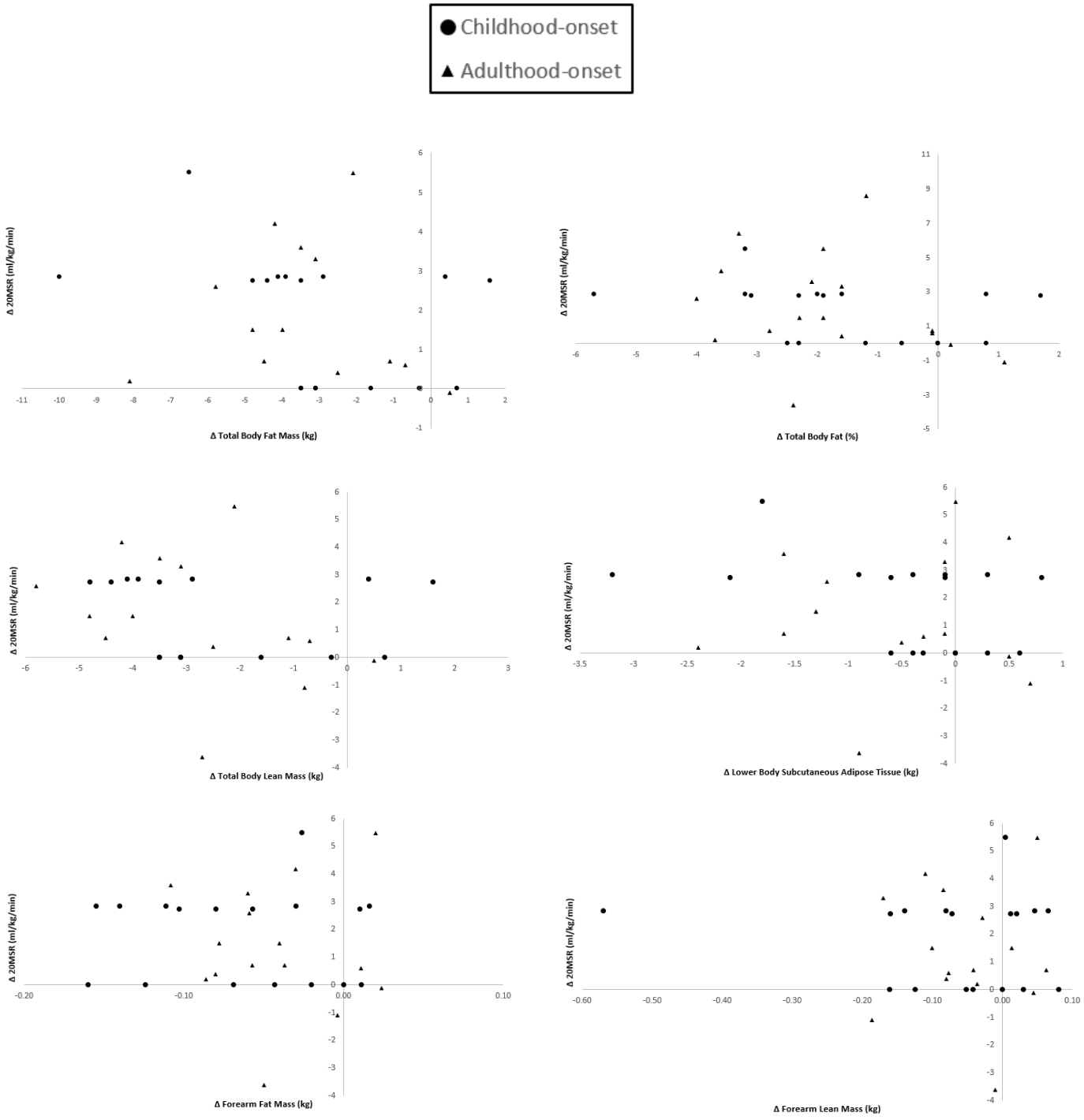
STAGE	WEEKS	FREQUENCY (Sessions/week	INTENSITY (% HRR)	DURATION (Minutes/Session)
Start-up	1	3	40-50	10-15
	2	3-4	40-50	15-20
	3	3-4	50-60	15-20
	4	3-4	50-60	20-25
Improvement	5-7	3-4	60-70	20-25
	8-10	3-4	60-70	25-30
	11-13	3-4	65-75	25-30
	14-16	3-5	65-75	30-35
	17-20	3-5	70-85	30-35
	21-24	3-5	70-85	35-40
Maintenance	>24	3-5	70-85	30-60

Table adapted from ACMS's Guidelines for Exercise Testing and Prescription (2000)

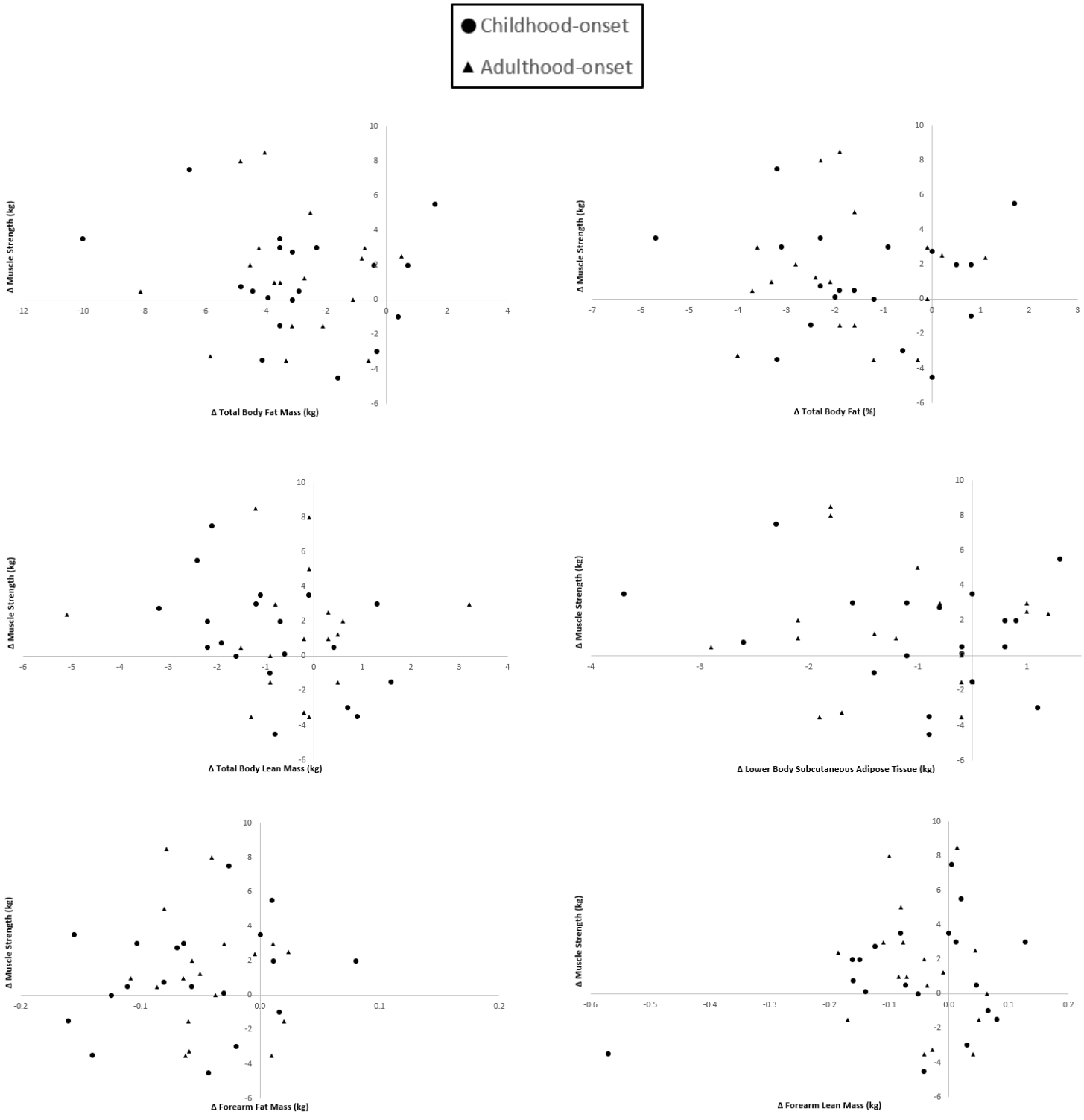
APPENDIX E: **Scatterplots of the relationship between changes from baseline to 12-weeks in the YMCA test and body composition by onset of obesity.**



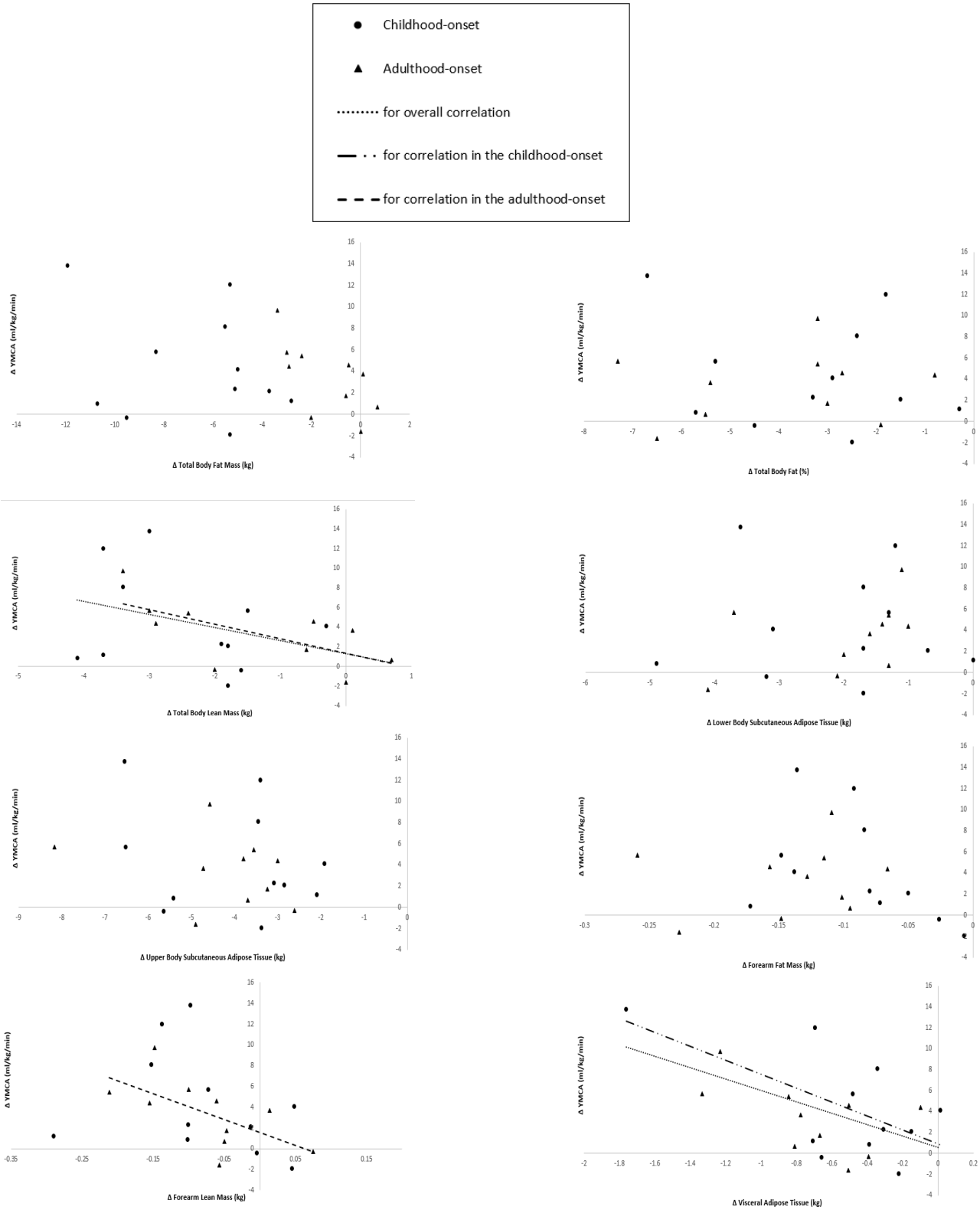
APPENDIX F: Scatterplots of the relationship between changes from baseline to 12-weeks in 20MSR and body composition by onset of obesity.



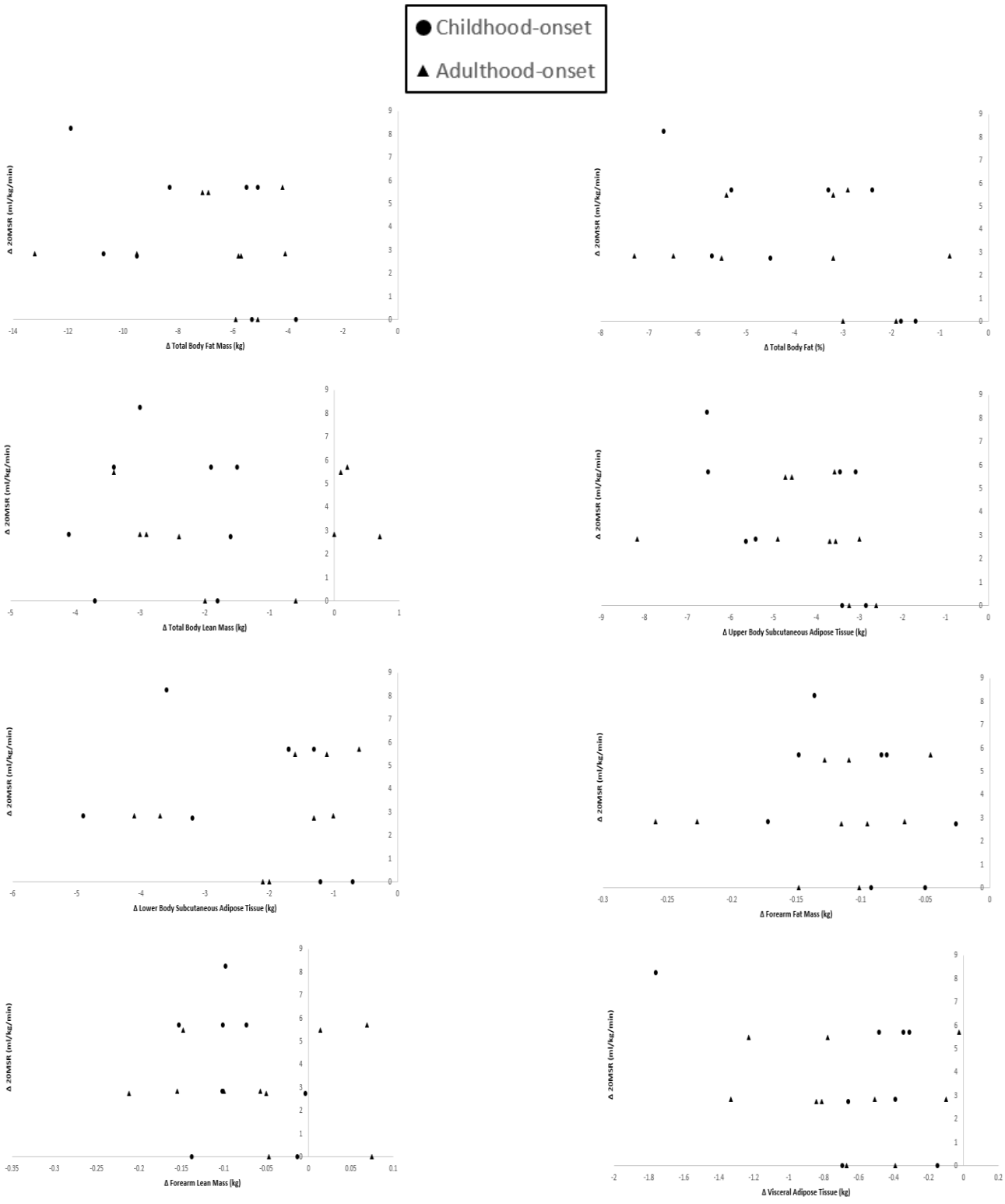
APPENDIX G: Scatterplots of the relationship between changes from baseline to 12-weeks in muscle strength and body composition by onset of obesity.



APPENDIX H: Scatterplots of the relationship between changes from baseline to follow-up in the YMCA test and body composition by onset of obesity.



APPENDIX L: Scatterplots of the relationship between changes from baseline to follow-up in 20MSR and body composition by onset of obesity.



APPENDIX M: Scatterplots of the relationship between changes from baseline to follow-up in muscle strength and body composition by onset of obesity.