EFFECTS OF LIFESTYLE-BASED INTERVENTIONS ON OBESITY AND RELATED METABOLIC RISK FACTORS WITH MINIMAL OR NO WEIGHT CHANGE

by

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Abstract

Background: Recent evidence suggests weight loss is not necessary to reduce obesity related co-morbidities. The principal finding within these reports is based on examination of group mean values. Accordingly, it is possible that within a given group, the subjects who failed to lose weight did not experience any health improvement, a finding masked by the exaggerated improvement in those who did lose weight. We sought to determine whether a gradient exists between the inter-individual change in bodyweight and corresponding changes in body composition and metabolic risk factors in response to minimal or no weight loss.

Methods: Total adipose tissue (AT) and skeletal muscle (SM) were determined by magnetic resonance imaging (MRI) in 46 men and 42 women participating in lifestyle-based programs designed to reduce obesity and related metabolic risk factors. Visceral AT (VAT) and abdominal subcutaneous AT (ASAT) were calculated from a single image at the L4-L5 inter-vertebral space. Glucose uptake was calculated using a hyperinsulinemic-euglycemic clamp procedure. Blood pressure (BP) was determined using an electronic cuff or manually using standard procedures. Waist circumference (WC) was taken at the level of the last rib.

Results: Bodyweight did not change in men or women ($p>0.10$). Collapsed across gender, with the exception of ASAT, SM, and systolic BP, all other anthropometric, body composition, and metabolic risk factor measures improved significantly following treatment ($p<0.05$). With few exceptions, regression analysis revealed that changes in bodyweight or WC were not associated with corresponding changes in body composition

measures or metabolic risk factors ($p>0.05$). To further consider whether a gradient existed between weight change or WC change on body composition and metabolic risk factors, subjects were cross-classified according to their level of weight/waist change (tertiles) and their respective change in either body composition or metabolic risk factor. Neither weight nor WC change tertile was related to any body composition or metabolic risk factor in a gradient fashion ($p>0.05$).

Conclusion: These findings reinforce and extend the observation that independent of gender, lifestyle-based interventions are associated with reductions in obesity and related metabolic risk factors despite minimal or no weight loss.

Co-Authorship

Andrew S. Palombella was solely responsible for the statistical analysis of all anthropometric, body composition, and metabolic risk measures, interpretation of the findings and preparation of the manuscript and thesis. Critical revisions were provided by Dr. Robert Ross.

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List of Abbreviations

ABAT	Abdominal adipose tissue
ASAT	Abdominal subcutaneous adipose tissue
AT	Adipose tissue
BMI	Body mass index
BP	Blood pressure
CRF	Cardiorespiratory fitness
CT	Computed tomography
CVD	Cardiovascular disease
FFA	Free-fatty acid
GLUT4	Insulin-regulated glucose transporter 4
HDL-C	High-density lipoprotein cholesterol
HOMA	Homeostatic model assessment
IL	Interleukins
MRI	Magnetic resonance imaging
MSL	Multiple symmetric lipomatosis
PAI-1	Plasminogen activator inhibitor 1
QUICKI	Quantitative insulin sensitivity check index
SAD	Sagittal abdominal diameter
SAT	Subcutaneous adipose tissue
SM	Skeletal muscle
TNF-α	Tumour necrosis factor alpha
T2D	Type 2 diabetes
VAT	Visceral adipose tissue
WC	Waist circumference

Chapter 1

Introduction

With more than 300, 000 deaths per year attributable to obesity in the United States[1], second only behind smoking as the main preventable cause of illness and premature death[2], the World Health Organization describes obesity as one of the most blatantly visible, yet most neglected public health problems[3]. Although increasing levels of overweight and obesity are associated with increased morbidity[4] and mortality[5] risk, it is now evident that the distribution of excess fat is the main predictor of health risk[6, 7]. Specifically, the excess accumulation of visceral adipose tissue (VAT) is strongly and independently associated with morbidity[8] and mortality[9].

Current health guidelines state that a clinically significant weight loss of 5 to 10% of bodyweight is necessary to reduce obesity-related morbidity and mortality[4, 10-12]. Accordingly, leading health authorities recommend multiple interventions and strategies, including dietary therapy, physical activity, behaviour therapy, pharmacotherapy, and surgery, as well as combinations of these strategies, to optimally reduce bodyweight[4, 13]. Increasing evidence suggests that clinically significant weight loss (>5%) is not necessary to reduce obesity related morbidities and mortality[14]. In fact, many individuals have shown reductions in abdominal obesity and metabolic risk, with improvements in cardiorespiratory fitness (CRF) in the absence of weight loss.

The following review will consider current knowledge regarding total, abdominal, and visceral obesity with regards to their respective associations with health risk. Insulin

resistance, along with methods of measurement, potential causes, and proven treatments will be examined. Finally, concepts related to lifestyle-induced changes in body composition and weight change, along with the association between weight loss and health benefit will also be considered.

Chapter 2

Review of Literature

2.1 Characterizing Obesity and Associated Health Risk

2.1.1 Total Obesity and Associated Health Risk

Overweight and obesity as measured by body mass index (BMI), defined as weight (kg) divided by height (m^2), has reached epidemic proportions in Canada. In fact, more than one in two Canadians are now overweight and 23% are considered obese[13], which translates into increased medical care and disability costs[15, 16]. Although there are a number of methods to assess obesity, the simple index of height and weight (BMI) developed by Quetelet was shown to predict total adiposity with an acceptable degree of accuracy[17]. Today, BMI remains the most common, indirect measurement of obesity related health risk in large population studies and in clinical settings. Evidence-based guidelines have been developed to define overweight and obese using BMI cutpoints[4]. These guidelines state that individuals with a BMI between 25 to 29.9 kg/m^2 are considered overweight, while those with a BMI $\geq$30 kg/m^2 are considered obese. BMI is also positively correlated with morbidity and mortality (Table 1), and that the relative risk for cardiovascular disease (CVD) risk factors increases in a graded fashion with increasing BMI in all population groups[4, 5].

It is well established that morbidity for a number of health conditions increases as bodyweight increases. Numerous studies have reported that overweight and obesity are

Table 1. Associations between BMI and health risks.

	Health Risks					
Reference	**Hypertension**	**T2D**	**CVD**	**Respiratory Problems**	**Cancer**	**Mortality**
Stamler (1978)[18]	RR = 2.0					
Colditz (1990)[19]		RR = 3.6				
Davies (1990)[30]				r = 0.54		
Chu (1991)[32]					RR = 3.0	
Chan (1994)[21]		RR = 42.1				
Willett (1995)[23]			RR = 3.56			
Walker (1996)[24]			RR = 1.29			
Ford (1997)[22]		HR = 11.24				
Huang (1997)[33]					RR = 1.24	
Rexrode (1997)[25]			HR = 3.1			
Calle (1999)[5]						RR = 2.58
Brown (2000)[26]			OR = 5.9			

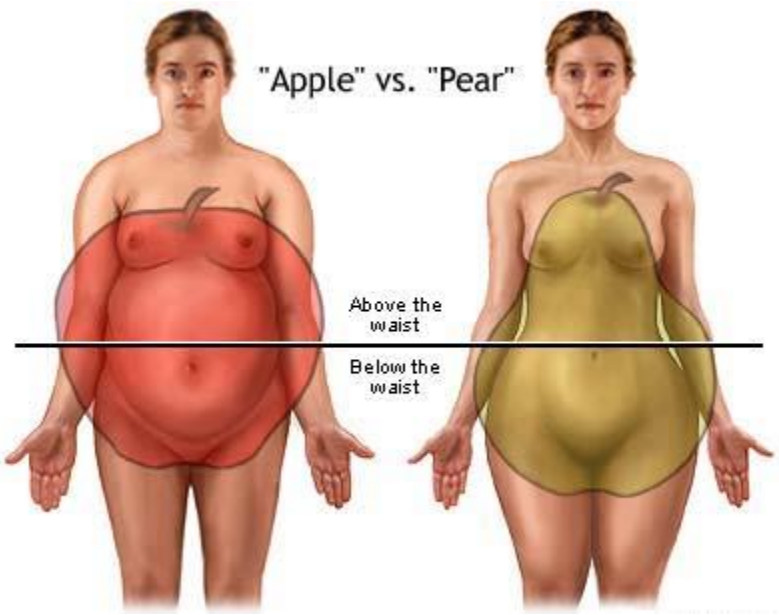
Abbreviations: CVD, cardiovascular disease; T2D, type 2 diabetes; RR, relative risk, r, correlation coefficient; HR, hazard ratio; OR, odds ratio.

associated with risk of hypertension[18, 19], type 2 diabetes (T2D)[20-22], CVD[23-26], osteoarthritis[27-29], respiratory problems[30, 31], cancer[32, 33], and mortality[4, 5]. Overweight and obesity are also associated with complications during pregnancy[34, 35], menstrual irregularities[36, 37], and psychological disorders[4]. Although the degree of obesity-related health risk is similar across all populations, the specific level of risk varies with ethnicity, age, and gender[4].

2.1.2 Abdominal Obesity and Associated Health Risk

Jean Vague's work in the 1950s was the first to identify that the location of body fat, not just the absolute amount, was an important indicator of obesity-related health risk[38]. Vague characterized two unique obesity phenotypes: gynoid obesity (pear-shaped), represented by body fat accumulation predominately in the buttocks, hips, and thighs, and android obesity (apple-shaped), represented by body fat accumulation in the abdomen (Figure 1)[38]. Although gynoid obesity was found to be a rather benign condition, android obesity was fairly malignant and associated with premature diabetes, atherosclerosis, gout, and uric calculous disease. Furthermore, Kissebah et al.[6] and Krotkiewski et al.[7] showed that for a given degree of adiposity, the distribution of fat played an important role in the development of the metabolic anomalies. They noted that abdominal obesity, rather than gynoid obesity, was a stronger correlate of fasting insulin, blood glucose and triglyceride levels, blood pressure (BP), and glucose tolerance[6, 7]. More recent studies also support the notion that the abdominal obesity phenotype, rather than total obesity, is the best predictor of health risk[39-41]. Although many have suggested

Figure 1. Android and gynoid obesity and associated health risk.



Fat accumulation in the abdomen
Greatest Health Risk
Associated with diabetes, atherosclerosis, & gout
Strongly predicts cardiovascular disease & death independent of age and BMI

Fat accumulation in the buttocks, hips, & thighs
Lower health risk
Benign condition

that the combined measurement of abdominal obesity and total obesity provides that best assessment of health risk[42-44], some believe that abdominal obesity alone sufficiently explains obesity related health risk[40]. Undeniably, the importance of abdominal obesity as a predictor of health risk is illustrated by its inclusion in the diagnostic criteria for the metabolic syndrome[45, 46].

The majority of recent studies utilize WC alone as the index of abdominal obesity. WC has been chosen as the abdominal measurement of choice due to its close association with VAT amount[47] and cardiovascular risk[48]. WC is the most practical and readily available anthropometric measurement for assessing a patient's abdominal fat content. Based on this evidence, the National Institutes of Health published sex-specific WC cut-points to define abdominal obesity[4]. Consequently, it was reported that independent of BMI, those with abdominal obesity (WC >102 and 88 cm in men and women, respectively) exhibited greater risk of hypertension, T2D, and dyslipidemia, than those individuals with normal WC values[49].

2.1.3 VAT and Health Risk

There are two distinct fat depots within the abdomen that may explain the association between WC and health risk: VAT and abdominal subcutaneous adipose tissue (ASAT). VAT is composed mainly of omental, mesenteric, and the retroperitoneal fat masses surrounding the organs and providing protective padding and a reserve of lipids[50]. As the name suggests, ASAT lies beneath the dermis of the skin and above the underlying fascia, and acts to insulate the body, absorb trauma, and is an energy source[51].

The quantification and analysis of these depots became possible with the use of imaging techniques such as computed tomography (CT) and MRI. Sparrow et al.[52] were the first to note an association between VAT and health risk as assessed by CT. Since that time, some report ASAT to be an independent predictor of health[53, 54], while the majority of literature indicates that VAT is a strong predictor of dyslipidemia[8, 55], blood glucose and plasma insulin levels[55-57], insulin sensitivity[8, 55, 58-60, 142], systemic inflammation[61], hypertension[62], CVD[63], T2D[64], and mortality[9], independent of ASAT (Table 2). The health risks associated with VAT are illustrated in Japanese sumo wrestlers and individuals with multiple symmetric lipomatosis (MSL), both of whom exhibit normal metabolic profiles, despite having large subcutaneous AT (SAT) depots[65, 66]. In addition, both sumo wrestlers and individuals with MSL have very little accumulation of VAT[65, 66]. Once sumo wrestlers retire, however, they accumulate large amounts of VAT, have decreased insulin sensitivity, and show an increased incidence of T2D and CVD[65]. Additionally, surgical intervention studies show that selective removal of VAT leads to significant improvements in metabolic profile, while SAT liposuction does not provide a similar benefit[67]. Finally, lifestyle intervention studies indicate that the reduction in VAT is associated with improvements in metabolic profile, independent of ASAT[68-71].

Although it is now well established that elevated VAT is deleterious to health, there is no consensus on the critical level of VAT above which metabolic disturbances are likely to be found. In both men and women, Després and Lamarche[72] found that a

Table 2. Associations between VAT and health risks independent of ASAT.

	Health Risks					
Reference	**Glucose/Insulin Dynamics**	**Inflammation**	**Hypertension**	**CVD**	**T2D**	**Mortality**
Lemieux (1996)[56]	r = 0.61					
Banerji (1997)[58]	r = -0.53					
Banerji (1999)[59]	r = -0.59					
Fujimoto (1999)[63]				OR = 1.57		
Boyko (2000)[64]					OR = 3.0	
Forouhi (2001)[61]		B = 0.95				
Rendell (2001)[57]	r = -0.49					
Janssen (2002)[142]	r = -0.44					
Ross (2002)[60]	r = -0.40					
Hayashi (2004)[62]			OR = 3.50			
Kuk (2006)[9]						OR = 1.83

Abbreviations: CVD, cardiovascular disease; T2D, type 2 diabetes; RR, relative risk, r, correlation coefficient; OR, odds ratio; β, standardized coefficient.

cross-sectional area of VAT at L4-L5 inter-vertebral space beyond 100cm^2 was associated with moderate disturbances in metabolic profile, whereas VAT areas >130cm^2 were associated with further deterioration and CVD. Although VAT amount is linked with serious health risk, the mechanisms describing this association are not fully understood.

2.2 The Link between VAT and Health Risk: Potential Mechanisms

2.2.1 Metabolically Driven Mechanism

VAT is metabolically different and more active than SAT, which may explain the potential link between VAT and health risk[73]. The lipolytic effect of catecholamines is weaker and the anti-lipolytic effect of insulin is more pronounced in SAT, as compared to VAT. VAT also has a greater number of β-adrenergic receptors[74]. The overall effect of these differences encourages a higher lipid turnover and exaggerated release of free-fatty acids (FFAs) from VAT. The elevated levels of FFAs in the circulation may lead to disordered hepatic metabolism, deposition of fat in the liver and skeletal muscle (SM), and resultant insulin resistance and associated metabolic disturbance[75].

2.2.2 The Portal Hypothesis

The vascular anatomy of VAT may be the key predisposing factor to complications of abdominal obesity[73]. Since VAT is drained by the portal venous system, it has a direct connection with the liver. An expanded VAT depot secretes many products, particularly FFAs, which are drained into the portal venous system, where the liver becomes exposed[76]. Chronic exposure of the liver to an elevated FFA flux can have

undesirable effects on the liver, including stimulation of gluconeogenesis, increased triglyceride synthesis, and inhibition of insulin breakdown[77]. As a result hyperglycemia, hyperlipidemia, and hyperinsulinemia develop[73]; all of which are known markers of health risk.

2.2.3 Adipocytokines

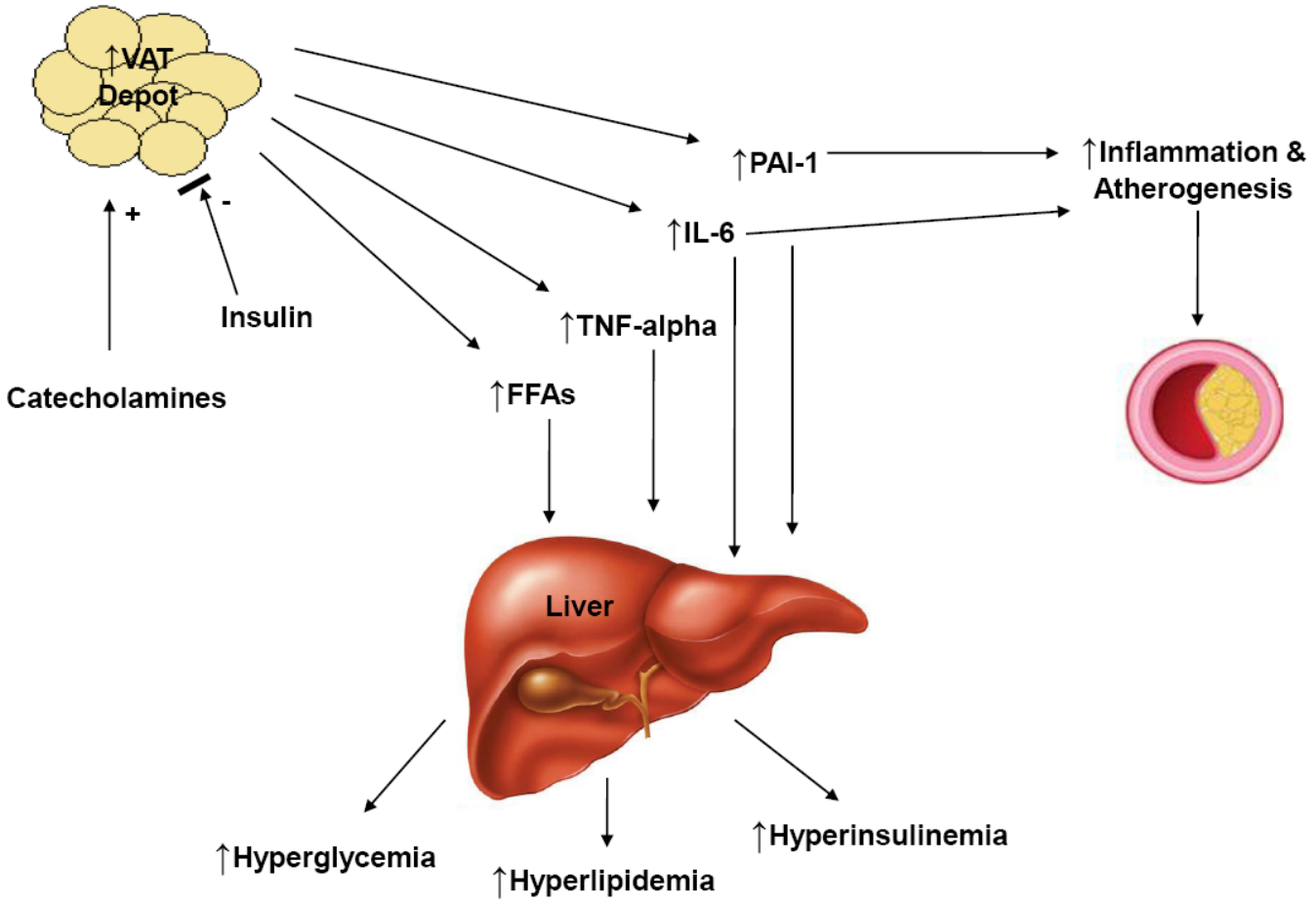
Adipocytes are not merely fat-storing cells, but they also act as an endocrine organ secreting a variety of hormones, cytokines, growth factors, and other bioactive substrates, known as adipocytokines[78]. VAT has been shown to produce significantly larger amounts of pro-inflammatory adipokines than SAT[79], including adiponectin, leptin, plasminogen activator inhibitor 1 (PAI-1), interleukins (IL), and tumour necrosis factor alpha (TNF-α). While high levels of circulating PAI-1, IL, and TNF-α impair insulin signaling in hepatocytes[80-82], PAI-1 and IL-6, in particular, also promote systemic inflammation and atherogenesis[80, 81]. The elevated secretion of these adipokines from VAT may explain the health risk associated with excess VAT (Figure 2).

2.3 Insulin Resistance

2.3.1 Insulin Resistance and Associated Health Risk

Insulin resistance is a clinical condition associated with a reduced response from adipose, skeletal muscle, and liver cells in response to a given insulin concentration[83, 84]. The pancreatic beta (β) cells attempt to secrete the amount of insulin necessary to maintain normal glucose concentrations. The more resistant an individual is

Figure 2. The link between VAT and health risk: Potential mechanisms.



Abbreviations: VAT, visceral adipose tissue; FFAs, free-fatty acids; TNF-alpha, tumour necrosis factor alpha; IL-6, interleukins-6; PAI-1, plasminogen activator inhibitor 1.

to insulin-mediated glucose uptake, the greater the extent of compensatory hyperinsulinemia[83]. Eventually the β-cells are unable to overcome insulin resistance through hypersecretion, glucose levels rise, and insulin resistance can then be characterized as T2D mellitus[85]. Insulin resistance is associated with obesity, hypertension[83, 86, 87], dyslipidemia[83, 86, 88-90], and CVD[86, 91-93]. Although the relationship among these conditions is complex, insulin resistance may be the primary initiating factor[94, 95].

2.3.2 Causes of Insulin Resistance

The cause of insulin resistance remains unknown; however, there is an inherited component, where insulin resistance and T2D rates increase if there is a history of T2D in first-degree relatives or a personal history of gestational diabetes[96]. Insulin resistance is often found in individuals with a high degree of adiposity, specifically visceral adiposity which produces significantly larger amounts of pro-inflammatory adipokines than SAT[79]. High levels of circulating PAI-1, IL, and (TNF-α) impair insulin signalling in hepatocytes[80-82]. Combined with an increased flux of FFAs from an expanded VAT depot to the liver can cause enhanced secretion of low density lipoproteins[97], elevated rates of gluconeogenesis, and reduced rates of insulin metabolism by the liver[98]. These changes in hepatic metabolism can lead to systemic hyperlipidemia, hyperglycemia, and hyperinsulinemia[82]. Additionally, hyperinsulinemia down-regulates the expression of the insulin-responsive glucose transporter (GLUT4)[99].

Finally, some medications have even been shown to promote insulin resistance. Glucosamine, a compound commonly used to treat osteoarthritis, a condition associated with both obesity and T2D, has been shown to increase the risk of insulin resistance and worsening vascular function[100]. Growth hormone replacement therapy is also associated with deteriorations in glucose metabolism[101].

2.3.3 Measuring Insulin resistance

There are many ways to measure and quantify insulin resistance, but the gold standard technique is the 3-hour hyperinsulinemic-euglycemic clamp, so called because the plasma glucose concentration is held constant at basal levels by a variable glucose infusion while insulin is infused at an extremely high rate[102]. Insulin is infused at ~40 $mU/m^2/min$, while glucose is infused at a rate which maintains a plasma glucose concentration of ~5 mmol/l. The rate of glucose infusion during the last 30 minutes of the clamp determines insulin sensitivity. High glucose infusion rates (≥7.1 mg/kg/min) indicate an individual that is insulin sensitive, while low glucose infusion rates (<4.7 mg/kg/min) indicate resistance to insulin[103].

Two alternative methods exist that simplify the measurement of insulin resistance. The Homeostatic Model Assessment (HOMA) method uses an equation so that insulin resistance can be estimated from fasting glucose and insulin levels[104]. The HOMA method correlates well with the hyperinsulinemic-euglycemic clamp ($R^2 = 0.88$)[105]. The Quantitative Insulin Sensitivity Check Index (QUICKI) method is derived using the

inverse of the sum of the logarithms of fasting glucose and insulin levels. The QUICKI method also correlates well with the hyperinsulinemic-euglycemic clamp ($r = 0.78$)[106].

2.3.4 Treatment of Insulin Resistance

Since insulin resistance often precedes the development of T2D by many years, identifying and treating it early encourages the development of good habits that may prevent or delay the onset of overt disease. There is considerable evidence that a single bout of 1 hour of exercise can improve glucose tolerance and reduce insulin resistance for up to 48 hours post-exercise[107] by increasing the number and activity of GLUT4 glucose transporters[108-110], and the content and activity of hexokinase[111], an enzyme that phosphorylates glucose. Additionally, the acute effect of exercise on insulin sensitivity may relate to depletion of muscle glycogen[112] or triglycerides[113]. In fact, an inverse relationship exists between muscle triglyceride content and insulin-stimulated glucose uptake[114]. Finally, repeated bouts of exercise over an extended period of time result in even greater improvements in insulin sensitivity[107], both with[69, 115] and without weight loss[69].

Insulin sensitivity may also improve within a few days of caloric restriction, before any significant weight loss occurs, while weight reduction leads to further improvement[96]. Metformin[116] and thiazolidinedione[117] increase insulin sensitivity, while sulfonylureas and exenatide improve β-cell function[118], and have been successfully used to treat diabetes. Unfortunately, these drugs are not labelled for treatment of isolated

insulin resistance, and the American Diabetes Association does not recommend drug therapy for the treatment of insulin resistance in the absence of diabetes[96].

2.4 Exercise with and without Weight Loss

2.4.1 Exercise with Weight Loss

Given the strong association between BMI and disease[4, 5], it seems appropriate that leading health authorities would suggest that treatments designed to reduce bodyweight represent the optimal strategies for decreasing morbidity and mortality risk[4, 11]. It is clear that weight loss of greater than 5% is associated with health benefit in a gradient manner[119]; leading health authorities to state that a clinically relevant weight loss of 5 to 10% of bodyweight is necessary for positive health benefit[4]. Multiple interventions and strategies designed for weight loss, including dietary therapy, physical activity, behaviour therapy, pharmacotherapy, and surgery, as well as combinations of these strategies are recommended by the National Institutes of Health[4]. In his review, Klein[12] examined the effect of weight loss on obesity-related disease and survival outcomes and revealed that weight loss is linked with decreases in CVD, insulin resistance, hypertension, dyslipidemia, morbidity, and mortality.

A weight loss of $\geq$ 2.25 kg is associated with a 40 to 50% reduction in coronary heart disease risk factors in both men and women[120]. Additionally, weight loss has been shown to decrease fasting blood glucose and insulin, and triglycerides in a gradient manner, while displaying an inverse relationship for high-density lipoprotein cholesterol (HDL-C) in obese patients with T2D[121]. Weight loss also decreases systolic and diastolic

BP in a dose-dependent manner[122]. Finally, modest weight loss decreases the respiratory disturbance index and improves sleep patterns in patients with sleep apnea[123], while decreasing liver fat content[124], and improving physical function and quality of life[125-127].

Unfortunately, despite short term success, most obese patients are unable to achieve long-term weight control using conventional treatments[128], even with the addition of pharmacotherapy[129]. In severely obese patients, diet, exercise, and drug therapy are extremely unsuccessful in the long-term. In fact, the recidivism rate for diet therapy is almost 100% at 5 years[130, 131]. The inability of most individuals to achieve long-term weight control success, combined with the inconsistent health risks associated with weight cycling[132-134], may lead some to question whether it is prudent to recommend that overweight adults should try to lose weight.

2.4.2 Exercise without Weight Loss

Stevens et al.[135] recommends that a change in bodyweight of less than 3% be considered weight maintenance, implying that a weight loss of less than 3% of bodyweight in response to an intervention be considered a failed attempt to reduce obesity and related metabolic risk factors. Although weight loss is associated with attenuated health risk, a recent review by Ross and Janiszewski[14] suggests that weight loss is not absolutely necessary to observe benefit. They examined the response of 20 studies of overweight and obese men and women participating in lifestyle-based interventions whose mean change in bodyweight were not considered clinically significant (< 5%). Despite the absence of weight change, many groups still had

significant reductions in abdominal obesity (e.g., VAT), metabolic risk, including glucose/insulin dynamics and dyslipidemia, and improvements in CRF, all of which are strong predictors of morbidity and mortality, independent of BMI[9, 40, 136]. It is important to note that the levels of obesity and health risk reduction seen in weight maintenance studies are less than those generally observed in response to weight loss greater than 5% (Figure 3).

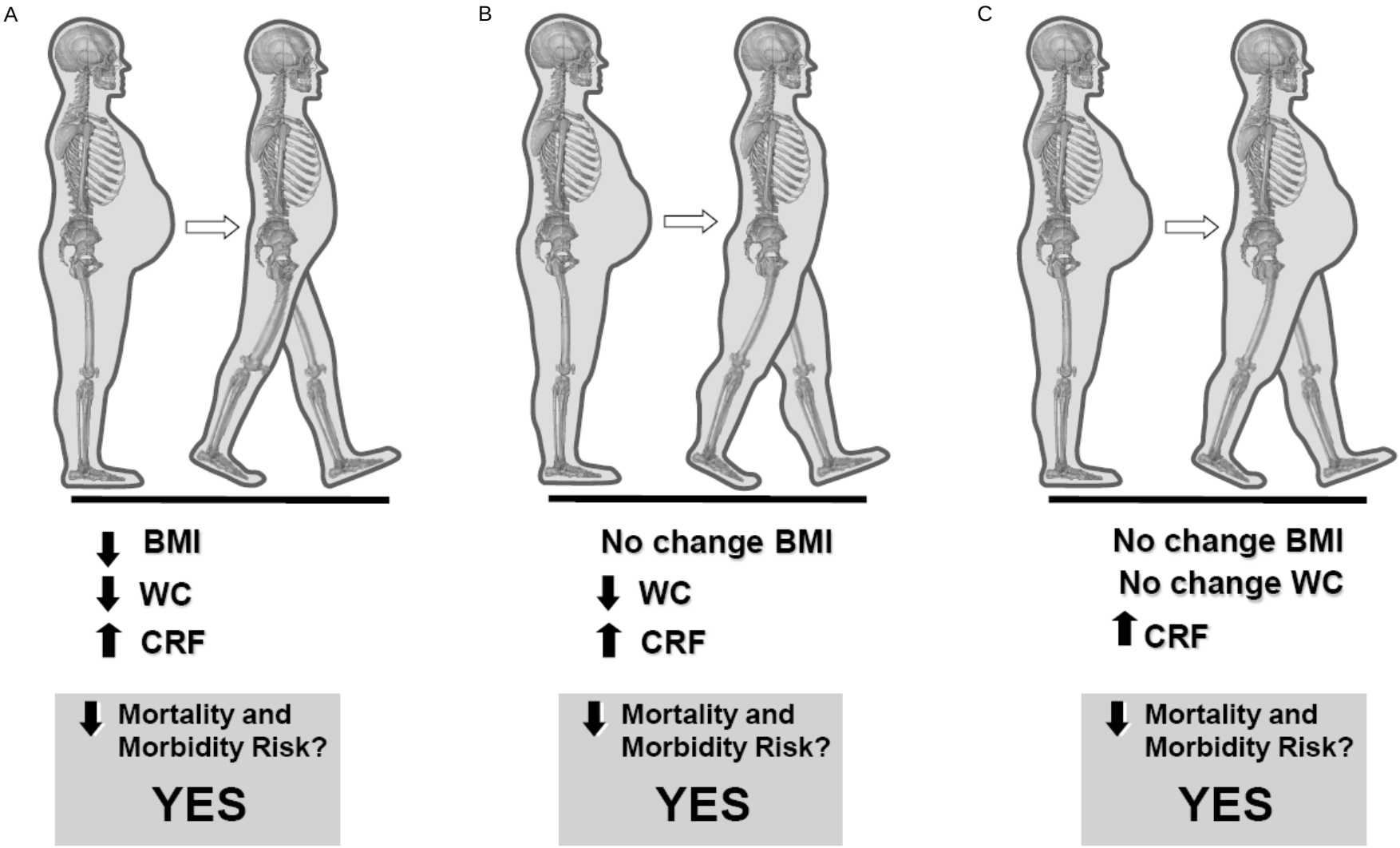
2.5 Exercise Modality

The American College of Sports Medicine's 2009 Position Stand states that moderate-intensity physical activity between 150 and 250 min/wk is effective to prevent weight gain, provide modest weight loss, or improve weight loss when combined with moderate diet restrictions; greater amounts of physical activity (>250 min/wk), however, are associated with clinically significant weight loss[11]. Current knowledge with respect to different exercise modalities (aerobic, resistance, combined) and their associated reductions in obesity and metabolic health risks will be considered below.

2.5.1 Aerobic Exercise

Aerobic exercise training improves the efficiency of the aerobic energy-producing systems that can improve cardiorespiratory endurance and includes walking, jogging, and dancing[4]. It is well established that increased aerobic physical activity is associated with marked reductions in bodyweight[4, 69, 115, 137], BP[4, 138, 139], dyslipidemia[4], WC[69, 115, 137], VAT[69, 115, 137], SAT[69, 115, 137], and improvements in glucose uptake [69, 115, 137] and CRF [69, 115, 137, 140]. Considerable literature supports the combination of a reduced caloric diet

Figure 3. Effects of weight loss, WC change, and CRF improvement on morbidity and mortality risk.



Abbreviations: BMI, body mass index; WC, waist circumference; CRF, cardiorespiratory fitness. (A) Decrease in bodyweight = greatest decrease in mortality and morbidity risk; (C) Smallest decrease in mortality and morbidity risk[14].

and increased aerobic activity to produce greater reductions in weight loss and health risks than diet or physical activity alone[4]; some studies, however, indicate that aerobic exercise combined with diet produces results that are no different than diet alone[141, 142].

2.5.2 Resistance Exercise

Without a modification in diet, substantial evidence indicates that resistance training is not suitable to reduce bodyweight[137, 143, 144]; it has been shown, however, to increase fat loss[145-148], total fat-free mass[137, 145, 146], and muscular strength[145, 146], with reductions in WC[137]. It has been suggested that resistance exercise can be used to maintain, or even increase resting metabolic rate and fat-free mass, thereby preventing AT gains in sedentary individuals[11, 149-151]. Following resistance exercise combined with caloric restrictions, Janssen et al.[142] observed no increase in SM, but significant within-group reductions in bodyweight and SAT and VAT were noted, although these were not significantly different from a diet-only group. Conversely, other studies combining resistance exercise with energy restriction report improved lean body mass compared to dieting alone[151, 152].

Several studies have observed significant reductions in fasting plasma insulin[153, 154] and glycated hemoglobin[155], with increases in glucose uptake[153, 154, 156] in healthy[153, 154] and type 2[156] and 1 diabetics[155]. While several studies have attributed the increased glucose uptake observed after resistance exercise solely to the increase in muscle mass[157-159], the majority of literature indicates that differences in the metabolic characteristics of SM are more important[160-163]. In fact, healthy[160-162] and T2D[162] individuals participating in resistance exercise exhibited significant increases in protein content of GLUT4[160-162], insulin receptor[162], and protein kinase B[162]. Insulin receptors bind to and phosphorylate a

substrate protein, which leads to an increase in the high affinity GLUT4 molecules, while protein kinase B is required for the insulin-induced translocation of GLUT4 to the plasma membrane.

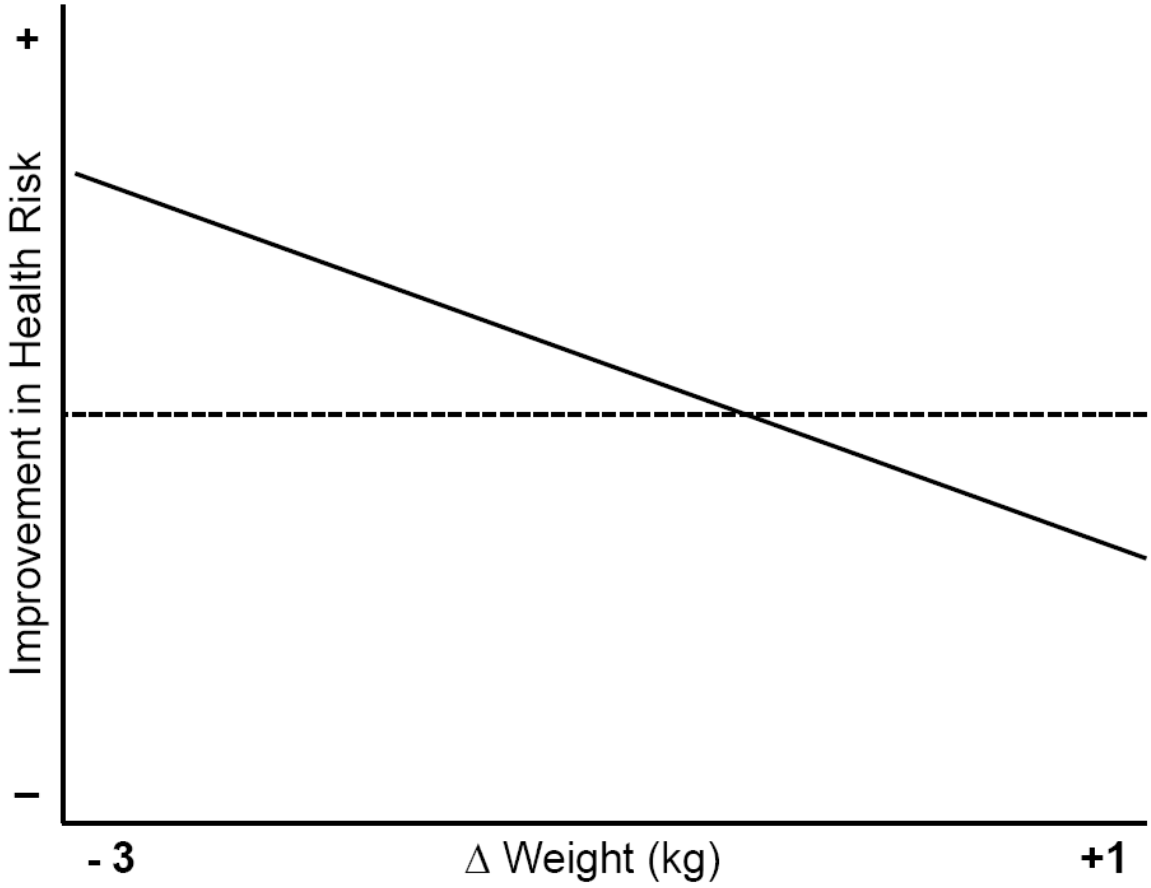
2.5.3 Combined Aerobic with Resistance Exercise

Although the American College of Sports Medicine[11] states that resistance exercise alone is not an effective weight reduction strategy, they do indicate that when combined with aerobic exercise, resistance exercise may increase loss of fat mass compared to resistance exercise alone. Davidson et al.[137] observed that a combined exercise group lost significantly more bodyweight and body fat, while significantly improving their insulin resistance compared to individuals completing only resistance exercise. In addition, Marks et al.[164] suggest caloric restriction and combined exercise to maintain fat-free mass and encourage body mass loss.

2.6 Individual Variation in Response to Exercise

Previous investigations have established that positive health benefits can be achieved in the absence of weight loss[14];however, it remains unknown if this observation is driven by individuals who did lose weight, albeit minimally **(**Figure 4). Accordingly, Bouchard and Rankinen[165] performed a review examining the inter-individual variation in response to regular exercise, while attempting to characterize the contributions of age, sex, race, and pre-training baseline levels. After examining VO_{2max}, heart rate, HDL-C, and systolic BP, they concluded that there is considerable heterogeneity in response to regular physical activity, where pre-training baseline levels had the greatest impact.

Figure 4. Health benefit driven by weight loss.



Additionally, an earlier study by Bouchard and colleagues[166] analyzed the response to exercise with a constant energy intake in identical twins. They discovered large individual differences in response to the exercise/diet protocol, although subjects with the same genotype were more comparable in responses (body fat, body energy, and VAT changes) than subjects with different genotypes.

2.7 Summary

Although obesity is only second behind smoking as the main preventable cause of illness and premature death in the United States, it remains one of the most neglected health problems. Indeed, increasing levels of overweight and obesity, as measured by BMI, are mirrored by increased risk for hypertension[19], T2D[20], CVD[26], and death[5]; it is evident, however, that the location of excess fat, rather than its absolute amount, is an important predictor of health risk[38]. Specifically, the excess accumulation of VAT is strongly and independently associated with morbidity[8] and mortality[9].

Although current health guidelines state that a clinically significant weight loss of 5 to 10% of bodyweight is necessary to reduce obesity related morbidity and mortality[4, 10-12], recent evidence suggests that obesity and related metabolic risk reduction is possible in the absence of weight loss[14]. Research indicates that reductions in obesity and health risk, including decreases in VAT and insulin resistance, are achievable with aerobic and/or resistance exercise, both with and without caloric restriction. Finally, the levels of obesity and health risk reduction seen in exercise without weight loss studies are less than those generally observed in response to weight loss greater than 5 to 10%.

Although previous investigations have established that positive health benefits can be achieved in the absence of weight loss[14], it remains unknown if this observation is

driven by individuals who did lose weight, albeit minimally**.** Using the anthropometric, body composition, and metabolic risk factor measures from four previous studies[69, 115, 137, 140], the aim of the investigation that follows was to determine whether a gradient exists between the inter-individual change in bodyweight and corresponding changes in body composition and metabolic risk factors in response to minimal or no weight loss.

Chapter 3

Manuscript

Effects of Lifestyle-Based Interventions on Obesity and Related Metabolic Risk Factors with Minimal or no Weight Change

INTRODUCTION

Current estimates suggest that more than one in two Canadians are overweight and approximately 23% are obese[13]. This represents a major public health problem as it is well documented that increasing levels of obesity, as commonly assessed using the BMI, are mirrored by increasing rates of morbidity and mortality[4, 5]. Accordingly, leading health authorities suggest that treatments designed to reduce bodyweight represent the optimal strategies for decreasing morbidity and mortality risk among obese individuals[4, 11]. Current guidelines state that a clinically relevant weight loss of 5 to 10% of bodyweight is necessary to reduce risk of CVD, T2D, and mortality[4, 10-12]. In fact, Stevens et al.[135] recently recommended that a change in weight of less than 3% be considered weight maintenance, while a weight loss of 5% or greater be considered clinically significant.

Increasing evidence suggests that weight loss is not absolutely necessary to reduce obesity related morbidities. For example, Ross and Janiszewski[14] examined the findings from 20 studies wherein overweight and obese men and women participated in lifestyle-based interventions and, the mean change in bodyweight was not considered clinically significant (i.e. < 5%). Despite the absence of clinically significant weight change, many groups showed reductions in abdominal obesity, metabolic risk, and improvement in CRF, all of which are strong predictors of health risk independent of BMI.

A limitation of the studies considered is that by examining the mean response of a group, it is possible that the subjects who failed to lose any weight did not experience any health improvement, a finding masked by the exaggerated improvement in those who did

lose weight, albeit minimally. Were this true, the observation that exercise without weight loss conveys a health benefit may be misleading, the implication of which would be significant when considering the public health message.

Therefore, the purpose of the current study was to determine whether a gradient exists between the inter-individual change in bodyweight and corresponding changes in body composition and metabolic risk factors in response to minimal or no weight loss. We hypothesize that the degree of weight change will not be associated with the degree of health improvement in response to an intervention with minimal or no weight loss.

METHODS

Subjects

Forty-six predominantly Caucasian men and 10 premenopausal and 32 postmenopausal women were recruited from the general public and participated in previously published exercise and/or diet-induced weight loss studies at Queen's University[69, 115, 137, 140]. Briefly, a total of 136 abdominally obese men and women, 60 to 80 years of age were recruited to participate in a study on the effects of resistance and/or aerobic exercise on risk factors for disease and disability[137]. In this study, within each gender, subjects were randomized to 1 of 4 groups for ~20 weeks: resistance exercise, aerobic exercise, resistance and aerobic exercise combined, or non-exercise control group (see "Interventions" below for further assignment information). Also, a total of 23 sedentary men (8 lean, 7 obese with T2D, and 8 obese without T2D) participated in a study on the effects of caffeine ingestion and chronic exercise on insulin sensitivity[140]. In this study, all subjects participated in a ~13-week aerobic exercise program (see "Interventions" below for further assignment information). Additionally, a total of 52 men and 54 women participated in 2 other studies (1 in each gender) comparing the effect of diet and aerobic exercise-induced weight loss on regional body composition and metabolic status[69, 115]. In these studies, within each gender, subjects were randomized to a control, diet-induced weight loss, exercise-induced weight loss, or an exercise without weight loss group (see "Interventions" below for further assignment information). All subjects in these prior studies were weight stable (± 2 kg) for at least 6 months prior to study, were non-smokers, had a sedentary lifestyle, and were not taking any medications to lower blood glucose levels; blood pressure and lipid lowering medications, however,

were allowed if the regimen was maintained throughout the trial. All participants gave informed consent prior to participation in accordance with the ethical guidelines set by Queen's University (Table 1).

Subjects for the current analysis included 46 men and 42 women from these studies who were overweight (BMI ≥25 kg/m^2) and/or had a WC ≥102cm (men) or ≥88cm (women) who experienced weight change (≤ -3% to ≤ +1%) during their intervention that was below the threshold thought to be clinically significant (e.g. below 5%).

Interventions

Eighteen of the 46 men were randomly assigned to a resistance exercise (n = 8), aerobic exercise (n = 2), or a combined exercise (n = 8) program for ~20 weeks, as described in detail elsewhere[137]. Additionally, fifteen of the 46 men were randomly assigned to an aerobic exercise without weight loss program for ~12 weeks, described in detail elsewhere[69]. The remaining thirteen men were assigned to an aerobic exercise without weight loss program for ~13 weeks, described in detail elsewhere[140].

Thirty two of the 42 women were randomly assigned to a resistance exercise (n = 12), aerobic exercise (n = 12), or a combined exercise (n = 8) program for ~20 weeks, described in detail elsewhere[137]. The remaining 10 women were randomly assigned to an aerobic exercise without weight loss program for ~14 weeks, described in detail elsewhere[115].

Diet

All subjects followed a weight maintenance diet (50% to 60% carbohydrate, 15% to 20% protein, and 20% to 30% fat) where they consumed self-selected foods for a 4- to

Table 1. Subject recruitment

	Study			
	Ross et al. (2000)[69]	**Ross et al. (2004)[115]**	**Lee et al. (2005)[140]**	**Davidson et al. (2009)[137]**
Total # of People in Original Study	52	54	23	136
# of People Utilized in our Study	15	10	13	50
Gender	Male	Female	Male (5 T2D)	32 Female 18 Male
Exercise Modality	Aerobic	Aerobic	Aerobic	14 Aerobic (12Female/2Male) 20 Resistance (12Female/8Male) 16 Resistance+Aerobic (8Female/8Male)
Intervention Duration	~12 Weeks	~14 Weeks	~13 Weeks	~20 Weeks
Total # of People Utilized in our Study	88 - 42 Female/46 Male			
# of People in each Exercise Modality	52 Aerobic Exercise – 22 Female/30 Male 20 Resistance Exercise – 12 Female/8Male 16 Resistance + Aerobic Exercise – 8 Female/8Male			

Abbreviations: # Number; T2D Type 2 diabetes.

5-week baseline period; although health food selection and preparation according to Canada's Food Guide was encouraged. During this period, bodyweight was monitored to determine the accuracy of the prescribed energy requirement and adjusted accordingly so that bodyweight was maintained. Fifty subjects[137] followed this diet throughout the entire exercise intervention period, whereas the remaining 38 participants [69, 115, 140] followed the weight maintenance diet but consumed enough calories to compensate for the energy expended during exercise. Monitoring of dietary intake for each participant helped to ensure that the composition and caloric intake of the prescribed diet was maintained throughout the intervention, and consequently, that the treatment effects were attributable to the exercise intervention.

Anthropometric Measures

Standing height was measured to the nearest 0.1 cm using a fixed stadiometer while the subject was barefoot and upright. Weight was measured to the nearest 0.1 kg on a calibrated balance, with the subject in light clothing and footwear removed. WC was taken at the level of the last rib to the nearest 0.1 cm after a normal expiration. BMI was calculated as weight in kg divided by height in m^2.

Maximal Oxygen Consumption

VO_{2max} was determined using a graded treadmill test and standard open circuit spirometry techniques before and after training (Sensor-Medics, Yorba Linda, CA).

Adipose Tissue and Skeletal Muscle

Whole body (~46 equidistant images) MRI data were obtained with a General Electric 1.5 Tesla magnet (Milwaukee, WI) using an established protocol described in detail elsewhere[168, 169]. Once acquired, the MRI data were transferred to computer work

stations for analysis using specially designed software (Tomovision Inc., Montréal, QC), the procedures for which are described elsewhere[169, 170].

VAT and ASAT depots were calculated using a single image at the L4-L5 inter-vertebral space. Total AT and SM volumes were determined using ~46 images. For total AT and SM, volume units (L) were converted into mass units (kg) by multiplying the volumes by the assumed constant density for AT (0.92 kg/L) and SM (1.04 kg/L)[171].

Insulin Sensitivity

Subjects consumed a self-reported weight maintenance diet consisting of at least 200 grams of carbohydrate for a minimum of 4 days before measurements of insulin sensitivity and were asked to avoid strenuous physical activity for 3 days preceding the studies. Post-treatment data were obtained 36 to 96 hours after the last exercise session. All studies were performed at about 8 am after a 10- to 14-hour overnight fast. An antecubital vein was catheterized for infusion of insulin and 20% glucose, and a hand vein was cannulated and placed in a heating pad for sampling of arterialized blood. Insulin was infused at a rate of 40 mU/m^2/min for 3 hours. Blood glucose was measured using an automated glucose analyzer (YSI 2300 Glucose Analyzer, YSI, Yellow Springs, OH) every 5 minutes in arterialized blood. Glucose uptake rate was calculated using the average exogenous glucose infusion rate during the final 30 minutes of euglycemia. Insulin was measured using a radioimmunoassay kit (Intermedico, Toronto, ON, Canada).

Blood Pressure

For fifty subjects, 5 consecutive measures of BP using an electronic cuff (BpTRU, Coquitlam, BC) at the upper right arm were taken, with one minute between

measurements. The average of these measurements was used to derive systolic and diastolic BP. For the remaining subjects (n=38), BP was measured manually using standard procedures.

Statistical Analysis

For all anthropometric, MRI, and metabolic risk factor variables, normal distribution was determined using a Shapiro-Wilk test. Data not normally distributed was normalized using a log transformation. Two-tailed independent-samples t-tests were used to assess baseline differences in anthropometric, MRI, and metabolic risk factors between males and females. Repeated measures ANOVAs were used to assess change (pre vs. post) for all variables in response to intervention. Gender was used as a between-subjects factor, while age and exercise modality were used as covariates in these analyses. Linear regression analyses were performed to assess the association between changes in anthropometric, MRI, and metabolic risk factors with the degree of weight or WC change. To further consider whether a gradient existed between weight change and/or WC change on body composition and metabolic risk factors, subjects were cross-classified according to their level of weight or waist change (tertiles) and their respective change in either body composition or metabolic risk factor. Univariate ANOVA was employed to determine whether differences existed between tertiles for all anthropometric, MRI, and metabolic risk factors. If differences existed between tertile groups ($p<0.05$), a tukey post-hoc test was performed to determine the location of difference. Gender, age, and exercise modality were used as covariates in these analyses. All statistical procedures were performed using SPSS 16.0 software (Chicago, IL).

RESULTS

Pre-treatment values for anthropometric, body composition, metabolic risk factors, and VO_{2max} values in men and women are presented in Table 1. The men were significantly younger and had higher values for bodyweight, WC, VAT, total SM, and VO_{2max}, but lower values for total AT, ASAT, and abdominal AT (ABAT) ($p<0.05$). Men also had higher values for diastolic BP, but lower values for glucose uptake ($p<0.05$).

The effect of treatment on all variables for men and women separately and combined are shown in Table 2. Analysis revealed no gender interaction for all variables except total AT; thus, we report our findings as collapsed across gender. Bodyweight did not change in men or women ($p>0.10$), however, a significant decrease in WC was observed ($p<0.05$). With the exception of ASAT, there were significant reductions in all adipose depots ($p<0.05$). Blood glucose decreased, while glucose uptake and VO_{2max} improved significantly ($p<0.05$).

As shown in Table 3, the regression analysis revealed that with few exceptions, changes in bodyweight or WC were not associated with corresponding changes in body composition variables or metabolic risk factors ($p>0.05$).

To further explore whether a gradient existed between weight change and/or WC change on body composition and metabolic risk factors, subjects were cross-classified according to their level of weight or waist change (tertiles) and their respective change in either body composition or metabolic risk factors. As shown in Table 4, with few exceptions, neither weight nor WC change tertile was related to any body composition or metabolic risk factor in a gradient fashion ($p>0.05$).

Finally, to illustrate the association between inter-individual changes in bodyweight and metabolic risk factors, the inter-individual changes in bodyweight, VAT, and glucose uptake are shown in Figure 1.

Table 2. Baseline characteristics.

	Men	Women
Age	54.9 ± 12.4 [46]	61.2 ± 12.9 [42]*
Anthropometrics		
Weight, kg	98.0 ± 9.4 [46]	82.1 ± 11.4 [42]*
BMI, kg/m^2	31.5 ± 3.6 [46]	30.9 ± 3.5 [42]
WC, cm	110.9 ± 6.9 [46]	101.6 ± 9.2 [42]*
MRI		
Total AT, kg	33.5 ± 6.1 [46]	37.6 ± 7.2 [41]*
ASAT L4-L5, cm^3	290.8 ± 81.2 [46]	388.2 ± 94.8 [41]*
VAT L4-L5, cm^3	203.9 ± 69.1 [46]	153.3 ± 52.5 [41]*
ABAT L4-L5, cm^3	494.8 ± 104.7 [46]	541.4 ± 109.5 [41]*
SM, kg	32.9 ± 3.8 [46]	20.9 ± 3.5 [41]*
Metabolic		
Blood Glucose, Mm	5.4 ± 1.3 [46]	5.1 ± 0.6 [37]
Glucose Uptake, mg/kg·SM/min	11.7 ± 5.3 [46]	18.0 ± 6.2 [37]*
Plasma Insulin, UI	9.8 ± 5.2 [45]	9.0 ± 5.6 [41]
Systolic BP, mmHG	124.7 ± 11.9 [39]	123.8 ± 14.2 [39]
Diastolic BP, mmHG	78.5 ± 8.1 [39]	73.7 ± 8.3 [39]*
VO_{2max}, ml/kg/min	32.1 ± 6.9 [46]	22.7 ± 4.1 [41]*

Data are means ± SD [N]. *indicates a significant difference between men and women ($p<0.05$). BMI Body mass index; WC Waist circumference; AT Adipose Tissue; ASAT Abdominal subcutaneous adipose tissue; VAT Visceral adipose tissue; ABAT Abdominal adipose tissue; SM Skeletal muscle; BP Blood pressure; VO_{2max} Maximal oxygen consumption.

Table 3. Absolute and relative changes in anthropometric, body composition, and metabolic risk measures following treatment.

	Men		Women		Collapsed Across Gender	
	Absolute Change	**Relative Change**	**Absolute Change**	**Relative Change**	**Absolute Change**	**Relative Change**
Anthropometrics						
Weight,kg	-0.7[b]	0.8%	-0.8	1.0%	-0.8	0.9%
BMI, kg/m^2	-0.2[b]	0.8%	-0.3	1.0%	-0.3	0.9%
WC, cm	-2.6	2.3%	-2.6	2.6%	-2.6*	2.4%
MRI						
Total AT, kg	-2.0[b]	6.1%	-1.5*,[b]	3.9%	-1.8*,[a]	5.0%
ASAT L4-L5, cm^3	-16.1	5.5%	-8.2[c]	2.1%	-12.4	3.7%
VAT L4-L5, cm^3	-18.3*	8.9%	-7.6*	4.9%	-13.3*,[b]	7.4%
ABAT L4-L5, cm^3	-34.4*	6.9%	-15.8	2.9%	-25.6*	4.9%
SM, kg	0.7	2.0%	0.4	1.8%	0.5	1.9%
Metabolic						
Blood Glucose, Mm	-0.3*	4.9%	-0.1	0.9%	-0.2*	3.2%
Glucose Uptake, mg/kg·SM/min	2.9*	24.7%	2.2	12.3%	2.6*	17.8%
Plasma Insulin, UI	-0.9	9.7%	-0.8	8.6%	-0.9	9.2%
Systolic BP, mmHG	-1.2	0.9%	-0.8	0.7%	-1.0	0.9%
Diastolic BP, mmHG	-0.7	0.9%	-1.6	2.2%	-1.2*,[b]	1.5%
VO_{2max}, ml/kg/min	5.0*	15.6%	2.5*,[b]	11.1%	3.8*,[b]	13.9%

Based on transformed variables; raw data is presented in table. * indicates an effect of time ($p<0.05$). [a] indicates an effect of time*gender ($p<0.05$). [b] indicates an effect of time*age ($p<0.05$). [c] indicates an effect of time*exercise modality ($p<0.05$). BMI Body mass index; WC Waist circumference; AT Adipose Tissue; ASATAbdominal subcutaneous adipose tissue; VAT Visceral adipose tissue; ABAT Abdominal adipose tissue; SM skeletal muscle; BP Blood pressure; VO_{2max} Maximal oxygen consumption.

Table 4. Relationship between changes in bodyweight and WC and changes in anthropometric, body composition, and metabolic risk factor variables in men (A), women (B), and genders combined (C).

A.

	Weight, kg	WC, cm	Total AT, kg	ASAT, cm^3	VAT, cm^3	ABAT, cm^3	SM, kg	Blood Glucose, Mm	Glucose Uptake, mg/kg·SM/min	Plasma Insulin, UI	SBP, mmHG	DBP, mmHG	VO_{2max}, ml/kg/min
Weight	1	.19*	.20*	.00	.02	.01	.02	.00	.01	.00	.06	.05	.09*
WC	.19*	1	.05	.03	.05	.00	.04	.00	.04	.01	.06	.02	.01

B.

	Weight, kg	WC, cm	Total AT, kg	ASAT, cm^3	VAT, cm^3	ABAT, cm^3	SM, kg	Blood Glucose, Mm	Glucose Uptake, mg/kg·SM/min	Plasma Insulin, UI	SBP, mmHG	DBP, mmHG	VO_{2max}, ml/kg/min
Weight	1	.00	.13*	.07	.00	.06	.07	.01	.00	.17*	.00	.12*	.00
WC	.00	1	.10*	.01	.02	.02	.02	.00	.00	.00	.02	.00	.00

C.

	Weight, kg	WC, cm	Total AT, kg	ASAT, cm^3	VAT, cm^3	ABAT, cm^3	SM, kg	Blood Glucose, Mm	Glucose Uptake, mg/kg·SM/min	Plasma Insulin, UI	SBP, mmHG	DBP, mmHG	VO_{2max}, ml/kg/min
Weight	1	.05*	.15*	.03	.01	.00	.00	.00	.01	.02	.01	.08*	.03
WC	.05*	1	.07*	.01	.00	.00	.00	.00	.02	.00	.02	.01	.01

R^2 based on transformed variables. * indicates significance. WC Waist circumference; AT Adipose Tissue; ASAT Abdominal subcutaneous adipose tissue; VAT Visceral adipose tissue; ABAT Abdominal adipose tissue; SM Skeletal muscle; BP Blood pressure; VO_{2max} Maximal oxygen consumption.

Table 5A. Relationship between anthropometric, body composition, and metabolic risk variables within tertiles of change in bodyweight.

	-3 to -1.5% Weight Change	-1.5 to -0.2% Weight Change	-0.2 to 1% Weight Change
Anthropometrics			
WC, cm	-3.0 ± 2.1 [29]	-3.2 ± 2.6 [29]	-1.6 ± 2.3 [30][3]
MRI			
Total AT, kg	-2.2 ± 1.1 [29]	-1.8 ± 1.4 [28]	-1.3 ± 1.1 [30][2, a]
ASAT L4-L5, cm^3	-15.8 ± 32.2 [29]	-14.6 ± 29.6 [28]	-6.9 ± 27.7 [30]
VAT L4-L5, cm^3	-11.3 ± 32.0 [29]	-16.3 ± 21.8 [28]	-12.3 ± 20.2 [30]
ABAT L4-L5, cm^3	-27.1 ± 39.7 [29]	-30.9 ± 39.7 [28]	-19.2 ± 34.9 [30]
SM, kg	0.5 ± 1.0 [29]	0.5 ± 0.8 [28]	0.6 ± 0.9 [30]
Metabolic			
Blood Glucose, Mm	-0.1 ± 0.5 [28]	-0.2 ± 0.4 [27]	-0.2 ± 0.5 [28]
Glucose Uptake, mg/kg·SM/min	1.9 ± 4.2 [28]	3.6 ± 3.7 [27]	2.3 ± 3.7 [28]
Plasma Insulin, UI	-2.2 ± 2.8 [29]	0.4 ± 3.8 [28]	-0.7 ± 4.4 [29][1]
Systolic BP, mmHG	0.7 ± 9.4 [26]	-2.1 ± 12.6 [23]	-1.6 ± 8.8 [29]
Diastolic BP, mmHG	1.1 ± 5.5 [26]	-1.5 ± 8.9 [23]	-2.9 ± 8.6 [29]
VO_{2max}, ml/kg/min	2.3 ± 3.5 [29]	4.4 ± 4.6 [29]	4.8 ± 4.8 [29][b]

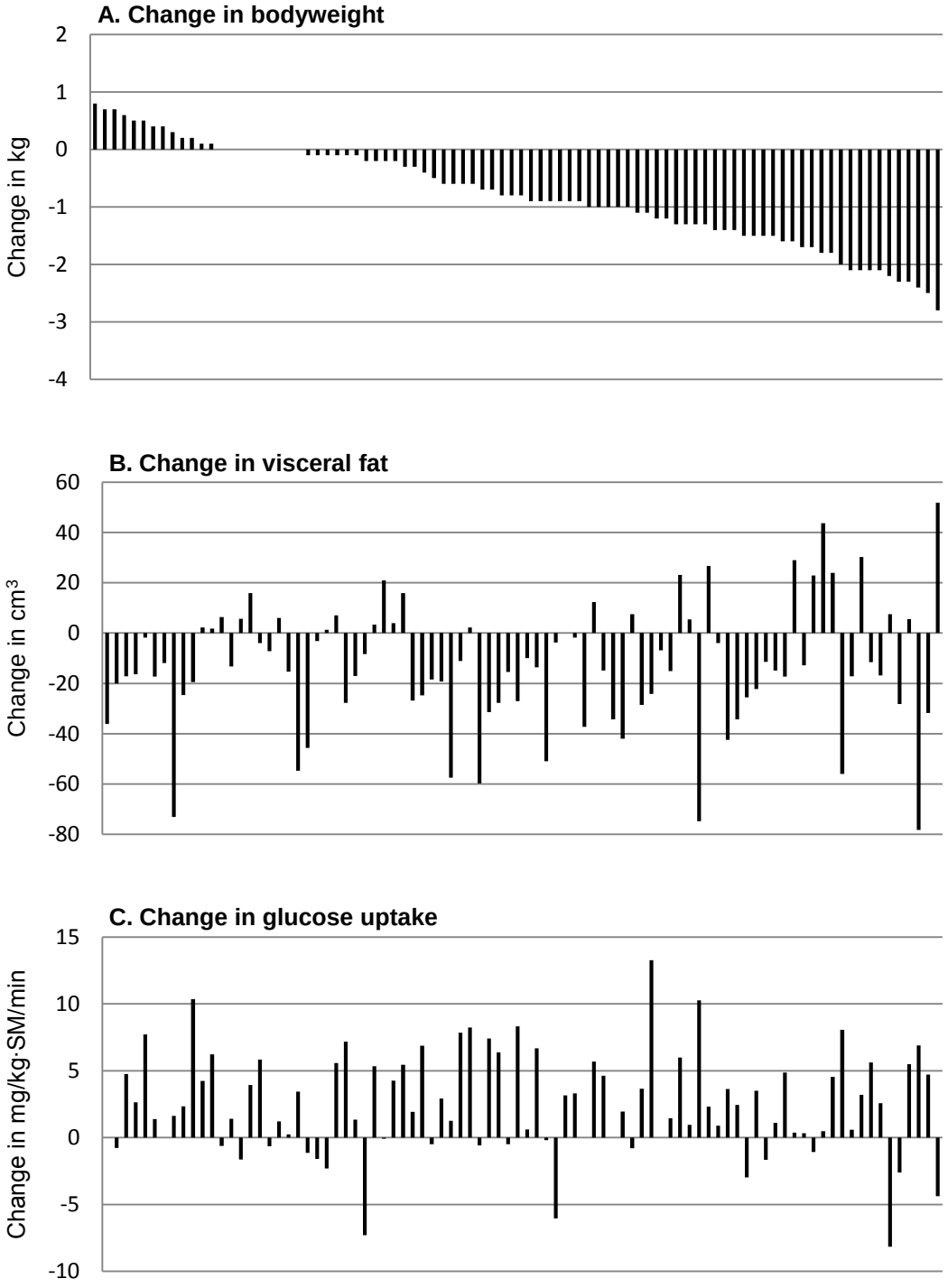
Based on transformed variables; raw data is presented in table. Data are means ± SD [N]. [1] indicates column 1 is significantly different than column 2 ($p<0.05$). [2] indicates column 1 is significantly different than column 3 ($p<0.05$). [3] indicates column 2 is significantly different than column 3 ($p<0.05$). [a] indicates an effect for gender ($p<0.05$). [b] indicates an effect for age ($p<0.05$). [c] indicates an effect for exercise modality ($p<0.05$). WC Waist circumference; AT Adipose Tissue; ASAT Abdominal subcutaneous adipose tissue; VAT Visceral adipose tissue; ABAT Abdominal adipose tissue; SM Skeletal muscle; BP Blood pressure; VO_{2max} Maximal oxygen consumption.

Table 5B. Relationship between anthropometric, body composition, and metabolic risk variables within tertiles of change in WC.

	-10 to -3.1% WC Change	-3.1 to -1.3% WC Change	-1.3 to 4% WC Change
MRI			
Total AT, kg	-1.9 ± 1.1 [29]	-2.1 ± 1.3 [31]	-1.2 ± 1.2 [27][3]
ASAT L4-L5, cm^3	-12.6 ± 30.7 [29]	-11.5 ± 27.9 [31]	-13.0 ± 31.9 [27]
VAT L4-L5, cm^3	-14.2 ± 27.1 [29]	-10.9 ± 25.1 [31]	-14.9 ± 23.3 [27]
ABAT L4-L5, cm^3	-26.9 ± 43.4 [29]	-22.5 ± 32.3 [31]	-27.9 ± 38.9 [27][a]
Total SM, kg	0.4 ± 0.9 [29]	0.9 ± 0.9 [31]	0.3 ± 0.9 [27]
Metabolic			
Blood Glucose, Mm	-0.2 ± 0.4 [29]	-0.1 ± 0.5 [29]	-0.3 ± 0.5 [25][a]
Glucose Uptake, mg/kgsm/min	3.4 ± 3.8 [29]	2.1 ± 4.2 [29]	2.2 ± 3.8 [25]
Plasma Insulin, UI	-1.2 ± 4.1 [29]	-0.7 ± 4.2 [31]	-0.7 ± 3.2 [26]
Systolic BP, mmHG	0.2 ± 10.3 [27]	-0.6 ± 6.6 [27]	-2.9 ± 13.1 [24]
Diastolic BP, mmHG	-0.7 ± 8.5 [27]	-0.4 ± 5.9 [27]	-2.4 ± 9.2 [24]
VO_{2max}, ml/kg/min	3.3 ± 4.4 [29]	3.5 ± 4.2 [30]	4.8 ± 4.8 [28][c]

Based on transformed variables; raw data is presented in table. Data are means ± SD [N]. [1] indicates column 1 is significantly different than column 2 ($p<0.05$). [2] indicates column 1 is significantly different than column 3 ($p<0.05$). [3] indicates column 2 is significantly different than column 3 ($p<0.05$). [a] indicates an effect for gender ($p<0.05$). [b] indicates an effect for age ($p<0.05$). [c] indicates an effect for exercise modality ($p<0.05$). AT Adipose Tissue; ASAT Abdominal subcutaneous adipose tissue; VAT Visceral adipose tissue; ABAT Abdominal adipose tissue; SM Skeletal muscle; BP Blood pressure; VO_{2max} Maximal oxygen consumption.

Figure 1. Individual changes in (A) bodyweight, (B) visceral fat, and (C) glucose uptake.



DISCUSSION

The primary finding of this study is that no relationship exists between the inter-individual change in bodyweight and corresponding changes in body composition and metabolic risk factors in response to minimal or no weight loss. Indeed, regardless of whether individuals gained some weight, had no weight change, or lost some weight (e.g., +1 to -3kg), aerobic and/or resistance exercise combined with a healthful diet resulted in significant reductions in obesity and related co-morbid conditions. Given current dogma that clinically significant weight loss (e.g., > 5%) is necessary to improve health, our findings have considerable relevance to public health. Indeed, the present study illustrates that regardless of the degree of weight change, most individuals who complete lifestyle-based interventions with minimal weight change will derive health benefits.

Leading health authorities state that a clinically relevant weight loss of 5 to 10% of bodyweight is necessary for positive health benefit[4], while others suggest that a change in weight of less than 3% should be considered weight maintenance[135]. Although it is clear that a lifestyle-induced weight loss of greater than 5% is associated with health benefit in a gradient manner[119], a growing body of literature suggests that clinically significant health improvements are associated with minimal or no change in bodyweight[14]. The current findings are consistent with prior studies[148, 172, 173], in that, based on the group response, we observed significant reductions in obesity and associated risk factors despite the absence of weight loss. However, as with prior studies, analysis based on the mean response of a group may be misleading, as it is possible that the reduction in obesity and related co-morbidities was driven entirely by those within the

group who lost weight. In response we examined the inter-individual response to lifestyle intervention and observed no relationship between weight change and corresponding improvement in obesity and related health risk factors. Stated differently, regardless of the degree of weight change ($\leq$ -3 to $\leq$ +1), health benefits were similar across individuals independent of gender.

That we observed a significant improvement in insulin sensitivity independent of weight loss and/or change may be partially explained by the significant reduction in VAT (see Figure 1), a strong predictor of insulin sensitivity[72]. Improvement in the metabolic efficiency of SM (e.g., increases in protein content of GLUT4) consequent to exercise may also contribute to the improvement in glucose and/or insulin dynamics[160-162].

A recent study by Dalle Grave and colleagues[174] observed a 52% drop-out rate at 12-months for obese subjects seeking treatment. While unrealistic baseline weight loss expectations were associated with attrition from treatment, more than 80% of those who withdrew stated concern for present or future health as the primary reason for seeking treatment. Combined with those of Dalle Grave[174], our findings are encouraging and have important implications not only for the development of public health policy, but also for individuals whose sole criteria for gauging obesity treatment success is reduction in weight. These findings stress the importance of constant dialogue and realistic weight loss expectations between the clinician and the treatment seeking individual, while acknowledging positive health benefit in the absence of weight loss.

It is noteworthy that in the present study, the duration of exercise was within the current health guidelines recommended by Canada's Physical Activity Guide to Healthy Active Living (30-60 minutes of physical activity 4-7 days/week)[175], while the healthful diet was easily followed using Canada's Food Guide[176]. Thus, the lifestyle program each individual was assigned to was very pragmatic, as evident by the high adherence rate, and has the potential to translate well outside of the laboratory setting. Additionally, there is health benefit in the absence of a strict diet, allowing individuals who find caloric restrictions difficult to continue with a healthy lifestyle.

It is important to note that the levels of obesity and health risk reduction observed in this study are less than those generally seen in response to weight loss, thus reinforcing current guidelines that recommend weight loss as the principal therapy for overweight and obese individuals[4, 11]. Our findings extend the current guidelines to suggest that exercise without weight loss represents another strategy for obesity and health risk reduction, especially for those individuals who are resistant to significant weight loss, which often occurs during the early stage of initiating a program of obesity reduction. Additionally, we observed (~14%) improvements in CRF, a measure of exercise capacity, that is associated with numerous reductions in health risk factors, CVD, and all-cause mortality independent of BMI[177-179].

Limitations of this study warrant mention. Since our study consists primarily of Caucasian men and women, it remains unclear whether the same is true for other ethnic groups.

The strengths of our study include the use of criterion methods, namely MRI for measurements of SM and AT volumes, and ASAT and VAT images. Also, the use of the hyplerinsulinemic-euglycemic clamp was essential in determining glucose disposal rates. Both MRI and the hyperinsulinemic-euglycemic clamp reinforced the rigor of our study design.

In summary, our study demonstrates that no gradient exists between the inter-individual change in bodyweight and corresponding changes in body composition and metabolic risk factors in response to minimal or no weight loss. Although the levels of obesity and health risk reduction in this study are less than those generally observed in response to weight loss greater than 5 to 10%, our findings have important clinical health implications. The resistance to weight loss that often occurs during the early stages of a behavioural change designed to reduce obesity may be extremely discouraging to an individual to the point of discontinuation. Recognition that changes in WC and/or CRF are occurring in the absence of weight change could be very encouraging for the individual, and this presents the clinician with an opportunity to acknowledge benefit.

Chapter 4

General Discussion

4.1 Implications of the Study

Although previous investigations have clearly established that clinically significant weight loss is not necessary to reduce obesity and related metabolic risk factors[14], it is unclear if those who did lose weight, albeit minimally, had exaggerated health improvement, possibly masking the diminished health of those who failed to lose any weight. No relationship exists between the inter-individual change in bodyweight and corresponding changes in body composition and metabolic risk factors in response to minimal or no weight loss, independent of gender. Furthermore, our findings corroborate previous reports, in that, based on a group response, we observed significant reductions in obesity and associated risk factors despite the absence of weight loss.

In accordance with previous reports of favoured AT reduction following lifestyle-based interventions both with and without clinically significant weight change[180, 181], independent of gender, we observed a greater reduction in VAT (7.4%) compared to ASAT (3.7%). As VAT is an independent predictor of morbidity and mortality, the fact that VAT is utilized more readily than ASAT, these results underline the importance of exercise as either a weight loss or weight maintenance tool.

Finally, WC, a simple marker of abdominal obesity and a strong predictor of morbidity and mortality independent of BMI[40, 49] was reduced (2.4%) significantly, while CRF, a measure of exercise capacity associated with reductions in health risks, CVD, and

all-cause mortality independent of BMI[177-179] was improved (13.9%) significantly. The aforementioned benefits of exercise in the absence of weight loss, including reductions in VAT and WC, as well as improvements in CRF should stress the importance of physical activity and encourage individuals to not gauge treatment success solely by weight loss.

4.2 Limitations of the Study

The use of a predominately Caucasian sample of men and women limits the generalization of our findings across other ethnic groups. Additionally, the omission of blood lipid measures due to our inability to detect a significant change may be caused by any number of things. Specifically, for a significant change in blood lipids to occur, a clinically significant weight loss may be necessary.

4.3 Strengths of the Study

The use of various criterion methods, namely MRI for measurements of SM and AT volumes, and ASAT and VAT images at L4-L5 inter-vertebral space, and the hyperinsulinemic-euglycemic clamp for measurements of glucose disposal rates.

4.4 Future Directions

As alluded to previously, although we found that no gradient exists between changes in bodyweight and corresponding changes in health risk, we did not detect a change in any of the blood lipids measured. Thus, an important future endeavour would be to confirm our findings and investigate whether blood lipids improve following lifestyle-based interventions with minimal or no weight loss in a larger study sample.

Additionally, it would be interesting to learn if these findings are applicable to other ethnic groups.

Furthermore, as it is well documented that excess accumulation of VAT is independently associated with morbidity and mortality, future studies should consider utilizing VAT images of the entire abdominal area, not just images at L4-L5 inter-vertebral space, to get a better understanding of VAT reduction following lifestyle-based interventions with minimal or no weight loss. In step, with the knowledge that various health benefits following acute bouts of exercise can be attributed to the improved metabolic efficiency of SM, it would be interesting to determine if health benefits following chronic bouts of exercise with minimal or no weight loss could be attributed to reductions in VAT.

Finally, given that leading health authorities recommend a clinically significant weight loss to improve health, our findings have considerable relevance to public health. Indeed, our findings place the clinician in a very positive position, where, through dialogue with the treatment seeking individual can acknowledge the benefits of weight loss, while stressing the importance of realistic weight loss expectations and identifying the positive health benefits associated with exercise combined with a healthful diet in the absence of weight loss.

Chapter 5

Summary and Conclusions

It is well established that increasing levels of obesity, as commonly assessed using BMI, are mirrored by increasing rates of morbidity and mortality[4, 5]. As a result, leading health authorities suggest treatments designed to reduce bodyweight, specifically a clinically relevant weight loss of 5 to 10%[4, 10-12]. Recent evidence, however, suggests that weight loss is not necessary to reduce obesity and related metabolic risk factors[14], but it remains unknown if this observation is driven solely by those individuals who did lose weight, albeit minimally. To our knowledge, this is the first study performed specifically examining whether a gradient exists between the inter-individual change in bodyweight and corresponding changes in body composition and metabolic risk factors in response to minimal or no weight loss. The novel finding of our study is that independent of gender, no relationship exists between the inter-individual change in bodyweight and corresponding changes in body composition and metabolic risk factors in response to minimal or no weight loss. Stated differently, regardless of the degree of weight change ($\leq$ -3 to $\leq$ +1), health benefits were similar across all individuals independent of gender.

From a clinical perspective, our results suggest that clinicians and treatment-seeking obese individuals look beyond the bathroom scale to gauge treatment success. In addition to measures of BMI in the assessment of health risk, clinicians should also include measures of WC and CRF to better predict health risk and possible benefits of treatment. As well as the link between WC and metabolic risk that may be explained by

its strong association with VAT (Ross et al, 1992), WC[182] and sagittal abdominal diameter (SAD)[183] have also been shown to be relatively strong anthropometric predictors of insulin resistance. With the knowledge that unrealistic baseline weight loss expectations are associated with attrition from treatment[174], these findings empower the clinician to stress realistic weight loss expectations, while acknowledging positive health benefits in the absence of weight loss. Future endeavours are needed to confirm and expand upon our findings with a larger study sample to arouse the notion that individuals participating in physical activity combined with a healthful diet in the absence of weight loss can attain clinically significant health improvements.

Chapter 6

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Appendix A

Informed Consent

CONSENT TO VOLUNTEER FOR PARTICIPATION IN A STUDY

TITLE: **Prevention and treatment of abdominal obesity and related insulin resistance in elderly men and women**

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You are invited to participate in a research study on the influence of aging and exercise on abdominal fat and insulin resistance. The following brief is intended to provide you with the details you should be aware of prior to your consent as a participant in this study. Please read the following information carefully and feel free to ask any question that you may have.

BACKGROUND INFORMATION

Many elderly people have problems keeping their blood glucose (sugar) levels normal, a condition referred to as "insulin resistance" by scientists and medical doctors. Although the reasons associating aging with insulin resistance are unclear, the increase in fat in the abdominal region is at least in part responsible for the increased insulin resistance. A reduction in physical activity with aging may also contribute to an increase in insulin resistance.

Recent studies have shown a relationship between muscle lipid (fat) content and insulin resistance in young healthy individuals and persons with diabetes. This is important as the amount of fat within the muscle increases with aging. Thus, muscle fat may partially explain why insulin resistance increases with age. However, at this time it is unknown whether or not muscle fat content is related to insulin resistance with aging.

Although muscle fat content is associated with insulin resistance, we also know that muscle fat content is increased in individuals who exercise on a regular basis. This is important because individuals who exercise on a regular basis are very insulin sensitive (opposite to insulin resistance). Thus, it appears that an increase in muscle fat content does not always suggest a person will become insulin resistant. An important question to ask then is whether the muscle fat in insulin resistant (e.g., sedentary elderly) and insulin sensitive (e.g., physically active elderly) individuals follows the same pattern. We will also be looking at whether the normal insulin sensitivity seen in physically active elderly persons is due to changes in skeletal muscle fat content.

Exercise is thought to be a good thing to do for reducing both abdominal fat and insulin resistance. However, whether aerobic (e.g., walking) or resistance-type exercise (e.g., weight lifting) is best for reducing either is unknown. Further, whether the two forms of exercise combined (aerobic and resistance exercise) is better than either one alone for reducing abdominal fat and insulin resistance is unknown. This is especially true for older persons.

Therefore, you are invited to participate in a study to assess the relationships between exercise, abdominal fat, muscle fat, and insulin resistance. We hope that the results of this study will provide a better understanding of the reasons for the age-related increase in insulin resistance. In addition, we hope to determine whether regular exercise, and more importantly what type of exercise, can prevent the insulin resistance common to the aging process. As insulin resistance is a major predictor of diabetes and cardiovascular disease, these results may have important implications for developing ways to prevent and treat diabetes and cardiovascular disease in elderly persons.

EXPLANATION OF PROCEDURES

Pre-participation screening

You will be required to have a medical exam prior to participation in this study. The examination will be performed by your family physician. In addition to the medical examination, you will have a fasting blood test to measure your blood sugar levels. This procedure is explained in further detail on page five (5) of this form.

Study Protocol

The study will be approximately 7 months in duration. The exercise part of the study will last 6 months. The 6-month exercise period will begin and end with a 3-week weight maintenance period - thus about 7 months in total. By volunteering to participate in this study, your name will be selected by chance and placed into one of the following four groups: (1) Control - no exercise, (2) Aerobic (walking) exercise, (3) Resistance exercise, (4) Aerobic and Resistance exercise.

Control Group: For the entire study the men and women in this group will consume a diet that will maintain bodyweight. Thus there will be no weight loss or exercise.

Aerobic Exercise Group: As a participant in the aerobic exercise group you will be asked to perform walking type exercise on a motorized treadmill for 30 minutes, 5 times per week, at about 65% of your cardiovascular fitness level (e.g., brisk walking) for the duration of the 6 month treatment period. During each exercise

session we will measure your heart rate every 5 minutes using an automated heart rate monitor. All of your exercise sessions will be by appointment and performed under supervision within our laboratory at Queen's.

Resistance Exercise Group: As a participant in this group you will be asked to perform a series of 10 exercises, 3 times per week, for the duration of the 6 month treatment period. Eight of the exercises will be performed using Nautilus strength training equipment and 2 using your own body weight (e.g., sit-ups). All resistance exercise sessions will be supervised by a qualified undergraduate or graduate level student and performed within Dr. Ross' laboratory at Queen's.

Aerobic and Resistance Exercise Program Combined: As a participant in this group you will perform an exercise regimen that combines resistance and aerobic exercise. The resistance exercise program will be the same as that described for the resistance exercise only group. In addition, the aerobic exercise will be performed at the same intensity (~65% of your cardiovascular fitness for 30 minutes) on 3 days of the week. In general, the aerobic exercise (e.g.,brisk walking) would be performed on the days when resistance exercise is not performed. Thus if you are a participant in this group you will exercise 6 days of the week.

Diet Program: All participants in each group will eat the same type of foods. The diet will consist of regular foods that you will buy and prepare yourself. All aspects of the diet plan will be explained to you by a nutritionist. The session will take place at the beginning of the study, with several additional sessions planned throughout to help you follow the diet plan. If someone else shops for your food or prepares your meals, or if you share those tasks with someone else, that person is invited to meet with the nutritionist as well. You will be required to record the food you eat each day for the duration of the study. All of your meetings with the nutritionist will be in Dr. Ross's laboratory within the Physical Education building at Queen's.

At the beginning of the study, using the diet records that you complete, the number of calories required to maintain your body weight will be determined. During the study we will ask you to maintain this caloric intake. In other words, eat an amount of food that would normally maintain your body weight. Thus any weight loss you experience will be the result of an increase in exercise.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a method for imaging or creating pictures of body structures or organs. MRI gives images in slices comparable to those produced by x-ray tomography (e.g., CT scan). One of the primary advantages of MRI is that it does not employ x-rays or other forms of radiation. Instead, a large magnet, a radio transmitter/receiver and a computer are used to gather chemical information from the body, and to produce images or pictures of internal anatomy. No harmful effects have been associated with MRI under existing conditions of use. It is important that you fill out the enclosed MRI questionnaire to determine if there is any reason why you should not have the MRI exam.

As mentioned, the MRI procedure is very similar to a scanner examination. You will be placed on a table and moved smoothly into the scanner. A loud-speaker within the magnet makes it possible for you to keep in constant contact with the staff. At all times the operator can see and hear you and if you need help or have questions, you can be removed from the machine if necessary. The whole procedure takes about 35 minutes and will be performed by appointment at Kingston General Hospital.

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) works the same way that MRI does. You will be positioned in the magnet as in the MRI test. The difference is that MRS does not provide pictures of the body. Instead, the radio signal emitted from the body is used to provide information about where the fat is positioned within your muscle. In other words, MRI provides pictures of muscle and fat, which tell us about the quantity of muscle and fat. Information obtained using MRS tells us something about the quality of muscle. As with MRI, the MRS procedure will be performed at Kingston General Hospital and will take about 30 minutes to complete.

Computerized Tomography (CT)

Computerized tomography or CT is another method that will be used to obtain information about the quality of your muscle and your liver. Unlike MRI, CT provides pictures of the muscle and liver that can be used to determine the

amount of fat in your liver and muscle. Specifically, two CT images of your mid-thigh will be obtained to measure the amount of fat in the muscle; one CT image of the liver will be obtained to determine the amount of fat in the liver. You will be asked to lie on an exam table while the CT scan is being performed. The entire CT procedure will take about 10 minutes.

Dual Energy X-Ray Absorptiometry (DEXA)

DEXA measures whole body fat, bone quality, and skeletal muscle. For this test you lie on your back on a table. The scanner moves above you measuring the transmission of X-rays from a source under the table. During this procedure you are asked to lie still for approximately 20 minutes. The radiation exposure involved with this test is approximately equivalent to one percent of a chest X-ray. This measurement will take place by appointment and be performed within the Department of Radiology at Kingston General Hospital.

Anthropometry (Skinfolds and Circumferences)

Many circumference measurements will be taken at numerous sites on your body. These measures can be used to derive estimates of body composition. In addition, through the use of skinfold calipers, skinfold thickness will be measured at 8 different sites on your body. The anthropometric measurements require about one hour to complete and will be obtained at the School of Physical and Health Education, Queen's University.

Bioelectrical Impedance

This is a very simple and safe procedure requiring no more than 5 minutes to complete. While you lie on your back, 2 electrodes will be placed on the surface of your right hand and foot. Two of the electrodes will introduce an alternating current that you can't feel into the body, while the other 2 record the resistance. The results are used to determine body composition. The bioelectrical impedance measurements will be obtained at the School of Physical and Health Education, Queen's University.

Assessment of Cardiovascular Fitness

We will measure your cardiovascular fitness (endurance) using a treadmill procedure. The test will begin at a level you can easily accomplish and will be advanced in stages, depending on your capacity to do so. We may stop the test at any time because of signs of fatigue or you may stop the test because of personal feelings of fatigue or discomfort.

The treadmill test involves risks comparable to any strenuous exercise situation. They include very rare instances of abnormal blood pressure, fainting, disorders of the heartbeat, and heart attack. Every effort will be made to minimize your risk by preliminary medical examination and observation during the test. Your fitness test will be conducted by a graduate student in the presence of a paramedic. You will perform the exercise test 3 times: once at the beginning, once after one month, and once at the end of the exercise training period.

Assessment of Muscular Strength

Improvement in muscular strength will be assessed before and at weeks 8, 16 and 24 using a 3-repetition maximum (3RM) test. The 3RM is defined as the maximal resistance that could be moved through the full range of motion for 3 repetitions.

Laboratory measurements (blood glucose (sugar) and lipid (fat) tests)

The measurement of how much sugar and fat are in your blood will be done at Hotel Dieu Hospital. To determine your ability to manage blood sugar you will be asked to perform two (2) separate tests. The first test, an Oral Glucose Tolerance Test or OGTT, will be performed after an overnight fast. You will be asked to arrive at the hospital at about 8am after an overnight fast (no eating after 7pm the night before). The first step of this test will involve a venipuncture with a needle and the removal of about 30 ml (3 tablespoons) of blood from a vein in your arm. The only risk from this procedure is possible local pain and bruising at the time of the blood test. In addition, you will be asked to drink a fluid that contains 75 grams of sugar (like an orange drink). At 30-minute intervals for 2 hours after drinking the sugar solution, a small amount of blood will be taken from a vein in your arm for the purpose of measuring the amount of sugar in the blood.

The second test will also be performed after an overnight fast, and, after having not exercised on the prior 3 days. This procedure will also be performed at Hotel Dieu Hospital. Having arrived at the hospital you will be asked to lie comfortably on a bed for about 4 hours. Catheters (needles) will be placed in a vein on the top of one hand and in a vein in both arms. A catheter in one arm vein will be used to give glucose (sugar) and insulin at a rate designed to keep blood sugar level normal for 3 hours. Every 5 minutes during this procedure a small amount of blood will be taken from a vein in your hand to measure blood sugar to ensure that it remains normal. A physician will monitor this procedure at all times.

The purpose of these tests is to determine your ability to maintain normal blood sugar levels (insulin sensitivity). Reduced sensitivity to insulin is a complication of aging and may be associated with diabetes mellitus, high blood pressure, and other health problems. These tests should not have any lasting side effects.

Summary of Appointments and Time Requirements

For the testing you will be required to make one 2-hour appointment at the Queen's University Physical Education Centre to complete the cardiovascular fitness, anthropometry, and bioelectrical impedance tests. We will arrange four appointments for you at Kingston General Hospital and Hotel Dieu Hospital. One $2^{1/2}$-hour appointment for the oral glucose tolerance test (Hotel Dieu Hospital); one 5-hour appointment for the insulin sensitivity and blood lipid/cholesterol tests (Hotel Dieu Hospital); one 2-hour appointment to complete the MRI, MRS, (Kingston General Hospital) and CT tests (Hotel Dieu Hospital); and one 30-minute appointment for the DEXA test. All of these appointments will be scheduled at a time that is convenient for you. Further, each of these tests will be performed twice, once at the beginning and once at the end of the treatment period.

Risks and Benefits

You will gain no direct benefit through participation in this study. Participation may involve some risks. The known risks are:

1) Insertion of a catheter in your arm or hand vein may cause bruising, bleeding, soreness or infection.

2) Computerized Tomography (CT). Participation in this research study will

involve a small radiation exposure (1.0 RAD or 2.0 RAD) from the CT scan to a small region of your thighs and chest (liver). For comparison, a radiation worker is allowed 5 RADS of whole body exposure per year.

3) The effective dose (the term used to describe your exposure to radiation) that you will receive during the Dual Energy X-ray Absorptiometry (DEXA) exam is approximately 5 microsieverts. The average background radiation that you are exposed to on a daily basis is estimated to be approximately 10 microsieverts. Thus the DEXA exam adds approximately half the daily background radiation.

For CT and DEXA, there is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects or cancer. However, the risk associated with the amount of radiation exposure you will receive from these procedures is considered to be very low and comparable to other everyday risks.

4) MRI or MRS has certain conditions which would exclude you from participating in this study. These include cardiac pacer, aneurysm clip, cochlear implant, intra-uterine device (IUD), shrapnel, neurostimulators or other metal devices. Metal objects present in the body could be moved by the large magnet involved in the MRI, and such movement could cause serious injury. Fear of closed spaces is also a reason you would be excluded from the study. No serious biological effects have been reported from being in a magnet. If you experience a fear of the confined space while in the magnet, you can terminate the study. Trained personnel are always in attendance during these studies.

5) The risk of receiving insulin (as in the test at Hotel Dieu Hospital in which your sensitivity to insulin is measured) is the development of hypoglycemia (blood sugar which is too low). Because we give you glucose (sugar) throughout the test, and, your blood sugar levels are measured every 5 to 10 minutes, the likelihood of your having a low blood sugar is very low. The symptoms of low blood sugar include increased sweating, fast heart rate, feeling shaky and/or hungry. In very rare cases when your blood sugar levels fall to low, seizures or death may occur.

6) The exercise test may cause muscle soreness or fatigue. In any individual

there is a minute risk of a heart attack or death from the exercise test. A trained paramedic or medical doctor will be present. If you develop chest pain the test will be stopped immediately.

You should inform the investigators if you have participated in any other research study during the previous year. This will help to ensure that you have not been exposed to a procedure in another study that may influence your ability or eligibility to participate in this one. You should understand that this study is a research study and may not be of direct benefit to you. If requested, a report will be generated for your medical record, which will include any information important for your medical care.

CONFIDENTIALITY

All information obtained during the course of this study is strictly confidential and your anonymity will be protected at all times. Your information will be kept in locked files and will be available only to Dr. Robert Ross and those working within his laboratory. Your identity will not be revealed in any description or publication.

In the event you that you are injured as a result of taking study medications or of the study procedures, medical care will be provided to you until resolution of the medical problem. By signing this consent form, you do not waive your legal rights nor release the investigator(s) and sponsors from their legal and professional responsibilities.

Financial remuneration will not be provided to you for participation in this study.

VOLUNTARY CONSENT

I have been given an opportunity to ask any questions concerning the procedures. All of my questions regarding the research project have been satisfactorily answered. I understand that my test results are considered confidential and will never be released in a form that is traceable to me, with the exception of my family physician or myself. I do understand that I am free to deny consent if I so desire, and may withdraw from the study at any time without prejudicing current or future medical care.

Should I have any questions about the study, I know that I can contact any of the following: Dr. Robert Ross (533-6583), Dr. Robert Hudson (533-2973), Dr. Janice Deakin, Head, School of Physical and Health Education (533-6601), Dr. Donald Brunet, Head, Department of Medicine (533-6327), or Dr. Albert Clark, Chair of the Ethics Review Board at Queen's (533-6081). A copy of this consent form will be provided me for my records. My signature below means that I freely agreed to participate in this study.

_____ _____

Date: **Volunteer's Signature**

_____

Witness' Signature

STATEMENT OF INVESTIGATOR

I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to participants in this study.

Principal Investigator's Signature **Date**

_____ _____

Appendix B

Sample of Statistical Analyses Used to Derive Manuscript Results

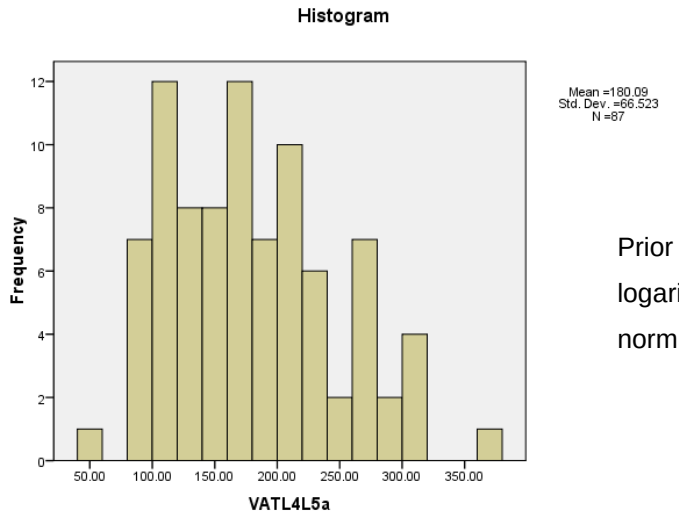
Example of a base-10 logarithm to normalize data

Tests of Normality

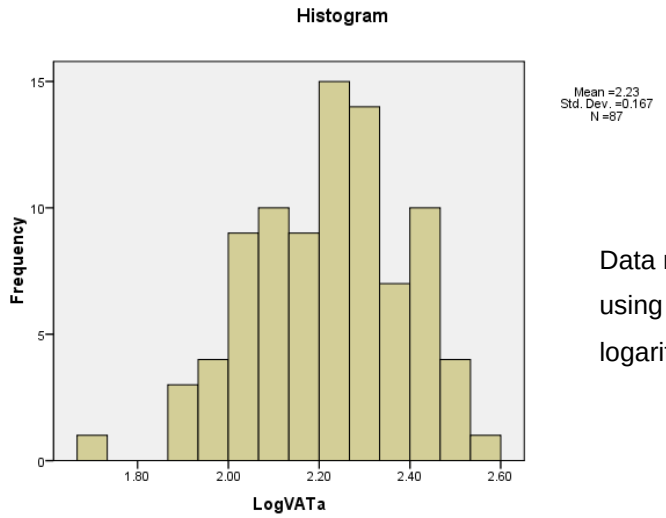
	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
VATL4L5a	.075	87	.200*	.970	87	.041
LogVATa	.078	87	.200*	.983	87	.333

a. Lilliefors Significance Correction

*. This is a lower bound of the true significance.



Prior to base-10 logarithm to normalize data.



Data normalized using a base-10 logarithm.

Example of independent-samples T-test

Group Statistics

	Gender	N	Mean	Std. Deviation	Std. Error Mean
WaistLR1	Female	42	1.0158E2	9.17920	1.41638
	Male	46	1.1087E2	6.97095	1.02781

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
WaistLR1	Equal variances assumed	3.367	.070	-5.376	86	.000	-9.29187	1.72854	-12.72809	-5.85566
	Equal variances not assumed			-5.310	76.278	.000	-9.29187	1.75001	-12.77711	-5.80663

Example of repeated measures ANOVA

Within-Subjects Factors

Measure:MEASURE_1

time	Dependent Variable
1	VO2kg1
2	VO2kg2

Between-Subjects Factors

		Value Label	N
Gender	1	Female	41
	2	Male	46

Descriptive Statistics

	Gender	Mean	Std. Deviation	N
VO2kg1	Female	22.7479	4.07933	41
	Male	32.1216	6.92637	46
	Total	27.7041	7.41564	87
VO2kg2	Female	25.2818	4.77414	41
	Male	37.1368	9.69892	46
	Total	31.5499	9.75959	87

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.
time	Pillai's Trace	.387	52.346[a]	1.000	83.000	.000
	Wilks' Lambda	.613	52.346[a]	1.000	83.000	.000
	Hotelling's Trace	.631	52.346[a]	1.000	83.000	.000
	Roy's Largest Root	.631	52.346[a]	1.000	83.000	.000
time * Age	Pillai's Trace	.164	16.244[a]	1.000	83.000	.000
	Wilks' Lambda	.836	16.244[a]	1.000	83.000	.000
	Hotelling's Trace	.196	16.244[a]	1.000	83.000	.000
	Roy's Largest Root	.196	16.244[a]	1.000	83.000	.000
time * ExerciseMode	Pillai's Trace	.022	1.830[a]	1.000	83.000	.180
	Wilks' Lambda	.978	1.830[a]	1.000	83.000	.180
	Hotelling's Trace	.022	1.830[a]	1.000	83.000	.180
	Roy's Largest Root	.022	1.830[a]	1.000	83.000	.180
time * Gender	Pillai's Trace	.029	2.517[a]	1.000	83.000	.116
	Wilks' Lambda	.971	2.517[a]	1.000	83.000	.116
	Hotelling's Trace	.030	2.517[a]	1.000	83.000	.116
	Roy's Largest Root	.030	2.517[a]	1.000	83.000	.116

a. Exact statistic

b. Design: Intercept + Age + ExerciseMode + Gender
Within Subjects Design: time

Example of linear regression

Variables Entered/Removed[b]

Model	Variables Entered	Variables Removed	Method
1	WeightChg[a]	.	Enter

a. All requested variables entered.

b. Dependent Variable: VATchg

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.101[a]	.010	-.001	25.04019

a. Predictors: (Constant), WeightChg

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	553.396	1	553.396	.883	.350[a]
	Residual	53295.965	85	627.011		
	Total	53849.361	86			

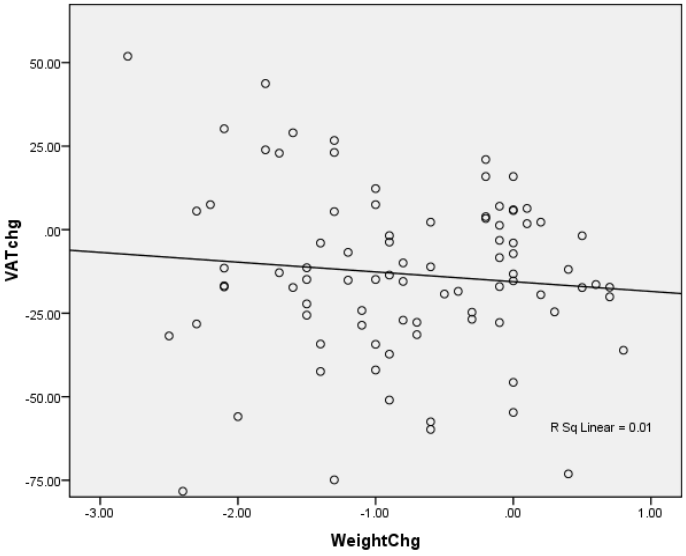
a. Predictors: (Constant), WeightChg

b. Dependent Variable: VATchg

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-15.558	3.625		-4.292	.000
	WeightChg	-2.919	3.107	-.101	-.939	.350

a. Dependent Variable: VATchg



Example of univariate ANOVA and tukey post-hoc test

Between-Subjects Factors

		Value Label	N
WeightChgPGroup	1	-3 to -1.5%	29
	2	-1.5 to -0.2%	29
	3	-0.2 to 1%	30

Descriptive Statistics

Dependent Variable:WaistChg

WeightChgPGroup	Mean	Std. Deviation	N
-3 to -1.5%	-3.0345	2.10480	29
-1.5 to -0.2%	-3.2017	2.59579	29
-0.2 to 1%	-1.5833	2.29032	30
Total	-2.5949	2.42548	88

Tests of Between-Subjects Effects

Dependent Variable:WaistChg

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	50.911[a]	5	10.182	1.812	.120
Intercept	31.189	1	31.189	5.549	.021
Gender	.186	1	.186	.033	.856
Age	3.266	1	3.266	.581	.448
ExerciseMode	.032	1	.032	.006	.940
WeightChgPGroup	48.641	2	24.320	4.327	.016
Error	460.904	82	5.621		
Total	1104.357	88			
Corrected Total	511.815	87			

a. R Squared = .099 (Adjusted R Squared = .045)

Multiple Comparisons

WaistChg
Tukey HSD

(I) WeightChgPGroup	(J) WeightChgPGroup	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
-3 to -1.5%	-1.5 to -0.2%	.1672	.61412	.960	-1.2977	1.6322
	-0.2 to 1%	-1.4511	.60898	.050	-2.9039	.0016
-1.5 to -0.2%	-3 to -1.5%	-.1672	.61412	.960	-1.6322	1.2977
	-0.2 to 1%	-1.6184*	.60898	.025	-3.0711	-.1657
-0.2 to 1%	-3 to -1.5%	1.4511	.60898	.050	-.0016	2.9039
	-1.5 to -0.2%	1.6184*	.60898	.025	.1657	3.0711

Based on observed means.
The error term is Mean Square(Error) = 5.469.

*. The mean difference is significant at the .05 level.